The PARTNER II Trial with Registries:

Placement of AoRTic TraNscathetER Valves Trial II

The Safety and Effectiveness of the SAPIEN XT™ Transcatheter Heart Valve with NovaFlex and Ascendra delivery systems in Intermediate and High Risk for Aortic Valve Surgery and Patients Who Cannot Undergo Surgery and the SAPIEN 3 Transcatheter Heart Valve with Associated Delivery Systems in High Risk or Inoperable Patients with Severe Symptomatic Aortic Stenosis

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Edwards SAPIEN XT™ and Edwards SAPIEN 3 Transcatheter Heart Valve Therapy

US IDE Pivotal Trial

Sponsor Trial #2010-12-US

IDE # G090216

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INVESTIGATIONAL PLAN SUMMARY

Title

The PARTNER II TRIAL "Placement of AoRTic TraNscathetER" Valves Trial" (US)
[Edwards Study 2010-12]

Purpose

The purpose of this trial is to establish the safety and effectiveness of the Edwards SAPIEN XT™ and the Edwards SAPIEN 3 Transcatheter Heart Valve device and delivery systems (transfemoral, transapical and transaortic), which are intended for use in patients with symptomatic, calcific, severe aortic stenosis.

Design

A prospective randomized, multi-center trial with two population cohorts for the Edwards SAPIEN XT™ device: 1) patients who are designated to have intermediate and high risk for surgical aortic valve replacement (operable) and 2) patients who are not suitable for aortic valve surgery (inoperable), and a single Cohort (S3 Cohort) for the Edwards SAPIEN 3 Transcatheter Heart Valve device (S3 THV): patients who are designated to have high risk (STS ≥ 8%) for aortic valve surgery (operable) and patients who cannot undergo surgery (inoperable).

Edwards SAPIEN XT™ Cohorts: For consistency with the terminology of The PARTNER I Trial, the operable cohort will be designated as Cohort A and the inoperable cohort will be designated as Cohort B. For both Cohorts of the trial, patients randomized to the test arm will receive the SAPIEN XT™ THV with either the NovaFlex family (transfemoral) or Ascendra family (transapical or transaortic) delivery systems. Valve delivery access is to be determined by site investigators and case review process. Cohort A and Cohort B study designs are further detailed below.

S3 Cohort: The S3 Cohort is a single arm non-randomized, historical- controlled study independently powered to compare transcatheter heart valve therapy with the first generation (SAPIEN THV) system to transcatheter heart valve therapy with the third generation (SAPIEN 3 THV) system in patients who either have high risk for surgery or cannot undergo surgery (inoperable).

The PARTNER Trial site investigative team (heart team) consists of dedicated representatives from cardiac surgery, interventional cardiology, echocardiology, neurology,

study coordination and other multi-disciplinary team members consistent with a heart failure clinic model.

Trial Cohorts and Additional Registries

There are various Cohorts and registries within the trial construct listed as follows:

SAPIEN XT:

- Cohort A: Intermediate and High Risk
- Cohort B: Inoperable (enrollment complete)
- Nested Registries (6): (enrollment complete)
- Continued Access Nested Registries (6)

SAPIEN 3:

- S3 Cohort: Operable High Risk and Inoperable

Cohort A

Cohort A is a 1:1 randomized, controlled study independently powered to compare transcatheter heart valve therapy with traditional, open-heart aortic valve surgery (AVR) in intermediate and high risk patients. For the purposes of this study, intermediate risk is defined as STS $\geq$ 4. The trial is a non-inferiority design. Patients randomized to the treatment arm of Cohort A will receive an Edwards SAPIEN XT™ THV with either transfemoral, transapical or transaortic delivery access, depending on patient anatomical factors and investigator heart team determination for optimal access approach. Patients in the control arm of Cohort A will receive a surgical bioprosthetic heart valve via aortic valve replacement surgery. The proposed randomized sample size is set to 2000 patients, based on both the statistically justified size and the need to allow for possible lost to follow-up and other trial contingencies.

Endpoints for Cohort A

The primary safety and effectiveness endpoint for Cohort A is a non-hierarchical composite of events: death (all cause) and disabling stroke. The primary endpoint analysis will occur after the last patient enrolled reaches two year follow-up. Trial arm comparison will be a non-inferiority analysis.

The secondary safety and effectiveness endpoint is a non-hierarchical composite of various adverse events. The endpoint will be evaluated at two time points: (1) acute, covering events occurring out to 30 days or hospital discharge, whichever is longer; and (2) longer-term, covering events from 31 days to the 2 year closing date of the primary endpoint. As requested by the FDA the specific components of the composite are:

- all stroke and TIA
- myocardial infarction
- major vascular complication (VARC)
- life-threatening bleeding (VARC)
- reoperation or catheter-based intervention for:
  - valve thrombosis, valve displacement, or other valve placed
  - procedure-related complication
- pericarditis
- hemolysis
- mediastinitis
- endocarditis
- moderate or severe aortic insufficiency (VARC)
- possible or significant aortic stenosis (VARC)
- permanent pacemaker insertion
- new mitral valve dysfunction
- acute kidney injury (VARC)

Secondary Efficacy and Safety Endpoints for Cohort A Labeling

The p-values generated as a result of statistically analyzing the endpoints listed in this section will be Hochberg-adjusted to account for multiplicity. See Section 7.9 for more details on the Hochberg method and more detailed descriptions of these analyses.

1. Days alive and out of hospital (DAOH) to one year
2. NYHA at the one year visit
3. 6MWT at the one year visit
4. Valve area at the one year visit
5. Total aortic regurgitation at the one year visit
6. Device success (Cohort B only)
7. 6MWT improvement from baseline to one year

Cohort B

Cohort B is a 1:1 randomized, controlled study independently powered to compare transcatheter heart valve therapy with the first generation (SAPIEN THV) system to transcatheter heart valve therapy with the second generation (SAPIEN XT™ THV) system in patients who cannot undergo surgery (inoperable). Patients in the control arm of Cohort B will receive an Edwards SAPIEN™ THV with RetroFlex3 (transfemoral). Patients in the treatment arm of Cohort B will receive an Edwards SAPIEN XT™ THV with NovaFlex (transfemoral). The randomized sample size has been set to 500 patients, to allow for possible lost to follow-up and other trial contingencies.

Endpoints for Cohort B

The primary safety and effectiveness endpoint is a non-hierarchical composite of death (all cause), disabling stroke, and rehospitalization for symptoms of aortic stenosis and/or complications of the valve procedure. The primary endpoint analysis will occur after the last patient enrolled reaches one year follow-up. Trial arm comparison will be a non-inferiority analysis.

The secondary safety and effectiveness endpoint is a non-hierarchical composite of all stroke, major vascular complications and reintervention. Trial arm comparison will be a non-inferiority analysis analyzed with the Hochberg adjustment.

Endpoints S3 Cohort

The S3 Cohort consists of both operable high risk and inoperable patients, who will receive the Edwards SAPIEN 3 THV.

The S3 Cohort is a single arm non-randomized, historical- controlled study independently powered to compare transcatheter heart valve therapy with the first generation (SAPIEN THV) system to transcatheter heart valve therapy with the third generation (SAPIEN 3 THV) system in patients who either have high risk for surgery or cannot undergo surgery (inoperable). S3 THV will be available in 23, 26, and 29 mm sizes. The historical control group from the PARTNER I trial is described in detail in Section 15.0.

Total enrollment in the S3 Cohort will be 500 as justified in the sample size section below in this protocol.

It is anticipated that the enrolling sites are experienced SAPIEN sites therefore no roll-in will be permitted.

Endpoints for the S3 Cohort

Statistical analysis for the S3 Cohort will be based on comparison to a historical control group consisting of randomized Cohort A and Cohort B Test arm patients from the PARTNER I trial who received the Edwards SAPIEN THV. There will be no concurrent control.

The primary effectiveness endpoint for the S3 Cohort is a comparison of total aortic regurgitation at 30 days between Test (S3 THV) and historical control (SAPIEN THV). The analysis is a non-inferiority analysis. Superiority will be tested sequentially if non-inferiority is demonstrated.

The primary safety endpoint for the S3 Cohort is a non-hierarchical composite event of death, all stroke and major vascular complication at 1 year in accordance to PARTNER I definitions. PARTNER I definitions were selected to provide consistency and avoid adjudication bias. Importantly the components of the composite endpoint were selected to reflect the clinical impact of the design differences between S3 THV and SAPIEN THV. The analysis is a non-inferiority analysis. Superiority will be tested sequentially if non-inferiority is demonstrated.
For the primary effectiveness endpoint, the PARTNER I data will be reevaluated by the same ECHO Core Lab evaluating the S3 THV data. Common definitions will be used.

Secondary Efficacy and Safety Endpoints for S3 Labeling

The p-values generated as a result of statistical analyses for the endpoints listed in this section will be Hochberg-adjusted to account for multiplicity. See Section 7.9 for more details on the Hochberg method and more detailed descriptions of these analyses.

1. Days alive and out of hospital (DAOH) to one year
2. NYHA at the one year visit
3. Valve area at the one year visit

Additional Registries (NR1, NR2, NR3, NR4, NR5 and NR6)

In addition to the randomized Cohorts A and B, six single arm prospective registries are included in The PARTNER II Trial:

NR1: Inoperable Transapical Registry. Patients deemed eligible for Cohort B but do not have eligible transfemoral access may be enrolled into a registry for transapical delivery of the 23mm or 26mm SAPIEN XT™ THV. A maximum of 100 patients may be enrolled in this arm. Primary endpoint of this registry is freedom from mortality at one year. Non-powered secondary endpoints for

safety and effectiveness will be consistent with additional secondary endpoint analyses for both Cohorts A and B and as described below. Patients previously enrolled as a Cohort A control may not be enrolled in this registry.

NR2: Inoperable Registry for Transfemoral delivery of the 23mm or 26mm SAPIEN XT™ in 6-7mm transfemoral arteries. Upon close of enrollment for the randomized inoperable cohort (Cohort B), patients with transfemoral vessels 6-7mm may be enrolled in a registry. The importance of this registry is to ensure enough data is collected for labeling the NovaFlex in the inoperable patients with 6 – 7 mm vessels. More women can be treated that may have been otherwise excluded in Cohort B, due to small vessel sizes. A maximum of 100 patients may be enrolled in this arm. Primary endpoint of this registry is freedom from mortality, major vascular complications and major bleeding at 30 days. Non-powered secondary endpoints for safety and effectiveness will be consistent with additional secondary endpoint analyses for both Cohorts A and B and as described below.

NR3: Registry for Transcatheter Heart Valve in Aortic Surgical Valve Implantation (THV-SV). Enrollment in this registry is indicated for use in patients with failing aortic bioprosthetic surgical valve in patients with a surgical mortality or major morbidity ≥ 50% and meeting the sizing requirements for 23mm or 26mm SAPIEN XT™ THV. A maximum of 100 patients may be enrolled in this arm. Primary endpoint of this registry is freedom from mortality at one year. Non-powered secondary endpoints for safety and effectiveness will be consistent with additional secondary endpoint analyses for both Cohorts A and B and as described below. Guidelines developed and approved by the PARTNER Trial Executive Committee for the THV-SV registry are provided in Appendix R.

NR4: Inoperable Transaortic Registry. Patients deemed eligible for Cohort B but do not have eligible transfemoral access may be enrolled into a registry for transaortic delivery of the SAPIEN XT™ THV (23 mm or 26 mm). A maximum of 100 patients may be enrolled in this arm. Primary endpoint of this registry is freedom from mortality at one year. Non-powered secondary endpoints for safety and effectiveness will be consistent with additional secondary endpoint analyses for both Cohorts A and B and as described below. Patients previously enrolled as a Cohort A control may not be enrolled in this registry.

NR5: Inoperable Transfemoral Registry for the delivery of 29 mm SAPIEN XT™ in ≥ 7mm femoral arteries. A maximum of 50 patients may be enrolled in this arm. Primary endpoint of this registry is freedom from mortality at one year. Non-powered secondary endpoints for safety and effectiveness will be consistent with additional secondary endpoint analyses for both Cohorts A and B and as described below. Patients previously enrolled as a Cohort A control may not be enrolled in this registry.

NR6: Inoperable Transapical Registry for the delivery of 29 mm SAPIEN XT™ for Cohort B that do not have eligible transfemoral access. A maximum of 50 patients may be enrolled in this arm. Primary endpoint of this registry is freedom from mortality at one year. Non-powered secondary endpoints for safety and effectiveness will be consistent with additional secondary endpoint analyses for both Cohorts A and B and as described below. Patients previously enrolled as a Cohort A control may not be enrolled in this registry.

Continued Access Registries (NR1, NR2, NR3, NR4, NR5 and NR6)

FDA approved Amendment 3.0 (dated March 2013) for the Continued Access for the Registries. The purpose is to provide Continued Access for Registry patients (NR1, NR2, NR3, NR4, NR5 and NR6) for the study devices and obtain additional safety and effectiveness data for the PARTNER II Trial Inoperable candidates. The Edwards SAPIEN XT™ device and NovaFlex /Ascendra delivery systems (transfemoral, transapical and transaortic) used in these Registries are intended for use in inoperable patients with severe symptomatic, calcific aortic stenosis.

All primary and secondary safety and efficacy endpoints, follow-up visits, visit exam requirements and statistical analysis remain unchanged from the PARTNER II Protocol Version 4.0 (August 2012).

Enrollment will consist of a maximum of 500 continued access patients. Enrollment is not capped per Registry. Rather, enrollment will close when the number of patients enrolled in the Registries reach 500. Enrollment will continue until the date on which the trial sponsor is aware that the designated sample size has been obtained. Patients who havealready signed the informed consent form at that time will be allowed to be treated, provided that treatment assignment is completed within 30 days of the consent date.

Additional Safety Endpoints to be Evaluated:

1. Freedom from major vascular complications (VARC)
2. Freedom from all neurological events all stroke and TIA (VARC)
3. Freedom from myocardial infarction
4. Freedom from acute kidney injury (VARC)
5. Freedom from access site infections
6. Freedom from new permanent pacemaker
7. Freedom from atrial fibrillation at each visit

8. Procedure related complications composites: two endpoints based on VARC definitions
9. For Cohort A only, a non-hierarchical composite of all stroke, major vascular complications and reintervention. The endpoint will be evaluated at 30 days and 2 years.
10. Freedom from transfusion

Additional Effectiveness Endpoints:

1. Total days alive and out of hospital (from date of index procedure)
2. Clinical improvement per NYHA Class (from baseline)
3. Clinical improvement per Quality of Life instruments: (Cohort A: KCCQ, EQ5D, SF36 Cohort B: KCCQ, EQ5D, SF12)
4. Clinical improvement per 6 Minute Walk Test (from baseline)
5. Mean ICU and total index procedure hospital length of stay

Additional Trial Arm Valve Performance Endpoints:

1. Freedom from major aortic paravalvular leak
2. Improvement in hemodynamic function: effective orifice area
3. Improvement in hemodynamic function: mean gradient
4. Freedom from structural valve deterioration
5. Total aortic regurgitation

Neurological Outcomes

The PARTNER Trial Cohorts A and B signaled increased neurological outcomes [strokes and transient ischemic attacks (TIA)] versus control arms. Assessments of disability related to neurological events were limited in The PARTNER Trial, therefore warranting further study. The PARTNER II Trial Executive and Steering Committees recognize the clinical importance of potential neurological outcomes for patients undergoing cardiovascular procedures and recommended enhanced provisions for ascertainment, analysis and oversight of neurological outcomes in The PARTNER II Trial.

As a result, The PARTNER II Trial study oversight includes a Neurological Outcomes Principal Investigator to the Executive Committee (Thomas Brott, MD, Mayo Clinic Florida) as well as the addition of a dedicated neurologist to each study site team as well as the DSMB and the CEC committees. All neurological events in this Trial will undergo assessment and classifications for causality and severity through dedicated review by a CEC neurologist, followed by periodic DSMB reviews for overall outcomes. Stopping rules for stroke outcomes are included in the DSMB charter.

Also established in this protocol are neurological instruments (NIHSS, Modified Rankin Scale and Barthel Index) that will be administered in both treatment and control arms at baseline, post procedure, discharge, 30 days, 6 months, 1 year and annually through 5 years. To ensure the highest level of quality and consistency in neurological assessments, the assessments should be performed by a neurologist or a neurology fellow. If the neurologist or neurology fellow is not available within the time of the prescribed visit window, a certified team member may perform the tests. However, given the importance of procedure related neurological outcomes, the post procedure assessment must be performed a neurologist or neurology fellow.

Primary Analytical Subset

For the primary safety and effectiveness endpoint, the primary analytical subset will be the Intent-To-Treat population defined at time of randomization. For secondary endpoints the primary analytical subset will be the As-Treated population.

Analysis subsets for the S3 Cohort are specified in Section 15.0.

Enrollment

Enrollment will consist of a maximum of 4200 patients, including approximately 250 roll-ins; 2000 patients randomized on a 1:1 basis in Cohort A; 500 patients randomized on a basis of 1:1 in Cohort B, approximately 50 patients who may be randomized after the 2000 and 500 totals have been achieved. Additionally, up to 100 patients will be enrolled in each of the four registries (NR1, NR2, NR3, NR4) and 50 patients each in NR5 and NR6. Continued Access Registries (N1, NR2, NR3, NR4, NR5, NR6) will consist of a maximum of 500 patients. S3 Cohort will consist of a maximum of 500 patients.

For each Cohort (A and B), enrollment will continue until the date on which the trial sponsor is aware that the designated sample size has been obtained. Patients who have already signed the informed consent form at that time will be allowed to be randomized, provided that this additional randomization is completed within 30 days of the consent date. These additional patients will be considered part of the analysis cohort, and no subset analysis will be performed related to randomization before or after the 2000 and 500 totals had been met.

Sites that have not previously used either the SAPIEN™ or the SAPIEN XT™ devices will be allowed up to 3 roll-in patients per delivery system prior to initiating randomization (2 roll-ins, if the first 2 are successful). Roll-in patients will not be pooled with randomized patients for data analysis, and will not count toward the randomized sample size.
To ensure enrollment is representative and balanced across study sites, no site will enroll more than 15 percent of the total in either cohort or implant approach.

S3 Enrollment:
A total enrollment of 500 is requested for the S3 THV.Enrollment will continue until the date on which the trial sponsor is aware that the designated sample size has been obtained. Patients who have already signed the informed consent form at that time will be allowed to be enrolled, provided that this enrollment and implant is completed within 30 days of the consent date. These additional patients will be considered part of the analysis cohort, and no subset analysis will be performed related to enrollment before or after the prespecified total has been met.

Eligibility

For Cohorts A, B and Additional Registries prior to stratification, patients must meet the fundamental enrollment criteria of severe, symptomatic, calcific aortic stenosis with quantifiable and documented source records. Upon meeting these eligibility criteria, the site investigators (per site heart team assessment) shall then determine the patient's risk for operative morbidity and mortality. Patients determined to be operable must have a minimum STS score of $\geq$ 4. Patients deemed inoperable must have documented evidence that the risk for mortality or serious irreversible morbidity is $\geq$ 50% as determined by the examining cardiac surgeon investigator. A third assessment,

regarding optimal valve delivery access (transfemoral, transapical or transaortic) is determined as follows: transapical or transaortic approach will be assigned in patients with iliofemoral vessels less than 6.0 mm; and transfemoral access will be assigned in patients with vessels greater than 7.0 mm. Access approach in patients with vessel size between 6.0 mm and 7.0 mm will be decided by the heart team.

S3 Eligibility:

Patients must meet the fundamental enrollment criteria of severe, symptomatic, calcific aortic stenosis with quantifiable and documented source records. Upon meeting these eligibility criteria, the site investigators (per site heart team assessment) shall then determine the patient's risk for operative morbidity and mortality. Patients determined to be operable must have a minimum STS score of ≥ 8. Patients deemed inoperable must have documented evidence that the risk for mortality or serious irreversible morbidity is ≥ 50% as determined by the examining cardiac surgeon investigator. A third assessment, regarding optimal valve delivery access (transfemoral, transapical or transaortic) is determined as follows: transapical or transaortic approach will be assigned in patients with iliofemoral vessels less than 5.5 mm; and transfemoral access will be assigned in patients with vessels greater than 6.5 mm. Access approach in patients with vessel size between 5.5 mm and 6.5 mm will be decided by the heart team.

After these assessments are made, the study candidate's qualifying criteria are presented via The PARTNER II Trial case review process where experienced trial investigators, members of the Executive and/or Steering Committee will adjudicate the cohort and access decision. Upon case review approval, the supporting evidence for the cohort and access assessments (transfemoral, transapical or transaortic) and the names of the review committee members will be documented in the medical record and case report forms. Once the review and the eligibility criteria are documented, the patient can be enrolled in the trial. Of note, it is essential that at least one site investigator (surgeon) must have personally examined the patient to make a determination of operability.

Follow-up

For end point analyses, study patients will undergo clinical follow-up:

- Cohort A: Discharge, 30 days, 6 months, 1 and 2 years
- Cohort B, S3 Cohort and all registries; Discharge, 30 days, 6 months and 1 year All Cohorts annually thereafter for a minimum of 5 years post index procedure. There will be a phone follow-up at the analysis close date of each Cohort. Additional phone follow-ups may be performed as needed, to obtain up to date survival information for use in regulatory submissions.

Clinical Sites

Up to a total of 60 sites

Study Duration

Initial enrollment:	March 2011
Anticipated enrollment completion:	March 2013

S3 Cohort:

Initial enrollment:	Upon FDA Approval
Anticipated enrollment completion:	9-12 months post FDA approval

	Cardiology	Cardiovascular Surgery
Principal Investigators	**Martin B. Leon, MD** Columbia University Medical Center	**Craig R. Smith, MD** Columbia University Medical Center
Co-Principal Investigators	**Susheel Kodali, MD** Columbia University Medical Center	**Vinod Thourani, MD** Emory University Hospital

The PARTNER II Trial Executive Committee

The PARTNER II Trial Executive Committee is comprised of four Interventional Cardiologists and four Cardiac Surgeons who are leaders in their respective specialties and experienced clinical trialists. Additionally, the committee includes a sponsor representative and enlists the counsel of specialists in biostatistics, neurology, geriatric medicine and medical cardiology.

Interventional Cardiologists	Martin B. Leon, MD	Columbia University Medical Center New York, NY
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	John G. Webb, MD	St. Paul's Hospital Vancouver, British Columbia, Canada
Cardiovascular Surgeons	Craig R. Smith, MD	Columbia University Medical Center New York, NY
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	Lars G. Svensson, MD	Cleveland Clinic Foundation, Cleveland, OH
Neurologist	Thomas Brott, MD	Mayo Clinic Florida
Sponsor	Jodi J. Akin, MSN	Edwards Lifesciences LLC Irvine, CA
Specialty Advisor	Eugene Blackstone, MD Statistics	Cleveland Clinic Foundation

Patient Screening and Procedure Management Steering Committee

A steering committee has been chartered and selected by The PARTNER Trial Executive Committee with the objective of providing leadership and guidance to sites and investigators in The PARTNER II Trial with specific focus on patient selection processes, procedural management and periodic review of procedure complications for educational purposes. The committee is comprised of ten members: five interventional cardiologists and five cardiac surgeons who participated in The PARTNER Trial and are experienced with both patient screening and procedure management for transcatheter heart valve

therapy and critical aortic stenosis patient management. The committee is responsible for the conduct of the patient review calls, as well as the conduct of teaching case reviews on a routine basis.

The PARTNER II Trial Patient Selection and Procedure Management Steering Committee

Cardiac Surgeons

- Todd Dewey, Medical City Dallas
- Wilson Szeto, University of Pennsylvania
- Vinod Thourani, Emory University
- Mathew Williams, Columbia University

Interventional Cardiologists

- William Fearon, Stanford University
- Susheel Kodali, Columbia University
- Samir Kapadia, Cleveland Clinic Foundation
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1.0 Introduction

1.1.1 A fatal, debilitating progressive disease: severe, symptomatic aortic stenosis

Prolonged average life expectancy has resulted in an aging population and consequently, an increase in the number of patients with acquired, calcific, severe, symptomatic aortic stenosis (AS). The standard of care therapy for patients suffering from severe AS is aortic valve replacement surgery (AVR). In the aged population, many patients are too sick to be operated or have comorbidities that preclude the option for surgery [1].

AS is a progressive, debilitating and life-threatening disease if left untreated. Affected individuals are typically > 65 years of age. The pathology involves progressive calcification of the leaflet bodies which limits normal cusp opening during systole. Cellular aging and degeneration have been implicated in this form of the disease and diabetes mellitus and hypercholesterolemia are risk factors.

The pathophysiology of AS includes an increase in afterload, progressive hypertrophy of the left ventricle, and a decrease in systemic and coronary blood flow as consequences of valve obstruction. 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, especially when associated with congestive heart failure. Death in general, including sudden death, occurs primarily in symptomatic patients. 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 [2]. Gardin [3] reported that among symptomatic patients with moderate-to-severe AS treated medically, mortality rates after the onset of symptoms were approximately 25% at 1 year and 50% at 2 years. More than 50% of deaths were sudden.

Grading the severity of AS is based on a variety of hemodynamic and natural history data. According to the ACC/AHA guideline authors, AS is best described as a continuum. In patients with moderate-to-severe AS, valve area may decline up to $0.3cm^2$ per year and the systolic pressure gradient across the valve can increase by as much as 15-19 mmHg per year, with a higher rate of progression observed in elderly patients with coronary artery disease (CAD) and chronic renal insufficiency. These guidelines were updated again in 2008 [4]. 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 [5].

Echocardiographic criteria for determining the severity of AS, as defined by the 2006 published practice guidelines of the joint ACC/AHA Task Force are described below in Table 1.1.1-1.

Table 1.1.1-1 Criteria for Determining Severity of Aortic Stenosis

Indicator	Mild	Moderate	Severe
Jet velocity (m/s)	< 3.0	3.0 - 4.0	> 4.0
Mean Gradient (mmHg)	< 25	25 - 40	> 40
Valve area (cm^2)	> 1.5	1.0 - 1.5	< 1.0
Valve area index (cm^2/m^2)			< 0.6

1.1.2 Treatment options prior to introduction of transcatheter aortic valve replacement (TAVR)

Treatment options for patients suffering from symptomatic aortic stenosis include palliation of symptoms without valve replacement (non-surgical standard therapy) or surgical aortic valve replacement (AVR). Treatment options are determined by patient risk for morbidity or mortality after surgery and patient choice. Non-surgical treatment options including balloon aortic valvuloplasty have been demonstrated to lead to shortened life expectancies and poor quality of [6-8]. Patients considered poor candidates for AVR typically present with significant morbidities or anatomical limitations (such as severely calcified aorta, chest wall radiation, etc) [9]. Also a state of frailty may lead to a patient or physician decision to forego surgery.

Surgical AVR has been demonstrated to have excellent long term outcomes for patients with aortic valve stenosis {Bouma, 1999 #5392}[6-7, 10] including patients who were operable but had predicted high risk for surgery (by STS PROM > 10 [8, 11].

1.1.3 Transcatheter aortic valve replacement (TAVR)

Transcatheter aortic valve replacement (TAVR) was first performed in man in 2002 [12] and was followed by European commercialization 2007 [13-14]. Today more than 15,000 patients have undergone TAVR worldwide, and there is a proliferation of published literature supporting the safety and feasibility of the first generation balloon expandable system (SAPIEN). The Edwards THV clinical research program includes more than 5000 patients enrolled in 10 clinical studies which include first in man, feasibility, pivotal randomized controlled trials and post market registries. Results from these trials have been publicly reported in the scientific congresses and journals. The references are provided in [15-22]. The PARTNER (I) Trial has produced the most conclusive evidence of the safety and effectiveness of the Edwards SAPEN THV in high risk surgical (Cohort A) and inoperable patients with symptomatic aortic stenosis (Cohort B) [23]. These are summarized below.

1.1.4 The PARTNER Trial Cohort A

The PARTNER Trial Cohort A primary analysis was published in the NEJM[24]in July, 2011 Comparison of Transcatheter and Surgical Aortic Valve Replacement for Aortic Stenosis in Patients at High-Risk for Operation. The trial randomly assigned 699 patients at 26 centers with severe aortic stenosis who were high-risk for operation to either AVR or TAVR (transfemoral or transapical approach) using a balloon expandable bovine pericardial valve. The primary end point was death from any cause at 1 year and the primary hypothesis was that TAVR is non-inferior to AVR. The authors concluded: In patients with severe aortic stenosis who are at high-risk for operation, TAVR and AVR had similar survival after 1 year, although there were important differences in peri-procedural hazards. (Clinical Trials.gov number: NCT00530894.)

Report Results: After TAVR and AVR, death from any cause at 30 days was 3.4% vs. 6.5% (P=0.07) and at 1 year was 24.2% vs. 26.8% (difference -2.6%, 95% upper confidence limit 3.0%, pre-defined margin 7.5%; P = 0.001 for non-inferiority). Rates of all neurologic events (i.e., all strokes and transient ischemic attacks) were higher in the transcatheter group than in the surgical group at 30 days (5.5% vs. 2.4%, P = 0.04) and at 1 year (8.3% vs. 4.3%, P = 0.04). At one year, all strokes and TIA after TAVR compared with AVR at one year were more frequent at 27 (8.3%) vs. 13 (4.3%) (P=0.04). Major vascular complications were more frequent after TAVR (11.0% vs. 3.2%, P<0.001), whereas major bleeding (9.3% vs. 19.5%, P<0.001) and new-onset atrial fibrillation (8.6% vs. 16.0%, P<0.001) were more frequent after AVR. Symptom improvement favored TAVR at 30 days, but was similar after 1 year. Para-valvular regurgitation was more frequent after TAVR than AVR (P<0.001).

Conclusions: In patients with severe aortic stenosis who are at high-risk for operation, TAVR and AVR had similar survival after 1 year, although there were important differences in peri-procedural hazards. (Clinical Trials.gov number: NCT00530894.)

Two year results from The PARTNER Trial Cohort A were published online (March, 2012) in NEJM. The authors noted:

Background

The Placement of Aortic Transcatheter Valves (PARTNER) trial showed that among high-risk patients with aortic stenosis, the 1-year survival rates are similar with transcatheter aortic-valve replacement (TAVR) and surgical replacement. However, longer term follow-up is necessary to determine whether TAVR has prolonged benefits.

Methods

At 25 centers, we randomly assigned 699 high-risk patients with severe aortic stenosis to undergo either surgical aortic-valve replacement or TAVR. All patients were followed for at least 2 years, with assessment of clinical outcomes and echocardiographic evaluation.

Results

The rates of death from any cause were similar in the TAVR and surgery groups (hazard ratio with TAVR, 0.90; 95% confidence interval [CI], 0.71 to 1.15; P = 0.41) and at 2 years (Kaplan–Meier analysis) were 33.9% in the TAVR group and 35.0% in the surgery group (P = 0.78). The frequency of all strokes during follow-up did not differ significantly between the two groups (hazard ratio, 1.22; 95% CI, 0.67 to 2.23;

P = 0.52). At 30 days, strokes were more frequent with TAVR than with surgical replacement (4.6% vs. 2.4%, P = 0.12); subsequently, there were 8 additional strokes in the TAVR group and 12 in the surgery group. Improvement in valve areas was similar with TAVR and surgical replacement and was maintained for 2 years. Paravalvular regurgitation was more frequent after TAVR (P<0.001), and even mild paravalvular regurgitation was associated with increased late mortality (P<0.001).

Conclusions

A 2-year follow-up of patients in the PARTNER trial supports TAVR as an alternative to surgery in high-risk patients. The two treatments were similar with respect to mortality, reduction in symptoms, and improved valve hemodynamics, but paravalvular regurgitation was more frequent after TAVR and was associated with increased late mortality. (Funded by Edwards Lifesciences; ClinicalTrials.gov number, NCT00530894.)

Based on these data, a premarket approval application for high risk operable patients is currently under review with the FDA.

1.1.5. The PARTNER Trial Cohort B

The PARTNER Trial Cohort B primary analysis was published in the NEJM[24] (Transcatheter Aortic Valve Implantation for Aortic Stenosis in Patients who Cannot Undergo Surgery**)** in October 2010. This trial evaluated the outcomes of TAVR versus standard therapy (medical management including balloon aortic valvuloplasty) in patients who were considered to be at a > 50% risk of mortality or irreversible morbidity after surgical AVR, as assessed by the study team including an examining cardiac surgeon Reported Results: 358 inoperable AS patients (STS score 11.7±6.0%) were randomized at 21 centers (17 from the U.S.). At 1 year follow-up, all-cause mortality decreased from 50.7% with standard therapy to 30.7% with TAVI; hazard ratio, 0.55; 95% confidence interval, 0.40 to 0.74 (P<0.001). The composite of all-cause mortality and repeat hospitalization decreased from 71.6% with standard therapy to 42.5% with TAVI; hazard ratio, 0.46; 95% confidence interval, 0.35 to 0.59 (P<0.001). In 1 year survivors, TAVI reduced cardiac symptoms (NYHA class I or II, 74.8% vs. 42.0%, P<0.001). At 30 days, At one year, TAVR was associated with more frequent strokes 19 (11.2%) vs. 8 (5.5%) ; P = 0.06) and major vascular complications (16.8% vs. 1.1%; P<0.001). In the year after TAVI, there was no deterioration in bioprosthetic valve function (stenosis and regurgitation) assessed by echocardiography.

Two year results from The PARTNER Trial Cohort **B** were published online (March, 2012) in NEJM. The authors noted:

Background

Transcatheter aortic-valve replacement (TAVR) is the recommended therapy for patients with severe aortic stenosis who are not suitable candidates for surgery. The outcomes beyond 1 year in such patients are not known.

Methods

We randomly assigned patients to transfemoral TAVR or to standard therapy (which often included balloon aortic valvuloplasty). Data on 2-year outcomes were analyzed.

Results

A total of 358 patients underwent randomization at 21 centers. The rates of death at 2 years were 43.3% in the TAVR group and 68.0% in the standard-therapy group

(P<0.001), and the corresponding rates of cardiac death were 31.0% and 62.4% (P<0.001). The survival advantage associated with TAVR that was seen at 1 year remained significant among patients who survived beyond the first year (hazard ratio, 0.58; 95% confidence interval [CI], 0.36 to 0.92; P = 0.02 with the use of the log-rank test). The rate of stroke was higher after TAVR than with standard therapy (13.8% vs. 5.5%, P = 0.01), owing, in the first 30 days, to the occurrence of more ischemic events in the TAVR group (6.7% vs. 1.7%, P = 0.02) and, beyond 30 days, to the occurrence of more hemorrhagic strokes in the TAVR group (2.2% vs. 0.6%, P = 0.16). At 2 years, the rate of rehospitalization was 35.0% in the TAVR group and 72.5% in the standard-therapy group (P<0.001). TAVR, as compared with standard therapy, was also associated with improved functional status (P<0.001). The data suggest that the mortality benefit after TAVR may be limited to patients who do not have extensive coexisting conditions. Echocardiographic analysis showed a sustained increase in aortic-valve area and a decrease in aortic-valve gradient, with no worsening of paravalvular aortic regurgitation.

Conclusions

Among appropriately selected patients with severe aortic stenosis who were not suitable candidates for surgery, TAVR reduced the rates of death and hospitalization, with a decrease in symptoms and an improvement in valve hemodynamics that were sustained at 2 years of follow-up. The presence of extensive coexisting conditions may attenuate the survival benefit of TAVR. (Funded by Edwards Lifesciences; ClinicalTrials.gov number, NCT00530894.)

1.1.5.1 Stroke and TAVR

The finding of an early higher hazard of stroke in TAVR versus AVR is a subject of keen interest and has inspired the trial investigators to perform further analysis of this clinically important event in The PARTNER Trial. The results of this investigation were published by Miller et al (Transcatheter (TAVR) versus surgical (AVR) aortic valve replacement: Occurrence, hazard, risk factors, and consequences of neurologic events in the PARTNER trial. April, 2012. JCVITS).

The following is the abstract from this publication: Background: All neurologic events in the PARTNER randomized trial comparing transcatheter aortic valve replacement (TAVR) with surgical aortic valve replacement (AVR) were analyzed. Methods: High-risk patients with aortic stenosis were stratified into transfemoral (TF, n ¼ 461) or transapical (TA, n ¼ 196) strata based on their arterial anatomy and randomized: 657 received treatment assigned (‘‘as treated’’), 313 underwent AVR, and 344 TAVR. Neurologic events were prospectively adjudicated by an independent Clinical Events Committee. Multivariable, multiphase hazard analysis elucidated factors associated with increased likelihood of neurologic events. Results: Forty-nine neurologic events (15 transient ischemic attacks, 34 strokes) occurred in 47 patients (TAVR, n=31;AVR, n=16). An early peaking high hazard phase occurred within the first week, which

declined to a constant late hazard phase out to 2 years. The risk in the early phase was higher after TAVR than AVR, and in the TAVR arm in patients with a smaller aortic valve area index. In the late risk phase, the likelihood of neurologic event was linked to patient-related factors in both arms (''non-TF candidate,'' history of recent stroke or transient ischemic attack, and advanced functional disability), but not by treatment (TAVR vs AVR) or any intraprocedural variables. The likelihood of sustaining a neurologic event was lowest in the AVR subgroup in the TF stratum during all available follow-up. Conclusions: After either treatment, there were 2 distinct hazard phases for neurologic events that were driven by different risk factors. Neurologic complications occurred more frequently after TAVR than AVR early, but thereafter the risk was influenced by patient- and disease-related factors. (J Thorac Cardiovasc Surg 2012;143:832-43).

Given the clinical importance of stroke, stroke is being further investigated in The PARTNER II Trial and is included in the composite primary endpoint. Additional efforts to recognize and reduce the incidence and impact of stroke after TAVR is ongoing.

1.1.6 Quality of Life in Inoperable patients after TAVR: Results fromThe PARTNER Trial

The Quality of Life sub-study results of The PARTNER Trial were reported at the American Heart Association Scientific Congress by Dr. David Cohen (Nov. 2010) and published in Circulation [27]. Dr. Cohen reported that in this population, TAVR was superior to standard therapy in effectiveness as demonstrated by improved Quality of Life instruments (SF-12 physical p=0.0055; SF-12 mental p=0.0006; Kansas City Cardiomyopathy Instrument p<0.0001 and EuroQOL p=0.0035) and six minute walking distance (p=0.007) after 1-year follow-up.

1.1.7 Second generation platform: SAPIEN XT™ with NovaFlex* Delivery and Ascendra 2 (*NovaFlex refers to NovaFlex or NovaFlex+).

Recent outcomes of the first randomized Edwards SAPIEN THV studies have concluded that balloon expandable TAVR should be recognized as the standard of care for inoperable patients and is an acceptable alternative to AVR in selected high risk patients. Also reported were significant outcomes related to the study device versus standard therapy control, such as stroke, major vascular complications and major bleeding events which had significant impact on overall mortality. (It should be noted that 78% of patients in the standard therapy arm were treated with 1 or more balloon aortic valvuloplasties).These findings were consistent with earlier published reports. Despite the high-risk nature of the population studied, it is widely held that iterative improvements in the profile of the delivery system may reduce these important adverse events as well as support expansion of the study population to include patients previously excluded due to anatomical limitations

The design initiative for the second generation Edwards THV Valve and Delivery system was to reduce the delivery system profiles (both transfemoral and transapical) to address vascular, bleeding and possibly embolic complications. In 2008 the Edwards SAPIEN XT THV with the NovaFlex delivery system was introduced in European multicenter prospective, non-randomized clinical trials (PREVAIL EU- transfemoral and PREVAIL TA - transapical). Safety and effectiveness was demonstrated in support of the CE Mark which was conferred in April, 2010. A report has been provided to FDA in support of the PARTNER II Trial IDE approval and the outcomes are summarized below. Five year follow-up in the PREVAIL Study is ongoing and a prospective consecutive post-market registry (SOURCE XT) is also underway.

1.1.8 Executive Summary PREVAIL TF and TA Studies

Based upon these findings and feedback from advisors and investigators, a second generation system has been developed, Edwards SAPIEN XT™ transcatheter heart valve and its delivery systems for transfemoral (NovaFlex) and transapical (Ascendra 2). The main SAPIEN XT valve design features include: change of the valve stent from stainless steel to cobalt chromium; change of the pericardial leaflets from an open to a semi-closed, coapted configuration, and the addition of a third valve size (29 mm). These devices were studied under two separate feasibility protocols in the European Union.

The PREVAIL EU (TF) Study (Study # 2008-04) is a comprehensive feasibility study that was designed to assess the safety and effectiveness of the Edwards SAPIEN XT™ valve and delivery systems. The Study commenced with early versions of the delivery system (RetroFlex3™, RetroFlex4™) which were modified and then obsoleted for the SAPIEN XT™ platform based on early observations in the Study. The PREVAIL EU Study was then expanded and amended to ensure that a meaningful sample of patients were enrolled in order to thoroughly evaluate the final design iteration of 18 French (for 23 mm THV) and 19 French (for 26 mm THV) NovaFlex™ delivery system. The NovaFlex™ delivery system incorporates a novel off-balloon valve crimping procedure enabling the use of a smaller introducer sheath combined with an in vivo valve-over-balloon alignment maneuver prior to valve crossing and delivery. In total, 212 patients from 11 European hospitals in four countries were enrolled in this study of which 198 patients received a SAPIEN XT valve, 149 of these “as treated” patients were enrolled under the NovaFlex™ protocol amendment.

Similarly, the PREVAIL TA Study (Study # 2009-06) is a comprehensive feasibility study also designed to assess the safety and effectiveness of the Edwards SAPIEN XT™ valve and transapical Ascendra /Ascendra 2 delivery systems. The Study was initiated with 23 mm and 26 mm valve sizes and was augmented with a new 29 mm valve size in response to user requests for patients with larger native aortic valve annulus diameters. The PREVAIL TA Study was also amended and expanded to thoroughly evaluate the larger 29 mm valve size. In total, 213 patients from 20 European hospitals

were enrolled in this study, of which 118 were enrolled under the SAPIEN XT™ 29 mm protocol amendment. A total of 207 patients received a SAPIEN XT valve and are considered "as treated" patients.

Both the PREVAIL EU (TF) and PREVAIL TA studies were designed to support the approval of a US Pivotal Trial (The PARTNER II Trial) evaluating Edwards SAPIEN XT™ with the NovaFlex™ and Ascendra/Ascendra 2™ delivery systems. As would be expected under a US IDE Trial, both studies were conducted in a GCP compliant manner.

Table 1.1.8-1 below summarizes the key demographics, procedural information and interim results of the primary and secondary endpoints of both As Treated study populations. Table 1.1.8-2 summarizes hemodynamic and effectiveness outcomes in the As Treated populations of both studies.

Table 1.1.8-1 Demographics and Outcomes

	PREVAIL EU Transfemoral NovaFlex Delivery System N = 149 As Treated	PREVAIL TA Transapical N = 207 As Treated
Enrollment Dates	12/2008 – 12/2010	12/2009 - 2/2011
Demographics		
Mean ± SD Age (years)	83.6 ± 5.6	81.2 ± 5.5
Gender Female (%)	67.4	30.0
Mean EuroSCORE (%)	22.5 ± 10.7	24.5 ± 8.0
STS-PROM (%)	9.9 ± 7.9	7.7 ± 4.9
Peripheral Vascular Disease (%)	2.2	34.3
Congestive Heart Failure (%)	47.1	60.4
Procedural Information		
Procedure time (min)	92.3 ± 42.2	94.6 ± 31.6
Fluoroscopy time (min)	18.9 ± 8.2	6.7 ± 3.9
Valve at intended site (%)	97.1	97.6
Conversion to open heart surgery (%)	2.2	0.5
Arterial access diameter (mm) Right	8.2 ± 1.5	NAP
Arterial access diameter (mm) Left	7.7 ± 0.8	NAP

End point	Safety Event	30 Day KM (%)	1 Year KM (%)	30 Day KM (%)	1 Year KM (%)
1°	Death	92.0	82.4	92.4	78.9
2°	Conduction defect requiring permanent pacemaker	91.1	87.3	88.5	87.7
	Myocardial infarction	99.3	97.0	99.0	97.8
	Perivalvular Leak (3+ or 4+)	97.1	94.1	98.5	97.2
	Reoperation	97.8	94.9	99.0	96.8
	Stroke-Embolic Origin	96.9	93.0	NAP	NAP
	Stroke-Embolic/Ischemic Origin	NAP	NAP	98.0	96.5
	Valve embolization	99.3	99.3	99.5	99.5
	Vascular Access-Related Complication	88.3	88.3	99.5	99.5
	Vascular Access-Related Complication-Thoracic	NAP	NAP	99.0	98.0
	Vascular Access-Related Complication-Ventricular	NAP	NAP	99.5	98.7
	Vascular Complication (Not Access-Related)	97.8	96.5	99.5	99.5
Data Extract		10 February 2011		17 March 2011	

NAP = not applicable for that data set

Table 1.1.8-2 Hemodynamic Performance and NYHA Classification

Hemodynamic Performance		PREVAIL TA Transapical N = 207 As Treated	PREVAIL TA Transapical N = 207 As Treated
		All valve sizes	29mm
EOA (cm²)	Baseline	0.7 ± 0.2	0.8 ± 0.2
	30 Day	1.8 ± 0.5	2.8 ± 4.2
	6 Month	1.7 ± 0.6	1.9 ± 0.6
Mean Gradient (mmHg)	Baseline	40.2 ± 15.6	38.5 ± 14.2
	30 Day	9.4 ± 4.7	8.2 ± 3.4
	6 Month	9.9 ± 4.4	8.3 ± 3.0
PVL >3+	30 Day	4.1%	1.3%
	6 Month	2.0%	0.0%

Hemodynamic Performance		PREVAIL TA Transapical N = 207 As Treated	PREVAIL TA Transapical N = 207 As Treated
NYHA Classification	Interval		
III & IV	Baseline	84.0%	84.2%
	30 Day	22.0%	22.9%
	6 Month	13.0%	9.3%
Data Extract		17 March 2011	17 March 2011

The combined 30 day freedom from mortality of 90.0% is considered acceptable in the early learning curve, as there were no roll-in patients and procedure success improved over time. No deaths were directly associated with vascular access complications such as dissection, rupture or bleeding.

Modest improvements in vascular access complications have been seen in this study, despite enthusiasm by the investigator group to attempt 18F sheath introduction into vessels that were small and more diseased than first appreciated. A 3.5% reduction in the incidence of vascular access complication was seen with the NovaFlex™ when compared to subjects who were treated with the RF3 delivery system. The off-balloon concept of mounting for the RF4 and NovaFlex™ delivery systems required additional in-servicing but gained quick acceptance by the investigator group. Modifications of the handle locking mechanism and the tip of the delivery system flex catheter have been incorporated as a result of direct investigator involvement and feedback.

The objective of the feasibility cohort of the PREVAIL TA Trial was to demonstrate comparable safety (including mortality) and performance outcomes with the SAPIEN XT valve and Ascendra/ Ascendra 2 delivery systems. SAPIEN XT THV was designed to provide a transcatheter heart valve for patients with severe aortic stenosis who present with a range of annular diameters including those between 18 mm and 27 mm for the sizes 23 mm, 26 mm and 29 mm devices. The PREVAIL TA study has been able to demonstrate that the SAPIEN XT stent design iteration to achieve a crimped profile reduction in combination with a larger diameter THV will meet the size requirements of the majority of patients that are now being selected for TAVR therapy. The mortality rate of 7.4% at 30 days is significantly lower than those rates seen in earlier transapical cohorts and is similar to that seen in transfemoral patients. Freedom from adverse event rates are also comparable or better than those seen in earlier trials with 99.1% freedom from myocardial infarction, 98.0% freedom from stroke and 100.0% freedom from structural valve deterioration at 30 days.

In both of the PREVAIL trials, the SAPIEN XT THV has demonstrated that all sizes of the SAPIEN XT perform hemodynamically as anticipated, with mean effective orifice areas that are progressively larger across the valve sizes and mean gradients that are lower as the valve size increases. The largest EOA and lowest gradients are seen with the 29 mm device. Perivalvular leak continues to be observed, but the incidence of

moderate 3+ or severe 4+ leaks requiring a surgical intervention remains low. Valve embolization was reduced in these series and there were no reports of leaflet dysfunction in situations of low cardiac output or low valve placement. This is a positive result of the valve leaflet modification and semi-closed coaptation of the SAPIEN XT. The implantation of a permanent pacemaker post index procedure is higher than what has been reported in earlier studies but still appears to be within the ranges reported for surgical AVR. The appearance of 3° AV block within the first few days after the replacement of the valve is the primary reason for pacemaker implantation after a TAVR procedure. There does however seem to be less reluctance to implant a pacemaker in patients who experience other arrhythmias that may not be directly related to a transcatheter valve but occur early after the index procedure.

In conclusion, data collected to date in these clinical investigations for the 23 mm, 26 mm and 29 mm SAPIEN XT THV provides objective evidence that: procedural outcomes with the SAPIEN XT™ THV and either the NovaFlex or Ascendra / Ascendra 2 delivery systems are within safe and reasonable ranges for the intended patient population.

1.1.9 Transcatheter Valve in a surgical bioprosthetic valve implantation (THV-SV) for structural valve deterioration

Biological heart valve substitutes have been valves of choice for surgical AS therapy in the older patient population since the 1960s [28]. Generally, xenografts have benefit in terms of no or reduced need for anticoagulation and good hemodynamic function.

The most common non-fatal valve-related complication of a bioprosthetic device are intrinsic changes to the leaflets known as primary tissue failure due to structural valve deterioration (SVD) [29]. The signs and symptoms of SVD in the aortic position mimics that of native valve stenosis with or without insufficiency and the pathophysiology is similar. SVD may be seen starting 10 - 15 years post implantation and generally occurs gradually and is age dependent with patients older than age 65 at initial implant experiencing a less than 10% chance of requiring a reoperation up to 15 years [30-31].

Reoperative procedures in patients with degenerated bioprostheses are technically feasible but challenging. Reduction of morbidity and mortality is a primary goal of the surgical AVR reintervention. Many patients are in higher surgical risk categories as they have not been regularly evaluated and are referred too late thus often being in congestive heart failure with compromised hemodynamics, multiorgan comorbidities, advanced age and poor functional condition. The accompanying comorbidities significantly affect the operative risk of mortality and in these cases a reoperative mortality rate as high as 19% has been reported [32-34]. Emergency reoperation carries an even higher mortality rate with reports between 22.6% and 44% [35-37].

The ”valve-in-surgical valve” concept (THV-SV) was first reported with failed conventional biological valves and the insertion of mechanical valve substitutes by Campanella [38] in 1990 and Raffa [39] in 1991 followed by Stassano [40] and Paterson [41] in 1993.

Numerous THV-SV experiences with Edwards SAPIEN and the Medtronic CoreValve have been published since 2007 in both elective and emergency situations. Wenaweser and colleagues [42] reported the first human THV-SV in a degenerated Mitroflow pericardial valve (Sorin Group, Vancouver, BC, Canada) with a Medtronic CoreValve THV (Irvine, California USA) in 2007. Walther and colleagues [43] followed in 2008 with the first Edwards SAPIEN implant within an Edwards PERIMOUNT pericardial prosthesis. As with transcatheter aortic valve implantations (TAVI) performed for native aortic valve stenosis the majority of the cases presented are in patients with multiple severe co-morbidities, high risk assessment scores and a limited prognosis for a conventional cardiac surgery procedure. The Edwards SAPIEN and Medtronic CoreValve transcatheter devices have been implanted in a wide variety of failed bioprostheses manufactured by different companies including stented and stentless aortic and stented mitral valves with relatively good success. [44-69]. One center has reported a successful SAPIEN VinV implantation in a homograft first implanted in 1996[47].

Publications or presentations to date document SAPIEN THV-SV in more than 200 patients with degenerated bioprostheses. The procedure has been reported to be feasible and safe by the authors and the available immediate hemodynamics reported to be reasonable and related to the internal diameter offered by the host bioprosthesis. It is important that the inner diameter of the surgical bioprosthesis be determined and is found to be adequate to allow full deployment of the transcatheter valve and not create stenoses [70].

Other authors with clinical experience document various advantages of THV-SV in this patient population. Positioning of the SAPIEN THV is simplified when used in devices that have a radiopaque frame or struts. A standard direct transapical access avoids the long travel distance associated with the transfemoral approach and enables excellent device stability during deployment. Procedural times appear to be comparatively shorter, and patients enjoy a quick recovery period. Paravalvular leaks also appear to be fewer and less severe. [50].

Challenges identified by the authors include:

- Identifying the appropriate landing zone in devices that that do not have radiopaque markers and are not obviously visible on fluoroscopy
- Correct THV stent to surgical valve sizing to
    - Avoid patient/prosthesis mismatch and enable adequate hemodynamics
    - Avoid distortion, insufficiency and early degeneration of the THV

- Appropriate anchoring of the THV – especially in stentless valves or homografts where aortic root calcification is prominent but have limited leaflet mineralization
- Impedance to valve crossing by pannus, calcification and thick leaflets
- The need for balloon pre-dilation of the failed device
- The likelihood of embolization of particulate matter and/or the risk of calcium displacement from the failed device
- Proper evaluation of aortic sinus morphology to avoid coronary ostia occlusion and possible compression of underlying coronary vessels.

Transcatheter Valve in Surgical Valve Registry (NR3)

The aim of this registry is to evaluate the safety and effectiveness of transfemoral or transapical implantation of the Edwards SAPIEN XT THV into a degenerated conventional aortic bioprosthesis on the beating heart using a minimally invasive approach in a prospective model.

The underlying assumption is that inoperable patients with a predicted surgical mortality or major comorbidity of 50% or greater face an extraordinary risk of a re-do operation for a failed xenograft would also benefit from a valve re-replacement undergoing transcatheter placement of the Edwards SAPIEN XT THV bioprosthesis. Given the increased risk of mortality and morbidity of reoperative AVR surgery for such high risk patients, there has been an interest in the development of an alternative less invasive technique for patients with a failed bioprosthesis.

Recent advances in transcatheter procedures have made sternal-sparing, beating heart valve replacement therapy possible. Clinical studies have demonstrated reasonable safety and effectiveness of transcatheter heart valve implantation in both transapical and transfemoral access procedures.

In order to maximize the risk-benefit for potential treatment subjects, only adult patients who are severely symptomatic and are considered by the multidisciplinary heart team to be a high risk for in-hospital mortality following reoperative biological valve replacement surgery will be considered for enrollment.

1.1.10 Transcatheter Transaortic Access Approach

Since its inception in 2002 and European market release in 2007, the approach to replacing the native aortic valve using a transcatheter valve has evolved from the original antegrade, transseptal approach [71], which suffered early catastrophic complications to more reproducible and improved early outcomes with the use of retrograde transfemoral [71] and transapical approaches [44, 72]. Additionally, a subclavian approach has been introduced and reported [73-81].

In some patients, due to unique anatomic characteristics or co-morbid conditions, it is necessary to consider another access route. Direct access through the ascending aorta, also known as the transaortic (TAO) approach has also been recently published and is gaining more attention [82-85].

TAO access is defined as introducing the THV directly into the ascending aorta and retrograde to the diseased aortic valve via a minimally invasive right 2nd or 3rd intercostal space mini-thoracotomy or mini-sternotomy, which is a partial sternotomy extending from the suprasternal notch to the right 3rd or 4th interspace. Although the first and second generation Edwards Lifesciences transapical delivery systems (trade names "Ascendra" and "Ascendra 2", respectively) were developed primarily for transapical delivery of the SAPIEN and/or SAPIEN XT THV, these devices also have been used by surgeons to deliver and deploy the THV via the transaortic approach in particular cases.

Bapat, et al. [82] published the first description of a successfully implanted SAPIEN device via the TAO route. The patient was an 84-year-old woman with critical AS (valve orifice area 0.6 cm^2; mean transaortic gradient 46 mm Hg, peak transaortic valve gradient 94 mm Hg), significant comorbidities (severe kyphoscoliosis, chronic pulmonary disease with poor lung function, and peripheral vascular disease), a EuroSCORE of 26% and was considered a poor candidate for surgical aortic valve replacement (SAVR). She was excluded from both TF and TA approaches due to a tortuous descending aorta and small (<7 mm) femoral arteries and prior medical history of chest radiation after a left mastectomy.

Under general anesthesia, the patient's ascending aorta was exposed through an upper partial sternotomy using fluoroscopy and three-dimensional transesophageal echo (TEE) guidance. A transapical delivery device was used for this transaortic retrograde deployment; with the valve loaded in a reverse orientation relative to the conventional TA approach. Balloon aortic valvuloplasty (BAV) was performed with a 20 mm balloon before deploying a 23 mm valve. Prior to closing, an aortogram confirmed good valve position with minimal leakage and normal coronary flow. Two hours after the surgery the patient was extubated; hospital discharge followed after only 5 days. The authors concluded that the transaortic route via a partial sternotomy may be a viable option when conventional approaches such as SAVR, and TF- and TA-AVR are not possible, or when the patient presents with poor lung function.

Bapat, et al. [86] have also reported their experience in a single-center series of 17 patients declined for TF-TAVR from January 2008 to March 2011, in whom the TAO procedure was performed based on anatomy, risk, LV function and significant respiratory disease. The TAO-TAVR patients received the SAPIEN or SAPIEN XT THV using the Ascendra or Ascendra 2 delivery system. Exposure of the ascending aorta was achieved for the TAO approach via a J-shaped upper partial sternotomy with an aortic puncture site that is free from calcification. Sheath alignment was coaxial to the plane of the aortic annulus, and adequate space between the tip of the sheath and

the aortic valve was maintained to allow full expansion of the balloon during deployment of the device. The authors recommended a minimum distance of 5 cm when using the Ascendra delivery device and SAPIEN valve: 3 cm for the balloon and 2 cm for the sheath.

The TAO approach achieved 100% successful valve implantation, although one patient had greater than grade 2 aortic regurgitation after the procedure. Additionally, one patient later underwent elective drainage for pericardial effusion. At 30 days, the TAO group had a mortality of 11.8%. Overall mortality rate was 23.5% at a mean follow up of 162 $\pm$ 154 days.

This series of 17 patients represents the largest collective experience reported to date, on patients who have successfully received a SAPIEN or SAPIEN XT valve via the transaortic route. The authors believe the transaortic route is a viable delivery route for AVR patients with significant respiratory disease concomitant with reduced respiratory reserve, or chest wall abnormalities that preclude a transapical approach. They suggest selection of the TAO approach when "in addition to FEV1/FVC ratio <70%, either the absolute value of FEV1 was <1 liter or FEV1< 60% of the predicted value."

The authors believe that the TAO approach avoids complications involving the left ventricular puncture such as late pseudo-aneurysm formation and new apical wall motion abnormalities (both hypokinetic or akinetic) attributed to the purse-string closure technique with associated regional myocardial necrosis. Further, they believe the TAO approach more closely mirrors the TF approach, and is less invasive than the TA approach. It is hoped that the TAO procedure will result in less post-operative pain than a left-sided thoracotomy that results from rib retraction, intercostal nerve injury, and invasion of the pleural space. The associated pain with respiration may indirectly contribute to the respiratory morbidity through impaired expiratory flow rate, and may adversely impact other lung function tests. The use of the TAO approach may also avoid the risk of peri-operative LV apical bleeding, and post-procedure respiratory morbidity associated with these adverse events. Another potential advantage is the familiarity of surgeons with this approach and a shorter learning curve, since the procedure is already used in minimally-invasive SAVR and endovascular stent procedures. However, in patients with a prior history of CABG, a slight variation may be required.

Additional papers describing the TAO experience have been published by Raja and colleagues [87], where a successful TAO implantation of a SAPIEN valve was reported in a 67-year-old woman with a history of total right pneumonectomy and accompanying distortion of normal chest anatomy, and a history of chronic atrial fibrillation and by Etienne, et al. [88] who reported their positive SAPIEN TAO experience in three female patients with severe AS and low ejection fractions seen at their institution in Belgium between June and September 2010.

Etienne and colleagues [89] also present the first case of a 26mm SAPIEN valve implanted via the transaortic route in combination with an Embol-X device (Edwards Lifesciences LLC, Irvine, CA), an anti-embolic filter. The filter was directly inserted in the distal ascending aorta and remained in place during the TAVR procedure with the aim of reducing peri-procedural neurologic events. The 80-year-old male patient was contraindicated for the transfemoral approach due to severe peripheral vascular disease (PVD). The patient had a history of COPD and an ejection fraction of 18%. Access to the mid ascending aorta was gained through a 6 cm J-shaped upper ministernotomy. Using TEE guidance, two separate puncture sites, one for the Ascendra delivery device and one for the Embol-X device, were chosen in areas to minimize the risk aortic plaque disruption. The anti-embolic device was deployed "as soon as retrograde crossing as the aortic valve was performed." It remained in place during dilatation of the native aortic valve, deployment of the SAPIEN, and removal of the delivery system. The Embol-X device was carefully examined after removal and trapped multiple emboli were visible in the filter. A cerebral MRI was performed the day before (day -1) and 48 hours after the procedure (day +2) in order to assess and quantify the presence of cerebral emboli. The postoperative course was uneventful and no clinical neurological complications were noted. Importantly, no new lesions were detected in the MRI images. Insertion and retrieval of the Embol-X filter was without complication.

In 2009, a cardiac surgery team at the German Heart Center in Munich [80] published the first successful case of a Medtronic CoreValve device implanted via the transaortic route. The patient was an 80-year-old woman with critical AS (EOA 0.45cm², mean gradient 48mmHg) and a Logistic EuroSCORE of 29.2%. A TF procedure could not be performed due to severe calcification of the femoral, iliac, and subclavian arteries. A BAV was performed before implanting a 29 mm CoreValve with fluoroscopy guidance. The procedure was successful, and trace aortic regurgitation without stenosis was confirmed via intraoperative aortography and echocardiographic analysis.

Olsen and coworkers [90] report the conversion of a surgical AVR to a transcatheter procedure using a CoreValve in a 73-year-old female patient. After initiation of cardiopulmonary bypass and aortotomy, it was recognized that the severity of calcification involving the proximal aorta, aortic annulus and coronary ostia precluded conventional AVR. Consequently, the CoreValve was placed directly through the open ascending aorta in the arrested heart. To facilitate closure of the aortotomy, cold water was continuously poured over the CoreValve Nitinol frame to reduce its expanded diameter. The patient was discharged on the 11th postoperative day with a valve gradient of 14 mmHg and an ejection fraction between 40% and 45%.

Bruschi, et al. [83] published on two cases at their institution in Italy using a direct TAO approach via a right minithoracotomy for TAVR. Both female patients aged 83 years and 60 years had severe symptomatic AS complicated by comorbidities and were found to be ineligible for TF and axillary artery access due to small vessel size in both patients.

BAV was performed in both patients using a 22 mm Nucleus balloon, prior to retrograde deployment of a 26 mm CoreValve prosthetic valve under fluoroscopic visualization. Mean aortic gradient decreased to 5 mm Hg or less, and aortic regurgitation was graded as trivial. Within 24 hours, both patients were extubated in the intensive care unit (ICU). Unfortunately, both patients developed complete atrioventricular block, which required permanent pacemaker implantation. The authors concluded that the TAO approach allowed easier manipulation of the THV device while avoiding some of the potential complications of a transapical approach, such as myocardial puncture and mitral or aortic valve trauma from stiff catheters, as well as disruption of the LV or formation of a false aneurysm in the apical puncture site. The authors also assert that this direct approach can avoid dislodging of atherosclerotic material that occurs with aortic arch passage during the transfemoral approach.

In another paper by Bruschi, et al. [91], the authors published their single-center experience, from May 2008 to July 2010, treating six of 92 patients with severe symptomatic AS by TAO access who were not offered surgery due to extreme risk. Twelve patients were declined transfemoral TAVR due to iliac-femoral arteriopathy, small vessel size, extreme tortuosity, calcification, or abdominal aorta aneurysm. Comorbidities in the six TAO patients included vasculopathy, chronic renal insufficiency, pulmonary hypertension, obesity, lymphoma, COPD, and diabetes with logistic EuroSCOREs ranging from 5-51%. Six patients received a CoreValve prosthetic valve using the TAO approach via a right mini-thoracotomy deployed after BAV under angiographic and fluoroscopic guidance. In the direct aortic access group implantation was successful in five cases (83%). Immediate hemodynamic results included a reduction in the mean aortic gradient to $\leq$ 5 mm Hg; two patients had grade 1-2 aortic regurgitation; the remaining three patients had none. All patients who survived were extubated in the ICU within the first 24 hours. Complications in the TAO survivors included new permanent pacemaker implantation in two patients due to complete atrioventricular block. At discharge the patients were asymptomatic with good prosthesis function confirmed by echocardiography, with a mean transvalvular aortic pressure gradient of 12 mm Hg. Hospital length of stay in this sub-group was a mean of 16 days (range 7-28 days).

During a follow-up period that ranged from 1-11 months, the direct aortic access group benefited from NYHA functional class improvement, and returned to their normal activities limited only by their preoperative comorbidities. One patient required a right thoracoscopic decortication 35 days after the procedure. At 6 months, the mean transvalvular aortic pressure gradient was 9 ± 4 mmHg with trivial paravalvular leak.

In summary, in high risk/inoperable THV candidates, diverse patient anatomic characteristics and clinical comorbidities have in some patients necessitated the search for alternative methods of device delivery. From the literature, the TAO approach has been recently introduced for patients who are excluded from TF, TA or subclavian/transaxillary delivery options due to small caliber, heavily calcified, tortuous arteries, chest wall abnormalities, poor respiratory function or poor left ventricular

function. The subclavian/transaxillary approach is another access route that has been used as an option for patients precluded from TF and TA procedures however, in the elderly population, the subclavian artery can be less compliant and more friable [92-93] and have some of the same limitations as seen in the TF approach, such as diameter restrictions and in some patients arterial wall calcifications. More than 30% of patients in the Bapat series of 17 patients who received a SAPIEN device transaortically also had a history of prior CABG. They caution that a possible compromise to a patent left internal mammary artery (LIMA) graft during a subclavian procedure should be considered before electing the subclavian route.

It has been suggested that the TAO approach provides an even more stable and direct platform for valve positioning and delivery. It may also avoid some of the disadvantages of the TA approach related to complications of the thoracotomy and puncturing of the left ventricle especially in patients with a low ejection fraction. In addition, hemostasis of the ascending aorta may be more easily achieved and a drain would only need to be placed intrapericardially and not in the pleural space. For patients with complex anatomic cardiac conditions such as those described by Raja and colleagues, TAO access with off-pump transcatheter replacement of the aortic valve may be the only means to provide definitive AVR therapy. Additionally, the TAO procedure facilitates the concomitant use of embolic capture or deflection filters that may help to reduce the number of peri-procedural embolic events during TAVR in this already fragile and susceptible population.

1.1.11 Expandable Introducer Sheath

The femoral artery is the most common route of vascular access used for interventional devices. Favorable iliofemoral arterial anatomy; including luminal diameter, calcification, and tortuosity are important anatomical determinants for successful device introduction and vessel access [94]. The common femoral artery (CFA) is the primary access site for interventional procedures and is considered to be ideal because of its relatively large size and compressibility [95]. Because of its larger size, puncture of the femoral artery is ideally performed at the level of the common femoral artery, usually at the femoral head. The diameter of the common femoral artery has been correlated to age, sex, and body surface area (BSA) [94]. Using vascular ultrasound, the mean diameter was reported to be 10.4±1.1mm in 24 healthy males with a mean age of 66.8±7.0 years of age and 9.2±0.9mm in 25 healthy females with a mean age of 67.9±8.5 years [96]. However, in a population of similarly aged men and women with comorbid conditions, such as diabetes and atherosclerosis, the mean common femoral arterial diameter was measured to be 6.0±1.0mm in 79 women at 69±14 years of age and 7.5±1.2mm in 121 men at 63±13 years of age [95].

Diameter of the femoral artery is only one consideration when determining the access, even in the absence of calcification, the anatomy of the vessel changes with increasing age. The intimal layer thickens, and the smooth muscle in the media deteriorates, which increases wall stress, causes cellular hypertrophy and arterial wall stiffening.

Arterial stiffening is also associated with atherosclerosis which is characterized by an excessive inflammatory and fibroproliferative response that leads to the deposition and build-up of plaque leading to a gradual thickening of arterial wall and a decline in the number of smooth muscle fibers. As these lipids accumulate, the vessel lumen begins to occlude, reducing the luminal size, and gradually becoming calcified.

Understanding the degree of calcification as well as the lumen diameter is essential in determining the adequacy of a vessel for endovascular treatments. The minimal vessel diameter required in the absence of calcium can be slightly smaller than the outer diameter of the introducer sheath as the artery can stretch somewhat to accommodate the introducer. In the presence of arterial wall calcification, oversizing the introducer sheath increases the risk of dissection or rupture during sheath insertion or removal [97]. Focal areas with smaller diameters can be transversed with caution and vessel tortuosity is not necessarily considered a limitation for the transfemoral approach, as long as the artery straightens after the insertion of a stiff guidewire. These caveats stress the importance of proper patient screening in the planning for vascular access. On the other hand, its significance may diminish as the profile of delivery systems decreases [94].

The Edwards SAPIEN THV and its delivery systems have been well characterized in more than 5000 patients enrolled in nine clinical studies from first-in-man trials (iREVIVE, RECAST [98], to feasibility studies (REVIVE, REVIVAL [22], PARTNER EU, PREVAIL-EU) a commercial registry (SOURCE) and a US IDE clinical study (PARTNER). SOURCE was initiated shortly after authorization for CE Marking was conferred for the Edwards SAPIEN THV. The SOURCE Registry follows the outcomes in a consecutive group of patients treated in 34 European centers, of which the patients from 32 centers were reported. Results of over 400 transfemoral patients during the first year of commercialization were reported for SOURCE and despite high acute procedural success rates of 95.6%, high vascular access complication rates were reported at 17.9% [99]. Recent publications of these studies are summarized in the following table. Additionally a multi-center series describing 339 patients receiving TAVR under the Canadian Ministry of Health Special Access provision is included [100]. In this series, 168 patients received TAVR via the transfemoral approach and high access complications were persistent despite mounting procedural learning curves and training. Table 1.1.11 - 1 summarizes the vascular access complications in these publications.

Table 1.1.11 - 1 - Vascular Access Complications

Study	# Patients	Vascular Access Complications
REVIVE II	106	15.5% [22]
REVIVAL II	55	12.7% [101]
PARTNER EU	61	27.9% (17/61) [21]
SOURCE	454	17.9% (91/83) [99]
Canadian Experience	168	13.1% (22/168) [100]
PARTNER	179	30.7% (55/179) [23]

Vascular complications in TAVR with the Edwards SAPIEN THV and RetroFlex platform may be attributed to the large profile of the introducer sheath required for device delivery and the presence of significant peripheral vascular disease in a large percentage of patients. The literature suggests however that vascular complication rates and associated mortality inversely correlates with operator experience, careful procedural planning, including diligent patient screening, anticipating possible vascular complications, and, most importantly, reducing the profile of the device [94, 97, 102-104]. A lower profile device would also provide an opportunity for more patients to be treated, who were previously excluded because of anatomical constraints.

Delivery of a transcatheter THV via transfemoral access is preceded by the placement of an introducer sheath in the ilio-femoral vasculature with an internal dimension that will accept the diameter of a SAPIEN or SAPIEN XT valve crimped onto its respective delivery catheter.

There still remains however a patient population where vessel tortuosities or eccentric deposits of calcification may require a somewhat smaller introducer sheath. The Edwards Expandable Sheath was developed to incorporate expansion properties as a means to safely introduce large diameter interventional devices into the vascular system and is available in sizes 16F and 18F (outer diameter 6.7mm and 7.2mm respectively) for delivery with the 23mm and 26mm SAPIEN XT THV[1]. The required access vessel diameters remain unchanged when using the 16F and 18F expandable sheaths for delivery of a 23mm and 26mm THV; however the outer diameters of the Edwards Expandable Sheath are reduced when compared to the respective NovaFlex

[1] Edwards Expandable Sheath is also available in a 20F size (8.0mm OD) for delivery of a 29mm SAPIEN XT THV.

Introducer Sheaths. This reduction in initial profile will aid in reducing the forces that the vessel experiences during sheath insertion and is expected to reduce trauma that the vessel experiences when the sheath is introduced. The sheath expansion will aid in providing reduced insertion force when tracking the respective NovaFlex Delivery Systems through the sheath while only momentarily expanding the access vessel to accommodate the device.

All sheaths have a working length of 36cm. The sheath set is provided EO sterilized and consists of an unexpandable section that maintains vessel hemostasis around the sheath during the procedure and an expandable sheath with a hydrophilic coating that provides access into the common femoral artery connected to a hub that contains valves that maintain hemostasis when devices are introduced. The expandable sheath is constructed of a high density polyethylene (HDPE) and TecoFlex coextruded outer layer with a specially folded expandable polytetrafluoroehtylene (PTFE) seam and a distal tip of low density polyethylene (LDPE) with a radiopaque marker band of platinum iridium.

Tchetche, D et al [105] compared the 30 day outcome and vascular complications between the Edwards SAPIEN THV and Medtronic CoreValve at a single-center, limited study. Forty-five patients had TAVR; 24 received the Edwards SAPIEN THV via surgical exposure of the common femoral and 21 received the Medtronic CoreValve via percutaneous pre-closure of the common femoral. All patients underwent general anesthesia for the procedure. Vessel diameters ranged from 7mm to 10.8mm with the Edwards group and 6.24mm to 9.06mm with the CoreValve group. The following table summarizes this experience.

Table 1.1.11 - 2 - 30 Day TAVR Vascular Complications

Thirty-day outcome and vascular complications after TAVR using both the Edwards SAPIEN and Medtronic CoreValve bioprostheses in a mixed population [105]		
Group	Edwards SAPIEN THV	Medtronic CoreValve
N =	24	21
Common femoral diameter	8.9±1.4mm	7.65±1.41mm
Common femoral access	Surgical exposure	Percutaneous with single Prostar XL™
Vascular complication rate	2/24 (8.3%)	2/21 (9.5%)
Vascular complication	1-extensive injury of CFA and EIA requiring iliofemoral bypass 1-vascular surgery redo due to retroperitoneal bleed following successful surgical repair	2-arterial injury requiring surgical arterial repair
Outcome of vascular complication patients	Both were discharged from the hospital	Both were discharged from the hospital
Length of hospital stay	13.54±5.6 days	10.05±0.5
Procedural success	100%	95.2%
30-d survival	100%	90.5%

Vessel diameters were found to be statistically different between the two groups (p=0.047) because the CoreValve was the only device that can treat patients with vessel diameters 6 to 8mm in combination of native annulus diameters between 24 and 27mm. There was no statistical difference in vascular complication rates between the two groups (p=0.89). However the length of hospital stay was significantly higher in the Edwards group due to the surgical exposure versus the percutaneous preclosure of the CoreValve group (p=0.049). This suggests that successful percutaneous preclosure of the common femoral artery can lead to quicker mobilization of the patient, quicker recovery time, and shorter hospital stays. Reduction in sheath profile would make arterial pre-closure more feasible however caution is still advised in patients with extensive peripheral vascular disease [106].

In summary, the Edwards Expandable Sheath is smaller in profile compared to currently marketed sheaths used with the Edwards SAPIEN THV platform and is comparable to the introducer sheath profile of the currently marketed SAPIEN XT THV platform. The scientific literature suggests that a smaller profile sheath is beneficial in reducing the risks of major vascular complications, as well as increasing the efficacy of percutaneous access and closure.

1.1.12 SAPIEN 3 Clinical History

Twenty-five clinical cases have been performed with the Edwards SAPIEN 3 THV System (model 9600TFX – Initial 19 cases with SAPIEN 3 THV Version 3.1 and the remaining 6 cases with SAPIEN 3 Version 3.1RR) under the Special Access Provision (SAP) in Canada that provides devices that are not licensed or not covered by an investigational protocol for compassionate care cases. Twenty-one of these cases were performed with early version of the Edwards Commander transfemoral delivery system (Version 0) and Edwards Expandable Sheath set and accessories in the first half of 2012; 19 of them with the 26mm system and 2 with the 29mm system. The remaining 4 cases were performed with the 26mm Certitude System: 3 of which were implanted via the transapical approach, and one via the transaortic approach.

All 25 patients receiving the S3 THV presented with were severe symptomatic calcific aortic stenosis requiring aortic valve replacement (AVR) and were at intermediate or higher risk for open chest surgery due to co-morbidities.

All patients underwent successful device implantation. There were no minor or major vascular complications and no minor or major bleeds. No post-dilation of the S3 THV was necessary and no patient required implantation of a second THV due to malpositioning or malfunction of the initial implant. In one patient, the 14F eSheath kinked as a result of very tortuous iliac arteries; after exchanging for a 16F eSheath, the procedure was completed successfully.

Results from the initial cohort of 15 patients have been documented in a journal article that is currently in press. Of these initial 15 patients, one patient developed permanent, and two patients transient, left bundle branch block immediately after valve deployment. One patient with new transient third degree and then permanent second-degree atrio-ventricular block underwent permanent pacemaker implantation. All patients were discharged home after median of 3 (range, 2-12) hospital days.

At 30-day follow-up there were no deaths, myocardial infarctions, minor or major strokes, transient ischemic attacks, minor or major bleeds and minor or major vascular complications. All patients were in NYHA class I or II at 30 day follow-up.

Mean transaortic gradient was reduced from 42.2 ± 10.3 mmHg to 11.9 ± 5.3 mmHg at discharge ($p < 0.001$) and 11.9 ± 5.3 mmHg at 30 days follow-up. The aortic valve area increased from 0.7 ± 0.2 cm2 to 1.5 ± 0.2 cm2 at discharge ($p < 0.001$) and 1.5 ± 0.3 cm2 at 30 days follow-up. Paravalvular regurgitation as assessed by TTE at discharge was none in 2 (13%), trivial in 9 (60%) and mild in 4 (27 %) patients. No patient had more than mild paravalvular regurgitation assessed by intra-procedural TEE, pre-discharge TTE, or 30 days follow-up TTE. One out of fifteen patients had a bi-cupid aortic valve. Despite the delicate native valve geometry, paravalvular regurgitation was absent.

The SAPIEN 3 System is currently undergoing clinical investigation in a multi-center study being conducted in Europe. The study will investigate the safety and performance of the SAPIEN 3 System for transfemoral, transapical, and transaortic approaches in patients with intermediate or high surgical risk for open chest surgery. Valve sizes of 23, 26, and 29mm will be used. Enrollment completion is anticipated in the fall of 2013.

1.2 Literature Review

The purpose of this review is to summarize publications and publically presented abstracts primarily in the year 2010 on the worldwide experience with transcatheter heart valves (THV) in the treatment of degenerative aortic valve stenosis. The review includes single and multicenter experiences, controlled trials, case reports on complications, an update and assessment of the THV patient population, an assessment of alternative and adjunct treatments and emerging developments in the field. The selection criteria for the documents presented include assessments of the following: 1) similarity of the device in the documents to the Edwards SAPIEN™ THV and SAPIEN XT™ devices 2) similarity of the patients or study populations in the documents compared to those that are treated with SAPIEN™ THV 3) conditions of the use of the device in the literature including uses of these devices in positions other than the aortic (i.e. mitral or tricuspid), and excludes literature related to pulmonary transcatheter implantation.

The SAPIEN™ THV (current model 9000TFX and prior models 9000 and 9000MIS; formerly known as the Cribier-Edwards aortic bioprosthesis) has been in clinical use since 2002. European CE mark authorization was granted in August 2007 for the model 9000TFX Edwards SAPIEN™ THV with the transfemoral RetroFlex delivery system and in January 2008 for use with the transapical Ascendra delivery devices. In March 2010 the Edwards SAPIEN XT transcatheter heart valve (THV) ("SAPIEN XT") was granted CE mark authorization for sizes 23 and 26 mm for use with the NovaFlex™ delivery system and is intended for use in symptomatic patients with severe calcific aortic stenosis (AS) requiring aortic valve replacement (AVR), who are at high risk for open-chest surgery due to comorbidities. The NovaFlex+ delivery system with the Edwards expandable sheath was granted CE mark authorization in May 2011 and December 2010, respectively. The Ascendra 2 delivery systems and accessory devices are intended for use during transapical AVR, received CE authorization in July 2010 and a larger size 29 mm SAPIEN XT™ THV with Ascendra Delivery System was approved for transapical use in February 2011 and with NovaFlex+ for transfemoral use in April 2012. Ascendra+ received CE mark authorization for transapical and transaortic access in May 2012. These devices represent the newest generation of the Edwards Lifesciences transapical THV platform.

The literature presented in this review were obtained using an automated literature search that was performed weekly using PubMed, an online resource that is available to the general public and maintained by the National Center for Biotechnology Information (NCBI), and located at the National Institute of Health (NIH). The following search terms were used to

establish the automated alerts:

- Aortic stenosis
- Aortic valve implantation
- Aortic valve replacement
- Cardiothoracic surgery outcomes
- CoreValve
- Cost effectiveness AND aortic valve
- DirectFlow
- EuroSCORE
- High risk AND aortic valve surgery
- JenaValve
- Percutaneous aortic valve
- Quality of life AND aortic valve
- Sadra
- SAPIEN
- Subclavian
- Symetis
- TAVI / TAVR
- Transapical
- Transcatheter aortic valve
- Transfemoral
- Valve replacement surgery
- Valve-in-valve

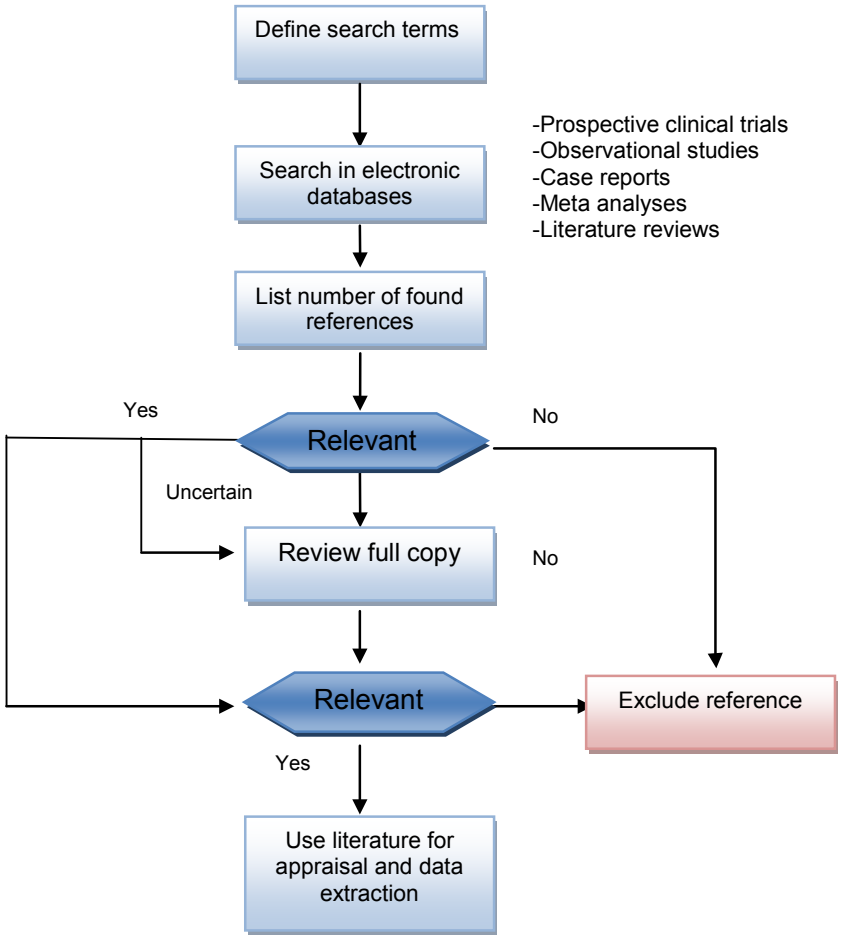
In addition to using PubMed, the following journals were also screened weekly for new publications using the automated e-mail alert feature of AMEDEO for articles relevant to the cardiovascular topic of "Valvular Heart Disease."

- Am Heart J
- Am J Cardiol
- Ann Thorac Cardiovasc Surg
- Ann Thorac Surg
- Cardiol Young
- Cardiovasc Surg
- Catheter Cardiovasc Interv
- Chest
- Circulation
- Clin Cardiol
- Eur Heart J
- Eur J Cardiothorac Surg
- Heart
- Int J Cardiol
- J Am Coll Cardiol
- J Am Soc Echocardiogr
- J Card Surg
- J Heart Valve Dis
- J Thorac Cardiovasc Surg
- Mayo Clin Proc
- N Engl J Med
- Pediatr Cardiol
- Semin Thorac Cardiovasc Surg
- South Med J
- Thorac Cardiovasc Surg

Automated search results were first filtered for duplicates. Articles relevant to Transcatheter Aortic Valve Implantation (TAVI) also referred to as Transcatheter Aortic Valve Replacement (TAVR) were selected and reviewed for applicable content, indexed by topic, and maintained within an EndNote® Master Library. EndNote® is a software program that allows references to be organized, and facilitates filtered searches.

Figure 1.0-1 describes the literature search and selection process used for this literature review.

Figure 1.0-1: Identification and selection of literature



The initial search result of PubMed for peer-reviewed journal articles published in the year 2010 produced 4446 references. AMEDEO search resulted in 1046 references. Following an additional review to remove citations in multiple categories, each citation was then assigned to a group deemed most relevant based on the abstract or full text. The references for this review were filtered using the following criteria:

- Limited to papers published from November 2009 to December 31, 2010.
- Limited to English language
- Limited to human subjects
- Limited to articles for which abstracts were available (excepting articles pertaining to Adverse Events).

The previous generations of SAPIEN THV have been implanted clinically since 2002 and commercially available since 2007 therefore, articles reporting on animal studies, in vitro testing and the history of heart valve evolution and development were not selected for this review, and are not considered relevant to this document. Prior literature reviews are available in the Clinical Investigator Brochures for the Edwards studies PREVAIL-EU, PREVAIL TA, PARTNER-EU, TRAVERCE, REVIVE, PARTNER IDE and PARTNER II IDE. Table 1.2-1 indicates the search results for the keywords searched for this review.

Table 1.2-1: Keyword Search Results

Keywords Searched	Search Result
Aortic Stenosis	1363
Aortic Valve Implantation	800
Aortic Valve Replacement	649
Cardiothoracic Surgery Outcomes	272
CoreValve	74
EuroSCORE	181
Percutaneous Aortic Valve	52
SAPIEN	62
Subclavian	485
TAVR	130
Transapical	99
Transcatheter Aortic Valve	180
Valve replacement surgery	34
Valve in Valve	20
High Risk & Aortic Valve Surgery	3
Quality of Life & Aortic Valve	25
Sadra	3
Transfemoral	13
JenaValve	1
Total PubMed Results	4446
Duplicates (approximation)	923
Articles of Interest	606
Discussed in the Review	132

The review is organized into 15 sections (inclusive of references) to facilitate reading and understanding and include: TAVR background; pathophysiology of aortic stenosis; recent findings and decision making on operability in surgical AVR (SAVR); screening and treatment for TAVR; current measures of operable risk, preparing patients for TAVR; updated single and multi-center study results of use of the SAPIEN THV; review and update of the literature on other methods and outcomes of transcatheter aortic valve implantation technologies; competitive experience; review and summary of complications reported with SAPIEN and other technologies; utilization and affects of anticoagulants, and conclusions. This review does not discuss the use of transcatheter valves in previously implanted aortic bioprostheses. In the background and etiology

sections articles published before 2010 are included to support the documentation of aortic stenosis and the evolution. The full literature review described above is available in EXHIBIT 4 of the IDE.

1.3 Design Rationale for The PARTNER II Trial

The PARTNER I Trial has served as the basic source of ideas and assumptions for The PARTNER II Trial design. Given the significance of the dismal fate of the Cohort B control patients in The PARTNER I Trial as published in the NEJM, the investigators have determined that a randomized trial against a medical management control is no longer feasible. Therefore a device versus device non-inferiority trial has been deemed as the best possible trial design in the absence of an FDA approved THV device.

Recent collaboration among multi-disciplinary world leaders in transcatheter heart valve therapy through The Valve Academic Research Consortium (VARC) and input from the Food and Drug Administration has also influenced the design and endpoint definitions of this protocol.

Other considerations are also noted below:

- The PARTNER II Trial is informed by the results of The PARTNER Trial, with particular care paid to potential complications of the transcatheter heart valve. Accordingly, more rigorous neurological assessments and implementation of a Procedure Management Steering Committee have been added to the trial conduct.

- Major complications of major vascular complications and stroke have been shown to significantly impact one year mortality (treatment arm) and major bleed and new onset atrial fibrillation (control arm, Cohort A) in The PARTNER Trial. For purposes of equipoise therefore stroke, major vascular complications and major bleed have been incorporated as important primary and secondary safety endpoints.

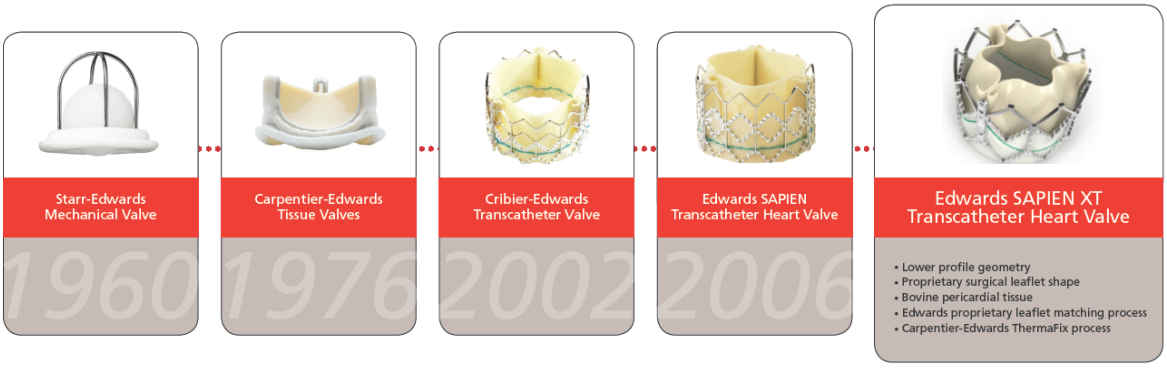
- The PARTNER II Cohort A has a lower risk population, therefore the primary endpoint has a longer term follow-up time-point (2 years) for primary safety and effectiveness analysis. There is a paucity of data for both treatment and control at 2 years. Therefore the assumptions for sample size and non-inferiority endpoint ranges are based on approximate event rates.

- The PARTNER II Trial inoperable cohort has different endpoints than the pre-specified endpoint of The PARTNER I (mortality). The primary safety and effectiveness endpoint is appropriate for comparing the two different transcatheter heart valve models. The assumptions for control performance are based upon the published PARTNER I Trial results.

- It is not anticipated that there will be statistically significant differences between Test and Control in both cohorts of The PARTNER II Trial. Trial arm comparisons for endpoint evaluation are based on non-inferiority.
- Secondary safety and effectiveness endpoints are intended to carefully evaluate device performance (implant and its delivery system) and clinical improvement measures as a means to assess risk to benefit.
- Numerous follow-up and statistical analysis items have been changed based on The PARTNER I Trial experience. For PARTNER II, these specifications are now prospective.
- It cannot be assumed that the patient population for PARTNER II Cohort B is the same as the population in PARTNER because of the lack of a true "standard therapy" control group and the differences in study design between the two trials (device vs. device as opposed to device vs. standard therapy) will modify the selection criteria for non-surgical patients. Therefore, pooled comparisons to PARTNER data may be limited in value.
- Best practices for procedure management were surveyed from The PARTNER I Trial sites and have been incorporated in The PARTNER II Trial.

2.0 General Overview of the Study Valve Technology

Edwards Lifesciences has pioneered three generations of heart valve implants over the past 50 years, starting with the first mechanical heart valve in 1960, followed by the introduction of bioprosthetic tissue valves in 1976 and the advancement of bovine pericardial bioprostheses in the 1980´s. The evolution of valve replacement therapy was expanded with the acquisition of the transcatheter heart valve technology in 2002. Edwards's research and development expertise in bioprosthetic heart valves was applied to the development of the first generation SAPIEN™ transcatheter heart valve (THV) in 2006 and the introduction of the second generation Edwards SAPIEN XT™ THV in 2008. The SAPIEN valve is commercially available in Europe and is currently under premarket approval status with FDA and remains an investigational device in the US.



For The PARTNER II Trial, it is recommended to utilize an Edward's surgical aortic valve bioprosthesis for Cohort A control patients. The Edwards SAPIEN™ (first generation) and Edwards SAPIEN XT™ (second generation) devices are catheter-delivered heart valves that combine a balloon expandable stent and bioprosthetic valve technology and are indicated for patients who are high risk for AVR or patients who are deemed to be inoperable due to co-morbid conditions. The frame height of both devices is designed for proper placement within the native aortic annulus without interfering with the surrounding anatomy, minimizing the risk of atrioventricular block and disruption of mitral valve leaflet function.

The Edwards SAPIEN THV is comprised of a radiopaque, stainless steel expandable support structure (stent), with an integrated unidirectional trileaflet tissue valve, and a polyethylene terephthalate (PET) fabric cuff. The valve tissue is fabricated from three equal sections of bovine pericardium that have been preserved in low concentration solutions of buffered glutaraldehyde to fully crosslink the tissue, while preserving its flexibility and strength. It is treated with the Edwards ThermaFix™ process. The valve tissue component is firmly affixed to the frame within the fabric cuff at its inflow aspect and to attachment bars on the commissural posts at its outflow aspect using polytetrafluoroethylene (PTFE) sutures. The valve is available in sizes 23 mm and 26 mm and is delivered with the leaflets in an open position. The THV is intended to be

implanted in a native annulus size range comparable to the transesophageal echocardiography (TEE) measurements cited in Table 2.0-1 below:

Table 2.0-1 SAPIEN THV Sizes

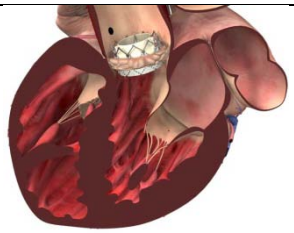
Native Valve Annulus Size (TEE Measurement)	**THV Size**	**Profile Height**
18-22 mm	23 mm	14.3 mm
21-25 mm	26 mm	16.1 mm

The Edwards SAPIEN XT transcatheter heart valve (model 9300TFX) is comprised of a balloon-expandable, radiopaque, nickel cobalt chromium frame, trileaflet bovine pericardial tissue valve, and polyethylene terephthalate (PET) fabric. It is treated according to the Edwards ThermaFix process and is packaged, and terminally sterilized in glutaraldehyde. The valve is available in three sizes 23 mm, 26 mm and 29 mm manufactured with the pericardial leaflets in a semi-closed, coapted configuration.

The THV is intended to be implanted in a native annulus size range comparable to the transesophageal echocardiography (TEE) measurements cited in Table 2.0-2 below:

Table 2.0-2 SAPIEN XT THV Sizes

Native Valve Annulus Size (TEE Measurement)	**THV Size**	**Profile Height**
18-22 mm	23 mm	14.3 mm
21-25 mm	26 mm	17.2 mm
24-27 mm	29 mm	19.1 mm

Edwards SAPIEN™ Model 9000TFX	Edwards SAPIEN XT™ Model 9300TFX	THV In Situ
		

Delivery of the THV is preceded by dilation of the stenotic native aortic valve by means of balloon aortic valvuloplasty (BAV). Predilation tests the expansion capacity of the native valve and prepares the annulus for implantation of the study valve. For the NovaFlex delivery system, the THV is carefully mounted and crimped proximal to the balloon. The delivery system is then inserted into the femoral artery (retrograde approach), through the introducer sheath or the Expandable Sheath, respectively and into a straight section of the descending aorta. At this point, the balloon catheter is brought underneath the valve, in the correct location for valve delivery. The steerable delivery system is then advanced over the aortic arch and delivered to the site of the native stenotic aortic valve.

For the Ascendra delivery systems, the valve is crimped onto the balloon, using a specially designed crimping device. The delivery system is then inserted in the left ventricular apex (antegrade approach), through the introducer sheath, and delivered to the site of the native stenotic aortic valve.

Both the SAPIEN and SAPIEN XT THV are positioned and deployed across the stenotic native valve under rapid ventricular pacing. The balloon delivery system and catheterization accessories are then removed. These minimally invasive approaches are intended to be performed under local and/or general anesthesia using sterile technique with echocardiographic and fluoroscopic guidance for visualization.The SAPIEN 3 system was designed to improve the ease of use and procedure related adverse events such as paravalvular leak, major vascular complications and major bleeding. The SAPIEN 3 system consists of:

- Edwards SAPIEN 3 transcatheter heart valve;
- Edwards Commander Delivery System (transfemoral)
- Edwards Certitude Delivery System (transapical/transaortic)

The inflow aspect of the SAPIEN 3 THV contains an external layer of PET with integral scalloped geometry that is intended to acutely fill the voids between the valve frame

and native annulus caused by eccentric calcium deposits and enhance the chronic re-endothelialization process to create a tissue bridge across these voids.

Table 3.0 SAPIEN 3 THV Sizes

Native Valve Annulus Size (TEE Measurement)	THV Size	Profile Height
18-22 mm	23 mm	18 mm
21-25 mm	26 mm	20 mm
24-28 mm	29 mm	22.5 mm

Delivery of the THV is preceded by dilation of the stenotic native aortic valve by means of balloon aortic valvuloplasty (BAV). Predilation tests the expansion capacity of the native valve and prepares the annulus for implantation of the study valve. For the Commander delivery system, the THV is carefully mounted and crimped proximal to the balloon. The delivery system is then inserted into the femoral artery (retrograde approach), through the introducer sheath or the Expandable Sheath, respectively and into a straight section of the descending aorta. At this point, the balloon catheter is brought underneath the valve, in the correct location for valve delivery. The steerable delivery system is then advanced over the aortic arch and delivered to the site of the native stenotic aortic valve.

For the Certitude delivery systems, the valve is crimped onto the balloon, using a specially designed crimping device. For transapical access, the delivery system is then inserted in the left ventricular apex (antegrade approach), through the introducer sheath, and delivered to the site of the native stenotic aortic valve. For transaortic access, the delivery system is inserted in the ascending aorta using a standard surgical technique (e.g. partial J-sternotomy or right parasternal mini thoracotomy), through the introducer sheath, and delivered to the site of the native stenotic aortic valve.

2.1 Indications for Use

The size 23, 26 and 29 mm SAPIEN XT THVs are indicated for use in patients with severe, symptomatic, calcific aortic stenosis with a STS score ≥4, or in a previously implanted, failing aortic bioprosthetic surgical valve in patients with a surgical mortality or major morbidity ≥ 50%.

The size 23, 26 and 29 mm SAPIEN 3 THVs are indicated for use in high risk patients with severe, symptomatic, calcific aortic stenosis with a STS score ≥8 or inoperable as defined above,

Devices included for use (See appendix O).

3.0 Risks and Benefits Analysis

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

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

- Abnormal lab values (including electrolyte imbalance)
- Allergic reaction to antithrombotic therapy, contrast media, anesthesia or device materials
- Aortic valve thrombosis/occlusion
- Anemia
- Aneurysm
- Angina
- Arrhythmia including ventricular fibrillation (VF) and ventricular tachycardia (VT)
- Arthralgia
- Bleeding / Bruising
- Cardiogenic shock / pulmonary edema
- Cardiovascular injury including perforation or dissection of vessels, ventricle, myocardium or valvular structures that may require intervention
- Conduction system injury (defect) which may require a permanent pacemaker
- Embolization including air, calcific/thrombotic valve material or thrombus
- Exercise intolerance or weakness
- Femoral AV fistula or pseudoaneurysm
- Fever
- GI symptoms
- Headache
- Heart failure
- Heart murmur
- Hematologic dyscrasia
- Hematoma
- Hemorrhage requiring transfusion or intervention
- Hepatic enzyme changes
- Hypertension or hypotension
- Infection including septicemia and endocarditis
- Inflammation
- Ischemia, limb or myocardial
- Myalgia
- Myocardial infarction

- Infection, pain or changes at the access site
- Paralysis
- Pericardial effusion or cardiac tamponade
- Peripheral ischemia or nerve injury
- Permanent disability
- Pleural effusion
- Post operative encephalopathy
- Pulmonary edema
- Renal insufficiency or renal failure
- Reoperation
- Respiratory insufficiency or respiratory failure
- Restenosis
- Retroperitoneal bleed
- Shock
- Silent cerebral edema
- Stroke/transient ischemic attack, clusters or neurological deficit
- Syncope
- Vasovagal response
- Vessel spasm
- Vessel thrombosis / occlusion

Additional potential risks associated with the use of the THV, delivery system, and/or accessories include:

- Acute coronary occlusion
- Allergic/immunologic reaction to the implant
- Aortic annulus dissection/rupture/trauma
- Arrhythmia including AV block, Atrial fibrillation/Atrial flutter
- Aortic valve insufficiency
- Blood loss requiring blood transfusion
- Cardiac arrest
- Cardiac failure or low cardiac output
- Cardiogenic shock
- Cognitive impairment
- Conduction disturbance including AV block requiring pacemaker
- Coronary flow obstruction/transvalvular flow disturbance
- Device degeneration
- Device embolization
- Device explants
- Device malfunction requiring intervention/surgery
- Device migration or malposition requiring intervention
- Device thrombosis requiring intervention

- Emergency cardiac surgery
- Endocarditis
- Hemolysis
- Injury to aortic and/or mitral valve
- Mechanical failure of delivery system, and/or accessories
- Mediastinitis
- Mediastinal bleeding
- Non-emergent reoperation
- Nonstructural dysfunction
- Paravalvular or transvalvular leak
- Structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from the stent posts, leaflet retraction, suture line disruption of components of a prosthetic valve, thickening, stenosis)
- Valve deployment in unintended location
- Valve regurgitation
- Valve stenosis
- Valve thrombosis

3.1 Efforts to minimize procedure risks

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

3.1.1 Site and investigator criteria

- Interventional cardiologists must be experienced and skilled in percutaneous, structural heart interventions (BAV).

- To qualify for participation in The Partner II Trial, cardiovascular surgeons must have performed at least 100 total intermediate risk open AVR operations (STS≥4) as well as maintain over the most recent three years an average of 30 or more open aortic valve operations per year. Strong interdepartmental collaboration between cardiac surgery and interventional cardiology operators must be demonstrated and is to be assessed by an experienced PARTNER trial study team. The study site team must be trained in the use of the investigational devices prior to enrollment of study patients. (See Appendix A for details on the training program).

- The procedure setting must include a fixed C-arm angiography imaging capability in the cath lab or operative suite and/or a hybrid catheterization/operating room suite.

- The study site must have an adequately staffed research department with a minimum of one dedicated study coordinator.
- The study site must demonstrate an organized and disciplined approach to screening, enrolling and follow-up of study patients in a “PARTNER clinic” style of multi-disciplinary team members.

3.1.2 Best practices aimed at minimizing procedure-related risks

The study management, monitors, field staff, Co-PIs and the Executive Committee will help to assess and determine site and investigator eligibility and ongoing ability to participate in the study- based upon such factors as enrollment status, the research coordination and clinic support, visit, protocol and data compliance, partnership of disciplines at the site level and overall commitment to the demands of the trial. Additionally, The Patient Selection and Procedure Outcomes Steering Committee will convene routinely to review procedure complications, interesting cases and share important lessons with the trial community via web conferences, The PARTNER II Trial web portal and other means of communications.

3.1.3 Potential Benefits

Implantation of the transcatheter heart valve may result in improved valvular function, acute alleviation of symptoms related to aortic stenosis and improved quality of life in inoperable and high risk patients (see section 1.0).

4.0 The PARTNER II Trial Design and Study Purpose

Design

A prospective randomized, multi-center trial with two population cohorts for the Edwards SAPIEN XT™ device: 1) patients who are designated to have intermediate and high risk for surgical aortic valve replacement (operable) and 2) patients who are not suitable for aortic valve surgery (inoperable), and a single Cohort (S3 Cohort) for the Edwards SAPIEN 3 Transcatheter Heart Valve device (S3 THV): patients who are designated to have high risk (STS ≥ 8%) for aortic valve surgery (operable) and patients who cannot undergo surgery (inoperable).

Edwards SAPIEN XT™ Cohorts: For consistency with the terminology of The PARTNER I Trial, the operable cohort will be designated as Cohort A and the inoperable cohort will be designated as Cohort B. For both Cohorts of the trial, patients randomized to the test arm will receive the SAPIEN XT™ THV with either the NovaFlex family (transfemoral) or Ascendra family (transapical or transaortic) delivery systems. Valve delivery access is to be determined by site investigators and case review process. Cohort A and Cohort B study designs are further detailed below.

S3 Cohort: The S3 Cohort is a single arm non-randomized, historical- controlled study independently powered to compare transcatheter heart valve therapy with the first generation (SAPIEN THV) system to transcatheter heart valve therapy with the third generation (SAPIEN 3 THV) system in patients who either have high risk for surgery or cannot undergo surgery (inoperable).

Trial Cohorts and Additional Registries:

There are two distinct trial cohorts with discrete eligibility criteria and trial designs. Additionally, four registries are included in The PARTNER II Trial as described herewith.

Cohort A

Cohort A is a 1:1 randomized, controlled study independently powered to compare transcatheter heart valve therapy with traditional, open-heart aortic valve surgery (AVR) in intermediate and high risk patients. For the purposes of this study, intermediate risk is defined as STS $\underline{\geq}$ 4. The trial is a non-inferiority design. Patients randomized to the treatment arm of Cohort A will receive an Edwards SAPIEN XT™ THV with either transfemoral, transapical or transaortic delivery access depending on patient anatomical factors and investigator heart team determination for optimal access approach. Patients in the control arm of Cohort A will receive a surgical bioprosthetic

heart valve via aortic valve replacement surgery. The proposed randomized sample size is set to 2000 patients, based on both the statistically justified size and the need to allow for possible lost to follow-up and other trial contingencies.

Endpoints for Cohort A:

The primary safety and effectiveness endpoint for Cohort A is a non-hierarchical composite of events: death (all cause) and disabling stroke. The primary endpoint analysis will occur after the last patient enrolled reaches two year follow-up. Trial arm comparison will be a non-inferiority analysis.

The secondary safety and effectiveness endpoint is a non-hierarchical composite of various adverse events. The endpoint will be evaluated at two time points: (1) acute, covering events occurring out to 30 days or hospital discharge, whichever is longer; and (2) longer-term, covering events from 31 days to the 2 year closing date of the primary endpoint. As requested by the FDA the specific components of the composite are:

- all stroke and TIA
- myocardial infarction
- major vascular complication (VARC)
- life-threatening bleeding (VARC)
- reoperation or catheter-based intervention for: valve thrombosis, valve displacement, or other valve placed
- procedure-related complication
- pericarditis
- hemolysis
- mediastinitis
- endocarditis
- moderate or severe aortic insufficiency (VARC)
- possible or significant aortic stenosis (VARC)
- permanent pacemaker insertion
- new mitral valve dysfunction
- acute kidney injury (VARC)

Secondary Efficacy and Safety Endpoints for Cohort A Labeling:

- Days alive and out of hospital (DAOH) to one year
- NYHA at the one year visit
- 6MWT at the one year visit

- Valve area at the one year visit
- Total aortic regurgitation at the one year visit
- Device success (Cohort B only)
- 6MWT improvement from baseline to one year

The p-values generated as a result of statistically analyzing the endpoints listed in this section will be Hochberg-adjusted to account for multiplicity. See Section 7.9 for more details on the Hochberg method and more detailed descriptions of these analyses.

Cohort B

Cohort B is a 1:1 randomized, controlled study independently powered to compare transcatheter heart valve therapy with the first generation (SAPIEN THV) system to transcatheter heart valve therapy with the second generation (SAPIEN XT™ THV) system in patients who cannot undergo surgery (inoperable). Patients in the control arm of Cohort B will receive an Edwards SAPIEN™ THV with RetroFlex3 (transfemoral). Patients in the treatment arm of Cohort B will receive an Edwards SAPIEN XT™ THV with NovaFlex (transfemoral). The randomized sample size has been set to 500 patients in order to allow for possible lost to follow-up and other trial contingencies.

Endpoints for Cohort B

The primary safety and effectiveness endpoint is a non-hierarchical composite of death (all cause), disabling stroke, and rehospitalization for symptoms of aortic stenosis and/or complications of the valve procedure. The primary endpoint analysis will occur after the last patient enrolled reaches one year follow-up. Trial arm comparison will be a non-inferiority analysis.

The secondary safety and effectiveness endpoint is a non-hierarchical composite of all stroke, major vascular complications and reintervention. Trial arm comparison will be a non-inferiority analysis analyzed with the Hochberg adjustment.

S3 Cohort

The S3 Cohort consists of both operable high risk and inoperable patients, who will receive the Edwards S3 THV. The S3 Cohort is a single arm non-randomized, historical- controlled study independently powered to compare transcatheter heart valve therapy with the first generation (SAPIEN THV) system to transcatheter heart valve therapy with the third generation (SAPIEN 3 THV) system in patients who either have high risk for surgery or cannot undergo surgery (inoperable).

S3 THV will be available in 23, 26, and 29 mm sizes. The historical control group from the PARTNER I trial is described in detail section 15.0.

Total enrollment in the S3 Cohort will be 500 as justified in the sample size section below in this protocol.

It is anticipated that the enrolling sites are experienced SAPIEN sites therefore no roll-in will be permitted.

Endpoints for the S3 Cohort

Statistical analysis for the S3 Cohort will be based on comparison to a historical control group consisting of randomized Cohort A and Cohort B Test patients from the PARTNER I trial who received the Edwards SAPIEN THV. There will be no concurrent control.

The primary effectiveness endpoint for the S3 Cohort is a comparison of total aortic regurgitation at 30 days between Test (S3 THV) and SAPIEN. The analysis is a non-inferiority analysis. Superiority will be tested sequentially if non-inferiority is demonstrated.

The primary safety endpoint for the S3 Cohort is a non-hierarchical composite of death, all stroke and major vascular complication at 1 year in accordance to PARTNER I definitions. PARTNER I definitions were selected to provide consistency and avoid adjudication bias. Importantly the components of the composite endpoint were selected to reflect the clinical impact of the design differences between S3 THV and SAPIEN. The analysis is a non-inferiority analysis. Superiority will be tested sequentially if non-inferiority is demonstrated.

For the primary effectiveness endpoint, the PARTNER I data will be reevaluated by the same ECHO Core Lab evaluating the S3 data. Common definitions will be used.

Secondary Efficacy and Safety Endpoints for S3 Labeling

The p-values generated as a result of statistically analyzing the endpoints listed in this section will be Hochberg-adjusted to account for multiplicity. See Section 7.9 for more details on the Hochberg method and more detailed descriptions of these analyses.

1) Days alive and out of hospital (DAOH) to one year
2) NYHA at the one year visit
3) Valve area at the one year visit

Registries (NR1, NR2, NR3, NR4, NR5 and NR6)

In addition to the randomized Cohorts A and B, six single arm prospective registries are included in The PARTNER II Trial.

NR1: Inoperable Transapical Registry. Patients deemed eligible for Cohort B but do not have eligible transfemoral access may be enrolled into a registry for transapical delivery of the 23mm or 26mm SAPIEN XT™ THV. A maximum of 100 patients may be enrolled in this arm. Primary endpoint of this registry is freedom from mortality at one year. Non-powered secondary endpoints for safety and effectiveness will be consistent with additional secondary endpoint analyses for both Cohorts A and B and as described below. Patients previously enrolled as Cohort A control may not be enrolled in this registry.

NR2: Inoperable Registry for Transfemoral delivery of the 23mm or 26mm SAPIEN XT in 6-7mm transfemoral arteries. Upon close of enrollment for the randomized inoperable cohort (Cohort B), patients with transfemoral vessels 6-7mm may be enrolled in a registry. A maximum of 100 patients may be enrolled in this arm. Primary endpoint of this registry is freedom from mortality, major vascular complications and major bleeding at 30 days. Non-powered secondary endpoints for safety and effectiveness will be consistent with additional secondary endpoint analyses for both Cohorts A and B and as described below.

NR3: Registry for Transcatheter Valve in aortic Surgical Valve Implantation (THV-SV). Enrollment in this registry is indicated for use in patients with failing aortic bioprosthetic surgical valve in patients with a surgical mortality or major morbidity ≥50% and meeting the sizing requirements for 23mm or 26mm Edwards SAPIEN XT THV. A maximum of 100 patients may be enrolled in this arm. Primary endpoint of this registry is freedom from mortality at one year. Non-powered secondary endpoints for safety and effectiveness will be consistent with additional secondary endpoint analyses for both Cohorts A and B and as described below. Guidelines developed and approved by the PARTNER Trial Executive Committee for the THV-SV registry are provided in Appendix R.

NR4: Inoperable Transaortic Registry. Patients deemed eligible for Cohort B but do not have eligible transfemoral access may be enrolled into a registry for transaortic delivery of the SAPIEN XT™ THV (23 mm or 26 mm). A maximum of 100 patients may be enrolled in this arm. Primary endpoint of this registry is freedom from mortality at one year. Non-powered secondary endpoints for safety and effectiveness will be consistent with additional secondary endpoint analyses for both Cohorts A and B and as described below.

NR5: Inoperable Transfemoral Registry for the delivery of 29 mm SAPIEN XT™ in ≥ 7mm femoral arteries. A maximum of 50 patients may be enrolled in this arm. Primary endpoint of this registry is freedom from mortality at one year. Non-powered secondary endpoints for safety and effectiveness will be consistent with additional

secondary endpoint analyses for both Cohorts A and B and as described below. Patients previously enrolled as a Cohort A control may not be enrolled in this registry.

NR6: Inoperable Transapical Registry for the delivery of 29 mm SAPIEN XT™ for Cohort B that do not have eligible transfemoral access. A maximum of 50 patients may be enrolled in this arm. Primary endpoint of this registry is freedom from mortality at one year. Non-powered secondary endpoints for safety and effectiveness will be consistent with additional secondary endpoint analyses for both Cohorts A and B and as described below. Patients previously enrolled as a Cohort A control may not be enrolled in this registry.

Additional Safety Endpoints To Be Evaluated

1. Freedom from major vascular complications (VARC)
2. Freedom from all neurological events (all stroke and TIA) (VARC)
3. Freedom from myocardial infarction
4. Freedom from acute kidney injury (VARC)
5. Freedom from access site infections
6. Freedom from new permanent pacemaker
7. Freedom from atrial fibrillation at each visit.
8. Procedure related complications composites: two endpoints based on VARC definitions
9. For Cohort A only, a non-hierarchical composite of all stroke, major vascular complications and reintervention. The endpoint will be evaluated at 30 days and 2 years.
10. Freedom from transfusion.

Additional Effectiveness Endpoints

1. Total days alive and out of hospital (from date of index procedure)
2. Clinical improvement per NYHA Class (from baseline)
3. Clinical improvement per Quality of Life instruments: (Cohort A: KCCQ, EQ5D, SF36 Cohort B: KCCQ, EQ5D, SF12)

4. Clinical improvement per 6 Minute Walk Test (from baseline)
5. Mean ICU and total index procedure hospital length of stay

Additional Trial Arm Valve Performance Endpoints

1. Freedom from major aortic paravalvular leak
2. Improvement in hemodynamic function: effective orifice area
3. Improvement in hemodynamic function: mean gradient
4. Freedom from structural valve deterioration
5. Total aortic regurgitation

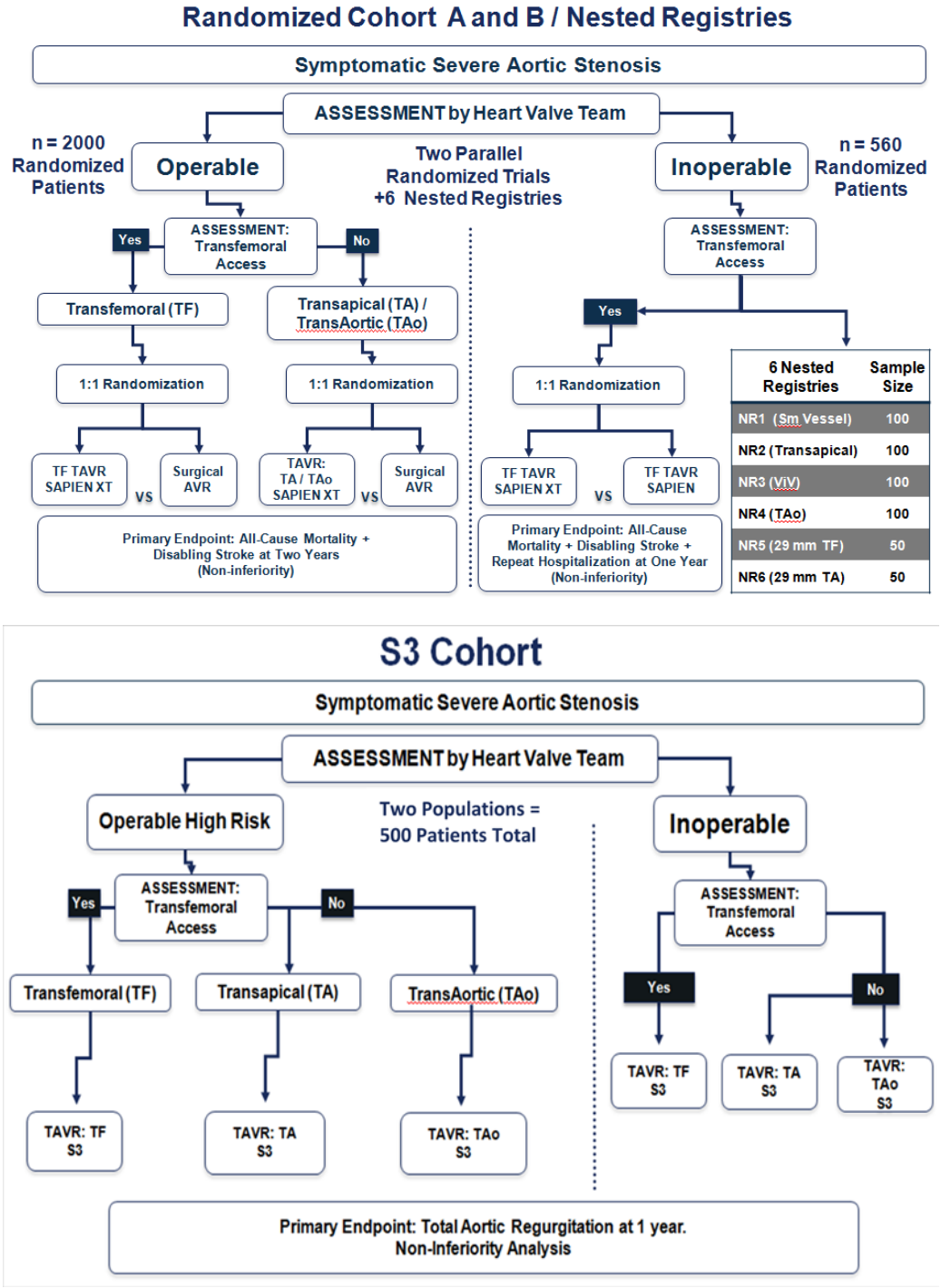
4.1 Neurological Outcomes

The PARTNER Trial Cohorts A and B signaled increased neurological outcomes versus control arms. Assessments of disability related to neurological events were limited in The PARTNER Trial, therefore warranting further study. The PARTNER II Trial Executive and Steering Committees recognize the clinical importance of potential neurological outcomes for patients undergoing cardiovascular procedures and recommended enhanced provisions for ascertainment, analysis and oversight of neurological outcomes in The PARTNER II Trial.

As a result, The PARTNER II Trial study oversight includes a Neurological Outcomes Principal Investigator to the Executive Committee (Thomas Brott, MD, Mayo Clinic Florida) as well as the addition of a dedicated neurologist to each study site team as well as the DSMB and the CEC committees. All neurological events in this Trial will undergo assessment and classifications for causality and severity through dedicated review by a CEC neurologist, followed by periodic DSMB reviews for overall outcomes. Stopping rules for stroke outcomes are included in the DSMB charter.

Also established in this protocol are neurological instruments (NIHSS, Modified Rankin Scale and Barthel Index) that will be administered in both treatment and control arms at baseline, post procedure, discharge, 30 days, 6 months, 1 year and annually through 5 years. To ensure the highest level of quality and consistency in neurological assessments, the assessments should be performed by a neurologist or a neurology fellow. If the neurologist or neurology fellow is not available within the time of the prescribed visit window, a certified team member may perform the tests. However, given the importance of procedure related neurological outcomes, the post procedure assessment must be performed a neurologist or neurology fellow.

4.2 The PARTNER II Trial Study Scheme and Primary Analytical Subset



For the primary safety and effectiveness endpoint, the primary analytical subset will be the Intent-To-Treat population defined at time of randomization. For secondary endpoints the primary analytical subset will be the As-Treated population.

A subset of these secondary endpoints will be selected for potential labeling claims, including formal adjustment for multiple comparisons.

Analysis subsets for the Sapien 3 Cohort are specified in Section 15.0.

4.3 Enrollment Enrollment will consist of a maximum of 4200 patients, including approximately 250 roll-ins; 2000 patients randomized on a 1:1 basis in Cohort A; 500 patients randomized on a basis of 1:1 in Cohort B, approximately 50 patients who may be randomized after the 2000 and 500 totals have been achieved. Additionally, up to 100 patients will be enrolled in each of the four registries (NR1, NR2, NR3, NR4) and 50 patients each in NR5 and NR6. Continued Access Registries (N1, NR2, NR3, NR4, NR5, NR6) will consist of a maximum of 500 patients. S3 Cohort will consist of a maximum of 500 patients.

For each Cohort (A and B), enrollment will continue until the date on which the trial sponsor is aware that the designated sample size has been obtained. Patients who have already signed the informed consent form at that time will be allowed to be randomized, provided that this additional randomization is completed within 30 days of the consent date. These additional patients will be considered part of the analysis cohort, and no subset analysis will be performed related to randomization before or after the 2000 and 500 totals had been met.

Sites that have not previously used either the SAPIEN or the SAPIEN XT devices will be allowed up to 3 roll-in patients per delivery system prior to initiating randomization (2 roll-ins, if the first 2 are successful). Roll-in patients will not be pooled with randomized patients for data analysis, and will not count toward the randomized sample size.

To ensure enrollment is representative and balanced across study sites, no site will enroll more than 15 percent of the total in either cohort or implant approach.

S3 Enrollment:
Enrollment will consist of 500 patients.

Enrollment will continue until the date on which the trial sponsor is aware that the designated sample size has been obtained. Patients who have already signed the informed consent form at that time will be allowed to be enrolled, provided that this enrollment and implant is completed within 30 days of the consent date. These additional patients will be considered part of the analysis cohort, and no subset analysis will be performed related to enrollment before or after the prespecified total has been met.

4.4 Follow-up

For end point analyses, study patients will undergo clinical follow-up:

- Cohort A: Discharge, 30 days, 6 months, 1 and 2 years ;
- Cohort B, S3 Cohort and All Registries: Discharge, 30 days, 6 months and 1 year;
- All Cohorts will undergo follow up annually for a minimum of 5 years post index procedure. There will be a phone follow-up at the analysis close date of each Cohort. Additional phone follow-ups may be performed as needed, to obtain up to date survival information for use in regulatory submissions.

5.0 Patient Population and Study Visits

Patients are screened for severe, symptomatic calcific aortic stenosis. Prior to stratification into the operable and inoperable cohorts, patients must meet the fundamental enrollment criteria of severe, symptomatic, calcific aortic stenosis with quantifiable and documented source records. Upon meeting these eligibility criteria, the site investigators (per site heart team assessment) shall then determine the patient's risk for operative morbidity and mortality. Patients determined to be operable must have a minimum STS score of $\geq$ 4. Patients deemed inoperable must have documented evidence that the risk for operative mortality is $\geq$ 50% as determined by the examining cardiac surgeon investigator. For Cohort A patients, a third assessment, regarding optimal valve delivery access (transfemoral, transapical or transaortic) is determined by the site heart team. Patients with arterial access < 6.0 mm shall receive transapical or transaortic delivery; patients with arterial access > 7.0 mm shall receive transfemoral delivery. Patients who are candidates for Edwards SAPIEN XT ™ and have arterial access between 6.0 and 7.0 mm vessels shall have the access determined by the heart team.

For the S3 THV, patients with arterial access < 5.5 mm shall receive transapical or transaortic delivery; patients > 6.5 mm shall receive transfemoral delivery unless the access vessels show extreme tortuosity and/or calcification or if there is concern about passing the delivery system across the aortic arch. Patients between 5.5 and 6.5 mm vessels shall have the access determined by the Heart Team based on anatomical and comorbid considerations. Patients that are not candidates for TF will undergo further assessment for the best surgical approach. The choice between TA and TAo represents a complex medical decision. The Heart Team will choose the approach which in their judgment appears to be best for the patient.

After these assessments are made, the study candidate's qualifying criteria are presented via The PARTNER Trial case review process where experienced trial investigators, members of the Executive and/or Steering Committee will adjudicate the cohort and access decision. Upon case review approval, the supporting evidence for the cohort and access assessments (transfemoral, transapical or transaortic) and the names of the review committee members will be documented in the source documents and case report forms. Once the review is documented and the eligibility criteria are documented, the patient can be enrolled in the trial. Of note, it is essential that at least one site investigator (surgeon) must have personally examined the patient to make a determination of operability.

5.1 Cohort A: Defining the Intermediate Risk Operable Patient

Patients are considered "intermediate risk" for surgical aortic valve replacement if their STS PROM is > 4. A survey of the STS data base was conducted (March 2011) to

ascertain an appropriate intermediate risk designation. For isolated AVR an STS score >4 represented 22.3% of patients and for combination AVR and coronary artery bypass grafting STS score >4 represented 44.5%. When examining the STS database by terciles and quartiles, the top 30% of the STS database showed a mean score 3.2; top quartile STS of 3.7 and top tercile STS of 2.9. For combination AVR plus CABG, the top 30% was STS of 5.3, top quartile STS of 6.0 and top tercile STS of 5.0. Candidates for aortic valve replacement may present with one or more comorbidities that are considered "unsupported" in the STS risk calculator due to insufficient numbers of patients in the STS dataset. Investigators may petition the Executive Committee for consideration of eligibility for patients with STS <4 if intermediate risk consistent with the study population can be demonstrated.

Such conditions may include but are not limited to:

- Advanced liver disease
- Porcelain aorta
- Complications with prior cardiac surgery (mediastinitis, prolonged intubation, etc)
- Malignancy
- Chest deformity (pectus excavatum, mastectomy, irradiation)
- Subdural hematoma
- Blood dyscrasia
- Refusal of blood products (Jehovah's witness)
- Immobility, malnutrition

In addition patients with particularly severe comorbidities may not be represented in sufficient numbers to model increased risk in the traditional STS scoring system.

Examples would be extremes of:

- pulmonary disease
- obesity
- non-graftable coronary disease

It is at the Investigator's discretion to present compelling evidence to The PARTNER II Trial Executive Committee for exemptions to the STS requirement. This is expected to be of rare occurrence and must be well documented in the study records.

5.2 S3 Cohort: Defining the "Operable High Risk Patient"

To assure that patients are of operable high risk to justify qualification, an STS score of ≥ 8 has been selected. This score represents patients in less than the top decile of risk in the STS National Registry Database*. The following data ensure that this score represents the extreme end of risk in the currently available surgical population in the US.

A candidate who does not meet the STS score criteria of ≥ 8 can be included in the study if a peer review by at least two investigators (not including the enrolling surgeon) concludes and documents that the patient's predicted risk of operative mortality is ≥15%. The surgeon's assessment of operative comorbidities not captured by the STS score must be documented.

Such conditions may include but are not limited to:

- Advanced liver disease
- Porcelain aorta
- Complications with prior cardiac surgery (mediastinitis, prolonged intubation, etc)
- Malignancy
- Chest deformity (pectus excavatum, mastectomy, irradiation)
- Subdural hematoma
- Blood dyscrasia
- Refusal of blood products (Jehovah's witness)
- Immobility, malnutrition
- Pulmonary disease
- Obesity
- Non-graftable coronary disease

5.3 Cohort B: Defining the "Inoperable" Patient

In the absence of a specific tool for assessment of inoperability, high-risk patients not eligible for the surgical arm are deemed "inoperable" based on a consensus assessment by 2 cardiovascular surgeons and a cardiac interventionalist. At least one surgeon deeming the patient inoperable must have performed a physical assessment of the patient. Most inoperable patients have elevated STS risk scores including one or more STS risk elements that exceed thresholds considered safe for operation. A common example is respiratory disease, for which the STS risk-scoring threshold usually signals increased risk in operable patients, but which may be severe enough in a given patient to explain inoperability (see definition in Section 8.0). Other "inoperable" patients, regardless of STS score, are rendered inoperable by severe co-morbidities of the low-prevalence, high-heterogeneity variety that are difficult to represent statistically and are not part of the STS risk model. Common examples include liver disease, porcelain aorta, chest wall abnormalities, and frailty (see definitions in Section 8.0). It must be acknowledged that "inoperable" is frequently an integration of multiple dimensions of an individual patient in whom no simple, single-factor quantifiable line can be drawn between operable and "inoperable." Surgeons are required to ask themselves "Before TAVR, would I operate on this patient?" The answer must be "no." To minimize subjective influences, patients declared "inoperable" must be presented for conference-call review when one or more surgeons from the Executive Committee and

or the Patient Selection and Procedure Steering Committee are on the call, and one of the surgeons must be on the call to answer any questions. Furthermore, source documentation supporting the assessment must be included in the patient's study binder and documentation of the decision of inoperability is required (operability risk assessment form). A record of case reviews including the name of the surgeon (who actually physically evaluated the patient) and the names of the conferring surgeons and their decisions will be kept in the study master file and will include documentation of the non-STS comorbidities assessed as leading to the inoperable assessment.

5.4 Inclusion Criteria

All Candidates for this study (Cohorts A and B) must meet the following criteria:

1. Patient has senile degenerative aortic valve stenosis with echocardiographically derived criteria: mean gradient > 40 mmHg or jet velocity greater than 4.0 m/s and an initial aortic valve area (AVA) of $\leq$ 0.8 cm^2 or indexed EOA < 0.5 cm^2/m^2. Qualifying echo must be within 45 days of the date of the procedure.

2. Patient is symptomatic from his/her aortic valve stenosis, as demonstrated by NYHA Functional Class II or greater.

3. The heart team agrees (and verified in the case review process) that valve implantation will likely benefit the patient.

4. The study patient or the study patient's legal representative has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site.

5. The study patient agrees to comply with all required post-procedure follow-up visits including annual visits through 5 years and analysis close date visits, which will be conducted as a phone follow-up.

Once eligibility in accordance to the above criteria is established, patients are assessed for operability. Patients who are candidates for AVR must meet the criteria set forth in Section 5.3.1 and patients who are deemed not to be candidates for surgery must meet the criteria set forth in Section 5.3.2. All candidates must meet the above criteria in order to be stratified into Cohort A or Cohort B.

5.4.1 Additional Eligibility Criteria Specific to Cohort A

Inclusion Criteria:

1. STS ≥ 4.
2. Heart team (including examining cardiac surgeon) agrees on eligibility including assessment that TAVR or AVR is appropriate.
3. Heart team agrees (a priori) on treatment strategy for concomitant coronary disease (if present).
4. Study patient agrees to undergo surgical aortic valve replacement (AVR) if randomized to control treatment.

Exclusion Criteria:

1. Heart Team assessment of inoperability (including examining cardiac surgeon).
2. Evidence of an acute myocardial infarction ≤ 1 month (30 days) before the intended treatment [defined as: Q wave MI, or non-Q wave MI with total CK elevation of CK-MB ≥ twice normal in the presence of MB elevation and/or troponin level elevation (WHO definition)].
3. Aortic valve is a congenital unicuspid or congenital bicuspid valve, or is non-calcified.
4. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).
5. Preexisting mechanical or bioprosthetic valve in any position (NR3).
6. Complex coronary artery disease :
    a. Unprotected left main coronary artery
    b. Syntax score > 32 (in the absence of prior revascularization)
7. Any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days of the index procedure (unless part of planned strategy for treatment of concomitant coronary artery disease). Implantation of a permanent pacemaker is not excluded.
8. Any patient with a balloon valvuloplasty (BAV) within 30 days of the procedure (unless BAV is a bridge to procedure after a qualifying ECHO).
9. Patients with planned concomitant surgical or transcatheter ablation for Atrial Fibrillation.

10. Leukopenia (WBC < 3000 cell/mL), acute anemia (Hgb < 9 g/dL), Thrombocytopenia (Plt < 50,000 cell/mL).
11. Hypertrophic cardiomyopathy with or without obstruction (HOCM).
12. Severe ventricular dysfunction with LVEF < 20%.
13. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
14. Active upper GI bleeding within 3 months (90 days) prior to procedure.
15. A known contraindication or hypersensitivity to all anticoagulation regimens, or inability to be anticoagulated for the study procedure.
16. Native aortic annulus size < 18 mm or > 27 mm as measured by echocardiogram.
17. Clinically (by neurologist) or neuroimaging confirmed stroke or transient ischemic attack (TIA) within 6 months (180 days) of the procedure.
18. Renal insufficiency (creatinine > 3.0 mg/dL) and/or renal replacement therapy at the time of screening.
19. Estimated life expectancy < 24 months (730 days) due to carcinomas, chronic liver disease, chronic renal disease or chronic end stage pulmonary disease.
20. Expectation that patient will not improve despite treatment of aortic stenosis
21. 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.
22. It is known that the patient is currently enrolled in the PARTNER I Trial or was withdrawn from the PARTNER I Trial prior to endpoint analysis.
23. Active bacterial endocarditis within 6 months (180 days) of procedure.
24. Patient refuses aortic valve replacement surgery.

5.4.2 Specific Criteria for Cohort B

Inclusion Criteria

1. The heart team agrees that medical factors preclude operation, based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. Specifically, the probability of death or serious, irreversible morbidity is ≥ 50%. The surgeons' consult notes shall

specify the medical or anatomic factors leading to that conclusion and include a printout of the calculation of the STS score to additionally identify the risks in the patient (some medical factors and definitions are provided in Section 8.0). At least one of the cardiac surgeon assessors must have physically evaluated the patient. All Cohort B patients must be approved by the Patient Selection and Procedure Management Steering or Executive Committee (at least 2 member votes, one must be a cardiac surgeon).

2. The heart team agrees the patient is likely to benefit from valve replacement.

Exclusion Criteria

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

1. Evidence of an acute myocardial infarction ≤ 1 month (30 days) before the intended treatment [(defined as: Q wave MI, or non-Q wave MI with total CK elevation of CK-MB ≥ twice normal in the presence of MB elevation and/or troponin level elevation (WHO definition)].
2. Aortic valve is a congenital unicuspid or congenital bicuspid valve, or is non-calcified.
3. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).
4. Preexisting mechanical or bioprosthetic valve in any position (see NR3).
5. Any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days of the index procedure. Implantation of a permanent pacemaker is not excluded.
6. Any patient with a balloon valvuloplasty (BAV) within 30 days of the procedure (unless BAV is a bridge to procedure after a qualifying ECHO).
7. Patients with planned concomitant surgical or transcatheter ablation for Atrial Fibrillation.
8. Leukopenia (WBC < 3000 cell/mL), acute anemia (Hgb < 9 g/dL), Thrombocytopenia (Plt < 50,000 cell/mL).
9. Untreated clinically significant coronary artery disease requiring revascularization.
10. Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of screening evaluation.

11. Need for emergency surgery for any reason.
12. Hypertrophic cardiomyopathy with or without obstruction (HOCM).
13. Severe ventricular dysfunction with LVEF < 20%.
14. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
15. Active upper GI bleeding within 3 months (90 days) prior to procedure.
16. A known contraindication or hypersensitivity to all anticoagulation regimens, or inability to be anticoagulated for the study procedure.
17. Native aortic annulus size < 18 mm or > 25 mm as measured by echocardiogram. (See NR5 and NR6).
18. Clinically (by neurologist) or neuroimaging confirmed stroke or transient ischemic attack (TIA) within 6 months (180 days) of the procedure.
19. Renal insufficiency (creatinine > 3.0 mg/dL) and/or renal replacement therapy at the time of screening.
20. Estimated life expectancy < 24 months (730 days) due to carcinomas, chronic liver disease, chronic renal disease or chronic end stage pulmonary disease.
21. Expectation that patient will not improve despite treatment of aortic stenosis.
22. Significant aortic disease, including marked tortuosity (hyperacute bend), aortic arch atheroma [especially if thick (> 5 mm), protruding or ulcerated] or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe “unfolding” and tortuosity of the thoracic aorta.
23. Iliofemoral vessel characteristics that would preclude safe placement of 22F or 24F introducer sheath such as severe obstructive calcification, severe tortuosity or minimum average vessel size less than 7 mm. (see NR1, NR2 and NR4).
24. 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.
25. It is known that the patient is currently enrolled in the PARTNER I Trial or was withdrawn from the PARTNER I Trial prior to endpoint analysis.
26. Active bacterial endocarditis within 6 months (180 days) of procedure.

5.4.3 Specific Criteria for Registry 1 (NR1) and Registry 4 (NR4)

Inclusion: Same criteria as Cohort B Including non-femoral access.

Exclusion: Same criteria as Cohort B.

5.4.4 Specific Criteria for Registry 2 (NR2)

Inclusion: Same criteria as Cohort B Including non-femoral access

Exclusion: Same criteria as Cohort B, except for exclusion 22 which is modified (italicized) for NR2 as follows.

- Iliofemoral vessel characteristics that would preclude safe placement of 22F or 24F introducer sheath such as severe obstructive calcification, severe tortuosity or minimum average vessel size less than 6 mm.

5.4.5 Specific Criteria for Registry 3 (NR3)

Inclusion:

1. Stenosed or insufficient surgically implanted bioprosthetic valve in the aortic position.
2. NYHA class >II.
3. Heart team consensus that the risk of surgical mortality or major morbidity ≥ 50%.

Exclusion:

1. Bioprosthetic valve labeled external diameter < 21mm.
2. Surgical or transcatheter valve in another position on the same side of the heart (mitral and tricuspid rings are not an exclusion).
3. Hemodynamic instability defined as requiring inotropic, pressor, or mechanical support.
4. Infectious endocarditis within 6 months.
5. Bacteremia within 1 month.
6. Intra-cardiac thrombus or vegetation.
7. Acute myocardial infarction ≤ 1 month (30 days) before the intended treatment [defined as: Q wave MI, or non-Q wave MI with total CK elevation ≥ twice normal in the presence of MB elevation and/or troponin level elevation (WHO definition)].
8. Percutaneous coronary intervention or implantation of a permanent pacemaker within 7 days of the index procedure.

9. Leukopenia (WBC < 3000 cell/mL), acute anemia (Hgb < 9 g/dL), thrombocytopenia (Plt < 50,000 cell/mL).
10. Hypertrophic cardiomyopathy with obstruction (HOCM).
11. Severe ventricular dysfunction with LVEF < 20%.
12. Active upper GI bleeding within 3 months (90 days) prior to procedure requiring transfusion.
13. Inability to be anticoagulated for the study procedure.
14. Stroke or transient ischemic attack within 6 months (180 days).
15. Renal Insufficiency (creatinine > 3.0 mg/dL) and/or renal replacement therapy at the time of screening.
16. Estimated life expectancy < 24 months.
17. 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.
18. The patient requires emergency surgery for any reason.
19. Xenograft or THV in another position.
20. Index valve has moderate or severe paravalvular regurgitation.
21. Index valve is unstable or rocking.
22. Extensive, severe non-revascularized coronary disease.
23. Increased risk of coronary obstruction by prosthetic leaflets (non-stented or internally stented valve which might extend above a coronary ostium).
24. Increased risk of embolization (non-stented and non-calcified valve).

Registry patients follow the Cohort A Schedule of Events (Table 5.0.0).

See Appendix R for the Transcatheter Heart Valve in Surgical Heart Valve Registry Guidelines.

Safety, effectiveness and durability have not been fully characterized or assessed for valve-in-valve procedures.

5.4.6 Specific Criteria for Registry 5 (NR5)

NR5: Inoperable Transfemoral Registry for the delivery of 29 mm SAPIEN XT™ in > 7mm femoral arteries. A maximum of 50 patients may be enrolled in this arm. Primary endpoint of this registry is freedom from mortality at one year. Non-powered secondary endpoints for safety and effectiveness will be consistent with additional secondary endpoint analyses for both Cohorts A and

B and as described below. Patients previously enrolled as a Cohort A control may not be enrolled in this registry.

5.4.7 Specific Criteria for Registry 6 (NR6)

NR6: Inoperable Transapical Registry for the delivery of 29 mm SAPIEN XT™ for Cohort B that do not have eligible transfemoral access. A maximum of 50 patients may be enrolled in this arm. Primary endpoint of this registry is freedom from mortality at one year. Non-powered secondary endpoints for safety and effectiveness will be consistent with additional secondary endpoint analyses for both Cohorts A and B and as described below. Patients previously enrolled as a Cohort A control may not be enrolled in this registry.

5.4.8 Continued Access Registries (NR1, NR2, NR3, NR4, NR5, NR6)

FDA approved Amendment 3.0 (dated March 2013) for the Continued Access for the Registries. The purpose is to provide Continued Access for Registry patients (NR1, NR2, NR3, NR4, NR5 and NR6) for the study devices and obtain additional safety and effectiveness data for the PARTNER II Trial Inoperable candidates. The Edwards SAPIEN XT™ device and NovaFlex /Ascendra delivery systems (transfemoral, transapical and transaortic) used in these Registries are intended for use in inoperable patients with severe symptomatic, calcific aortic stenosis.

All primary and secondary safety and efficacy endpoints, follow-up visits, visit exam requirements and statistical analysis remain unchanged from the PARTNER II Protocol Version 4.0 (August 2012). Enrollment will consist of a maximum of 500 continued access patients.

Enrollment is not capped per Registry. Rather, enrollment will close when the number of patients enrolled in the Registries reaches 500. Enrollment will continue until the date on which the trial sponsor is aware that the designated sample size has been obtained. Patients who have already signed the informed consent form at that time will be allowed to be treated, provided that treatment assignment is completed within 30 days of the consent date.

5.4.9 Criteria for S3 Cohort

Inclusion Criteria

1. STS ≥ 8
2. Patient has senile degenerative aortic valve stenosis with echocardiographically derived criteria: mean gradient > 40 mmHg or jet velocity greater than 4.0 m/s and an initial aortic valve area (AVA) of ≤ 1.0 cm2. Qualifying echo must be within 45 days of the date of the procedure.
3. Patient is symptomatic from his/her aortic valve stenosis, as demonstrated by NYHA Functional Class II or greater.
4. The heart team agrees (and verified in the case review process) that valve implantation will likely benefit the patient.
5. The study patient or the study patient's legal representative has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site.
6. The study patient agrees to comply with all required post-procedure follow-up visits including annual visits through 5 years and analysis close date visits, which will be conducted as a phone follow-up.
7. For inoperable patients: The heart team agrees that medical factors preclude operation, based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. Specifically, the probability of death or serious, irreversible morbidity is ≥ 50%. The surgeons' consult notes shall specify the medical or anatomic factors leading to that conclusion and include a printout of the calculation of the STS score to additionally identify the risks in the patient (some medical factors and definitions are provided in Section 8.0). At least one of the cardiac surgeon assessors must have physically evaluated the patient. Inoperable patients must be approved by the Patient Selection and Procedure Management Steering or Executive Committee (at least 2 member votes, one must be a cardiac surgeon).

Exclusion Criteria

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

1. Evidence of an acute myocardial infarction ≤ 1 month (30 days) before the intended treatment [(defined as: Q wave MI, or non-Q wave MI with total CK elevation of CK-MB ≥ twice normal in the presence of MB elevation and/or troponin level elevation (WHO definition)].
2. Aortic valve is a congenital unicuspid or congenital bicuspid valve, or is non-calcified.
3. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).
4. Pre-existing mechanical or bioprosthetic valve in any position.
5. Any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days of the index procedure. Implantation of a permanent pacemaker or ICD is not considered exclusion criteria.
6. Any patient with a balloon valvuloplasty (BAV) within 30 days of the procedure (unless BAV is a bridge to procedure after a qualifying ECHO).
7. Patients with planned concomitant surgical or transcatheter ablation for Atrial Fibrillation.
8. Leukopenia (WBC < 3000 cell/mL), acute anemia (Hgb < 9 g/dL), Thrombocytopenia (Plt < 50,000 cell/mL).
9. Untreated clinically significant coronary artery disease requiring revascularization.
10. Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance within 30 days of screening evaluation.
11. Need for emergency surgery for any reason.
12. Hypertrophic cardiomyopathy with or without obstruction (HOCM).
13. Severe ventricular dysfunction with LVEF < 20%.
14. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
15. Active upper GI bleeding within 3 months (90 days) prior to procedure.
16. A known contraindication or hypersensitivity to all anticoagulation regimens, or inability to be anticoagulated for the study procedure.
17. Native aortic annulus size < 18 mm or > 28mm as measured by echocardiogram.
18. Clinically (by neurologist) or neuroimaging confirmed stroke or transient ischemic attack (TIA) within 6 months (180 days) of the procedure.
19. Renal insufficiency (creatinine > 3.0 mg/dL) and/or renal replacement therapy at the time of screening.
20. Estimated life expectancy < 24 months (730 days) due to carcinomas, chronic liver disease, chronic renal disease or chronic end stage pulmonary disease.
21. Expectation that patient will not improve despite treatment of aortic stenosis.

22. Significant aortic disease, including marked tortuosity (hyperacute bend), aortic arch atheroma [especially if thick (> 5 mm), protruding or ulcerated] or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe “unfolding” and tortuosity of the thoracic aorta.
23. Iliofemoral vessel characteristics that would preclude safe placement of 14F or 16F introducer sheath such as severe obstructive calcification, severe tortuosity or minimum average vessel size less than 5.5 mm.
24. 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.
25. It is known that the patient is currently enrolled in the PARTNER I Trial or was withdrawn from the PARTNER I Trial prior to endpoint analysis.
26. Active bacterial endocarditis within 6 months (180 days) of procedure.

5. 5 Study Patient Screening

The screening phase of the trial is designed to meet two objectives:

1. Patient Consent.

2. Determine study patient eligibility, cohort assignment (operability), access site for THV procedure and eligibility for the registries.

5. 5.1 Patient Consent

Informed Consent must be obtained prior to the screening procedures or baseline tests. Upon completion of the screening process and prior to treatment assignment, the patient’s case will be presented for peer review. Treatment assignment may occur after the patient has met all requirements and has been accepted for enrollment by peer review. Refer to Appendix B of the Protocol, for associated forms.

5.5.2 Patient Screening

A unique aspect of this trial is the formal joint collaboration of co-principal investigators (a designated interventional cardiologist and a designated cardiac surgeon) at each site. Both co-principal investigators will be involved in the patient selection and screening process. All patients evaluated for severe aortic stenosis in medical and surgical departments that are very high risk candidates for AVR should be screened for study eligibility. The screening assessments are described below. The screening of patients in both departments will be conducted by one or more study team members. The study team will be responsible for ensuring and reporting study patient screening for study eligibility. Cumulative screening and enrollment logs will be maintained in the

electronic database by study sites. Reasons for screen failures will be documented on the enrollment logs.

The following screening data will be collected for all study patients prior to enrollment (see Table 5.0-0). All cardiac medications and all medications given for cardiovascular effect (long-acting nitrates, diuretics, cardiac glycosides, etc.) may be continued at their prescribed dosages.

- Operability Risk Assessment Form
- Medical history, pertinent physical examination [includes blood pressure, height, weight, history of stroke, and all major systems findings]
- CCS status of angina
- Syntax Score (Cohort A)
- NYHA classification
- Number of hospitalizations for symptoms of aortic stenosis during the past 6 months
- STS Risk Score
- Logistic EuroSCORE
- Comprehensive transthoracic echocardiogram, including assessment of aortic valve gradients (mean and peak), areas, indices, degree of regurgitation, left ventricle systolic function (global and segmental)
- Thoracic x-ray, an abdominal angiogram, and CT angiograms or MRI, and with complete visualization of both iliacs and femorals to the aorta. In the situation where patients have compromised renal function that precludes the use of contrast agents, MR imaging may be used as an alternative. CT scans are strongly recommended, particularly in patients with femoral arteries less than 7 mm; (≤ 180 days before procedure). Patients with previously documented inadequate femoral access (Iliofemoral vessel characteristics that would preclude safe placement of 14F22F or 16F24F introducer sheath (14F or 16F for S3) such as severe obstructive calcification, severe tortuosity or minimum average vessel size less than 6 mm (23 and 26 mm THV minimum vessel size ≥ 5.5 mm / 29 mm THV minimum vessel size ≥ 6.0 mm for S3) don't require repeat testing. Supporting documentation must be presented during the case presentation process and filed in the patient's study binder.
- Left and right heart catheterization to assess the severity of aortic stenosis and severity of coronary artery disease if applicable (≤ 90 days before procedure)

An operability risk assessment form will be completed prior to enrollment of the patient. Essential to the eligibility criteria of the Cohort B and the S3 Cohort patient is the surgical assessment of operability. These assessments must be made by a qualified cardiac surgeon who has physically examined the patient and then assessed by independent reviewers as previously described. Risk scores should not be used as an assessment of inoperability. Screening assessments must be completed within 30 days of patient enrollment unless otherwise specified.

5.5.3 Case Review Process

The PARTNER II Trial operations include a case review process prior to enrollment of patients. After site assessments are made, the study candidate's qualifying criteria are presented via The PARTNER II Trial case review process where experienced trial investigators, members of the Executive and/or Steering Committee will adjudicate the cohort and access decision. Upon case review approval, the supporting evidence for the cohort and access assessments (transfemoral, transapical or transaortic) and the names of the review committee members will be documented in the medical record and case report forms. Once the review and the eligibility criteria are documented, the patient can be enrolled in the trial. Of note, it is essential that at least one site investigator (surgeon) must have personally examined the patient to make a determination of operability.

5.6 Enrollment

After completion of the following items, the patient is enrolled in the trial:

- Completion of screening assessments;
- Meets all of the inclusion and none of the exclusion criteria;
- Operability Risk Assessment Form is completed;
- Case presentation and approval per case review process
- Signed Informed Consent
- Treatment assignment in EDC (electronic data capture)

It is strongly encouraged to enroll patients as close to the planned procedure date as possible.

Day 0 is defined to be the scheduled day of the index procedure for all subjects and all visits. If a subject has been randomized but not implanted within 90 days of randomization, Day 0 will be defined to be the date of randomization + 90 days. This

Day 0 will then be used to schedule that subject's Day 30, 6-month, 1-year, and all subsequent assessments according to Table 5.0. In the very unlikely event that a given subject has an Index Procedure after this rule has already been applied to them, Day 0 will be re-defined to correspond to the Index Procedure date. Furthermore, the Day 30, 6-month, 1-year, and all subsequent assessments will be scheduled according to this re-defined Day 0 regardless of whether or not this causes assessments to be duplicated. Patient data listings will be created for all such patients so that the data captured at earlier visits (and subsequently duplicated) is completely reported; however, these data will not be used in statistical analyses.

To ensure enrollment is representative and balanced across study sites, no site will enroll more than 15 percent of the total in either cohort or implant approach.

5.7 Treatment Assignment in Cohort A and B

At the time of enrollment into the trial, patients will be randomized to treatment versus control. The randomization is on the basis of 1:1 (Test: Control). Subjects will be randomized according to a computer generated randomization scheme. The study procedure should occur within two weeks (14 days) of treatment assignment.

5.8 Treatment Assignment in S3 Cohort

At the time of enrollment into the trial, patients will be assigned to treatment. The study procedure should occur within two weeks (14 days) of treatment assignment.

5.9 Baseline Assessments: Prior to Procedure

The following baseline data (in addition to the screening assessments) will be collected for all study patients prior to procedure (see Table 5.0-0). Baseline assessments must be completed within 30 days of patient enrollment unless otherwise specified.

Cardiopulmonary:

- 12 Lead ECG
- Chest X-Ray

Functional Assessments:

- 6MWT
- QOL (Cohort A: KCCQ, EQ5D, SF36 Cohort B / S3 Cohort: KCCQ, EQ5D, SF12)

- Frailty Index
- Mini-Mental State Examination;(MMSE) (Appendix G)

Clinical Laboratory Tests:

- CBC with differential and platelet count
- Complete metabolic panel including sodium, potassium, creatinine and BUN
- Liver panel including AST and ALT
- Albumin
- B-type natriuretic peptide (BNP)
- Plasma free hemoglobin
- Haptoglobin
- PTT or PT/INR
- CK/CKMB and/or Troponins ≤ 72 hours before the procedure

Neurological Assessments:

All study sites must have a dedicated neurologist on the study team.

The neurological instruments (NIHSS, Modified Rankin Scale and Barthel Index) will be administered in both treatment and control arms at baseline, post procedure, discharge, 30 days, 6 months, 1 year and annually through 5 years. To ensure the highest level of quality and consistency in neurological assessments, the assessments should be performed by a neurologist or a neurology fellow. If the neurologist or neurology fellow is not available within the time of the prescribed visit window, a certified team member may perform the tests. However, given the importance of procedure related neurological outcomes, the post procedure assessment must be performed a neurologist or neurology fellow.

Cohort B patients at study sites participating in the neuro sub-study will be assessed by a neurologist or a neurology fellow at Baseline, Discharge, 30 Day, 6 Months and 1 year.

Cohort A, S3 Cohort and Registries

- National Institutes of Health Stroke Scale (NIHSS) (Appendix F) performed by a Neurologist or neurology fellow. If a study patient demonstrates symptoms of a neurological event and an abnormal NIHSS, a CT or MRI brain scan must be performed and the patient should be evaluated by a neurologist or neurology fellow;
- Modified Rankin Scale (MRS) (Appendix L);

- Barthel Index for any patient with a previous stroke (to be performed immediately before the performance of the MRS) (Appendix L).
- A neurologist or neurology fellow will perform the above tests. If the neurologist or neurology fellow is not available at the time of patient's visit, a certified team member may perform the tests.

Cohort B

- National Institutes of Health Stroke Scale (NIHSS) (Appendix F) performed by a certified team member. If a study patient demonstrates symptoms of a neurological event and an abnormal NIHSS, a CT or MRI brain scan must be performed and the patient must be evaluated by a neurologist or neurology fellow. If participating in the Neuro Sub-Study Cohort B, a neurologist or neurology fellow will perform the examination.
- Modified Rankin Scale (MRS) (Appendix L);
- Barthel Index for any patient with a previous stroke (to be performed immediately before the performance of the MRS).
- A neurologist or neurology fellow should perform the above tests. If the neurologist or neurology fellow is not available at the time of patient's visit, a certified team member may perform the tests.

5.10 Procedure Assessments

Total procedure time is defined as the time from skin incision to the time of skin incision access closure. The following invasive hemodynamic data must be collected pre and post implant:

- Echo assessments of mean and peak AV gradients
- LV pressure measurements for valve area calculation
- Cardiac output and cardiac index
- A supra-aortic angiogram or TEE for valve performance and coronary patency;
- Fluoroscopic imaging implanted valve (Appendix P)
- Medications given for cardiovascular effect including anti-platelet/anti-thrombins
- Adverse Event Assessment

5.11 Procedure Details

5.11.1 Device Preparation

A detailed description of device preparation and required equipment is supplied in the Study Devices Instructions for Use (Appendix O). An Edwards Clinical Specialist will attend all study cases. At least one member of the site team will be trained on study device preparation to assure site independence for case support post-approval.

Devices included for use (See Appendix O):

5.11.2 Procedure Recommendations

Surveys were conducted in The PARTNER Trial sites to assess best practices for access, anesthesia and anticoagulation /anti-thrombin therapy. Some recommendations are provided in Table 5.9-0 and are described below.

5.11.3 Recommended Antiplatelet/Anticoagulation Regimen

Table 5.9-0 outlines the recommended antiplatelet regimen. The categories were developed by The PARTNER II Trial Patient and Procedure Management Steering Committee. There are no current validated guidelines in this specific study population, however, the literature was surveyed and used as guidance for the following proposed guidelines. Patients will be assessed by the heart team for Category of Stroke Risk prior to prescribing treatment regimen. The Category will be documented in the discharge case report form. Committee Categories are based on CHAD score for stroke risk [107]. NOTE: The CHAD score only applies to patients in Atrial Fibrillation (AF) and has not been validated in non-AF patient populations; therefore the CHAD score reference was used as one among many guidelines to establish the risk stratification for intensity of anticoagulation regimen.

5.11.4 Antibiotic Prophylaxis

Study patients should be prophylactically treated for endocarditis per the recommendations of the American Heart Association [108].

5.11.5 Contrast Media

Careful management of contrast media is required for these patients. Accurate measurement of the dye used will be captured in the case report form.

Table 5.9-0

	AVR	TAVR
Access	Sternotomy or mini-sternotomy	Femoral surgical cut down
Anesthesia	General	General/Conscious sedation
Anti-coagulation regimen pre procedure		
	Aspirin 81-100 mg QD	Aspirin 81-100 mg QD
	• Patients with BMS within one month or drug eluting stent (DES) within 12 months should be continued on Clopidogrel/prasugrel prior to their procedure • Patients in atrial fibrillation on warfarin should be bridged with LMW or UF heparin prior to the procedure • Patients with persistent or paroxysmal atrial fibrillation, not on anticoagulation, will not be required to have a TEE to rule out LA thrombus prior to procedure. If intra-procedural TEE during TAVR reveals thrombus, procedure will be aborted and delayed until patient has been on warfarin or dabigatran for 30 days. In patients in the surgical group with LA clot seen on intraoperative TEE, procedure can proceed per surgical standard of care	• Patients with BMS within one month or DES within 12 months should be continued on Clopidogrel/prasugrel prior to their procedure • Patients in atrial fibrillation on warfarin should be bridged with LMW or UF heparin prior to the procedure • Patients with persistent or paroxysmal atrial fibrillation, not on anticoagulation, will not be required to have a TEE to rule out LA thrombus prior to procedure. If intra-procedural TEE during TAVR reveals thrombus, procedure will be aborted and delayed until patient has been on warfarin or dabigatran for 30 days. • In patients under concomitant TAVR/PCI, the following is recommended in addition to ASA • Transfemoral TAVR – Clopidogrel loading with either 300mg or 600mg prior to the procedure • Transapical/Transaortic TAVR – Clopidogrel loading with 300mg just prior to the procedure
Anti-coagulation regimen-intraprocedural		
	Heparin will be given to achieve/ maintain ACT≥250 sec.	Heparin will be given to achieve/ maintain ACT≥250 sec.
Anti-coagulation regimen-post procedure		

Category I for Stroke Risk No atrial fibrillation, No recent stents	• ASA 81mg qd • Clopidogrel 75qd started 24 hours post surgery for at least one month if clinically safe and at the discretion of the surgical team. In centers that use warfarin post surgical AVR, Clopidogrel will not be started	• ASA 81mg qd • Clopidogrel 300mg load within 6 hours of procedure (either pre or post) • Clopidogrel 75mg qd for at least one month post procedure
Category II for Stroke Risk No atrial fibrillation, recent stents	• ASA 81mg qd • Clopidogrel should not be discontinued prior to surgery if patient had BMS within one month or DES in 12 months • Clopidogrel 75qd started 24 hours post surgery if clinically safe and continued for at least one month post surgical AVR in those with BMS and a total of 12 months for those with DES	• ASA 81mg qd • Clopidogrel 75mg qd should be continued prior to the procedure and after the procedure without interruption for at least one month after BMS and 12 months after DES
Category III for Stroke Risk Atrial fibrillation, no recent stents	• ASA 81mg qd • Patients should be started on warfarin or dabigatran 24 hours post AVR if clinically safe and this should be continued for at least one month or indefinitely if possible. If clinically safe, patient's being started on warfarin should be bridged with unfractionated or low molecular weight heparin until INR therapeutic. • If patients are not a candidate for warfarin or dagibatran, Clopidogrel 75mg qd (in addition to ASA 81 mg) can be considered as an alternative	• ASA 81mg qd • Patients 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, patients started on warfarin should be bridged with unfractionated or low molecular weight heparin until INR therapeutic. • If patients are not a candidate for warfarin or dagibatran, Clopidogrel 75mg qd can be considered as an alternative

Category IV for Stroke Risk Atrial fibrillation, recent stents	• ASA 81mg qd • Clopidogrel 75mg qd for at least one month post BMS or 12 months post DES • Patients should be started on warfarin or dabigatran 24 hours post AVR if clinically safe and continued indefinitely. If clinically safe, patients being started on warfarin should be bridged with UF or LMW heparin until INR therapeutic.	• ASA 81mg qd • Clopidogrel 75mg qd for at least one month post BMS or 12 months post DES • Patients should be started on warfarin or dabigatran 24 hours post TAVR if clinically safe and continued indefinitely. If clinically safe, patient's being started on warfarin should be bridged with UF or LMW heparin until INR therapeutic.
Antibiotic Prophylaxis	Study patients should be prophylactically treated for endocarditis per the recommendations of the American Heart Association	Study patients should be prophylactically treated for endocarditis per the recommendations of the American Heart Association

Note: Any changes to anticoagulation regime from study visit to study visit will be noted on the Case Report Form (CRF) including reason for change.

5.11.6 Radiation Precautions

Radiation exposure will be documented at each study visit in the CRF, with options to record whether chest x-ray, including additional plain x-rays, MRI, CT scans and all fluoroscopy procedures were performed. In the event that a dose isn't recorded; such as a plain X-ray, an average dose will be assigned for each applicable test. A trigger will be applied in the database such that when the cumulative estimated radiation exposure calculation exceeds 150 to 250 Gy/cm^2 for any study patient, the site coordinator and investigator will be notified and a follow-up visit advised to assess patient for skin reaction.

Additional precautions:

Substantial radiation dose level (SRDL) - The operator should be notified promptly if SRDL was exceeded. The SRDL is a trigger level to initiate follow-up of a radiation dose that might produce a clinically relevant injury in an average patient. Some suggested values for the SRDL are a skin dose of 3 Gy, a KAP of 500 Gy/cm^2, or an air kerma at the interventional reference point of 5 Gy (NCRP 2010). For cardiology procedures, a KAP between 150 and 250 Gy/cm^2 may be more appropriate, depending

on the radiation field size and the specific protocols. These values could indicate peak skin doses greater than 2 Gy in a single procedure.

The operator should write an appropriate note in the patient's medical record, stating that a substantial radiation dose has been administered, and indicating the reason ([109]; NCRP 2010). This information may be included in the post-procedure notes. Patients with reported KAP between 150 and 250 Gy/cm^2 must be further evaluated for radiation injury and the event must be reported as a serious adverse event in the case report form.

Acute evaluation - When the SRDL has been exceeded, clinical follow-up is essential for early detection and management of skin injuries (NCRP 2010; [110]). The patient should be advised of the possibility of a skin injury due to a tissue reaction, and should be told to examine the beam entrance site at 2-4 weeks after the procedure. The operator should be notified if any skin changes are seen. Patients who have not previously notified the operator should be contacted by telephone at approximately 30 days after the procedure, in order to ensure that a skin injury is not missed.

Long-term evaluation - If a skin injury is suspected, the interventionalist should see the patient at an office visit, and should arrange for appropriate follow-up care (NCRP 2010; [110]).

The physician responsible for the patient's care should be informed of the possibility of radiation effects.

5.11.7 Transcatheter Heart Valve in Transcatheter Heart Valve (THV in THV)

Severe aortic insufficiency in transcatheter heart valve procedures is rare and long term outcomes are unknown. Patients with failed transcatheter heart valve evidenced by severe aortic insufficiency post THV implantation may undergo surgical valve replacement or THV in THV as a bail-out option, depending on the estimated risk of surgical mortality by the cardiovascular surgeon. There is limited data available on the safety and effectiveness of THV in THV, therefore patients must be informed of known and unknown risks and implanting operators are to pay careful attention to valve sizing and placement to avoid incidence of severe insufficiency.

See Appendix R for the Transcatheter Heart Valve in Surgical Heart Valve Registry Guidelines.

5.12 Post-Procedure Assessments

Study patients will be continuously monitored clinically, hemodynamically, and electrocardiographically during catheterization for all local, systemic side effects and complications. After completion of the procedure, all study patients will be monitored per institutional standard of care. Subsequent monitoring will be continued according to

institutional standard of care. The post procedure time period is within 24 – 48 hours from the time the patient exits the cath lab / operating room unless otherwise noted. See Table 5.0-0, Schedule of Events.

- Current cardiac medications and all medications given for cardiovascular effect;
- CK/CKMB and/or Troponins will be performed to monitor the patient's cardiac enzymes at 3 different time intervals: 1) the first lab draw post procedure (within 8 hours of exit from the cath lab / operating room) 2) the second lab draw 6 – 8 hours after the first lab draw 3) the third lab draw 6 – 8 hours after the second lab draw.
- CBC with differential and platelet count; PTT or PT/INR; Metabolic Panel including sodium, potassium, creatinine and BUN.
- 12 Lead ECG
- Adverse Event assessment.

Neurological Assessments

Cohort A,Registries and S3 Cohort

- National Institutes of Health Stroke Scale (NIHSS) (Appendix F) performed by a Neurologist or neurology fellow. If a study patient demonstrates symptoms of a neurological event and an abnormal NIHSS, a CT or MRI brain scan must be performed and the patient should be evaluated by a neurologist or neurology fellow;
- Modified Rankin Scale (MRS) (Appendix L);
- Barthel Index (Appendix L) for any patient with a stroke or a change in neurological status.
- A neurologist or a neurology fellow will assess the Cohort A,Registries and S3 Cohort patients at Baseline, Post Procedure and Discharge. If the neurologist or neurology fellow is not available at the time of patient's baseline or discharge visit, a certified team member may perform the tests. A neurologist or neurology fellow must perform the Post Procedure assessment. For the S3 Cohort, a certified team member may perform the post procedure assessment.
- Patients that have suffered a stroke or TIA will be assessed by a neurologist or neurology fellow.
- If the patient has suffered a stroke the NIHSS, MRS and Barthel Index will be performed at all subsequent visits.

- Patients with stroke or TIA should report for follow-up within 30 to 90 days from the onset of the stroke or TIA, and the examination will include the NIHSS, Modified Rankin Scale, and the Barthel Index.

5.13 Discharge Procedures

The following data will be collected for all study patients within 24 hours of the date of discharge from the index hospitalization. See Table 5.0-0. If patient is discharged over a weekend or holiday, the discharge tests may be completed on the last weekday prior to discharge.

Systems:

- Pertinent physical examination [includes blood pressure, height, weight, major systems findings;
- Medications given for cardiovascular effect including anti-platelet/anti-thrombins;
- Adverse Event assessment;

Neuro:

Cohort A, Registries and S3 Cohort

- National Institutes of Health Stroke Scale (NIHSS) (Appendix F) performed by a Neurologist or neurology fellow. If a study patient demonstrates symptoms of a neurological event and an abnormal NIHSS, a CT or MRI brain scan must be performed and the patient should be evaluated by a neurologist or neurology fellow;
- Modified Rankin Scale (MRS) (Appendix L);
- Barthel Index (Appendix L) for any patient with a stroke or a change in neurological status.
- A neurologist or a neurology fellow will assess the Cohort A, all Registries and S3 Cohort patients at Baseline, Post Procedure and Discharge. If the neurologist or neurology fellow is not available at the time of patient's baseline or discharge visit, a certified team member may perform the tests.
- Patients that have suffered a stroke or TIA will be assessed by a neurologist or neurology fellow.
- If the patient has suffered a stroke the NIHSS, MRS and Barthel Index will be performed at all subsequent visits.

    - Patients with stroke or TIA should report for follow-up within 30 to 90 days from the onset of the stroke or TIA, and the examination will include the NIHSS, Modified Rankin Scale, and the Barthel Index.

Cohort B

- NIHSS (Appendix F) performed by a certified team member. If participating in the Neuro Sub-Study, a neurologist or neurology fellow will perform the examination.
- Modified Rankin Scale (MRS) (Appendix L); If participating in the Neuro Sub-Study, a neurologist or a neurology fellow will perform the test.
- Barthel Index (Appendix L) done if stroke or change in neurological status (to be performed immediately prior to the MRS). If participating in the Neuro Sub-Study, a neurologist or a neurology fellow will perform the test.
- A neurologist or neurology fellow should perform the above tests. If the neurologist or neurology fellow is not available at the time of patient's visit, a certified team member may perform the tests.
- Patients that have suffered a stroke or TIA will be assessed by a neurologist or neurology fellow.
- If the patient has suffered a stroke the NIHSS, MRS and Barthel Index will be performed at all subsequent visits.
- Patients with stroke or TIA should report for follow-up within 30 to 90 days from the onset of the stroke or TIA, and the examination will include the NIHSS, Modified Rankin Scale, and the Barthel Index.

Cardiac:

- CCS status of angina;
- NYHA classification;
- Standard 12-lead ECG ;
- Chest X-ray examination;
- Comprehensive transthoracic echocardiogram (TTE).

Clinical Laboratory Tests:

- B-type natriuretic peptide (BNP).
- CBC with differential and platelet count; PTT or PT/INR; Metabolic Panel including sodium, potassium, creatinine and BUN.

Other:

- Category per Table 5.9-0 for prescription of anticoagulation regime

5.14 Follow-Up Procedures

Follow-up procedures will be conducted at the intervals specified in Table 5.0-0. Blood draws will be performed at the specified intervals and according to hospital standard or medication regimen. Patients will be informed that some of the data that are collected at scheduled follow-ups as well as at unscheduled visits, including the echocardiogram, ECG and the Quality of Life questionnaires, may be sent to the respective independent core lab for analysis.

The determination of the specified study endpoints such as survival, valve function and combined clinical events, will require rigorous clinical follow-up and quality data collection. After patient index hospitalization, the clinical research coordinator will contact the patient or the patient's private physician by telephone for general symptomatic screening and scheduling of follow-up contacts. Planned long absences from the area should be recorded to facilitate continued ability to contact a study patient. If a patient cannot be reached for a follow-up visit, the investigator will document on the follow-up data form, the efforts undertaken to contact the patient, referring physicians, including internists as well as cardiologists, family members, or other alternate contacts noted in the study patient's records. These efforts should include 3 attempts of telephone contacts at separate dates and times, and a registered letter. If the patient cannot be reached in any way for their follow-up visits and misses the scheduled visit, new efforts will be undertaken to locate them at subsequent follow-up visits. In the event that the patient's implanted valve is explanted, the patient needs to be continued to be followed for the duration of the study.

Follow-up visit intervals are as follows: 30 (-7, +14) days, 6 months (±30 days), 12 months (±60 days), and then annually (± 60 days) for a minimum of 5 years. A telephone follow-up will occur at the primary analysis close date (see Section 7.2); this follow-up must occur on or after that close date (+14 days). In the event that an adverse neurological event is reported by the patient, the patient will be asked to return to the clinic for examination by a neurologist or a neurology fellow. Additional phone follow-ups may be performed as needed to obtain up to date survival information for use in regulatory submissions.

For all patients at all visits, the time clock starts on the date of the first implant attempt, whether or not the implant is successful. If no implant attempt occurs within 90 days of randomization, the time clock will start on the 90th day post-randomization, and site visits will be scheduled accordingly. In the rare event that such a patient later has a first implant attempt, the time clock will be re-set to zero on this date, and site visits will be scheduled accordingly, even if they duplicate previously scheduled site visits.

5.14.1 Thirty Day Follow-Up Visit

The following data will be collected for all study patients at 30 days (within 7 days before and 14 days after the 30 day date). (Table 5.0-0)

Systems:

- Pertinent physical examination [includes blood pressure, height, weight, major systems findings;
- Medications given for cardiovascular effect including anti-platelet/anti-thrombins;
- Adverse Event assessment

Neuro:

- NIHSS (Appendix F) performed by a certified team member. If participating in the Neuro Sub-Study Cohort B, a neurologist or neurology fellow will perform the examination.
- Modified Rankin Scale (MRS) (Appendix L);
- Barthel Index (Appendix L) for any patient with a stroke or a change in neurological status.
- A neurologist or neurology fellow will perform the above tests. If the neurologist or neurology fellow is not available at the time of patient's visit, a certified team member may perform the tests.
- Patients that have suffered a stroke or TIA will be assessed by a neurologist or neurology fellow.
- A neurologist or neurology fellow should perform the above tests. If the neurologist or neurology fellow is not available at the time of patient's visit, a certified team member may perform the tests.
- If the patient has suffered a stroke the NIHSS, MRS and Barthel Index will be performed at all subsequent visits.
    - Patients with stroke or TIA should report for follow-up within 30 to 90 days from the onset of the stroke or TIA, and the examination will include the NIHSS, Modified Rankin Scale, and the Barthel Index.

Cardiac:

- CCS status of angina
- NYHA classification
- Standard 12-lead ECG
- Comprehensive transthoracic echocardiogram (TTE)

Functional Assessments:

- 6MWT
- QOL (Cohort A: KCCQ, EQ5D, SF36 Cohort B and S3 Cohort: KCCQ, SF-12, EQ 5D)

Clinical Laboratory Tests:

- CBC with differential and platelet count
- Albumin
- B-type natriuretic peptide (BNP)
- Plasma free hemoglobin
- Haptoglobin

Non-Invasive Studies:

- Chest X-ray examination
- Fluoroscopic imaging implanted valve (required if CXR indicates abnormalities related to valve integrity and position and for Adverse Events related to worsening valve function) (See protocol for assessment in Appendix P)

5.14.2 Six Month Follow-Up Visit

The following data will be collected for all study patients at 6 months: ±30 days. (See Table 5.0-0).

Systems:

- Pertinent physical examination [includes blood pressure, weight, major systems findings
- Medications given for cardiovascular effect including anti-platelet/anti-thrombins;
- Adverse Event assessment

Neuro:

- NIHSS (Appendix F) performed by a certified team member. If participating in the Neuro Sub-Study Cohort B, a neurologist or neurology fellow will perform the examination.
- Modified Rankin Scale (MRS) (Appendix L);
- Barthel Index (Appendix L) for any patient with a stroke or a change in neurological status.
- A neurologist or neurology fellow should perform the above tests. If the neurologist or neurology fellow is not available at the time of patient's visit, a certified team member may perform the tests.
- Patients that have suffered a stroke or TIA will be assessed by a neurologist or neurology fellow.

- If the patient has suffered a stroke the NIHSS, MRS and Barthel Index will be performed at all subsequent visits.
    - Patients with stroke or TIA should report for follow-up within 30 to 90 days from the onset of the stroke or TIA, and the examination will include the NIHSS, Modified Rankin Scale, and the Barthel Index.

Cardiac:

- CCS status of angina
- NYHA classification

5.14.3 One Year Follow-Up Visit

The following data will be collected for all study patients at ±60 days. (Table 5.0-0).

Systems:

- Pertinent physical examination [includes blood pressure, weight, major systems findings
- Medications given for cardiovascular effect including anti-platelet/anti-thrombins
- Adverse Event assessment

Neuro:

- NIHSS (Appendix F) performed by a certified team member. If participating in the Neuro Sub-Study Cohort B, a Neurologist or neurology fellow will perform the examination.
- Modified Rankin Scale (MRS) (Appendix L);
- Barthel Index (Appendix L) for any patient with a stroke or a change in neurological status.
- A neurologist or neurology fellow should perform the above tests. If the neurologist or neurology fellow is not available at the time of patient's visit, a certified team member may perform the tests.
- Patients that have suffered a stroke or TIA will be assessed by a neurologist or neurology fellow.
- If the patient has suffered a stroke the NIHSS, MRS and Barthel Index will be performed at all subsequent visits.

- Patients with stroke or TIA will report for follow-up within 30 to 90 days from the onset of the stroke or TIA, and the examination will include the NIHSS, Modified Rankin Scale, and the Barthel Index.

Cardiac:

- CCS status of angina
- NYHA classification
- Standard 12-lead ECG
- Chest X-ray examination
- Fluoroscopic imaging implanted valve (required if CXR indicates abnormalities related to valve integrity and position and for Adverse Events related to worsening valve function) (See protocol for assessment in Appendix P)
- Comprehensive transthoracic echocardiogram (TTE)

Clinical Laboratory Tests:

- CBC with differential and platelet count
- Complete metabolic panel including sodium, potassium, creatinine and BUN
- Albumin
- B-type natriuretic peptide (BNP)
- Plasma free hemoglobin
- Haptoglobin.

Functional Assessments:

- 6MWT
- QOL (Cohort A: KCCQ, EQ5D, SF36 Cohort B and S3 Cohort: KCCQ, SF-12, EQ 5D)

5.14.4 Two Year Visit (Cohort A)

The following data will be collected for all study patients within 60 days before and 60 days after the 2-year date of the index procedure. (see Table 5.0-0).

Systems:

- Pertinent physical examination [includes blood pressure, weight, major systems findings

- Medications given for cardiovascular effect including anti-platelet/anti-thrombins
- Adverse Event assessment

Neuro:

- NIHSS (Appendix F) performed by a certified team member. If participating in the Neuro Sub-Study Cohort B, a Neurologist or neurology fellow will perform the examination.
- Modified Rankin Scale (MRS) (Appendix L);
- Barthel Index (Appendix L) for any patient with a stroke or a change in neurological status.
- A neurologist or neurology fellow should perform the above tests. If the neurologist or neurology fellow is not available at the time of patient's visit, a certified team member may perform the tests.
- Patients that have suffered a stroke or TIA will be assessed by a neurologist or neurology fellow.
- If the patient has suffered a stroke the NIHSS, MRS and Barthel Index will be performed at all subsequent visits.
    - Patients with stroke or TIA will report for follow-up within 30 to 90 days from the onset of the stroke or TIA, and the examination will include the NIHSS, Modified Rankin Scale, and the Barthel Index.

Cardiac:

- CCS status of angina
- NYHA classification
- Standard 12-lead ECG
- Chest X-ray examination
- Fluoroscopic imaging implanted valve (required if CXR indicates abnormalities related to valve integrity and position and for Adverse Events related to worsening valve function) (Appendix P)
- Comprehensive transthoracic echocardiogram (TTE)

Clinical Laboratory Tests:

- CBC with differential and platelet count
- Albumin
- Complete metabolic panel including sodium, potassium, creatinine and BUN
- Liver panel including AST and ALT

- B-type natriuretic peptide (BNP)
- Plasma free hemoglobin
- Haptoglobin
- PTT or PT/INR

Functional Assessments:

- 6MWT
- QOL (KCCQ, EQ 5D, SF-36)

5.14.5 Analysis close date Telephone Follow-Up

- Survival
- Hospitalization
- Adverse Event Assessment
- Medications given for cardiovascular effect including anti-platelet/anti-thrombins

5.14.6 Three to Five Year Follow-Up Visit (Cohort A)

The following data will be collected for all study patients annually (± 60 days) for a minimum of 5 years from the scheduled date of the index procedure. (see Table 5.0-0).

Systems:

- Pertinent physical examination [includes blood pressure, weight, major systems findings
- Medications given for cardiovascular effect including anti-platelet/anti-thrombins
- Adverse Event assessment

Cardiac:

- CCS status of angina
- NYHA classification
- Chest X-ray examination;
- Fluoroscopic imaging implanted valve (required if CXR indicates abnormalities related to valve integrity and position and for Adverse Events related to worsening valve function) (See Appendix P)
- Comprehensive transthoracic echocardiogram (TTE)

Clinical Laboratory Tests:

- B-type natriuretic peptide (BNP)

Neuro:

- NIHSS (Appendix F) performed by a certified team member. If participating in the Neuro Sub-Study Cohort B, a Neurologist or neurology fellow will perform the examination.
- Modified Rankin Scale (MRS) (Appendix L);

- Barthel Index (Appendix L) for any patient with a stroke or a change in neurological status.
- A neurologist or neurology fellow will perform the above tests. If the neurologist or neurology fellow is not available at the time of patient's visit, a certified team member may perform the tests.
- Patients that have suffered a stroke or TIA will be assessed by a neurologist or neurology fellow.
- If the patient has suffered a stroke the NIHSS, MRS and Barthel Index will be performed at all subsequent visits.
    - Patients with stroke or TIA will report for follow-up within 30 to 90 days from the onset of the stroke or TIA, and the examination will include the NIHSS, Modified Rankin Scale, and the Barthel Index.

Functional Assessments:

- QOL (KCCQ, , EQ 5D, SF-36)

5.14.7 Two to Five Year Follow-Up Visit (Cohort B and S3 Cohort)

The following data will be collected for all study patients annually (± 60 days) for a minimum of 5 years from the scheduled date of the index procedure. (Table 5.0-0).

Systems:

- Pertinent physical examination [includes blood pressure, weight, major systems findings
- Medications given for cardiovascular effect including anti-platelet/anti-thrombins;
- Adverse Event assessment

Cardiac:

- CCS status of angina
- NYHA classification
- Chest X-ray examination
- Fluoroscopic imaging implanted valve (required if CXR indicates abnormalities related to valve integrity and position and for Adverse Events related to worsening valve function) (Appendix P)
- Comprehensive transthoracic echocardiogram (TTE)

Clinical Laboratory Tests:

- B-type natriuretic peptide (BNP)

Neuro:

- NIHSS (Appendix F) performed by a certified team member. If participating in the Neuro Sub-Study Cohort B, a neurologist or neurology fellow will perform the examination.
- Modified Rankin Scale (MRS) (Appendix L);
- Barthel Index (Appendix L) for any patient with a stroke or a change in neurological status.
- A neurologist or neurology fellow will perform the above tests. If the neurologist or neurology fellow is not available at the time of patient's visit, a certified team member may perform the tests.
- Patients that have suffered a stroke or TIA will be assessed by a neurologist or neurology fellow.
- If the patient has suffered a stroke the NIHSS, MRS and Barthel Index will be performed at all subsequent visits.
    - Patients with stroke or TIA will report for follow-up within 30 to 90 days from the onset of the stroke or TIA, and the examination will include the NIHSS, Modified Rankin Scale, and the Barthel Index.

Functional Assessments:

- QOL (KCCQ, EQ 5D, SF-12).

5.15 Assurance of thorough follow-up

The clinical research coordinator and principal investigators will instruct patients and their families about the importance of follow-up assessment during the consenting process. Additionally, the site coordinators will contact the patients after index procedure to ensure timely scheduling of follow-up visits. In-window visit compliance will be carefully assessed by site and compliance below 80% at any time will be reviewed

closely by study leadership and may result in suspension of enrollment. Routinely, reports will be provided to the site Investigator and coordinators to track trends, identify issues and to ensure timely feedback about follow-up compliance. Reports will be provided to the PARTNER II Trial Executive Committee on a routine basis.

5.16 Study Patient Withdrawal

All study patients are required to complete clinical follow-up for all designated study visits. A careful review of these requirements must be communicated to the patient and family members prior to obtaining the study consent. Patients who cannot make study visits due to physical or geographical constraints should be encouraged to complete as many assessments within the planned visit as possible, including under the study investigator, however examinations by referring physicians are acceptable. A study patient that has been withdrawn from the study will not be replaced and may impact the ITT analysis.

5.17 Neurology Testing

All patients in The PARTNER II Trial will undergo baseline and follow-up neurological testing (NIHSS, Modified Rankin Scale and Barthel Index) for stroke assessment. The NIHSS and Modified Rankin Scale will be performed by certified test personnel at Baseline, Discharge, 30 days, 6 month, one year and within 30 to 90 days after an occurrence of stroke or TIA. In addition to the above timelines, the Cohort A patients will have neurological testing at Post Procedure and at the 2 year follow-up interval. All sites will designate a dedicated neurologist to the study (heart team) and should perform the required tests. Additional neurocognitive testing may be performed at the discretion of the neurologist. All tests and person performing tests will be documented on the CRFs. Patients with stroke or TIA will be examined within 30 to 90 days from the onset of the stroke or TIA, and the examination will also include the NIHSS, Modified Rankin Scale, and the Barthel Index; for such patients for whom the identification of the stroke or TIA occurred beyond 90 days from onset, the examination will be expedited, so it can take place as close to the 90 day mark as possible.

Table 5.0-0 Schedule of Events: Cohort A and Registries

	Screening	Baseline	During procedure	Post Procedure	Discharge	30 D Follow-Up (-7 days; +14 days)	6 M Follow-up (± 30 days)	1 Yr Follow-Up (± 60 days)	2 Yr Follow-Up (± 60 days) Cohort A Only	Telephone Follow-up after analysis close date (+14days)	Annual Follow-Up ≥5 Y (± 60 days)
Physical assessment and Patient interview											
Operability Risk Assessment	X										
Informed Consent	X										
Medical History	X										
Physical Exam	X				X	X	X	X	X		X
CCS Angina	X				X	X	X	X	X		X
NYHA Classification	X				X	X	X	X	X		X
Syntax Score	X										
Cardiac Medications		X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X	X	X	X	X
NIHSS		X[1]		X[1]	X[1]	X	X	X	X		X
Modified Rankin Scale		X[1,]		X[1]	X[1]	X	X	X	X		X

	Screening	Baseline	During procedure	Post Procedure	Discharge	30 D Follow-Up (-7 days; +14 days)	6 M Follow-up (± 30 days)	1 Yr Follow-Up (± 60 days)	2 Yr Follow-Up (± 60 days) Cohort A Only	Telephone Follow-up after analysis close date (+14days)	Annual Follow-Up ≥5 Y (± 60 days)
Barthel Index		X[1, 2]		X[1]	X[1]	X	X	X	X		
Risk Score Assessments: ▪ STS Risk Score Logistic EuroSCORE	X X										
Six Minute Walk Test (6MWT)		X				X		X	X		
MMSE	X										
Frailty Index		X									
Lab Measurements											
CBC with Differential and Platelet Count		X		X	X	X		X	X		
PTT or PT/INR		X		X	X				X		
CK/CKMB and/or Troponins		X[3]		X[4]							

	Screening	Baseline	During procedure	Post Procedure	Discharge	30 D Follow-Up (-7 days; +14 days)	6 M (± 30 days) Follow-up	1 Yr Follow-Up (± 60 days)	2 Yr Follow-Up (± 60 days) Cohort A Only	Telephone Follow-up after analysis close date (+14days)	Annual Follow-Up ≥5 Y (± 60 days)
Metabolic Panel (Sodium, Potassium, Creatinine, BUN)		X		X	X			X	X		
Liver Panel (ALT, AST)		X							X		
Albumin		X				X		X	X		
BNP		X			X	X		X	X		X
Plasma Free Hemo-globin & Haptoglobin		X				X		X	X		
Non-Invasive Tests											
ECG		X		X	X	X		X	X		
Chest X-ray		X			X	X		X	X		X
Transthoracic Echocardiogram (TTE)	X				X	X		X	X		X
Fluoroscopic imaging implanted valve			X			X[5]		X[5]	X[5]		X[5]
Invasive Tests											

	Screening	Baseline	During procedure	Post Procedure	Discharge	30 D Follow-Up (-7 days; +14 days)	6 M (± 30 days) Follow-up	1 Yr Follow-Up (± 60 days)	2 Yr Follow-Up (± 60 days) Cohort A Only	Telephone Follow-up after analysis close date (+14days)	Annual Follow-Up ≥5 Y (± 60 days)
CT Thoracic/Abdomen with visualization of iliac and femoral arteries	**X**										
Cardiac Catheterization	**X**										
Supra-aortic angiogram or TEE			**X**								
Invasive Hemodynamics			**X**								
Quality of Life Questionnaire											
Cohort A KCCQ, EQ5D, SF36		**X**				**X**		**X**	**X**		**X**

[1] A neurologist or a neurology fellow will assess the Cohort A and all Registries patients at Baseline, Post Procedure and Discharge. If the neurologist or neurology fellow is not available at the time of patient's baseline or discharge visit, a certified team member may perform the tests. A neurologist or neurology fellow must perform the Post Procedure assessment.

[2] Barthel Index for any patient with a previous stroke.

[3] Baseline CK/CKMB and/or Troponins are required ≤ 72 hours before the procedure.

[4] Post Procedure CK/CKMB and/or Troponins are required at 3 different time intervals: 1) the first lab draw post procedure (within 8 hours of exiting the cath lab or operating room) 2) the second lab draw 6 – 8 hours after the first lab draw 3) the third lab draw 6 – 8 hours after the second lab draw.

[5] For patients with abnormal chest x-ray findings related to valve integrity and position and patients with Adverse Events related to worsening valve function.

Table 5.0-1 Schedule of Events: Cohort B

	Screening	Baseline	During procedure	Post Procedure	Discharge	30 D Follow-Up (-7 days; +14 days)	6 M (+ 30 days) Follow-up	1 Yr Follow-Up (± 60 days)	Telephone Follow-up after analysis close date (+14days)	Annual Follow-Up ≥5 Y (± 60 days)
Physical assessment and Patient interview										
Operability Risk Assessment	X									
Informed Consent	X									
Medical History	X									
Physical Exam	X				X	X	X	X		X
CCS Angina	X				X	X	X	X		X
NYHA Classification	X				X	X	X	X		X
Cardiac Medications		X	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X	X	X	X
NIH Stroke Score Assessment		X[1]			X[1]	X[1]	X[1]	X[1]		X
Modified Rankin Scale		X[1,]			X[1, 2]	X[1, 2]	X[1, 2]	X[1, 2]		X

	Screening	Baseline	During procedure	Post Procedure	Discharge	30 D Follow-Up (-7 days; +14 days)	6 M (+ 30 days) Follow-up	1 Yr Follow-Up (± 60 days)	Telephone Follow-up after analysis close date (+14days)	Annual Follow-Up ≥5 Y (± 60 days)
Barthel Index		X[1, 2]			X[1, 2]	X[1, 2]	X[1, 2]	X[1, 2]		
Risk Score Assessments: STS Risk Score Logistic EuroSCORE	X X									
Six Minute Walk Test (6MWT)		X				X		X		
MMSE	X									
Frailty Index		X								
Lab Measurements										
CBC with Differential and Platelet Count		X		X	X	X		X		
PTT or PT/INR		X		X	X					
CK/CKMB and/or Troponins		X[3]		X[4]						

	Screening	Baseline	During procedure	Post Procedure	Discharge	30 D Follow-Up (-7 days; +14 days)	6 M (+ 30 days) Follow-up	1 Yr Follow-Up (± 60 days)	Telephone Follow-up after analysis close date (+14days)	Annual Follow-Up ≥5 Y (± 60 days)
Metabolic Panel (Sodium, Potassium, Creatinine, BUN)		X		X	X			X		
Liver Panel (ALT, AST)		X								
Albumin		X				X		x		
BNP		X			X	X		X		X
Plasma Free Hemo-globin & Haptoglobin		X				X		X		
Non-Invasive Tests										
ECG		X		X	X	X		X		
Chest X-ray		X			X	X		X		X
Transthoracic Echocardiogram (TTE)	X				X	X		X		X
Fluoroscopic imaging implanted valve			X			X[5]		X[5]		X[5]
Invasive Tests										

	Screening	Baseline	During procedure	Post Procedure	Discharge	30 D Follow-Up (-7 days; +14 days)	6 M (+ 30 days) Follow-up	1 Yr Follow-Up (± 60 days)	Telephone Follow-up after analysis close date (+14days)	Annual Follow-Up ≥5 Y (± 60 days)
CT Thoracic/Abdomen with visualization of iliac and femoral arteries	**X**									
Cardiac Catheterization	**X**									
Supra-aortic angiogram or TEE			**X**							
Invasive Hemodynamics			**X**							
Quality of Life Questionnaire										
Cohort B KCCQ, EQ5D, SF12		**X**				**X**		**X**		**X**

[1] Cohort B: Designated sites participating in the NeuroSub-Study must have tests performed by a neurologist or neurology fellow. Neuro Sub-Study sites must also have a neurologist or neurology fellow perform the MRS and Barthel Index.

[2] Barthel Index for any patient with a previous stroke.

[3] Baseline CK/CKMB and/or Troponins are required ≤ 72 hours before the procedure.

[4] Post Procedure CK/CKMB and/or Troponins are required at 3 different time intervals: 1) the first lab draw post procedure (within 8 hours) 2) the second lab draw 6 – 8 hours after the first lab draw 3) the third lab draw 6 – 8 hours after the second lab draw.

[5] For patients with abnormal chest x-ray findings related to valve integrity and position and patients with Adverse Events related to worsening valve function.

Table 5.0-2 Schedule of Events: S3 Cohort

	Screening	Baseline	During procedure	Post Procedure	Discharge	30 D Follow-Up (-7 days; +14 days)	6 M (± 30 days) Follow-up	1 Yr Follow-Up (± 60 days)	Telephone Follow-up after analysis close date (+14days)	Annual Follow-Up 2-5 Y (± 60 days)
Physical assessment and Patient interview										
Operability Risk Assessment	X									
Informed Consent	X									
Medical History	X									
Physical Exam	X				X	X	X	X		X
CCS Angina	X				X	X	X	X		X
NYHA Classification	X				X	X	X	X		X
Cardiac Medications		X	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X	X	X	X
NIHSS		X[1]		X[1]	X[1]	X	X	X		X
Modified Rankin Scale		X[1,]		X[1]	X[1]	X	X	X		X
Barthel Index		X[1, 2]		X[1]	X[1]	X	X	X		
Risk Score Assessments: STS Risk Score Logistic EuroSCORE	X X									
Six Minute Walk Test (6MWT)		X				X		X		
MMSE		X								
Frailty Index		X								
Lab Measurements										

	Screening	Baseline	During procedure	Post Procedure	Discharge	30 D Follow-Up (-7 days; +14 days)	6 M (± 30 days) Follow-up	1 Yr Follow-Up (± 60 days)	Telephone Follow-up after analysis close date (+14days)	Annual Follow-Up 2-5 Y (± 60 days)
CBC with Differential and Platelet Count		X		X	X	X		X		
PTT or PT/INR		X		X	X					
CK/CKMB and/or Troponins		X[3]		X[4]						
Metabolic Panel (Sodium, Potassium, Creatinine, BUN)		X		X	X			X		
Liver Panel (ALT, AST)		X								
Albumin		X				X		X		
BNP		X			X	X		X		X
Plasma Free Hemo-globin & Haptoglobin		X				X		X		
Non-Invasive Tests										
ECG		X		X	X	X		X		
Chest X-ray		X			X	X		X		X
Transthoracic Echocardiogram (TTE)	X				X	X		X		X
Fluoroscopic imaging implanted valve			X			X[5]		X[5]		X[5]
Invasive Tests										
CT Thoracic/Abdomen with visualization of iliac and femoral arteries	X									
Cardiac Catheterization	X									

	Screening	Baseline	During procedure	Post Procedure	Discharge	30 D Follow-Up (-7 days; +14 days)	6 M (± 30 days) Follow-up	1 Yr Follow-Up (± 60 days)	Telephone Follow-up after analysis close date (+14days)	Annual Follow-Up 2-5 Y (± 60 days)
Supra-aortic angiogram or TEE			**X**							
Invasive Hemodynamics			**X**							
Quality of Life Questionnaire										
Cohort A KCCQ, EQ5D, SF-12		**X**				**X**		**X**		**X**

[1] A neurologist or a neurology fellow should assess the S3 Cohort patients at Baseline, Post Procedure and Discharge. If the neurologist or neurology fellow is not available at the time of patient's baseline, post-op or discharge visit, a certified team member may perform the tests.

[2] Barthel Index for any patient with a previous stroke.

[3] Baseline CK/CKMB and/or Troponins are required ≤ 72 hours before the procedure.

[4] Post Procedure CK/CKMB and/or Troponins are required at 3 different time intervals: 1) the first lab draw post procedure (within 8 hours of exiting the cath lab or operating room) 2) the second lab draw 6 – 8 hours after the first lab draw 3) the third lab draw 6 – 8 hours after the second lab draw.

[5] For patients with abnormal chest x-ray findings related to valve integrity and position and patients with Adverse Events related to worsening valve function.

6.0 Endpoint Data Collection and Adjudication

6.1 Electrocardiogram (ECG)

All ECGs will be sent to the ECG Core Lab (see Appendix C) for independent analysis of rhythm and occurrence of myocardial infarction. Data from the evaluation of the ECG will be transferred to the database management center for integration into the database and used in the adjudication of MI events.

6.2 Echocardiography (ECHO)

The pre-procedure TTE will be performed to assess risk factors and eligibility. Discharge and Follow-Up TTE will be performed at the intervals specified in Table 5.0-0. All echocardiograms will be independently analyzed by the Echocardiographic Core Lab (see Appendix C). The aortic valve effective orifice area (EOA) that will be used to assess the AVA effectiveness endpoint will be the aortic valve EOA after valvuloplasty, after final valve deployment, and at follow-up time points calculated from echocardiographic data using the continuity equation. The AVA calculated from cardiac catheterization data using the Gorlin formula will be used only to calculate an estimated AVA at baseline, after valvuloplasty and after final valve deployment at the time of the study valve implant.

6.3 Stroke/Neurological Assessments

Modified Rankin Scale, Barthel Index, and NIHSS exams will be performed by neurologists, neurology fellows or certified team members to ensure proper assessments for neurological and stroke outcomes. Documentation of training and certification for certified team members performing these tests will be kept in the study master file. All neurological events and sub-classifications will be assessed by an independent clinical events committee.

Cohort B (Neuro Sub-Study): Sites will be selected to be representative of high enrolling and novice sites and both academic and non-academic institutions, assign appropriate neurologist resources and deliver high quality, timely and complete data. For these participating centers, consecutively enrolled/randomized patients will undergo a screening (baseline), discharge, thirty days, 6 months, and one year evaluation by the site designated neurologist or neurology fellow and this assessment will be documented on the case report form. As stated above, patients with stroke or TIA will be examined at within 30 to 90 days from the onset of the stroke or TIA, and the examination will also include the NIHSS, Modified Rankin Scale, and the Barthel Index; for such patients for whom the identification of the stroke or TIA occurred beyond 90 days from onset, the examination will be expedited, so it can take place as close to the 90 day mark as possible.

6.4 Quality of Life

Quality of life will also be measured through standard surveys:

1) Kansas City Cardiomyopathy Questionnaire (KCCQ). The KCCQ is for the assessment of disability and quality of life impairment due to congestive heart failure.

2) EuroQOL. The EuroQOL is a generic health status instrument and rating scale (EQ-5D) that allows mapping of health status to population-level utility weights. This is an important metric for cost-effectiveness analysis.

3) SF12 / SF36. The SF (12 and 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. Cohort A will complete the SF36. Cohort B and S3 Cohort will complete the SF12.

The protocol describing this plan and the analysis to be used is located in Appendix D. Efforts to minimize bias in the scheduling and administration of the QOL questionnaire will be taken by ensuring that all patients, regardless of cohort assignment, are approached and instructed similarly.

6.5 Six Minute Walk Test

Each patient will be required to undergo a six minute walk test in accordance with the official statement (on the six minute walk test) of the American Thoracic Society [113] will be performed at baseline, 30 days and one year. Patients deemed clinically unable to perform the test are excluded from this requirement at the time of the required test. In other words, if a patient is ineligible for the test at baseline, they must be reassessed for eligibility again at 30 days and one year. Patients deemed clinically unable to perform the test will be assigned a value of 0 distance walked in all analyses. (An additional assignment is discussed in the statistical section of this protocol.)

If the patient is unable to perform the 6MWT for any reason, the reason must be documented in the case report form. A clinical justification documented in the medical record and reviewed and signed by the principal investigator will be accepted as an attempted 6MWT. Ineligibility criteria include (but not limited to) clinical criteria such oxygen dependency, neuromuscular limitations rendering patient wheel-chair bound, NYHA class 4, unstable angina, postural hypotension. A missed 6MWT for logistical reasons (i.e. patient not present in clinic, clinic not staffed adequately, etc.) will be treated as a missed test in the trial analysis.

6.6 Clinical Follow-up

The clinical follow-up will include capturing of all adverse events. These events must be recorded on the electronic case report forms provided by the database management center.

6.7 Histopathology Studies

Histopathology studies of explanted valves will be performed. Explants will be appropriately prepared and preserved and sent to the independent histopathology laboratory for macroscopic and microscopic analysis (according to FDA Heart Valve Guidance on Explant Analysis). Investigational valves that are removed during the THV procedure or prior to index hospitalization discharge will be returned to the Sponsor for evaluation. Valves explanted after index hospitalization discharge will be sent to the Histopathology Core Lab. Appendix E contains a complete explant protocol which includes detailed procedures for the histopathology studies.

Gross pathological examination of the entire valve and the support structure (i.e. and shape, if occurrence of intravascular trauma, tissue abrasion, uniformity of the frame, position the natural valve cusps) will be assessed.

The valves will be assessed for cusp excursion and the presence of leaflet fenestrations, rigidity tears, hematoma, thrombi and calcified nodules, cell proliferation tissue overgrowth, fibrous sheath, and local inflammatory reaction. (One half of each leaflet must be used for the quantitative determination of inorganic calcium and phosphate).

6.8 Clinical Event Adjudication

All events that are included in primary and secondary endpoint analyses will be adjudicated in accordance to a Clinical Event Committee Charter (Appendix J) and in accordance to the definitions listed in section 8.0 of this protocol.

7.0 Statistical Analysis

Unless otherwise specified, all analyses will be conducted within each Cohort (A and B). When trial arm comparisons are noted, they intend to represent comparison of treatment to control within a Cohort. Trial arms will not be compared solely between the two Cohorts for PMA submission purposes. However, the Sponsor reserves the right to produce integrated summaries of efficacy and safety spanning multiple studies (including Rest-of-World [ROW]) in support of any PMA application, as well as in support of publications. As many of the endpoints and analyses are identical for both Cohorts A and B, they are generally described only once within this section. It should be assumed that these analyses will be conducted within each Cohort.

Some analysis descriptions are included in this protocol. Further details are provided in two separate statistical analysis plans (SAPs), which have been developed in cooperation with the FDA. The Cohort A SAP corresponds to analyses specific to Cohort A data. The Cohort B SAP corresponds to analyses specific to Cohort B data. These plans include analyses not described in this protocol.

Furthermore, Section 10 of each of these documents enumerate the differences between the respective SAP and the presentation of statistical detail in this section of the main Protocol. The reader is encouraged to digest the contents of the Cohort A SAP and the Cohort B SAP, especially Section 10 of each.

Statistical analysis for the S3 Cohort is somewhat different than for the remainder of the trial. That analysis is described in Section 15.0.

7.1 Sample Size Computation

The sample size for Cohort A is based on the primary safety and effectiveness endpoint. The following data are taken from The PARTNER I Trial and are considered in the sample size assumptions. For Cohort B, The PARTNER I Trial provides reasonable assumptions in that the population is similar to the planned PARTNER II and for similar period of follow-up (1 year). For Cohort A, The PARTNER I Trial data provide some support for assumptions however the proposed population for PARTNER II A is of lower risk and the anticipated event rate can be assumed to be different. Additionally, Cohort A of PARTNER II has a longer follow-up period for the primary endpoint (mean 2 years).

The PARTNER I Trial Cohort A As Treated Event Rates

Event	30 day KM Event (Test)	30 day KM Event (Control)	One Year KM Event (Test)	One Year KM Event (Control)
Death	12 (3.4)	22 (6.5)	84 (24.2)	89 (26.8)
Major Stroke	13 (3.8)	7 (2.1)	17 (5.1)	8 (2.4)
Rehospitalization	15 (4.4)	12 (3.7)	58 (18.2)	45 (15.5)
Major Bleed	32 (9.3)	67 (19.5)	49 (14.7)	85 (25.7)
Major Vascular complications	38 (11.0)	11 (3.2)	39 (11.3)	12 (3.5)

The PARTNER I Trial Cohort B As Treated Event Rates

Event	30 day KM Event (Test)	30 day KM Event (Control)	One Year KM Event (Test)	One Year Event (Control)
Death	9 (5.0)	5 (2.8)	55 (30.7)	89 (49.7)
Major Stroke	9 (5.0)	2 (1.1)	14 (7.8)	7 (3.9)
Rehospitalization	10 (5.6)	18 (10.1)	40 (22.3)	79 (44.1)
Major bleed	30 (16.8)	7 (3.9)	40 (22.3)	20 (11.2)
Major vascular complications	29 (16.2)	2 (1.1)	30 (16.8)	4 (2.2)

The Cohort A primary endpoint of death (all cause) and disabling stroke will be evaluated once all subjects have reached 2 years. An event rate of 30% was used to calculate the Cohort A sample size. Assumptions were taken from The PARTNER I Trial two year event rate for death, major stroke and rehospitalization (35%) and then discounted to account for the lower risk population, and for lower stroke rates. Assuming a 1:1 randomization ratio, event rate of 30% in both trial arms and power 80%, 1744 patients would be needed. The randomized sample size has been set to 2000 patients in order to allow for possible lost to follow-up and other trial contingencies.

It is noted that the site-specific randomization lists for Cohort A will be stratified by incidence of baseline atrial fibrillation. The site-specific stratified randomization lists will be produced independently for the Transapical, Transfemoral, and Transaortic surgical approaches, yielding six 1:1 randomization lists per site. Blocks of random size (2, 4, or 6) will be used in the development of these lists.

The sample size was computed using PASS 2008 software, as shown in the table below.

Power	Alpha (1-sided)	Non-Inferiority Ratio	Failure Rate	N1	N2	Total N (Evaluable)	Total N (with 10% dropout)
80%	0.05	1.2	30%	872	872	1744	1938

The analysis will be based on the ratio of proportions, as a non-inferiority analysis. Let r_T denote the true event proportion in the Test arm, and r_C denote the true event proportion in the Control arm. The hypotheses are

$$H_0: \ r_T / r_C \geq 1 + \Delta$$

$$H_A: \ r_T / r_C < 1 + \Delta$$

The value Δ is the non-inferiority margin, and is taken to be 0.2. The test will be performed as a one-sided test at alpha = 0.05.

The specific non-inferiority margin for Cohort A was specified by the FDA.

The Cohort B endpoint would be evaluated based on a non-inferiority ratio of 1.35 at a one-sided alpha of 0.025. The feasibility assumptions are a 1:1 randomization ratio, event rate of 43.6% in both trial arms, and power 80%. The software produces a minimum statistically justified sample size of 458 patients. The randomized sample size has been set to 500 patients in order to allow for possible lost to follow-up and other trial contingencies.

It is noted that the site-specific randomization lists for Cohort B will be unstratified. The site-specific randomization lists will be produced independently for each site, yielding one 1:1 randomization list per site. Blocks of random size (2, 4, or 6) will be used in the development of these lists.

In analysis of cohort B data, there is no anticipation that there will be statistically significant differences between Test and Control. Additionally, it is anticipated that while the eligibility criteria for The PARTNER I and PARTNER II Trials (Cohort B) are essentially the same, due to multi-factors, future pooling of the two cohorts will have limitations. Where p-values are presented for direct trial arm comparisons, these p-values are for information only; confidence limits for trial arm differences will convey more clinically meaningful information. Some analyses will be described as formal non-inferiority analyses; the p-values are meaningful for these analyses.

7.2 Timing issues

Various data will be collected at specific follow-up times post-procedure and will be assigned to visit windows according to the limits defined in Section 5.12 of the protocol. See Section 3.2.1 of each SAP for additional visit window detail. Where analyses refer to data collected at nominal follow-up intervals, only visits within the specified window will be used for main analyses, regardless of the interval specified by the site on the case report form. Additional analyses are specified in the missing data Section 7.22.8. See Section 3 in the relevant SAP (Cohort A or B) for full details regarding the use of multiple imputation for primary analysis of the primary endpoint, as well as additional sensitivity analyses not presented in this Protocol.

- In analysis of time-dependent variables, one year will be defined as 365.25 days, and one month as 30.4375 (= 365.25/12) days.
- The scheduled day of the index procedure is defined to be Day 0 for all subjects and all visits.
- Any roll-in patients who do not receive the implant will be excluded from analyses. A separate report will be made of such patients if there are any.

The enrollment close date is the day that Edwards becomes aware that the sample size target has been met, based on patients randomized. Patients already consented on the enrollment close date will be allowed to be randomized provided that this randomization takes place within 30 days of the enrollment close date. Such patients, if any, will be analyzed together with other enrolled patients, and no separate analyses will be performed based on randomization before or after the enrollment close date.

For purposes of initial PMA submission, the analysis close date is day 365 following the last scheduled date of an index procedure, for Cohort B. Likewise, for purposes of initial PMA submission, the analysis close date is day 730 following the last scheduled date of an index procedure, for Cohort A. See Section 3.2.1 of each SAP for a reflection of this fact in the visit windows for analysis purposes. For any subsequent analyses, an analysis close date will be determined prior to beginning the analysis. Adverse events occurring after the analysis close date will not be considered in the initial PMA analysis.

Data depending on visit windows (such as NYHA) will be included in analysis if the visit window starts on or before the analysis close date and the visit occurs within the visit window.

Analyses referring to baseline values will use the values obtained during the baseline visits, and entered as baseline values in the clinical database. These values will not be re-measured, even if the implant is delayed.

7.3 Patient groups

7.3.1 Analysis populations

Additional analysis populations have been defined in the SAPs beyond those listed below. Please see Section 3.1 of each SAP and Section 10 of each SAP.

- Intent to Treat (ITT) population. The ITT population is defined to include all randomized subjects. Except where otherwise specified, this population will be used for endpoint analyses.
- As Treated population. The AT population is defined to include all subjects actually undergoing the index procedure. Except where otherwise specified, this population will be used for the analysis of adverse event analyses. The As Treated Test and Control arm assignment will be determined at the patient is brought into the procedure room or the induction of anesthesia/sedation, whichever occurs earlier. Any events related to the procedure, even if they occur prior to the implant of procedure valve will be counted in the "As Treated" arm. It is anticipated that randomized patients will receive the valve assigned. If there are any exceptions the valve actually used in the initial implant attempt will be used for determining the As Treated arm.
- Valve Implant population. This population is a subset of the As Treated Test and Control arms, consisting of those patients for whom the valve implant process is completed. Except where otherwise specified, this population will be used for all analyses of echocardiographic data.
- If it necessary to implant more than one valve (valve-in-valve) the patient will still be in the Valve Implant population. The final valve implanted will determine the assignment to Test or Control for the valve implant population.
- If any valve other than the Test or Control valve is implanted, the patient will not be considered part of the Valve Implant population.

Crossovers: It is expected that all valve implants will be based on the randomized assignment, and the protocol contains no provisions for any crossover. The definitions of the As Treated and Valve Implant populations prescribe the analyses in case the unexpected actually happens.

7.4 Primary and Secondary Endpoints

The March 2010 draft "Guidance for Industry: Non-Inferiority Clinical Trials" issued by CDER/CBER and addresses the issue of interpretability of non-inferiority results in clinical trials, and specifically the text on page 33 of this document states:

> "It is therefore important to conduct both ITT and as-treated analyses in NI studies. Differences in results using the two analyses will need close examination. The best advice for conducting an NI study is to be aware at the planning stage of these potential issues and to monitor the trial in a manner that minimizes these problems, as they can seriously affect the validity of an NI study."

Edwards agrees with this recommendation. The ITT and AT analyses of primary efficacy and secondary labeling non-inferiority endpoints will be presented with equal consideration. There will be no adjustment to Type I error rates for multiplicity beyond the Hochberg adjustment of secondary labeling endpoints already specified in Section 7.3.1 of the SAP. All other endpoints will be assessed with respect to patient populations as per the SAP. The Sponsor reserves the right to publish study results on the basis of either the ITT or AT or any other patient population as it deems appropriate.

The randomization of Cohort A will be conducted different than what was implemented for Cohort B. Please see Sections 2.1 and 10 of the Cohort A SAP. The text in the Cohort A SAP supersedes any other randomization text present in this main Protocol.

Furthermore, per the March 2010 draft "Guidance for Industry: Non-Inferiority Clinical Trials" issued by CDER/CBER, page 34, if the results of a primary endpoint non-inferiority assessment are statistically significant, a superiority assessment will be conducted using the same alpha = 0.025 error rate, with no Type I error adjustment needed. The Sponsor will request a claim of superiority on its product label if such a result is obtained. This applies separately to each Cohort discussed in this protocol.

7.4.1a Primary safety and effectiveness (Cohort A)

The primary safety and effectiveness endpoint is a non-hierarchical composite of events: death (all cause) and disabling stroke. Disabling stroke will be as evaluated by the CEC, using the definition contained elsewhere in this protocol.

Evaluation will be in the randomized intent to treat (ITT) trial arms. The evaluation will be performed at 2 years. Events occurring on day 730 or earlier will be included in the evaluation. Events occurring after day 730 will not be included.

Each patient is classified as Event Yes or a No for this composite endpoint. Multiple events, or multiple occurrences of the same event, will not be considered in the analysis.

The analysis will be based on the ratio of proportions, as a non-inferiority analysis. Let r_T denote the true event proportion in the Test arm, and r_C denote the true event proportion in the Control arm. The hypotheses are

$$H_0: \ r_T / r_C \ \geq \ 1 + \Delta$$

$$H_A: \ r_T / r_C \ < \ 1 + \Delta$$

The value Δ is the non-inferiority margin, and is taken to be 0.20. The test will be performed as a one-sided test at alpha = 0.05. The sample size, which is derived above, will produce a power of 85% for this endpoint.

If all patients have 2 year data, the confidence limits for the ratio of proportions will be computed using the default methodology of SAS® PROC FREQ.

It is reasonably likely that there will be some patients who are censored prior to 2 years, either due to withdrawal or lost to follow-up. If that should prove to be the case, an approach using ratios of Kaplan-Meier estimates will be used, as described in section 7.22.2 of this protocol.

7.4.2b Primary safety and effectiveness (Cohort B)

The primary safety and effectiveness endpoint for Cohort B is a non-hierarchical composite of death, disabling stroke, and rehospitalization. Death is all cause mortality. Disabling stroke will be evaluated by the CEC. Rehospitalization will consist of hospitalization for symptoms of aortic stenosis and hospitalization for complications of the valve procedure; both will be evaluated by the CEC.

Evaluation will be in the randomized intent to treat (ITT) trial arms. The evaluation will be performed at 1 year. Events occurring on day 365 or earlier will be included in the evaluation. Events occurring after day 365 will not be included.

Each patient is classified as Event Yes or a No for this composite endpoint. Multiple events, or multiple occurrences of the same event, will not be considered in the analysis.

The analysis will be based on the ratio of proportions, as a non-inferiority analysis. Let r_T denote the true event proportion in the Test arm, and r_C denote the true event proportion in the Control arm. The hypotheses are

$$H_0: \ r_T / r_C \ \geq \ 1 + \Delta$$

$$H_A: \ r_T / r_C \ < \ 1 + \Delta$$

The value Δ is the non-inferiority margin, and is taken to be 0.35. The test will be performed as a one-sided test at alpha = 0.025. Assuming a one year event rate in each arm of 45%, there will be 82% power to declare non-inferiority for this secondary endpoint.

If all patients have 1 year data, the confidence limits for the ratio of proportions will be computed using the default methodology of SAS® PROC FREQ.

It is reasonably likely that there will be some patients who are censored prior to 1 year, either due to withdrawal or lost to follow-up. If that should prove to be the case, an approach using ratios of Kaplan-Meier estimates will be used, as described in section 7.22.2 of this protocol.

7.5 Procedure related complications

There are two composite endpoints in this category.

Procedure related complications A:

This endpoint is a non-hierarchical composite of major vascular complication, major bleed, and reintervention for valve or procedure complications. Major vascular complication and major bleed will be evaluated by the CEC. Reintervention refers to events occurring after the index procedure. This endpoint will be evaluated at 30 days or discharge, whichever is later. Trial arm comparison will be a non-inferiority analysis.

Evaluation will be in the As Treated analysis population. Events occurring before the day of implant will not be considered in evaluation of this endpoint. For purposes of evaluating this endpoint, an event occurring on day 0 or later will be considered early if it occurs on day 30 or earlier, or if it occurs on or before the day of discharge from the index hospitalization.

Procedure related complications B:

This endpoint is a non-hierarchical composite of the events in the Procedure related complications A endpoint, together with all stroke (disabling and minor), renal failure, access site infection, new permanent pacemaker, or other important access problems. All components will be evaluated by the CEC. This endpoint will be evaluated at 30 days or discharge, whichever is later. Trial arm comparison will be a non-inferiority analysis.

Evaluation will be in the As Treated trial arms. The day of implant is day 0.

Events occurring before the day of implant will not be considered in evaluation of this endpoint. For purposes of evaluating this endpoint, an event occurring on day 0 or later will be considered early if it occurs on day 30 or earlier, or if it occurs on or before the day of discharge from the index hospitalization.

As an exception to the above, certain events that occur after randomization but before implant will be included. The inclusion will be when these events are due to conditions caused by changing medication in preparation for the implant.

For both composites

Each patient is classified as Event Yes or a No for this composite endpoint. Multiple events, or multiple occurrences of the same event, will not be considered in the analysis.

The analysis will be based on the ratio of proportions, as a non-inferiority analysis. Let r_T denote the true event proportion in the Test arm (XT), and r_C denote the true event proportion in the Control arm (SAPIEN). The hypotheses are

$$H_0: \ r_T / r_C \ \geq \ 1 + \Delta$$

$$H_A: \ r_T / r_C \ < \ 1 + \Delta$$

The value Δ is the non-inferiority margin, and is taken to be 0.35. The test will be performed as a one-sided test at alpha = 0.05. Confidence limits for the ratio of proportions will use the default methodology of SAS® PROC FREQ.

7.6 Secondary Endpoints

For the composite secondary endpoints defined below, each patient is classified as Event Yes or a No for the composite endpoint. Multiple events, or multiple occurrences of the same event, will not be considered in the analysis.

The analysis of composite events will be based on the ratio of proportions, as a non-inferiority analysis. Let r_T denote the true event proportion in the Test arm, and r_C denote the true event proportion in the Control arm (open surgery for cohort A, SAPIEN for cohort B). The hypotheses are

$$H_0: \ r_T / r_C \ \geq \ 1 + \Delta$$

$$H_A: \ r_T / r_C \ < \ 1 + \Delta$$

The value Δ is the non-inferiority margin. Unless otherwise specified, Δ is taken to be 0.35, and the test will be performed as a one-sided test at alpha = 0.05.

Confidence limits for the ratio of proportions will use the default methodology of SAS® PROC FREQ.

Where the analyses are based on differences instead of proportions, the exact details will be specified with each analysis.

7.7 Secondary safety and effectiveness (Cohort A)

Cohort A: The secondary safety and effectiveness endpoint is a non-hierarchical composite of various adverse events. The endpoint will be evaluated at two time points: (1) acute, covering events occurring out to 30 days or hospital discharge, whichever is longer; and (2) longer-term, covering events from 31 days to the 2 year closing date of the primary endpoint. As requested by the FDA the specific components of the composite are

- all stroke and TIA
- myocardial infarction
- major vascular complication (VARC)
- life-threatening bleeding (VARC)
- reoperation or catheter-based intervention for:
    - valve thrombosis, valve displacement, or other valve - or procedure-related complication
- pericarditis
- hemolysis
- mediastinitis
- endocarditis
- moderate or severe aortic insufficiency (VARC)
- possible or significant aortic stenosis (VARC)
- permanent pacemaker insertion
- new mitral valve dysfunction
- acute kidney injury (VARC).

Evaluation will be in the As Treated analysis population. For both analyses there will be censored data due to death; there is also the potential for censoring due to withdrawal or lost to follow-up. In evaluation of the primary endpoint the censoring was handled by Kaplan-Meier estimates. That method cannot be used for the acute analysis, because of the FDA request to extend the clock to discharge; this means that there is no fixed time at which to evaluate the Kaplan-Meier estimates.

For the acute endpoint each patient will be evaluated as having the composite event or not, based on the available data. A patient who is censored without experiencing any of the events will be considered to have not had any of the events, regardless of the time of censoring.

Events occurring before the day of implant will not be considered in evaluation of the acute phase of this endpoint. For purposes of evaluating this endpoint, an event occurring on day 0 or later will be considered early if it occurs on day 30 or earlier, or if it occurs on or before the day of discharge from the index hospitalization.

For the longer term analysis, the clock will start and stop at fixed times, in order to enable use of the same Kaplan-Meier analysis used in the primary endpoint evaluation. This method means that there may be a few events that are counted in both the acute and longer term analysis. Events occurring at day 30 or earlier will not be considered in evaluating this endpoint; patients who have no data past day 30 will not be included in the analysis.

7.8 Secondary safety and effectiveness (Cohort B)

This endpoint is a non-hierarchical composite of all stroke, major vascular complications and reintervention. All components will be evaluated by the CEC. This endpoint will be evaluated at 30 days and 1-year. Trial arm comparison will be a non-inferiority analysis.

Evaluation will be in the As Treated analysis population.

Events occurring before the day of implant will not be considered in evaluation of this endpoint. For purposes of evaluating this endpoint, an event occurring on day 0 or later will be considered early if it occurs on day 30 or earlier, or if it occurs on or before the day of discharge from the index hospitalization.

7.9 Secondary endpoints (Cohorts A and B)

Secondary endpoints have been chosen for use in labeling claims. A formal hypothesis test formulation of each of these specific endpoints is given below.

Multiplicity analysis for these endpoints is based on Hochberg's method, as described in Section 7.22.6. The order of presentation below is irrelevant for the application of Hochberg's method, and is not intended to create the appearance of a hierarchy. Hochberg will be applied in the two cohorts independently. Thus the multiplicity adjustment will apply within a cohort.

It should be noted that the analyses described below are for the specific purpose of analyzing the endpoints for labeling in accordance with the Hochberg procedure. Other analyses to be performed, including other missing data imputations, are described elsewhere in this protocol.

The analyses fall into three groups:

- The first 5 analyses are non-inferiority analyses of measurement variables, comparing Test to Control, similar to the analyses used in cohort A of PARTNER I. The analyses are based on confidence intervals for differences of the values.

- There is one analysis of a binary endpoint – device success. This analysis is for cohort B only, since there is no appropriate control group for cohort A.

- There is 1 analysis involving improvement of 6MWT from baseline. Edwards believes that this additional analysis is important because a similar analysis is generally reported in the literature for other treatments. Edwards acknowledges that because of the multiplicity correction, the inclusion of the additional analyses may reduce the possibility of obtaining statistical significance in the other analyses.

The basic analyses are described in this section. Treatment of missing data and other sensitivity analyses are discussed in Section 7.22.8

1. Days alive and out of hospital (DAOH) to one year. This test will be performed in the ITT trial arms.

The formal hypotheses are

$$H_0: DAOH_{Test} - DAOH_{Control} \leq - \Delta.$$

$$H_1: DAOH_{Test} - DAOH_{Control} > - \Delta.$$

The comparison will use the two-sample t-statistic, as a one-sided test at alpha = 0.05. The non-inferiority margin Δ = 35 days. This endpoint was not part of the PARTNER I per protocol analysis, and the standard deviation is higher than one might have anticipated. The chosen non-inferiority margin will give reasonable power for passing this endpoint.

The definition of DAOH, and methods for its computation, are described in section 7.11.5; the treatment of incomplete data is discussed in that section. The general methodology for DAOH is that specified for continuous variables in Section 7.22.3.

2. NYHA at the one year visit. This test will be performed in the ITT trial arms.

The formal hypotheses are

$$H_0: NYHA_{Test} - NYHA_{Control} \geq \Delta.$$

$$H_1: NYHA_{Test} - NYHA_{Control} < \Delta.$$

The comparison will use the two-sample t-statistic, as a one-sided test at alpha = 0.05. The non-inferiority margin $\Delta = 0.25$, which is the same that was used for the analysis of NYHA in the approved PARTNER I Cohort A protocol.

The t-test has been chosen for the simplicity of explaining the non-inferiority result to reviewers and panelists. The validity of the t-test in this situation is discussed in section 7.22.3. The general methodology for NYHA is that specified for continuous variables in Section 7.22.3.

Summary statistics will also be presented giving the counts in the various NYHA classes.

The analysis will be based on actual data only. Sensitivity analyses are discussed in section 7.22.8.

3. 6MWT at the one year visit. This test will be performed in the ITT trial arms.

The formal hypotheses are

$$H_0: 6MWT_{Test} - 6MWT_{Control} \leq -\Delta.$$

$$H_1: 6MWT_{Test} - 6MWT_{Control} > -\Delta.$$

The comparison will use the two-sample t-statistic, as a one-sided test at alpha = 0.05. The non-inferiority margin $\Delta = 70$ meters, which is the same that was used for the analysis of the 6 minute walk test in the approved PARTNER I Cohort A protocol. In this analysis, as in all other analyses of the 6MWT, patients unable to perform the walk due to a medical reason will be considered to have walked an actual distance of zero.

The general methodology for 6MWT is that specified for continuous variables in Section 7.22.3.

The analysis will be based on actual data only. Sensitivity analyses are discussed in section 7.22.8.

4. Valve area at the one year visit.

The formal hypotheses are

$$H_0: EOA_{Test} - EOA_{Control} \leq - \Delta.$$

$$H_1: EOA_{Test} - EOA_{Control} > - \Delta.$$

The non-inferiority margin $\Delta = 0.2$ $cm^{2.}$ This value is approximately half the difference of the mean area reported at 1 year and the value 1.2, which is sometimes set as the lower bound for evaluation of device effectiveness.

The general methodology for EOA is that specified for continuous variables in Section 7.22.3.

The analysis will be based on actual data only. Sensitivity analyses are discussed in section 7.22.8.

5. Total aortic regurgitation at the one year visit. This test will be performed in the valve implant population.

The formal hypotheses are

$$H_0: AR_{Test} - AR_{Control} \geq \Delta.$$

$$H_1: AR_{Test} - AR_{Control} < \Delta.$$

The comparison will use the two-sample t-statistic, as a one-sided test at alpha = 0.05. The non-inferiority margin $\Delta = 0.25$, which is the same that was used for the analysis of NYHA above in this protocol.

In order to create a numeric variable for analysis, the AR values will be converted as follows: None = 0, Trace = 1, Mild = 2, Moderate = 3, and Severe = 4. The t-test has been chosen for the simplicity of explaining the non-inferiority result to reviewers and panelists. The validity of the t-test in this situation is based on the same argument as for NYHA.

The analysis will be based on actual data only. Sensitivity analyses are discussed in section 7.22.8.

In addition to this analysis based on a numeric variable, counts for the various regurgitation classes will be presented.

The particular coding scheme and a discussion of its applicability are given in section 7.22.3 of this protocol,

6. Device success. This test will be performed in the As Treated population.

This analysis will be performed for cohort B only. (Although the device success itself will be computed for cohort A patients, there is no available control group in the Partner II trial.)

Each patient will be classified as a success or failure, according to the device success definition in section 8.0. For purpose of this particular endpoint analysis, a missing value of device success will be considered a failure.

The analysis will be based on the ratio of proportions, as a non-inferiority analysis. Let r_T denote the true failure proportion in the Test arm, and r_C denote the true failure proportion in the Control arm. The hypotheses are

$$H_0: \ r_T / r_C \ \geq \ 1 + \Delta$$

$$H_A: \ r_T / r_C \ < \ 1 + \Delta$$

The value Δ is the non-inferiority margin, and is taken to be 0.35. The test will be performed as a one-sided test at alpha = 0.05. Confidence limits for the ratio of proportions will use the default methodology of SAS® PROC FREQ.

7. 6MWT improvement from baseline to one year. This test will be performed in the As Treated Test arm.

$$H_0: 6MWT_{Baseline} = 6MWT_{1\text{-year.}}$$

$$H_1: 6MWT_{Baseline} \neq 6MWT_{1\text{-year.}}$$

The improvement for each patient will be computed as a signed number. The test will then be evaluated by the paired sample t- test, as a two sided test at alpha = 0.05.

The analysis will be based on actual data only. In this analysis, as in all other analyses of the 6MWT, patients unable to perform the walk due to a medical reason will be considered to have walked an actual distance of zero.

An alternative methodology is described in Section 7.22.8. The general methodology for 6MWT is that specified for continuous variables in Section 7.22.3.

7.10 Additional Secondary endpoints (Cohorts A and B)

The following events will be analyzed according to the analysis prescribed for adverse events. This analysis will be presented in the As Treated population.

- Freedom from major vascular complications
- Freedom from all neurological events (all stroke and TIA)
- Freedom from myocardial infarction
- Freedom from acute kidney injury (VARC)
- Freedom from access site infections
- Freedom from new permanent pacemaker
- Freedom from transfusion.
- Freedom from atrial fibrillation at each visit.

Atrial fibrillation is evaluated by the ECG core lab, based on data collected at scheduled visits. Evaluation will be based on pure percentages at each visit, without regard to the specific date of the ECG. The following percentages will be evaluated:

- Patients with atrial fibrillation at that visit.
- Patients with atrial fibrillation at that visit, who did not have atrial fibrillation reported at the baseline visit.
- Patients with a previously unreported atrial fibrillation at that visit. For the purpose of evaluating previously unreported events, the unscheduled visits will also be considered. The exact ECG dates will be used in this computation.
- If any patients have received ablation to treat atrial fibrillation, the analyses will be stratified accordingly.

7.11 Additional effectiveness endpoints (Cohorts A and B)

The descriptions in this section deliberately have some overlap with Section 7.9. The descriptions in 7.9 will be used in analyzing the secondary endpoints for labeling purposes.

1. Total days alive and out of hospital (from date of index procedure).

Total days alive and out of hospital post index procedure will be compared between trial arms in both cohorts. The Wilcoxon rank-sum test will be used to compare the trial arms in both the ITT and the AT analysis populations.

2. Functional improvement as measured by NYHA at 30 days and later scheduled visits.

   NYHA will be treated as a continuous variable and the paired sample t-test will be used to compare baseline and follow-up values. This analysis will be presented separately for each scheduled visit, and again by a repeated measures analysis. This improvement analysis will be presented separately by trial arm. Only actual data will be used in this analysis. Counts will be presented for NYHA classes at each visit, stratified by cohort and approach. This analysis will be presented in the ITT population, and again in the As Treated population.

3. Clinical improvement as measured by QOL at 30-days and later scheduled follow-up visits.

   The following instruments will be presented: KCCQ, EQ5D, and SF12 (Cohort B) and SF36 (Cohort A). The paired sample t-test will be used to compare baseline and follow-up values; each of the QOL measures will be used. This analysis will be presented separately for each scheduled visit, and again by a repeated measures analysis. This improvement analysis will be presented separately by trial arm. Only actual data will be used in this analysis. This analysis will be presented in the ITT population, and again in the As Treated population.

4. Functional improvement as measured by Six Minute Walk at 30-days, 1 year and 2 year follow-up visits. The paired sample t-test will be used to compare baseline and follow-up values. This analysis will be presented separately for each scheduled visit, and again by a repeated measures analysis. This analysis will be presented separately by trial arm. Only actual data will be used in this analysis. In this analysis, as in all other analyses of the six minute walk test (6MWT), patients unable to perform the walk due to a medical reason will be considered to have walked an actual distance of zero.

   Another analysis of improvement will be a responder analysis, in which each patient is considered to have improved or not. For each patient the six minute walk distance will be compared against baseline at the specified follow-up times. Based on text in the official statement of the American Thoracic Society [113], an improvement of 70 meters will be taken to be clinically significant. Thus, for the purposes of the six minute walk test (6MWT) responder analysis, patients that improve by more than 70 meters will be considered responsive. The proportion of patients who achieve clinical improvement (i.e. improvement of 70 meters) at each time point will be

computed and reported for each cohort and each trial arm. Patients that expire prior to the given follow-up time will be considered as not improved (i.e. they will be included in the denominator when computing the proportion of patients that achieve clinical improvement). Patients that are unable to perform the 6MWT for medical reasons will be considered as not improved. Patients with missing 6MWT for reasons other than death and inability to perform the test will be excluded from the analysis.

This analysis will be presented in the ITT population, and again in the As Treated population.

5. Mean ICU and total index procedure hospital length of stay. Length of index hospital stay and ICU days will be compared between ITT trial arms in both cohorts. It is anticipated that this variable will be heavily right skewed, and the Wilcoxon rank sum test will be used.

6. Days Alive and Out of Hospital (DAOH)

The DAOH variable is used in preference to days in hospital in order to account for potential differences in survival.

In order to avoid calculations with fractional days, the following method will be used.

- The time for which the patient is dead will include the death date and all days thereafter
- Each day that the patient is alive will be classified as a day in hospital or not; days of admission and discharge are counted as days in hospital.
- The maximum potential value of DAOH will be an integer, even though one year is set to 365.25 days for some other analyses in this protocol.
- The DAOH will be the number of days for which the patient is not dead or in hospital.

In the endpoint discussed in section 7.9.1 of this protocol the maximum potential value of DAOH for each patient will be 366 days. The DAOH would have this maximum value if the patient had never been hospitalized, and was known to be alive at the 1 year time point. It is realistic to assume that a few patients will be censored prior to the 1 year time point, due to withdrawal or lost to follow-up. To account for the reduced potential time the following correction will be made

- The DAOH will be computed as above, and the maximum potential DAOH will be calculated for each patient involved.

- The computed DAOH will be multiplied by the appropriate factor (366/maximum potential DAOH for this patient.)
- The resulting value will be rounded to the nearest integer. This rounded value will be used in all calculations.

In effect, this methodology computes the percent DAOH for each patient. The method used here has been chosen for ease of interpretation.

7.12 Additional Trial Arm Valve Performance (Cohorts A and B)

The descriptions in this section deliberately have some overlap with Section 7.3.3. The descriptions in 7.3.3 will be used in analyzing the secondary endpoints for labeling purposes.

1. Freedom from major aortic paravalvular leak

For each scheduled analysis, a patient will be considered a success if there is no paravalvular leak. The analysis will compare the trial arms and will present the p-value from Fisher's exact test, and confidence intervals for the difference and ratio of success rates. These analyses will be presented in the valve implant population; data after valve explants will not be included. No imputation will be made for missing data.

2. Valve performance measured by effective orifice area (EOA) and other echo variables at scheduled echo times.

For each patient the follow-up EOA will be compared against the preoperative EOA. For this purpose the paired sample t-test will be used.

EOA Responder Analysis 1:

- A patient will be considered a success if the increase from baseline is 50% or greater.
- A patient will be considered a failure if both the baseline and follow-up EOA are evaluable, and the success criterion is not met,

EOA Responder Analysis 2:

- A patient will be considered a success if the increase from baseline is 100% or greater, or if the follow-up EOA is > 1.5cm^2.
- A patient will be considered a failure if both the baseline and follow-up EOA are evaluable, and the success criterion is not met

EOA Responder Analysis 3:

- A patient will be considered a success if the follow-up EOA is > 1.25cm^2.
- A patient will be considered a failure if the follow-up EOA is evaluable, and the success criterion is not met

3. Valve performance measured by gradient and other echo variables at scheduled echo times.

Mean Gradient Responder Analysis:

- A patient will be considered a success if the decrease from baseline is 50% or greater.
- A patient will be considered a failure if both the baseline and follow-up mean gradient are evaluable, and the success criterion is not met,

Peak Gradient Responder Analysis:

- A patient will be considered a success if the decrease from baseline is 50% or greater.
- A patient will be considered a failure if both the baseline and follow-up peak gradient are evaluable, and the success criterion is not met,

Regurgitation Responder Analysis:

- A patient will be considered a success if the follow-up total aortic regurgitation is None, Trace or Mild.
- A patient will be considered a failure if the follow-up total aortic regurgitation is evaluable, and the success criterion is not met

Each of the above responder analyses will be presented for each visit with a scheduled echo, based only on data from that visit. The analyses will also be presented based on the first available echo with the corresponding echo variable evaluable.

The analyses will compare the trial arms. The analyses will present the p-value from Fisher's exact test, and confidence intervals for the difference and ratio of success rates. These analyses will be presented in the valve implant population; data after valve explants will not be included. No imputation will be made for missing data.

Additional regurgitation analysis: As an additional analysis, regurgitation will be analyzed as an ordinal categorical variable. The trial arms will be compared

using the Jonckheere-Terpstra test. The p-value from a chi-squared test will also be presented.

4. Freedom from structural heart deterioration

Freedom from structural heart deterioration will be analyzed via Kaplan-Meier methods. Test and Control will be compared.

Evidence of prosthetic valve dysfunction, at scheduled echo times: Aortic regurgitation at the various scheduled echo times will be presented in summary tables, showing each level separately. Summarized values will be presented for AR < 2+ and AR $\geq$ 2+. This analysis will be presented in the valve implant population; data after valve explants will not be included. Hemolysis, infection, thrombosis, and migration will be analyzed according to the analysis prescribed for adverse events.

7.13 Safety Variables

Adverse event analyses will be performed in the As Treated population. Events occurring after the analysis close date will not be included.

Adverse events to be analyzed include:

- The specific adverse events gathered on the CRFs.
- Any composite safety endpoints defined in this protocol or requested by the FDA, and all components thereof.
- Any additional events defined in Section 8.0.
- Death, cardiovascular death, non-cardiovascular death, unknown death, death related to the index procedure, death related to the device, death related to the valve.

Where AE's are adjudicated by the CEC, separate analyses will be presented for CEC adjudications and site evaluations. Where the CEC classifies events as major/minor two analyses will be given: one for major events only and one for all events.

Similarly, any composite analyses will be performed using just major events, and again using all events.

The CEC events with major/minor classifications include stroke, bleed, and vascular events. If there are others they will be treated as in the previous two paragraphs.

Specific analyses are:

- Intra-procedural adverse events will be analyzed as a proportion of patients experiencing the event. Test and Control will be compared.
- Perioperative adverse events will be analyzed as a proportion of patients experiencing the event. Test and Control will be compared. For the purpose of this analysis, the perioperative events will be defined as those occurring on days 0-30, or prior to discharge, whichever is later.
- As an additional data presentation, the count of events occurring on day 0-30 will be given. Each event will occur in either this count, or the count of late adverse events as described below.
- Late adverse events (> 30 days) will be analyzed by a constant hazard model, and upper one-sided confidence limits will be given for the rates. Test and Control will be compared.
- The time to first adverse event will be analyzed as a time dependent variable. Test and Control will be compared by the log-rank test. This analysis will be performed for each event type.
- Kaplan-Meier analyses will be presented for re-hospitalization-free survival, stroke-free survival and MI-free survival. Test and Control will be compared.

7.14 Additional Analyses

7.14.1 Blood Laboratory Data

Blood laboratory data will be reported by summary statistics by Cohort and treatment arm. No formal analyses will be performed of laboratory data as such. However, laboratory data will enter into the definition of certain adverse events, and those events will be analyzed as described above.

7.14.2 ECG data

ECG data will be reported by summary statistics by Cohort and treatment arm. No formal analyses will be performed of ECG data as such. However, ECG data will enter into the definition of certain adverse events, and those events will be analyzed as described above.

7.14.3 Baseline data

Baseline data will be reported by summary statistics, by Cohort with comparisons between trial arms; the comparisons will be performed overall, and additionally stratified by cohort and implant approach.

7.14.4 Chest X-ray

Chest X-ray data will be reported by summary statistics by Cohort and treatment arm. No formal analyses will be performed of Chest X-ray data as such. However, Chest X-ray data will enter into the definition of certain adverse events, and those events will be analyzed as described above.

7.14.5 Procedural variables

The various procedural variables will be presented as summary statistics by Cohort; Test and Control will be compared.

7.15 Follow-up compliance

Summary statistics will be presented to show the compliance with various requirements of the scheduled follow-up visits by Cohort and treatment arm.

For purposes of trial administration, a visit quality score will be assigned for each visit, according to the algorithm described below. Sites with poor results on the score may be told to slow down or even stop enrollment, pending improvement on the score.

Visit compliance will be evaluated on a 10 point scale. The purpose is to encourage sites to gather all information, while at the same time encouraging collection of partial information if a complete in-window follow-up evaluation is not possible.

Table 15.0-1

Item	Value
Survival information. (2 points)	
Visit date	1 point
Patient status indicating patient alive	1 point
NYHA value present	1 point
Echo performed	2 point
QOL completed.	1 point
NIHSS	2 points
6 minute walk test completed, or medical reason given for test not performed. If completed, the distance must be entered on the walk test form.	2 points
Total	10 points

Notes:

For each visit, the visit quality score will be computed beginning with the first data extract later than the end of the visit window.

If the visit is out of window the total score will be multiplied by 50%.

As a realistic matter, a telephone or letter visit cannot achieve a full 10 points.

If the study exit form shows a patient death prior to the expiration of the visit window, the visit will not be included in the visit quality score computation.

A score of zero will be assigned for an overdue or missed follow-up visit. When data are entered for an overdue visit, the score will be recomputed based on the visit information.

If the study exit form is completed showing patient withdrawal or formally declared lost to follow-up, then a score of zero will be assigned for the first follow-up visit following the study exit. Subsequent visits will not be included in the visit quality score computation.

7.16 Covariate analyses

Potentially relevant baseline and operative variables will be included in covariate models in an attempt to determine predictors of adverse events, including mortality. The specific adverse events to be considered are those evaluated by the CEC; where events are classified as major or minor, the major events will be analyzed. These analyses will be performed separately by trial arm.

It is noted that baseline atrial fibrillation has been added as a covariate to all adhoc model-based comparisons of TAVR to “control” for both Cohorts. The presence of baseline atrial fibrillation is formally evaluated with respect to the primary endpoint of Cohort A because baseline atrial fibrillation is a stratifying characteristic in the Cohort A randomization scheme. There is no planned formal atrial fibrillation assessment with respect to the primary endpoint of Cohort B because the Cohort B randomization schema did not include atrial fibrillation as a stratifying characteristic.

Potentially relevant baseline and operative variables will be included in covariate models in an attempt to determine predictors of adverse events, including mortality. The specific adverse events to be considered are those evaluated by the CEC; where events are classified as major or minor, the major events will be analyzed. These analyses will be performed separately by trial arm. Per FDA request, ‘GENDER’ as a main effect and ‘GENDER*TREAT’ as an interaction effect will be included as a predictor variable in covariate models for the primary efficacy and safety endpoint and also the secondary labeling endpoints listed in Section 7.3.1 of both SAPs. Additionally, ‘GENDER’ and ‘GENDER*TREAT’ will be entered into covariate models for the composite endpoints described in Sections 7.7 and 7.8 of the main Protocol. The analyses described in these Sections of the main Protocol are also presented in Section 7.3.2 of each SAP. If

statistically significant differences between males and females are found as a result of these FDA-requested covariate analyses, further exploration of additional covariates will be performed to determine if the effect of 'GENDER' on model outcomes may be explained.

- Perioperative adverse events will be analyzed by logistic regression for freedom from event, and by negative binomial regression where analysis of multiple events is reasonable.

- Late adverse events will be analyzed by regression based on a constant hazard model. The time clock starts after each event, allowing for consideration of multiple events and time after the last event. This analysis will use the methodology of SAS PROC LIFEREG.

- Where the constant hazard analysis does not seem appropriate, adverse events will also be analyzed by proportional hazards regression. This includes both the late analyses, and analyses over the entire time period.

- An additional analysis will attempt to find predictors of device success.

- Univariate analyses will keep missing predictors as missing, rather than imputing values.

- Final models will be developed using stepwise techniques. In order to prevent unnecessary loss of data, missing predictor variables will be imputed to the mean of the values in the cohort and approach to which each patient is assigned.

- ROC curves will be presented for prediction of 30-day mortality in the trial arms separately arm, using STS score, logistic EuroSCORE, and the frailty index as predictors. None of these instruments has been validated in a transcatheter valve implant population; the purpose of the analysis is to determine if any are a reasonable predictor, and which is better if relevant. Statistical significance of the ROC area, and comparison of the ROC curves, will be tested using the procedures available in SAS PROC LOGISTIC.

Covariate models for 30-day mortality will be developed using just trial covariates, and trial covariates in conjunction with the STS and EuroSCORE. Because of the construction of the EuroSCORE, the logit of the EuroSCORE will be used in such models.

Since the purpose of the covariate analyses is to build meaningful models, rather than to evaluate trial endpoints, the specification of predictor variables and stepwise techniques has appropriately been left informal.

7.17 Center comparisons

Baseline and outcome variables will be presented stratified by clinical site, with formal site comparisons appropriate for each variable type.

The primary endpoint will be reanalyzed using a model that contains a center effect. This model will produce confidence limits for the ratio of the event rates between Test and Control.

7.18 Additional composite endpoints

As an additional analysis two composite endpoints in the draft VARC document will be analyzed. These are the composite 30-day safety and composite 1-year effectiveness endpoints described in Section 8.0.

These analyses are for information only, as part of establishing a baseline for potential use of the VARC definitions in future studies.

The VARC document describes the endpoints as hierarchical, without specifying how the hierarchy will be created or analyzed. The analysis described below will meet the suggested hierarchy.

The components of the composite event are listed in the hierarchical order in Section 8.0. The safety endpoint has 6 components. A score for each patient will be created in the following manner.

- Each component is deemed to have occurred or not for that patient; multiple events do not matter.
- A score of 1 will be assigned for component 6 (repeat procedure) if the event occurred for that patient. A score of 2 will be assigned for component 5, a score of 4 for component 4, a score of 8 for component 3, a score of 16 for component 2, and a score of 32 for component 1.
- The score for the patient will be the sum of the scores for the components. Because the individual scores are powers of 2, no combination of lower events in the hierarchy can outweigh a higher event.
- The other components cannot be observed after death. No imputation will be made for the potential of other events occurring after death; because of the hierarchy this censorship will not meaningfully impact the analysis.
- No imputations will be made for patients with less than one year data for reasons other than death. The analysis will be presented on the basis of the available data only, and again with the partial data patients excluded from analysis.

The trial groups will be compared within each Cohort using the Wilcoxon rank-sum test. Because this test is non-parametric, any other score respecting the hierarchy would yield the same results.

A score for the composite effectiveness endpoint will be constructed in the same manner, except that there are only 3 components. Summary statistics will be presented.

The VARC may define additional composites prior to the analysis date of this trial. Those composite endpoints will be evaluated for scientific purposes only, and will not be included in regulatory submissions unless specifically requested by the FDA.

7.19 Additional improvement endpoints

Where the above analyses specify analysis of improvement from baseline in the Test arm, the analogous analysis will be performed in the Control arm. These analyses will be additional analyses for the benefit of the reviewers, and they are not included in the list of secondary endpoints for labeling.

7.20 Additional analysis for crossover patients

This protocol contains no provision for crossover between trial arms. If a patient does not receive the valve to which he was randomized, the change is reflected in the As Treated trial arm assignment.

7.21 Additional analysis for withdrawn patients

When patients have withdrawn, they are censored for analysis on the withdrawal date. To the extent allowed by individual IRBs, Edwards will attempt to use registries for determination of death dates.

If any such dates can be determined, additional analyses of the primary safety and effectiveness endpoint and all cause mortality will be performed using such data. The analysis will be performed at sites where the IRB is in agreement. Death dates will be taken from registries. Where no death information is found in a registry, patients will be assumed to have been alive 6 months prior to the date on which the registries are queried; this difference is intended to allow for lag in entering registry information.

7.22 General Statistical Methodology

7.22.1 Time-Dependent Variables

Time-dependent variables will be analyzed using the Kaplan-Meier algorithm, with standard errors computed by Greenwood's formula. Kaplan-Meier graphs will be presented for each trial arm and for other patient groups as appropriate. The number of patients-at-risk will be computed at exact time points, without reference to any nominal follow-up windows. These time-dependent variables include such analyses as time to death and time to various adverse events.

Time-dependent variables also include stroke-free survival, and any other event free survival analyses. In such analyses a patient will be considered to have an event at the first occurrence of death or the event(s) in the composite; patients who are event free will be censored.

The log-rank statistic will be used for any comparison among groups. Confidence limits for Kaplan-Meier estimates will be based on the Greenwood standard error.

It is Edwards's experience that some reviewers prefer to have log-rank comparisons accompanied by hazard ratios. Accordingly, whenever the log-rank test is presented for a group comparison, the hazard ratio and hazard ratio confidence limits will also be presented. This ratio will be computed by the proportional hazards algorithm, and will be presented whether or not it appears that the proportional hazards assumption is warranted.

Covariate analyses will be based on the proportional hazards model. Groups will be compared using the Cox proportional hazards algorithm. The hazard ratio and hazard ratio confidence limits will be presented.

Where appropriate, time-dependent variables will be analyzed using a constant hazard model. The numerator for rate estimates will be the total number of events (as distinguished from the number of patients with events), and the denominator will be the total follow-up time. Confidence limits will be computed using Cox's approximate chi-squared statistic, as recommended by Grunkemeier G, A.W., and Anderson W. [114]. Groups will be compared using Cox's approximate F-test.

Patients who have not experienced the event being analyzed will be censored as of the last date at which they are known to be free of the event. Generally this will be the last follow-up date, the date of some other event, or the death date.

Patients will also be censored at the time of withdrawal from the trial, even if later information is known to the trial sponsor.

Some time-dependent variables may be inherently interval censored; an example would be a yes/no variable that can be determined only at the time of x-ray

examinations. Such variables will be analyzed in two ways. Both of these methods are available in SAS PROC LIFEREG.

- Graphical displays of a single group will be presented using the non-parametric estimates produced by Turnbull's algorithm.
- Groups will be compared using a Weibull model.

7.22.2 Censoring in the primary safety and effectiveness endpoint

The primary safety and effectiveness analysis will be based on the ratio of proportions, for a combination of time dependent events in the first year. If all patients have complete endpoint data, the confidence limits for the ratio of proportions will be taken from the output of SAS® PROC FREQ, using the RELRISK option.

It is realistically likely that there will be some patients censored prior to endpoint, due to withdrawal or lost to follow-up, and that those patients will be event free on the censoring date. It would not be statistically valid to assume that the patients remained event free for the year; it would be equally invalid to assume that such patients experienced an event. If there are any such patients, the analysis will be modified in the following manner.

The event proportions r_T and r_C will be computed using the Kaplan-Meier algorithm. The standard errors s_T and s_C will be computed using Greenwood's formula. It is easy to verify that in the absence of censoring these are the same risks and standard errors produced by SAS PROC FREQ.

The ratio will be analyzed using a logarithmic transformation. The standard error of log(r) is s/r. Then log (r_T/ r_C) = log(r_T) – log(r_C), with standard error sqrt[(s_T/ r_T)2 + (s_C/ r_C)2]. From these formulas the confidence interval for the logarithm of the ratio can be computed, and then transformed back to produce confidence limits for the ratio itself.

It is easy to verify that in the absence of censoring the resulting confidence limits for the ratio are the same values produced by SAS PROC FREQ; this is not surprising, since PROC FREQ uses the logarithmic transformation to produce confidence limits for a ratio.

The formula for the standard error of the log transformation is discussed in the documentation for SAS PROC LIFETEST; it is also a straightforward derivation using the delta method.

7.22.3 Continuous and Ordinal Variables

For continuous variables, summary statistics will include means, standard deviations, medians and quartiles. Confidence limits will be computed using the t-distribution. Groups will be compared using t-tests or analysis of variance, with multiple comparisons performed using Scheffé's method. Where severe departures from normality are anticipated or observed, comparisons will also be performed using the Wilcoxon rank-sum test.

Except where otherwise specified, NYHA will be treated as a continuous variable in analyses, primarily because this method is the most common in cardiovascular literature. The validity of treating NYHA in this manner is demonstrated by Heeren and D'Agostino, [115] We note that the reference showed the validity of the t-test in samples as small as 20; in this trial it is anticipated that there will be at least 400 one-year NYHA values. The same reasoning applies to treatment of aortic and mitral regurgitation.

Note on the coding of regurgitation. The echo core lab evaluates regurgitation using 5 levels. The ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease only discussed 3 levels. In order to obtain the full value of the core lab evaluation, a 5 level coding scheme is needed. The one chosen is the simplest.

For both NYHA and regurgitation, it should also be noted that any non-parametric analysis based on the ordinal nature of the variables would implicitly use a coding scheme with integer levels, whether or not the coding scheme was made explicit.

Summary statistics for NYHA and regurgitation will also include counts for each class.

For ordinal variables, summary statistics will include medians and quartiles; means will also be presented when appropriate. Except where otherwise specified, group comparisons will be performed using the Wilcoxon rank-sum test.

7.22.4 Categorical Variables

For categorical variables, summary statistics will include counts and percentages. Confidence limits for binary variables will be computed using the exact binomial distribution.

Categorical variables will be compared by Fisher's exact test.

Stratified comparisons of categorical variables will be performed using the appropriate Mantel-Haenszel statistics.

These summary statistics by groups will be presented for NYHA, even though its analysis is by the t-test.

7.22.5 Count Variables

Some analyses (e.g. the number of adverse events in a fixed time period) will produce counts that can in principle range from 0 to an arbitrarily large number. It is anticipated that such counts will be more dispersed than allowed for in a Poisson model; accordingly the negative binomial model will be used for such analyses [116].

7.22.6 Multiplicity Adjustment

Formal multiplicity adjustment will apply to the specific list of secondary endpoints described in Section 7.9. These adjustments will be performed by the method of Hochberg, as described below.

In all other analyses, p-values will be presented as computed; reviewers and other readers can interpret the p-values as desired. In particular, the protocol contains a large number of secondary endpoints; safety endpoints, and additional analyses. The trial sponsor acknowledges that all of these analyses may be considered by reviewing agencies as part of the product approval evaluation.

Hochberg's method is described in the online documentation furnished with SAS, version 9 [117]. The rationale for using Hochberg's method is that the secondary endpoints are expected to all work in the same direction. Schulz and Grimes [118] give examples where use of other methods would lead to scientifically invalid conclusions in such a situation; Hochberg's method avoids most of these anomalies. This methodology was used in the MIRACLE trial [119], and is described in the FDA approved labeling for the InSync® ICD [FDA approved labeling for InSync ICD. [120]. The method was also used in the PARTNER I trial.

In order to describe the specific methodology of the Hochberg method, suppose that there are n endpoints being considered.

- If all the endpoints meet statistical significance at the 0.05 level, than all are considered to have passed the multiple comparisons test. The steps described below would not be taken.
- Otherwise
    - The endpoint with the highest p-value is removed from consideration.

- If all the remaining n – 1 endpoints meet statistical significance at the more strict level of 0.05/2 level, then all these n – 1 endpoints are considered to have passed the multiple comparisons test.

- Otherwise
  - The endpoint with the highest p-value is removed from consideration
  - The evaluation is repeated as above, now using 0.05/3.

- If necessary the process repeats. The very last endpoint would be evaluated at the significance level 0.05/n.

7.22.7 Exact Tests

Fisher's exact test has been specified for comparison of categorical variables. In presentations of the Wilcoxon rank sum test, the p-value will be the t-approximation produced by SAS PROC NPAR1WAY. Results of the exact test will be presented for all secondary endpoint analyses where the p-value produced by the t-approximation is in the range (0.04 – 0.06); in such cases the exact p-value will be used in preference to the t-approximation. In presentations of the Wilcoxon signed-rank test, the exact p-value will be used whenever it is directly produced by SAS. The Monte Carlo version of exact tests will be used when computationally necessary. A fixed seed will be used for all such tests. It is anticipated that the Monte Carlo methodology will be used for any center comparisons; it may also be necessary for trial arm comparisons.

7.22.8 Missing Data Imputation

Missing variables will not be imputed for planned analyses, except as specified in this section or elsewhere in the protocol.

For all analyses involving data collected in follow-up windows, the following additional analysis will be presented. Where an in-window value is not available, the earliest value obtained after the window will be used, if any such values are available. Values obtained before the window will not be used in this analysis, and dead patients will be treated as in the primary analysis.

Specific imputations for the secondary endpoints listed in Section 7.9 are described below. The primary analyses of all these endpoints are based on actual data only; these imputations are purely for sensitivity purposes. Edwards acknowledges that the FDA may change its judgment of the endpoints as a result of these sensitivity analyses; in particular the FDA may use imputation 3 described for the 6-minute walk test.

Additional sensitivity analyses will include tipping point analysis and multiple imputation. Details will be provided in the SAP.

Imputations also include best case and worst case analyses. In the worst case analysis, the value for Test patients is imputed to be the worst value consistent with observed data, and the value for Control patients is imputed to be the best value consistent with observed data. In the base case analysis the value for Test patients is imputed to be the best value consistent with observed data, and the value for Control patients is imputed to be the worst value consistent with observed data. Specifics are given for each of the endpoints. The sponsor does not accept that these best and worst case analyses have any validity, but acknowledges that the FDA has requested such analyses. These analyses are for PMA submission purposes only, and will not be performed for any scientific publications resulting from the trial.

DAOH

Best and worst case analysis: For a patient censored prior to 1 year, the best value for the missing days will be to assume that the patient is alive and out of hospital; the worst value will be to assume that the patient is in hospital.

NYHA

Patients who have died before the visit will be imputed to have NYHA 5.

Best and worst case analysis: For a missing value for reasons other than death, the best value will be to impute NYHA = 1 and the worst value will be to impute NYHA = 4.

Six-Minute Walk Test

For all analyses of the 6 Minute Walk Test, it is specified above that a patient who is medically unable to perform the test will be considered to have walked an actual distance of zero. An alternative methodology is the following: the 12.5 percentile of actually observed walk distances will be computed, separately by trial arm and visit. For follow-up visits only the in-window values will be included in this computation. (We note that it is possible that a few completed tests will report a distance of 0.)

Patients who have died before the visit will be imputed to have walked a distance equal to the percentile described above. This imputation is for purposes of the endpoints described in section 7.3.3, and will not be used in other analyses of the 6-minute walk test.

As an additional sensitivity analysis for 6MWT, all analyses will be repeated with patients unable to walk for medical reasons imputed to have a value equal to the percentile described above. This imputation will be used in all analyses of the 6-minute walk test.

Best and worst case analysis:

For a missing value for reasons other than death or medical reason for not performing the test, the best value will be to impute the longest distance actually observed for that trial arm and visit, and the worst case will be to impute a distance of zero.

Valve Area:

Best and worst case analysis:

For a missing value for reasons other than death, the best value will be to impute the largest area actually observed for that trial arm and visit, and the worst case will be to impute the smallest area actually observed for that trial arm and visit.

Aortic Regurgitation:

Best and worst case analysis:

For a missing value for reasons other than death, the best value will be to impute the lowest regurgitation actually observed for that trial arm and visit, and the worst case will be to impute the highest regurgitation actually observed for that trial arm and visit. (Presumably the lowest regurgitation will be None, and the highest will be either Moderate or Severe; the actual data will determine the imputation.)

Device success:

The definition of device success specifies the value for all patients, and no further imputation is needed.

For both NYHA and 6 minute walk test, the trial arm comparison will be re-evaluated using a linear model containing the baseline value and the change from baseline.

Edwards is willing to perform all other imputations requested by the FDA.

7.23 Periodic Analyses

Periodic analyses will be performed during the trial as required by the appropriate regulatory authorities and the DSMB. The sample size and endpoint time for this trial is fixed in advance, and not based on these periodic analyses. Accordingly, there is no adjustment to alpha.

7.24 Data from Other Trials

Endpoint analyses for this trial will be based on trial data only, without any attempt to incorporate data from other sources.

As additional analyses, the various endpoint variables in this protocol will be analyzed by comparing against the cohort B Test arm of the PARTNER I trial. No meaningful differences are anticipated, and the confidence intervals will be of more interest than the p-values.

To the extent required by regulatory authorities, data from other sources will be presented in the reference section. Unless otherwise requested, no attempt will be made to pool the various data from other sources, or to perform a formal meta-analysis.

7.25 Miscellaneous

Unless otherwise specified, confidence limits and hypotheses tests will be two sided, using α = 0.05.

Unless otherwise specified, the Wald p-values will be presented where available. This statement is not relevant for exact tests.

Unless otherwise specified, the precise form of each algorithm will be the default of SAS®, using the latest release generally available at the time of analysis. This will be version 9.1.3 or later. The purpose of this statement is to specify the algorithms; some or all of the actual analysis may be performed using other software packages.

Graphs will generally be created in SAS/GRAPH. Other graphics packages may be used.

7.26 Analysis for Registries (NR1, NR2, NR3, NR4, NR 5 and NR 6)

These six registries are for inoperable patients. There are no directly comparable controls for any of the registries. Certain analyses will be presented side by side with data from other cohorts or trials. These will be referred to below as informal comparisons; no p-values will be presented for any of the informal comparisons.

The following analyses will be performed for all six registries, using the methodology already described in this protocol for cohort B patients. The only p-values presented will be those for improvement from baseline.

- All cause mortality at 1 year.
- Six minute walk test improvement from baseline, and NYHA improvement from baseline.
- All adverse event analyses, both single event and composite.
- Device success.
- Procedural analyses.
- NYHA, walk, and echo analyses related to specific visits.
- Neurological analyses as appropriate.
- Hospital time.
- Follow-up compliance.

Because of the small sample size, covariate analyses will not be presented for the registries.

NR 1: Inoperable Transapical Registry. Informal comparisons will be the transapical patients from Partner I cohort A, including randomized Test, randomized Control, and non-randomized continued access.

NR2: Inoperable Registry for Transfemoral delivery of SAPIEN XT™ in 6-7mm transfemoral arteries. Informal comparisons will be the randomized Test and Control patients from Partner II Cohort B.

NR3: Registry for Transcatheter Heart Valve in Aortic Surgical Valve Implantation (THV-SV) Registry. Informal comparisons will be the transfemoral patients from Partner I cohort B, including randomized Test, randomized Control, and non-randomized continued access. Additional informal comparison will be the randomized Test and Control patients from Partner II Cohort B. If there are any transapical patients in this registry, the informal comparison will use Partner I Cohort A transapical Test and non-randomized continued access patients. An additional analysis for this registry will be to stratify results by the previous bioprosthetic valve model; this stratification will be restricted to cases where there are at least 5 implants for a given previous bioprosthetic valve model.

NR 4: Inoperable Transaortic Registry. Informal comparisons will be the transapical patients from Partner I cohort A, including randomized Test, randomized Control, and non-randomized continued access.

NR 5: Inoperable Transfemoral Registry for the delivery of 29 mm SAPIEN XT™ in $\geq$ 7mm femoral arteries. Informal comparisons will be the randomized Test and Control patients from Partner II Cohort B.

NR 6: Inoperable Transapical Registry for the delivery of 29 mm SAPIEN XT™ for Cohort B that do not have eligible transfemoral access. Informal comparisons will be the transapical patients from Partner I cohort A, including randomized Test, randomized Control, and non-randomized continued access.

8.0 Definitions

Term	Definition	Reference/ Justification
Adverse Event (AE)	An adverse event is any "untoward medical occurrence in a study patient" which does not necessarily have to have a causal relationship with a study device or treatment. An AE can therefore be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, temporary or permanent, whether or not related to the study valve implantation or BAV procedure. AE/SAE reporting is Investigator's Responsibility. All SAEs should be immediately reported to the sponsor and followed by supporting source documents related to the event.	ISO 14155-1:2009 GCP
Serious Adverse Event (SAE)	Adverse Event that: a) led to a death, b) led to a serious deterioration in the health of a study patient that • resulted in a life-threatening illness or injury, • resulted in permanent impairment of a body structure or body function, • required inpatient hospitalization or prolongation of existing hospitalization, • resulted in a medical or surgical intervention to prevent permanent impairment to body structure or a body function. Important medical events not resulting in the above should be assessed as an SAE. Any major or clinically significant adverse event occurring during and after the study valve implantation or BAV procedure: Death; life-threatening adverse event; in-patient hospitalization or prolongation of existing hospitalization; persistent or significant disability/incapacity; medically significant event (includes laboratory abnormalities). The following is not considered an SAE: Hospitalization for diagnostic or elective surgical procedures, planned at or before the enrollment for a pre-existing condition.	ISO 14155-1:2009 FDA (21 CFR 312.32 (a)
Adverse Device Effect (ADE)	Any untoward or unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device or any event that is a result of user error.	ISO 14155-1:2009

Term	Definition	Reference/ Justification
Serious Adverse Device Effect (SADE)	Adverse Device Effect that resulted in any of the consequences characteristics of a Serious Adverse Event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.	ISO 14155-1:2009
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
Access Site	Access site defined as any location (arterial or venous) traversed by a guide-wire, a catheter or a sheath (including the left ventricular (LV) apex and the aorta)	
Access Related Complication	Access Related defined as any adverse clinical consequence possibly associated with any of the access sites used during the procedure.	
Acute Kidney Injury	Change in serum creatinine (up to 72 h) compared with baseline Stage 1 Increase in serum creatinine to 150% to 200% (1.5 to 2.0 _ increase compared with baseline) or increase of 0.3 mg/dl (26.4 mmol/l) Stage 2 Increase in serum creatinine to 200% to 300% (2.0 to 3.0 increase compared with baseline) or increase between 0.3 mg/dl (26.4 mmol/l) and 4.0 mg/dl (354 mmol/l) Stage 3* Increase in serum creatinine to 300% (3 increase compared with baseline) or serum creatinine of 4.0 mg/dl (354 mmol/l) with an acute increase of at least 0.5 mg/dl (44 mmol/l) *Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.	VARC
AIDS	Acquired immune deficiency syndrome (AIDS) is an infectious disease caused by the human immunodeficiency virus (HIV). Indicate “Yes” on the Baseline CRF if the patient has a documented history of AIDS.	
Annular Dissection	Disruption or tear of the valve annulus extending to the aorta caused by mechanical injury from over sizing a balloon or the valve device itself.	STS

Term	Definition	Reference/ Justification
Aortic Dissection	1. Aortic dissection defined as Type A or B dissections that require surgical or percutaneous intervention. 2. Stanford Type B or Debakey Type 3 dissections that may be treated medically.	FDA
Aortic Stenosis	Aortic stenosis is classified as "severe" when the following are present: • Jet velocity > 4.0 m/s • Mean gradient > 40mmHg • Valve area < 1.0 cm^2 • Valve area index < 0.6cm^2/m^2	ACC/AHA p. e14, e18
Aortic Regurgitation by Echocardiography Special Considerations in Evaluating the Severity of Aortic regurgitation	Special Considerations in Evaluating the Severity of Prosthetic Aortic Regurgitation by Echocardiography 1. Acoustic shadows directly below the ventricular end of the prosthesis may obscure the jet width in the left ventricular outflow tract. 2. Eccentric jets may be cut obliquely in the parasternal window and risk overestimation. 3. Entrainment of the jet in the left ventricle outflow tract may lead to rapid broadening of the jet just after the vena contracta and lead to overestimation. 4. Very eccentric jets may impinge on the wall of the left ventricle outflow tract or anterior mitral valve leaflet ("coanda" effect) and lead to underestimation. 5. Width of the vena contracta may be difficult to accurately measure in the long axis due to the prosthesis. 6. Careful imaging of the neck of the paravalvular jet in the short axis at the level of the prosthesis might allow appreciation of the circumferential extent of the regurgitation (<10% mild, 10-20% moderate, >20% severe). 7. If the pressure half-time is < 200 ms suspect severe aortic regurgitation; if pressure half-time is > 500 ms consistent with mild aortic regurgitation; intermediate ranges difficult to quantify. 8. Holodiastolic flow reversal in the descending thoracic aorta is indicative of at least moderate aortic regurgitation; severe aortic regurgitation is suspected when the velocity time integral of the reverse flow approximates that of the forward flow. 9. Holodiastolic flow reversal in the abdominal aorta is indicative of severe aortic regurgitation. 10. Regurgitant volumes – measurement of the velocity time integral in the left ventricle outflow tract too	Valve Academic Research Consortium (VARC) [16]

<table>
<tr><th>Term</th><th>Definition</th><th>Reference/ Justification</th></tr>
<tr><td></td><td>close to the prosthesis may lead to overestimation of the velocity (due to proximal acceleration) and thus regurgitant volume.

AHA/ACC 2006 guidelines:

<table>
<tr><th></th><th colspan="3">Aortic Regurgitation</th></tr>
<tr><th></th><th>Mild</th><th>Moderate</th><th>Severe</th></tr>
<tr><td>Qualitative</td><td></td><td></td><td></td></tr>
<tr><td>Angiographic grade</td><td>1+</td><td>2+</td><td>3–4+</td></tr>
<tr><td>Color Doppler jet width</td><td>Central jet, width less than 25% of LVOT</td><td>Greater than mild but no signs of severe AR</td><td>Central jet, width greater than 65% LVOT</td></tr>
<tr><td>Doppler vena contracta width (cm)</td><td>Less than 0.3</td><td>0.3–0.6</td><td>Greater than 0.6</td></tr>
<tr><td>Quantitative (cath or echo)</td><td></td><td></td><td></td></tr>
<tr><td>Regurgitant volume (ml per beat)</td><td>Less than 30</td><td>30–59</td><td>Greater than or equal to 60</td></tr>
<tr><td>Regurgitant fraction (%)</td><td>Less than 30</td><td>30–49</td><td>Greater than or equal to 50</td></tr>
<tr><td>Regurgitant orifice area (cm2)</td><td>Less than 0.10</td><td>0.10–0.29</td><td>Greater than or equal to 0.30</td></tr>
<tr><td>Additional essential criteria</td><td></td><td></td><td></td></tr>
<tr><td>Left ventricular size</td><td></td><td></td><td>Increased</td></tr>
</table>
</td><td></td></tr>
<tr><td>Aortic Valve Stenosis criteria, Prosthetic</td><td>
<table>
<tr><th colspan="4">Prosthetic Aortic Valve Stenosis Criteria*</th></tr>
<tr><th>Parameter</th><th>Normal</th><th>Possible stenosis</th><th>Significant stenosis</th></tr>
<tr><td>Peak velocity (m/s)†</td><td><3</td><td>3-4</td><td>> 4</td></tr>
<tr><td>Mean gradient (mm Hg)†</td><td><20</td><td>20-35</td><td>>35</td></tr>
<tr><td>Doppler velocity index</td><td>=0.30</td><td>0.29 -0.25</td><td><0.25</td></tr>
<tr><td>Effective orifice area (cm^2)</td><td>>1.2</td><td>1.2-0.8</td><td><0.80</td></tr>
<tr><td>Contour of the jet velocity through the prosthetic valve</td><td>Triangular, early peaking</td><td>Triangular to intermediate</td><td>Rounded, symmetrical contour</td></tr>
<tr><td>Acceleration time (ms)</td><td><80</td><td>80-100</td><td>>100</td></tr>
<tr><td colspan="4">*In conditions of normal or near normal stroke volume (50 -70 mL)
†These parameter are more affected by flow, including concomitant aortic regurgitation.</td></tr>
</table>
</td><td>VARC</td></tr>
<tr><td>Arrhythmia</td><td>Variation from the normal rhythm of the heartbeat, encompassing abnormalities of rate, regularity, site of impulse origin, and sequence of activation. Indicate “Yes” on the Baseline CRF if the subject has a documented history of any of the following major arrhythmias: Atrial fibrillation/flutter; Tachyarrhythmia(s), such as Supra-Ventricular Tachycardia (SVT); Bradyarrhythmia(s), such as Sinus Bradycardia (SB); or Heart Blocks; such as Atrio-Ventricular Heart Block (AV Block), First/Second or Third Degree Heart Block. Patients are considered to have a major arrhythmia in the presence of the arrhythmia being treated or controlled by medication.</td><td></td></tr>
</table>

Term	Definition	Reference/ Justification
Baseline co-morbidities for STS PROM Calculation	Please consult: http://www.sts.org/sites/default/files/documents/STSAdultCVDataSpecificationsV2_73.pdf	STS[121]
Bleeding Event	Type of Bleeding: Life-threatening or Disabling Bleeding • Fatal bleeding OR • Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome OR • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery OR • Overt source of bleeding with drop in hemoglobin of ≥5 g/dL or whole blood of packed red blood cells (RBC) transfusion ≥4 units* Major Bleeding Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring transfusion of 2-3 units of whole blood/RBC AND Does not meet criteria of life-threatening or disabling bleeding. Minor Bleeding Any bleeding worthy of clinical mention (e.g. access site hematoma) that does not qualify as life-threatening, disabling or major. * Given one unit of packed RBC typically will raise blood hemoglobin concentration by 1 g/dL, an estimated decrease in hemoglobin will be calculated.	VARC/ CEC

Term	Definition	Reference/ Justification
Canadian Cardiovascular Society Classification (CCS)	Class 1 No limitation of ordinary activity. 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. Class 2 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. Class 3 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. Class 4 Inability to carry on any physical activity without discomfort. Angina syndrome may be present at rest.	Canadian Cardiovascular Society
CABG	Coronary artery bypass surgery.	
Cancer	Characterized by uncontrolled growth of the cells and the ability of these cells to migrate from the original site and spread to distant sites. Cancer may be benign or malignant. Indicate “Yes” and specify the type of cancer on the Baseline CRF if the patient has a documented history of a malignant cancer.	
Cardiomyopathy	A chronic disease of the myocardium in which the muscle is abnormally enlarged, thickened, and/or stiffened. Indicate “Yes” on the Baseline CRF if the patient has a documented history of cardiomyopathy.	
Carotid Disease	A condition where atherosclerosis develops within one or both of the carotid arteries. Indicated “Yes” on the Baseline CRF if the patient has a documented history of carotid artery disease. An example, of carotid artery disease would be a documented history of a carotid endarectomy.	
Cerebral Infarction	See “Stroke”.	
Cerebrovascular disease	See “Stroke”.	

<table>
<tr><th>Term</th><th>Definition</th><th>Reference/ Justification</th></tr>
<tr><td>CHADS 2 Score</td><td>The CHADS2 score is a widely used, validated assessment of stroke risk stratification in patients with non-valvular atrial fibrillation (AF). The CHADS2 score has been associated with stroke independent of AF, particularly in patients with coronary heart disease (CHD). The CHADS2 score can be computed from baseline characteristic: C=congestive heart failure (1 point), H= hypertension (1 point), A=age >75 yr (1 point), D= Diabetes (1 point), S=Stroke (2 points).

Annual Stroke risk
<table>
<tr><th>$CHADS_2$ Score</th><th>Stroke Risk %</th><th>95% CI</th></tr>
<tr><td>0</td><td>1.9</td><td>1.2–3.0</td></tr>
<tr><td>1</td><td>2.8</td><td>2.0–3.8</td></tr>
<tr><td>2</td><td>4.0</td><td>3.1–5.1</td></tr>
<tr><td>3</td><td>5.9</td><td>4.6–7.3</td></tr>
<tr><td>4</td><td>8.5</td><td>6.3–11.1</td></tr>
<tr><td>5</td><td>12.5</td><td>8.2–17.5</td></tr>
<tr><td>6</td><td>18.2</td><td>10.5–27.</td></tr>
</table></td><td>[122-123]</td></tr>
<tr><td>Chest Deformity (Chest deformities that would preclude an open chest procedure)</td><td>CT scan evidence of anatomy predicting intolerable risk, agreed upon by 3 surgeons from different institutions, or pulmonary function abnormalities considered inoperable and thought to be based on chest wall deformity. If this condition is not reported in the patient's medical record, consults must be obtained.</td><td></td></tr>
</table>

Term	Definition	Reference/ Justification
Coagulopathy	A pathologic condition that affects the ability of the blood to coagulate. Examples include hemophilia, drug-induced clotting disorder, thrombocytopenia and Von Willebrand's disease. Indicate “Yes” on the Baseline CRF if the patient has a documented history of a chronic coagulopathy disorder.	
Conduction Defect, Severe	1. Conduction Defect requiring implantation of permanent pacemaker. 2. Creation of permanent bundle branch block.	FDA
Congestive Heart Failure (CHF)	Usually a chronic, long-term condition, although it can sometimes develop suddenly. The condition may affect the right side, the left side, or both sides of the heart. Indicate “Yes” on the Baseline CRF if the patient has a documented history of CHF.	
Conversion To Bypass	Conversion to cardiopulmonary bypass is defined when patient is cannulated and heparinized.	FDA
Coronary artery disease (CAD)	Atherosclerosis of the coronary arteries. Indicate “Yes” on the Baseline CRF is the patient has a documented history of CAD.	
Delirium	Acute confusional state with fluctuating impairment in attention and cognition.	[124]
Dementia	Significant loss of intellectual abilities such as memory capacity, severe enough to interfere with social or occupational functioning. An example of dementia is Alzheimer’s Disease. Indicate “Yes” on the Baseline CRF if the patient has a documented history of dementia.	

Term	Definition	Reference/ Justification
Death	Cardiovascular Death Any one of the following criteria: Any death due to proximate cardiac disease cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure); Unwitnessed death and death of unknown cause (includes sudden cardiac death) All cardiovascular procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure; Death caused by noncoronary vascular conditions such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, or other vascular disease. Non-Cardiovascular Death Death is due primarily to an identifiable non-cardiovascular cause or etiology. Specific diagnoses may include respiratory failure, pneumonia, trauma, suicide, or any other non-cardiovascular defined causes (e.g., liver disease, malignancies etc.) not included in the previous categories.	CEC
Device Embolization	Device displacement from its initial annular implantation site so that it is no longer in its original position and is either in the left ventricle, aortic root or ascending/descending aorta.	
Device Fracture	The complete separation of any portion of the frame into two or more parts; as may be determined by radiography, computed tomography or magnetic resonance imaging.	
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.	
Device Migration	Device migration is defined x-ray confirmed movement of the study valve from its initial implantation site such that there is a change in valve orientation within the aortic outflow track resulting in a new ECHO confirmed flow disturbance (pre- and post- filmed documentation).	

Term	Definition	Reference/ Justification
Device Success	Device success is a 'technical' composite endpoint meant to characterize the acute device and procedural factors which underlie vascular access, delivery, and performance of the TAVI system. Successful vascular access, delivery and deployment of the device and successful retrieval of the delivery system. Correct position of the device in the proper anatomical location. Intended performance of the prosthetic heart valve (aortic valve area ≥1.2 cm2 and mean aortic valve gradient < 20 mm Hg or peak velocity < 3 m/s, without moderate or severe prosthetic valve AR) Only one valve implanted in the proper anatomical location. In evaluating the echo parameters, the first available value (discharge/7 day visit or later) will be used for each of the echo parameters above. Separate visits may be used for the three parameters. If success or failure cannot be determined due to missing or unevaluable echos, device success will be considered missing.	VARC
Diabetes Mellitus (DM)	A condition in which the pancreas no longer produces enough insulin or cells stop responding to the insulin that is produced, so that glucose in the blood cannot be absorbed into the cells of the body. The two main types of diabetes mellitus are insulin-requiring type 1 diabetes and adult-onset type 2 diabetes. Indicate "Yes" on the Baseline CRF if the patient has a documented history of DM. Indicate whether the DM is controlled by diet, oral medication or insulin.	
Dyslipidemia (Hyperlipidemia, Hypercholesterolemia)	Abnormality in, or abnormal amounts of, lipids and lipoproteins in the blood. Indicate "Yes" on the Baseline CRF if the patient has a documented history of dyslipidemia and/or is presently taking statin medication(s).	

Term	Definition	Reference/ Justification
Embolism	Free flowing blood clot or lesion material that is located in the systemic or pulmonary circulation. Any embolic event that occurs in the absence of infection after the immediate perioperative period (when anesthesia-induced unconsciousness is completely reversed). Peripheral embolic event is an operative, autopsy or clinically documented embolus that produces symptoms from complete or partial obstruction or a peripheral (noncerebral) artery. Patients who awaken with a myocardial infarction are excluded. Patients who have a myocardial infarction after the perioperative period are also excluded unless a coronary arterial embolus is shown to be the cause of the infarction by operation, autopsy or clinical investigation. Emboli proven to consist of nonthrombotic material (e.g., atherosclerosis, myxoma) are excluded.	STS
Emergent Bypass Surgery	Emergent bypass surgery is defined as urgent or emergent coronary bypass surgery < 30 days of the index treatment.	FDA

Term	Definition	Reference/ Justification
Emergent Cardiac Surgery	Emergent Salvage: The patient is undergoing CPR en route to the operating room or prior to anesthesia induction Emergent: The patient's clinical status includes any of the following: 1. Ischemic dysfunction of any of the following: a) ongoing ischemia including rest angina despite maximal medical therapy (medical and/or IABP); b) Acute Evolving Myocardial Infarction within 24 hours before surgery or c) pulmonary edema requiring intubation 2. Mechanical dysfunction (either of the following): a) shock with circulatory support; or b) shock without circulatory support. Urgent: ALL of the following conditions are met: Not elective status Not emergent status Procedure required during same hospitalization in order to minimize chance of further clinical deterioration Worsening, sudden chest pain, CHF, acute myocardial infarction (AMI), anatomy, IABP, unstable angina with intravenous (IV) nitroglycerin (NTG) or rest angina may be included. Elective: The patient's cardiac function has been stable in the days or weeks prior to the operation. The procedure can be deferred without increased risk of compromised cardiac outcome.	STS Definition of Cardiac Surgery Status
Encephalopathy	See "Delirium".	FDA
Endocarditis (Operated Valvular Endocarditis)	Any infection involving an operated valve. The diagnosis of operated valvular endocarditis is based on customary clinical criteria including an appropriate combination of positive blood cultures, clinical signs and histologic confirmation of endocarditis at reoperation or autopsy. Morbidity associated with active infection, such as valve thrombosis, thrombotic embolus, bleeding event or paravalvular leak is included under this category and is not included in other categories of morbidity.	STS [125] Suggested reference: Duke Criteria for Infective Endocarditis

Term	Definition	Reference/ Justification
Endocarditis, Remote	Lacking positive cultures, but with morphologic evidence of previous disease. Indicate "Yes" on the Baseline CRF if the patient has a documented history of endocarditis.	
Endpoints, VARC Composite Combined Efficacy at 1 Year	All-cause mortality Failure of current therapy for AS, requiring hospitalization for symptoms of valve-related decompensation (CEC adjudicated episodes of heart failure, angina, or syncope requiring an aortic valve procedure or intensification of medical management) Prosthetic heart valve dysfunction (aortic valve area < 1.2 cm^2 and mean aortic valve gradient > 20 mmHg, or moderate or severe prosthetic valve AR)	VARC
Endpoints, VARC Composite Combined Safety at 30 Days	All- cause mortality Disabling stroke Life-threatening (or disabling) bleeding Acute kidney injury - Stage 3 (including renal replacement therapy) Peri-procedural MI Major vascular complication Repeat procedure for valve-related dysfunction (surgical or interventional therapy)	VARC FDA
Event Free Survival	Survival from death, stroke, or emergent cardiac surgery during the index procedure hospitalization, plus freedom from death or clinically-driven hospitalization (adjudicated congestive heart failure, myocardial ischemia, or syncope treated by medicine, repeat aortic balloon valvuloplasty, or aortic valve replacement) from index hospital discharge.	
Explant (See Also "Reoperation")	Removal of the investigational valve implant for any reason.	STS/AATS
Frailty	Decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes (L. P. Fried). Documented major deficits in a combination of serum albumin, strength and physical performance, cognition, and activities of daily living.	[126]
Gastro-Intestinal (GI) disorder	A disorder of or relating to the gastrointestinal tract. Examples of a GI disorder are Crohn's Disease, irritable bowel syndrome, gastrointestinal esophageal reflux disease. Indicate "Yes" on the Baseline CRF if patient has a documented history of a GI disorder.	

Term	Definition	Reference/ Justification
Hemodynamic Collapse	Hemodynamic collapse is defined when the systolic blood pressure drops below 40mmHg or when there is electromechanical dissociation.	
Hemolysis	• Plasma Hgb > 40 mg/dl on two consecutive measurements within 24 hours. Laboratory values meeting this criteria should be listed as a major adverse event; or • Clinical diagnosis of hemolysis evidenced by laboratory testing such as serum Hgb, LDH, haptoglobin, bilirubin and/or urine bilirubin levels.	FDA
Highly Compromised Respiratory Disease	Home oxygen >2L/min, FEV1 <30% predicted, DLCO <15 or as above <30% although <50% if evidence of interstitial lung disease, FEF 25-75 <30% (measure of cough strength, <30%).	
Hypercholesterolemia	See “Dyslipidemia”.	
Hyperlipidemia	See “Dyslipidemia”.	
Hypertension	Systolic pressure > 140 or a diastolic pressure > 90 mm Hg. Indicate “Yes” on the Baseline CRF if the patient has a documented history of hypertension or is on medication to treat hypertension.	
Index Hospitalization	The beginning of the Index Hospitalization is defined as beginning on the day of the Index Procedure and continues until the patient is discharged from the Hospital.	
Index Procedure	The beginning of the Index Procedure is defined as the day and time when the patient enters the Cath Lab / OR.	
Infection	Known infection requiring intravenous antibiotics for other than prophylaxis, and/or extended hospitalization.	
Inoperable Pulmonary Function	FEV1 <1 liter, DLCO <30%, oxygen dependence at rest, PCO2 = PO2 on room air.	
Intracranial Hemorrhage	See “Stroke”.	
Liver Cirrhosis	Model for End-Stage Liver Disease (MELD) score $\geq$ 25 and/or Child-Pugh Classification of B – C (score 7 – 15), confirmed by a hepatology consult, assessed during a period of relative clinical stability, not during acute crisis. If this condition is not reported in the patient’s medical record, a consult must be obtained.	

Term	Definition	Reference/ Justification
Liver Disease	A chronic progressive condition that results in liver cell dysfunction and portal hypertension. Indicate "Yes" and report the degree (mild, moderate or severe) on the Baseline CRF if the patient has a documented history of liver disease.	
Lung Disease	Any condition causing or indicating impaired lung function. There are three types of lung disease: 1) airway: causes a narrowing or blockage of the airways (Examples: asthma, emphysema, chronic bronchitis) 2) lung tissue: affect the structure of the lung tissue, scarring or inflammation of the tissue (Examples: pulmonary fibrosis, sarcoidosis) 3) pulmonary circulation: causing clotting, scarring, or inflammation of the blood vessels. Indicate "Yes" on the Baseline CRF if the subject has a documented history of lung disease. Additionally, indicate whether the patient has a documented history of Chronic Obstructive Pulmonary Disease (COPD).	
Marfan's Syndrome	An inherited disorder of connective tissue characterized by abnormalities of the eyes, skeleton, and cardiovascular system. Indicate "Yes" on the Baseline CRF if the patient has a documented history of Marfan's syndrome.	
Mitral Valve Compromise	Mitral valve compromise defined as mitral injury producing a 1+ increase in mitral regurgitation (MR).	FDA
Mitral Valve Disease	Evidence of trace to severe valve leak, regurgitation or insufficiency. Indicate "Yes" on Baseline CRF if the patient has trace to severe leak, regurgitation or insufficiency as reported on the screening echocardiogram and/or other medical record.	

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. DESCRIPTION 0 No symptoms at all 1 No significant disability despite symptoms; able to carry out all usual duties and activities 2 Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance 3 Moderate disability; requiring some help, but able to walk without assistance 4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance 5 Severe disability; bedridden, incontinent and requiring constant nursing care and attention 6 Dead See Appendix L.	
Multiple Previous Interventions in the Presence of Advanced Multi-System Dysfunction	More than one previous cardiothoracic or vascular surgery.	
Myocardial Infarction	1. Peri-Procedural MI (beginning within 72 hours of the index procedure) as evidenced by: • New ischemic symptoms (e.g. chest pain or shortness of breath), OR • New ischemic signs (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment deviations – either elevation >1 mm or depression >1 mm in two or more contiguous leads, hemodynamic instability, or imaging evidence of new loss of viable myocardium or new wall motion abnormality), AND 2. Elevated cardiac biomarkers (preferably CK-MB) within 72 hours after the index procedure, consisting of 2 or more post-procedure samples that are > 6-8 hours apart with a 20% increase in the second sample	VARC/CEC

Term	Definition	Reference/ Justification
	and a peak value exceeding 10x the 99th percentile URL, or a peak value exceeding 5x the 99th percentile URL with new pathological Q waves in at least 2 contiguous leads. Spontaneous MI (> 72 hours after the index procedure) Any one of the following criteria: • Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with evidence of myocardial ischemia with at least one of the following: • ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]); • New pathological Q waves in at least 2 contiguous leads; • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. Pathological findings of an acute myocardial infarction. Any emergent PCI performed for acute St-elevation MI. Any administration of thrombolytics for acute MI.	
National Institute of Health Stroke Scale (NIHSS)	A method developed by the National Institutes of Health used to gauge the severity of a stroke. See Appendix F.	
Nonstructural Dysfunction	An abnormality, which is not intrinsic to the prosthetic valve (i.e. valve is structurally normal) resulting in stenosis or regurgitation. Examples of nonstructural dysfunction include entrapment by pannus, tissue or suture, paravalvular leak, inappropriate sizing or positioning, residual leak or obstruction from valve implantation or repair, and clinically important hemolytic anemia. See “paravalvular leak” for additional definitions	STS/AATS

Term	Definition	Reference/ Justification
Neurological Event	Stroke, Cerebral Infarction, Transient Ischemic Attack, Encephalopathy or Intracranial Hemorrhage per specified definitions (see individual definitions and criteria.)	VARC/FDA
New York Heart Association Classification (NYHA)	Class I: Patients with cardiac disease but without resulting limitations of physical activity. Class II: Patients with cardiac disease resulting in slight limitation of physical activity. Patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain. Class III: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation dyspnea, or anginal pain. Class IV: Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	New York Heart Association
Paravalvular Leak (See Also "Nonstructural Dysfunction")	Defined as any evidence of leakage of blood around the prosthesis between the device and the native annulus. Primary paravalvular leaks will be stratified by the following: All leaks: evidence of moderate to severe paravalvular insufficiency by echocardiography Minor leaks: A paravalvular leak graded < 3+ aortic insufficiency and does not require surgical intervention Major leaks: A paravalvular leak graded ≥ 3+ aortic insufficiency or requires surgical intervention	STS/AATS, FDA
Perforation Of The Free Myocardial Wall	These perforations will be categorized according to the severity as follows: Clinical perforation: Coronary perforation requiring additional treatment outside the protocol, or resulting in significant pericardial effusions, urgent open-chest surgery or death. "Clinical perforation" applies if either catheter drainage or open drainage is required. Pericardial hemorrhage/tamponade: Perforation with hemodynamic evidence of tamponade or pericardial hemorrhage.	FDA

Term	Definition	Reference/ Justification
Peripheral vascular disease (PVD)	The narrowing or blockage of blood vessels in the limbs. Indicate "Yes" on the Baseline CRF if the patient has a documented history of PVD. PVD may also be referred as peripheral artery disease (PAD). An example, of PVD or PAD would be a documented history of a peripheral bypass graft surgery.	
Porcelain Aorta	Thick, circumferential calcification involving most of the ascending aorta to an extent precluding conventional maneuvers necessary for AVR without aortic replacement. Conventional maneuvers include cannulation, aortic occlusion, aortotomy, and aortotomy closure.	
Pulmonary Hypertension	A mean pulmonary artery pressure greater than 25 mmHg. Indicate "Yes" on the Baseline CRF if the subject has pulmonary hypertension as noted on the screening cardiac catheterization report and/or other medical record.	
Pulmonic Valve Disease	Evidence of trace to severe valve leak, regurgitation or insufficiency. Indicate "Yes" on Baseline CRF if the patient has trace to severe leak, regurgitation or insufficiency as reported on the screening echocardiogram and/or other medical record.	
Pre-Existing Condition	A pre-existing condition is one that is present at the start of study treatment. A preexisting condition is not an adverse event unless it worsens as a result of the study treatment.	
Procedure Failure	Complication(s) arising during implantation of the prosthetic valve such as an inability to properly seat the valve in the annulus, size mismatch between the annulus and the prosthetic valve, or the need for more than one Edwards SAPIEN XT THV (valve in valve), or if a surgical valve is required to correct a paravalvular leak. The reasons for this difficulty may be due to the anatomic configuration of the annulus or a calcific valvular annulus.	
Radiated Sternum (Radiation for treatment of the sternum that precludes an open chest procedure)	Chronic, open skin defects, CT scan evidence of severe sternal bone destruction, CT evidence of indetectable plane between posterior sternal table and important mediastinal structures, extremely severe soft tissue atrophy, complete absence of reconstructive options based on plastic surgeon consult. If this condition is not reported in the patient's medical record, a consult must be obtained.	

Term	Definition	Reference/ Justification
Remote Endocarditis	See "Endocarditis, Remote".	
Recurrent Hospitalization Re-Hospitalization	Rehospitalization for symptoms of aortic stenosis and/or complications of the valve procedure If the index hospitalization for a patient is greater than 30 days, then hospital day 31 will count as a re-hospitalization for endpoint analysis.	
Renal Failure (Acute Kidney Injury)	Change in serum creatinine at up to 72 hours compared to pre-procedure value (baseline) Stage 1: Increase in serum creatinine to 150-200% (1.5-2.0 x increase compared with baseline) or increase of ≥ 0.3 mg/dl (≥26.4 µmol/L) Stage 2 Increase in serum creatinine to 200% to 300% (2.0 to 3.0 X increase compared with baseline) or increase between > 0.3 mg/dl (> 26.4 mmol/l) and < 4.0 mg/dl < 354 mmol/l) Stage 3*: Increase in serum creatinine to ≥300% (> 3 x increase compared with baseline) or serum creatinine of ≥ 4.0 mg/d (≥354 µmol/L) with an acute increase of at least 0.5 mg/dl (44 µmol/L) * Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria Patient requires chronic dialysis for > 30 days.	VARC
Renal Insufficiency	See "Acute Kidney Injury".	
Reintervention	Any intervention that repairs, alters or replaces a previously operated valve. Balloon aortic valvuloplasty Surgical aortic valve replacement Valve in valve	STS/AATS
Rheumatic Fever	Heart damage caused by rheumatic fever. Indicate "Yes" on the Baseline CRF if the patient has a documented history of rheumatic fever.	

Term	Definition	Reference/ Justification
Sternal Wound Infection	Deep sternal infection involving muscle, bone, and/or mediastinum. Must have one of the following: wound opened with excision of tissue (I&D); positive culture; treatment with antibiotics. Infection that is contiguous with the sternum on imaging will constitute involvement of the sternum.	STS/AATS
Stroke / Transient Ischemic Attack (TIA)	Stroke Diagnostic Criteria: Rapid onset of a focal/global neurological deficit with at least one of the following: • Change in level of consciousness • Hemiplegia • Hemiparesis • Numbness or sensory loss affecting one side of the body • Dysphasia/Aphasia • Hemianopia • Amaurosis fugax • Other new neurological sign(s)/symptom(s) consistent with stroke Duration of a focal or global neurological deficit ≥ 24 hours OR < 24 hours if: Therapeutic intervention(s) were performed: (e.g. thrombolytic therapy or intracranial angioplasty); OR • Available neuro-imaging documents a new hemorrhage or infarct; OR • The neurological deficit results in death. No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences)* Confirmation of the diagnosis by at least one of the following#: • Neurology or neurosurgical specialist • Neuro-imaging procedure (at least one of the following): - CT scan - MRI scan - Cerebral angiography Lumbar puncture (i.e. spinal fluid analysis diagnostic of	VARC/CEC

Term	Definition	Reference/ Justification
	intracranial hemorrhage). * Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuro-imaging studies. # If a stroke is reported without evidence of confirmation of the diagnosis by one of these methods, the event may be considered a stroke on the basis of the clinical presentation alone. Transient Ischemic Attack (TIA) New focal neurological deficit with rapid symptom resolution (usually 1 – 2 hours), always with 24 hours. Neuroimaging without tissue injury Disabling" stroke is defined as a mRS score of 2 or more at either at the 30 day or 90 day time period.	
Structural Valvular Deterioration (SVD)	Any change in valve function (a decrease of one NYHA functional class or more) resulting from an intrinsic abnormality of the valve that causes stenosis or regurgitation. Structural valve deterioration includes dysfunction or deterioration exclusive of infection or thrombosis as determined by reoperation, autopsy or clinical investigation. The term structural deterioration refers to changes intrinsic to the valve, such as wear, fracture, calcification, leaflet tear, and suture line disruption of components (e.g. leaflets).	STS/AATS
Sudden Death	See “Death”.	
Syncope	A temporary loss of consciousness due to generalized cerebral ischemia. Indicate “Yes” on the Baseline CRF if the patient has a documented history of syncope.	
Thromboembolic Event	See “embolism”.	STS/AATS

Term	Definition	Reference/ Justification
Thrombus (Valve Thrombosis)	An aggregation of platelet, fibrin, clotting factors, and other cellular elements exclusive of infection. Valve thrombosis is defined as any thrombus in the absence of infection attached to or near an operated valve that occludes part of the blood flow path or that interferes with function of the valve. A valve related thrombus may be confirmed by operation, autopsy, or diagnostically by such methods as echocardiography, angiocardiography, or magnetic resonance imaging.	STS/AATS
Transcatheter Heart Valve in Surgical Valve (THV-SV)	Implantation of a transcatheter heart valve (THV) in a pre-existing surgical valve (SV).	
Transcatheter Heart Valve in Transcatheter Heart Valve (THV-THV)	Occurs during the transcatheter heart valve (THV) implantation procedure when an initial THV has not resulted in an appropriately functioning manner requiring an additional THV(s) to be implanted within the originally placed THV. Causes may include, but are not limited to: severe paravalular leak.	
Transient Ischemic Attack (TIA)	See “Stroke”.	
Traumatic Cardiac Microangiopathic Hemolytic Anemia	The intravascular fragmentation of red blood cells characterized by low Hgb levels, schizocytes consisting of helmet cells, triangle cells and other fragmented forms. The red cells may show hypochromia if iron deficiency due to urinary loss of hemoglobin or hemosiderin is present. The plasma hemoglobin level is elevated and the serum haptoglobin concentration is diminished or absent. Hemosiderinuria is a constant finding, but hemoglobinuria may vary from none to large amounts. Serum LDH activity may be elevated. The leukocyte count may be normal or slightly elevated and the platelet count may be diminished. This anemic event is exclusive of infection or autoimmune disease. The anemia is considered mild if controlled by iron replacement, and severe if transfusion is necessary.	
Tricuspid Valve Disease	Evidence of trace to severe valve leak, regurgitation or insufficiency. Indicate “Yes” on Baseline CRF if the patient has trace to severe leak, regurgitation or insufficiency as reported on the screening echocardiogram and/or other medical record.	

Term	Definition	Reference/ Justification
Valve-Related Mortality	See "Death".	STS/AATS
Vascular/Access-Complications	Major Vascular Complications Any thoracic aortic dissection. Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, or compartment syndrome) leading to either death, need for significant blood transfusions (≥ 4 U), unplanned percutaneous or surgical intervention, or irreversible end-organ damage (e.g., hypogastric artery occlusion causing visceral ischemia or spinal artery injury causing neurological impairment) Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage Minor Vascular Complications Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula or pseudoaneuysms requiring compression or thrombin injection therapy, or hematomas requiring transfusion of ≥ 2 but, < 4 U) not requiring unplanned percutaneous or surgical intervention and not resulting in irreversible end-organ damage Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage Failure of percutaneous access site closure resulting in interventional (e.g., stent-graft) or surgical correction and not associated with death, need for significant blood transfusions (≥ 4 U), or irreversible end-organ damage.	VARC

Term	Definition	Reference/ Justification
* Note: The Valve Academic Research Consortium (VARC) consists of representatives from several independent Academic Research Organizations (Cardialysis, Rotterdam, the Netherlands, Cardiovascular Research Foundation, New York City, NY, Duke Clinical Research Institute, Durham, NC, and Harvard Clinical Research Institute, Boston, MA), several Surgery and Cardiology Societies (American Association of Thoracic Surgeons, American College of Cardiology, American Heart Association, European Association of CardioThoracic Surgeons, European Society of Cardiology, Society of Cardiac Angiography and Intervention, and Society of Thoracic Surgeons) and several independent expert scientists and consultants		

Table 7 Prosthetic Aortic Valve Regurgitation Criteria (Central and Paravalvular)

Prosthetic Aortic Valve Regurgitation Criteria (Central and Paravalvular)			
Parameter	**Mild**	**Moderate**	**Severe**
Valve structure and motion			
Bioprosthetic	Usually normal	Usually abnormal	Usually abnormal
Structural parameters			
Left ventricular size	Normal	Normal/mildly dilated	Dilated
Doppler parameters (qualitative or semiquantitative)			
Jet width in central jets (% LVO diameter): color*	Narrow (≤25%)	Intermediate (26-64%)	Large (≥65%)
Jet density: CW Doppler	Incomplete or faint	Dense	Dense
Jet deceleration rate (PHT, ms): CW Doppler†	Slow (>500)	Variable (200-500)	Steep (<200)
LV outflow vs. pulmonary flow: PW Doppler	Slightly increased	Intermediate	Greatly increased
Diastolic flow reversal in the descending aorta: PW Doppler	Absent or brief Early diastolic	Intermediate	Prominent, Holodiastolic
Circumferential extent of paraprosthetic AR (%)	<10	10-20	>20
Doppler parameters (quantitative)			
Regurgitant volume (mL/beat)	<30	30-59	>60
Regurgitant fraction (%)	<30	30-50	>50
* Parameter applicable to central jets and is less accurate in eccentric jets			
† Influenced by left ventricular compliance.			
AR = aortic regurgitation; CW = continuous wave; LVO = left ventricular outflow; PW = pulsed wave			

9.0 Study Committees

9.1 The PARTNER II Trial Executive Committee

The Executive Committee is responsible for the overall conduct of the trial. This committee meets periodically by teleconference to monitor study patient enrollment, clinical site progress, and protocol compliance. This committee is responsible for reviewing the final results, determining the methods of presentation and publication, and selection of secondary projects and publications by members of the Steering Committee. The committee is comprised of 8 study investigators (4 cardiovascular surgeons, and 4 interventional cardiologists), a QOL Medical Advisor, Echocardiography Expert and a Sponsor representative. A Neurologist will be appointed as an additional advisory member of the trial.

9.2 Patient Selection and Procedure Management Steering Committee

This Steering Committee will consist of an additional ten members of the study investigators (5 cardiac surgeons and 5 cardiologists). These members will have previously participated in the PARTNER Trial and are to be selected by the Executive Committee. The mission of this Committee is to provide leadership in The PARTNER II Trial with specific focus on patient selection processes, procedure development and case management oversight. The committee will participate in the weekly case review calls and will convene as a committee by quarterly meetings as well as ad-hoc web calls.

The committee members and advisors are listed below:

Interventional Cardiologists	Martin B. Leon, MD	Columbia University Medical Center New York, NY
	Jeffrey W. Moses, MD	Columbia University Medical Center New York, NY
	E. Murat Tuzcu, MD	The Cleveland Clinic Foundation Cleveland, OH
	John G. Webb, MD	St. Paul's Hospital Vancouver, British Columbia, Canada
Cardiovascular Surgeons	Craig R. Smith, MD	Columbia University Medical Center New York, NY
	D. Craig Miller, MD	Stanford University Medical Center Stanford, CA
	Michael J. Mack, MD	Medical City Hospital Dallas, TX
	Lars Svensson, MD	Cleveland Clinic Foundation Cleveland, OH
Sponsor	Jodi J. Akin, MSN	Edwards Lifesciences LLC Irvine, CA
Neurologist	Thomas Brott	Mayo Clinic Florida

Specialty Advisors	Robert Bonow, MD Eugene Blackstone, MD Statistics	Cleveland Clinic Foundation Cleveland, OH

9.3 Data Safety Monitoring Board (DSMB)

9.3.1 Independence of the DSMB

The DSMB is independent from the Sponsor, the investigators, or anyone involved in the medical care of the study patients. Members will not have scientific, financial, or other conflict of interest related to the Sponsor or the investigators. DSMB members must sign a non-conflict-of-interest statement in this regard.

The committee will be selected by the Executive Committee and managed independently by an academic research organization (Cardiovascular Research Foundation).

The members must have the following characteristics:

- working professionally as physicians or statisticians;
- at least one member with specific expertise in cardiothoracic surgery clinical trials;
- at least one member with significant prior experience as DSMB chairperson;
- no conflict of interest;
- no financial interest in Edwards Lifesciences;
- they will not be involved in the conduct of this trial in any other capacity, such as principal investigators, sub-principal investigators;
- they will not be engaged in any simultaneously occurring competitive trials;
- they should not be on the NIDPOE or debarred list of investigators.

Members will not serve on the DSMB, Clinical Event Adjudication Committee (CEC) or Operating Committee of a competing device trial. Members will not have any affiliation with the core laboratories, the data coordinating center, or the principal

investigator of the trial. The DSMB will function in accordance with Cardiovascular Research Foundation's SOPs and applicable regulatory guidelines.

The DSMB committee will review all safety data from the PARTNER II Trial in accordance to an established charter and make recommendations based upon the safety analyses. The same DSMB will be responsible for both cohorts, even if there is early submission on one cohort. It will also be responsible for developing a charter and establishing stopping rules for early termination of the trial. The frequency of the DSMB meetings will be determined prior to study commencement; however, the DSMB may call a meeting at any time if there is reason to suspect safety is an issue. DSMB oversight for this trial is expected to be rigorous with frequent review of all essential safety data.

Edwards Lifesciences will provide statistical support for the DSMB. The DSMB may also request the services of an independent statistician.

The DSMB chairperson will notify Edwards Lifesciences, by confidential memo, of any safety or compliance issues. They will also provide confidential recommendations, when necessary, of study termination based upon the safety stopping rules determined at study onset, or because a clinically significant result was identified in safety analyses of the data. All DSMB reports will remain strictly confidential, but will be made available to regulatory authorities.

Edwards will notify FDA if any member of the DSMB advises to terminate the study due to safety concerns.

9.3.2 Study Termination

The DSMB will monitor the rates of SAEs, major safety events, device and procedure failures and any device-related adverse events. The stopping rules will be developed in conjunction with the DSMB. In addition to the stopping rules, the DSMB may recommend stopping the study at any time, in the event of other unforeseen and/or excessive adverse effects or other safety concerns in the treated group.

9.4 Clinical Event Adjudication Committee

The Clinical Event Adjudication Committee (CEC) will be responsible for adjudicating endpoint related events reported during the trial per a charter and protocol endpoint definitions established a priori. The CEC under the direction of an academic research organization (ARO) will include specialists in neurology, cardiology and vascular surgery, as well as cardio-thoracic surgeons in clinical practice who are not participants in the study and who meet regularly throughout the study to adjudicate

events in an ongoing fashion. The CEC members must be independent from the investigational sites.

The CEC, under the Medical Director of the ARO, will operate under a detailed charter outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical event. These rules have been submitted to the Executive Committee for final approval. The charter is similar to the charter in The PARTNER I Trial and will undergo periodic review for effectiveness. Endpoint definitions are in large in line with the VARC recommendations. Members are provided data summaries from the clinical study in a blinded fashion without site or physician identification. All members of the CEC will be blinded to the primary results of the study. All CEC meeting minutes will remain strictly confidential, but will be made available to regulatory authorities upon request. Edwards Lifesciences will provide statistical support for the CEC. The CEC may also request the services of an independent statistician.

9.5 Publication Committee

Selected members of the Steering Committee will participate in a publications committee which will plan and review the study publication strategy and review proposed papers and presentations. An independent publications office is currently under development which will be staffed by independent statistical, programming, administrative and medical expertise and support. The committee Co-Chairman, Dr. Lars Svensson, Cleveland Clinic Foundation and Dr. Jeffrey Moses, Columbia University will develop the format for submission and review of proposed publications. The committee will ensure accuracy of data reporting and will provide editorial assistance and review as needed. Investigators will be required to submit requests for presentation or publication for committee review and approval. Papers or abstracts (other than methodology) from individual sites are not allowed without prior written consent from the publication Chairmen and the Executive Committee. No papers or presentations will be allowed prior to completion of study follow-up and a designated data extract sometime after the last patient has been followed for the primary set analysis. Any requests for sub-studies must be submitted to the Co-Chairman for formal review. Any sub-studies that would increase the potential risk to the patient will not be considered. The PARTNER II Trial Executive Committee encourages the study investigators to demonstrate an active interest in future sub-studies and will provide opportunities for participation in publication and presentation of the study data at the appropriate time.

9.6 Database Management

The database management center will provide data management through an electronic data capture (EDC) system. The database management center will also be responsible for providing clean data sets to DCRI for statistical analysis and reporting of the DSMB and CEC.

9.7 Investigator Access to the Data and Publication Policies

At the conclusion of the trial, a multi-center abstract reporting the primary results will be prepared and presented at a major cardiovascular meeting. A multi-center publication will also be prepared for publication in a reputable scientific journal. Secondary papers authored by Investigators who have contributed quality data and are in good standing with the trial conduct will be encouraged and supported by the Executive Committee and Sponsor. The publication of results from any single center experience within the trial is not permitted without prior written consent of the Executive Committee. If approved, the single center analysis must be derived from the study data base and core lab analyses as appropriate. Publication or presentation of the overall clinical study results of study devices which have not been released, and which still may be undergoing development, requires the prior written approval of Edwards Lifesciences. Notwithstanding the foregoing, after the publication of the primary data analysis of the Trial, Investigators are free to publish or present their own clinical study data study patient to review by Edwards Lifesciences and the Executive Committee prior to submission or presentation, but data analyses of site-specific results may occur only at intervals explicitly defined in the analysis plan. Publication or presentation of the Investigator's site specific clinical study results of devices which have not been market released and which still may be undergoing development, shall not include claims of device safety and effectiveness. If the Executive Committee or Edwards Lifesciences approves of the publication or presentation of the overall clinical results then Institutions and Investigators will comply with the protocol set forth in the Clinical Studies Agreement.

Publication or presentation of trial data prior to the primary publication or presentation may result in banning from future publications and or potential removal from participation in future studies. Additionally, all publications and presentations reflecting The PARTNER Trial data must be generated from core lab and official study data extracts from the study database.

10.0 Administrative Responsibilities

10.1 Institutional Review Board (IRB) Information

This protocol and the informed consent must be reviewed and approved by the appropriate IRB where the trial is to be conducted before enrollment of patients. Changes to the protocol that may increase the risk or present new risks to the patient, or may adversely affect the validity of the trial, must be approved in writing by Edwards Lifesciences, FDA and the IRB before the change is implemented.

10.1.1 Reviewing Institutions

Up to 60 sites will participate in the trial.

10.1.2 Institutional Review Board/EC Approval Letter

Institutional Review Board (IRB) approval to participate in this trial is required from each institution participating in this investigation. Prior to patient enrollment, a signed copy of the IRB approval letter must be submitted to Edwards Lifesciences certifying trial approval. Investigators are responsible for submitting and obtaining initial and continuing review of the trial at least annually unless otherwise directed by their IRB.

10.1.3 Informed Consent

Informed consent is mandatory and must be obtained from all study patients (or their legally authorized representative) prior to their participation in this trial.

The Informed Consent Form is included in Appendix B. Any modifications to the Informed Consent Form must be approved by Edwards Lifesciences and the IRB.

A copy of the IRB approved Informed Consent Form along with a copy of each patient's signed consent form must be maintained by each investigator in a designated clinical trial administrative file. A signed copy of the consent form must be given to each patient.

10.2 Confidentiality

All information and data sent to the data management center concerning study patients or their participation in this trial will be considered confidential. Only authorized data management center personnel will have access to these confidential files. Authorized personnel from the regulatory authorities have the right to inspect

and copy all records pertinent to this trial. All data used in the analysis and reporting of this evaluation will be without identifiable reference to the patient.

10.3 Data Monitoring and Quality Control

10.3.1 Electronic Case Report Forms (e-CRFs)

Electronic CRFs (e-CRFs) will be used to collect all patient data during the trial. Paper copies may be printed of the website. An e-mail notification will be sent to Edwards Lifesciences, the data management center and if applicable, CRO, when enrollment data are collected into the website. E-CRFs must be fully completed for each patient and signed electronically by the investigator and/or designee. If for any reason the eCRFs are unavailable or access to the electronic database is limited, paper CRF forms must be completed and submitted to the Study Manager.

10.3.2 Data Reporting

The Investigator or his/her designee is responsible for recording all data from the trial onto the e-CRFs supplied by the data management center.

The Investigator is required to provide an electronic signature on the appropriate e-CRF pages to verify that he/she has reviewed the recorded data.

Completed e-CRFs will be reviewed at the investigational site and remotely by authorized Edwards Lifesciences personnel at regular intervals throughout the trial. To this end, the Investigator must permit inspection of the trial paper files and patient e-CRFs by such representatives and/or responsible government agencies.

Data submission will be monitored closely. Sites with incomplete or outstanding CRFs may be prohibited from enrollment until data submission is current.

10.3.3 Data Review

All e-CRFs will be tracked at the data management center and missing or unclear data will be requested as necessary throughout the trial. Edwards Lifesciences and/or its data management center will request further documentation such as physician and/or cardiac catheterization lab procedure notes when complications or malfunctions are observed and reported.

For purposes of safety review and event adjudication the members of the DSMB and CEC will have access to all necessary safety and event data.

10.4 Records and Reports

10.4.1 Records

Records to be maintained by the investigator include:

- Clinical trial investigational plan and all amendments
- Signed clinical trial agreement
- Signed financial disclosure form
- IRB approval letter, including informed consent;
- IRB membership list;
- Correspondence relating to the trial;
- CVs for all investigators;
- Delegation of Authority Log;
- Clinical monitor sign-in log;
- Blank set of e-CRFs and instructions for completion;
- Patient screening/enrollment log;
- Lab certification and lab test normal ranges;
- Reports (includes annual reports, final reports from investigator and Sponsor).

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

- Signed Patient Informed Consent Form;
- All completed e-CRFs;
- Supporting documentation of any complications or serious adverse events.

Edwards Lifesciences requests that the investigator retain copies of procedure reports, procedure nursing notes and the results of any interventional procedures that occur after the trial procedure. Edwards Lifesciences reserves the right to secure data clarification and additional medical documentation on patients enrolled in this trial.

10.4.2 Reports

The data management center will make online reports on this investigation available for Edwards Lifesciences and if applicable, CRO, when necessary. Both real time reporting and ad hoc reporting tools are being developed.

10.5 Investigator's Final Report

Upon completion or termination of the Edwards Lifesciences PARTNER II Trial, the Principal Investigator must submit a final written report to Edwards Lifesciences and the IRB as required by the regulations. The report must be submitted within 3 months (90 days) of completion or termination of the trial.

10.6 Labeling: Instructions for Use

The Instructions for Use for use of the study device with the transfemoral, transapical and transaortic delivery systems are included with each shipment. The Instructions for Use for other approved devices are packaged with each device by their respective manufacturers.

10.7 Deviations from Protocol

The investigator will not deviate from the protocol without the prior written approval of Edwards Lifesciences except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the patient's risk or affect the validity of the trial. In medical emergencies, prior approval for protocol deviations will not be required, but the Edwards Lifesciences clinical research personnel must be notified within 2 days of the incident. Periodic monitoring of protocol compliance will be performed for each site. The Sponsor has the right to suspend enrollment at sites deemed to have excessive protocol compliance issues.

11.0 Adverse Event Reporting

All adverse events (AEs) will be reported by the Investigator and reviewed by the Sponsor in compliance with applicable regulations.

For the purpose of this protocol, an adverse event is any undesirable medical occurrence in a patient. This definition does not depend on a causal relationship with the device or the protocol requirements. Expected clinical and non-significant clinical adverse events will not be reported.

Adverse events may be volunteered by patients, elicited by the Investigator or designee, or collected via observation by the Investigator. All AEs will be assessed by the Investigator who will determine whether or not the event is related to the device and/or procedure, and whether or not the event meets serious criteria. If it is determined that an AE has occurred, the investigator should obtain all the information required to complete the AE Form of the CRF. Source documents as requested by the Safety Officer and in accordance with the CEC charter must be submitted to the Sponsor within a timely manner to ensure timely assessment and adjudication of the event as appropriate.

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

AE Reporting Period:

Adverse events are reported beginning from randomization until study patient participation has ended (i.e. completion of study or withdrawal of consent). Adverse events must be followed until resolution, AE has stabilized, or the study has been completed.

Pre-existing condition:

Pre-existing medical conditions or symptoms reported prior to device implantation will not be recorded as an AE. In the event there is a change in the pre-existing medical condition or symptoms due to the device or study related procedure, then an AE must be recorded.

Severity

The following categories of adverse event severity are to be used:

- Mild: Awareness of a sign or symptom that does not interfere with the patient's usual activity or is transient, resolves without treatment and with no sequelae.
- Moderate: Interferes with the patient's usual activity and/or requires symptomatic treatment.

- Severe: Symptom(s) causing severe discomfort and significant impact on the patient's usual activities and/or requires treatment.

Causality

The causal relationship to the device and the procedure should be rated as follows:

- None: The event is not associated with the device or procedure. There is no relation between the event and the device or procedure.
- Possibly Related: The temporal sequence between the device or procedure and the event is such that the relationship is not unlikely or there is no contradicting evidence that can reasonably explain the study patient's condition. There is a possibility of any relation between the event and the device or procedure.
- Related: The temporal sequence is relevant or the event abates upon device application completion/removal or the event cannot be reasonably explained by the patient's condition or comorbidities. The event is related or most likely associated with the device or procedure.
- Unknown: There is no evidence or relevant data available to assess the relationship between the event and the device or procedure.

Serious Adverse Events

An Adverse Event is considered serious if the event:

- Leads to death;
- Leads to a serious deterioration in the health of the study patient that:
  - Results in life-threatening illness or injury;
  - Results in a permanent impairment of a body structure or a body function;
  - Requires inpatient hospitalization or prolongation of existing hospitalization;
  - Results in medical or surgical intervention to prevent permanent impairment to body structure or a body function;

All Serious Adverse Events (SAE) must be reported to Edwards Lifesciences immediately. At the time of initial notification, the following minimal information must be provided:

- Identifiable patient: study patient number
- Identifiable reporter: study site
- Adverse event
- Causal relationship to device and procedure

Source documentation if available:

- The AE Forms of the CRF must be completed within 7 working days of awareness for all SAEs.

Source Documentation Collection

Following the report of any SAE, the site will provide to the Edwards Lifesciences Safety Officer (or Edwards Lifesciences designee) a copy of supporting documentation (such as hospitalization records, laboratory results, consultation report, autopsy results) related to the reported event as soon as possible.

Anticipated Adverse Events

Anticipated adverse events are AEs that have been identified as possible adverse events related to the investigational device or procedure.

Unanticipated Adverse Device Effects

Unanticipated adverse device effects (UADE) are defined as 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 study patients.

All UADEs must be reported to Edwards Lifesciences immediately upon the Investigator's awareness of the event. The AE Forms of the CRF must be completed with 7 working days for all UADEs. The Investigator is also responsible for notifying his/her EC/IRB of all UADEs occurring at his/her site no later than 10 days after the

investigator first learns of the effect (and any additional information as required by EC/IRB or local regulations).

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

Edwards will notify FDA as well as all participating clinical investigators and IRBs of all UADEs that occur during this study within 10 working days after he/she first receives notice of the effect. Investigators are responsible for reviewing information received about UADEs.

Contacting the Sponsor Regarding Safety

The name and telephone number of the individual who should be contacted regarding safety issues as well as the source documentation collection is listed on Contact list of this protocol.

Reasons for Withdrawal

Every patient should be encouraged to remain in the study until they have completed the protocol required follow-up period. If the patient discontinues prematurely from the study, the reason for discontinuation must be documented. Possible reasons for premature discontinuation may include, but are not limited to the following:

- Withdrawal of consent: Patient decides to withdraw from the study.
- Lost to follow-up: All patients should be encouraged to return to the clinic for evaluation during long term follow-up. Three separate telephone calls should be made to attempt to schedule a follow-up visit or obtain follow-up information. All attempts should be documented in the source documents. If the patient does not respond to the 3 telephone calls then the Investigator will send a certified letter to the study patient. The patient will be considered lost to follow-up if this communication is unsuccessful. Patients who discontinue prematurely will be included in the analysis of results, and will not be replaced.
- Death registries: In the event of a patient withdrawal or lost to follow-up, Edwards may opt to obtain the death certificate, search the Social Security Death Index and/or other death registries to obtain survival information.

12.0 Study Data Reporting and Processing

12.1 Study Data Collection

The electronic case report forms (e-CRFs) are designed to accommodate the study design and requirements. Modification of e-CRFs will only be made if deemed necessary by the Executive Operations and Steering Committees.

Other data and reports detailed in the following table should be made available to the sponsor and the respective core lab as outlined in Table 12.1.

Table 12.1-1 Responsibilities for Submitting Other Data

Type of Data	Prepared by Investigator For
QoL Forms: Baseline, 30 Day, 12 Month (KCCQ, EQ5D and SF12 (Cohort B) SF36 (Cohort A))	Edwards Lifesciences and QOL Core Lab
ECHOs: Baseline, Discharge, 30 Day, 12 month, and Annually thereafter to 5 Years Post Procedure, and Other	Echocardiography Core Lab
ECGs: Enrollment, 48 Hours Pre-Procedure, Discharge, 30 Day, and 12 Month, and Other	ECG Core Lab
Explanted Valves (post index procedure implantation)	Histology Core Lab
Supporting documentation of any SAEs	Edwards Lifesciences

12.2 Site Data Monitoring and Quality Control

Primary data collection based on source documented hospital chart reviews will be performed by study coordinators at each clinical site. Electronic CRFs will be completed online. All applicable eCRFs will be automatically available to the study coordinator as new patients are enrolled in the study.

All clinical sites will be monitored periodically by the sponsor or its designee for protocol adherence, accuracy of e-CRFs, and compliance to applicable regulations. Evident patterns of non-compliance with respect to these standards will be cause for the site to be put on probation. If corrective actions are not subsequently undertaken, the clinical site will be asked to withdraw from the trial. Periodic compliance reports will be provided to the Executive Operations Committee.

12.3 Recruitment Tracking

An online recruitment status report will be generated by the data management center automatically. The inclusion trend will allow identification of variations in recruitment frequency among sites. For a well-balanced study, a normal distribution in recruitment is expected; however, outliers will be routinely investigated for study compliance.

12.4 Data Processing and Quality Control

The online database will reside on a central server accessible through the Internet. Conventional data verification sub-routines will be extensively programmed to test entry and logical errors, while all individual (study patient based) case report forms will be linked for cross-reference. Periodic analysis of each data field (across cases) will be performed in order to examine the expected distributions of data, and to identify outliers for possible data errors.

Specific components of this process include:

12.4.1 Data Entry

The data entry is performed by a study coordinator on a dedicated website. All data entered is subjected to data type verification and range checking. The operator is notified of errors that may occur, and depending on the data verification sub-routines, the operator might need to resolve that error before moving to the next entry field.

12.4.2 Data Cleaning

All e-CRFs will be subjected to initial inspection for omitted data, data inconsistencies, and deviations. The resolution of data inconsistencies will be done using electronic tracking and will be resolved by the clinical site.

12.4.3 Data Editing

Each data record is evaluated with extensive electronic intra-form and inter-form edit checking on a regular interval. If an error is discovered the clinical site research coordinator will be notified. Corrections to the e-CRFs will be made by the research coordinator, approved by the investigator or designee and verified by the Sponsor.

12.4.4 Data Update

The cycle of data editing will be ongoing until all the data are clean. The Sponsor or designee will monitor the clinical site for source documentation verification. If further data entry associated with source documentation is discovered during the site visit, additional queries will be generated and will have to be addressed by the clinical site.

12.4.5 Data Back-up

Operational data is hosted for full security and availability with a leading third party hosting service partner that allows the data management center to provide its clients with the highest standards of availability and security:

- Hosting facility is a multi-level protected environment.
- Access is severely restricted with high-end user recognition technology.
- Multi-points backup of critical data is standard.
- Firewalls and other undisclosed technologies provide strong data security.
- Availability all year-round 24 hours a day.

12.4.6 Report Generation and Summary Statistics

A customized report is generated for record keeping and scheduling, serving as an overview of the current database and revealing the backlog in data processing. In addition, recruitment status, study patients' baseline characteristics, and summary statistics of non-endpoint data can be easily scanned for outliers, and protocol compliance by clinical site may be determined for immediate feedback.

12.5 Confidentiality and Protection of Study Files

Passwords will be issued to appropriate data management personnel to ensure confidentiality and protection of the data by allowing variable levels of access to the computer system.

13.0 Training

The training of appropriate clinical site personnel will be the responsibility of the Sponsor or its designee (see Appendix A). To ensure proper device usage, uniform data collection, and protocol compliance, the Sponsor or designee will present formal training sessions to relevant study site personnel in accordance to roles outlined in the Delegation of Authority, which will review the Instructions For Use of the device, the Investigational Plan, techniques for the identification of eligible patients, instructions on in-hospital data collection, methods for soliciting data from alternative sources, schedules for follow-up with the study site coordinators, and regulatory requirements. Detailed telephone, fax and email feedback regarding completion of forms will be provided by the Sponsor, and through regular site monitoring. The Sponsor reserves the right to enforce retraining for sites who have demonstrated study or procedure compliance issues.

14.0 Ethical and Regulatory Considerations

14.1 Role of Edwards Lifesciences

As the study sponsor of this clinical study, Edwards Lifesciences, has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the appropriate regulatory bodies. In this study, the sponsor will have certain direct responsibilities and may delegate other responsibilities to the CRO and the data management center.

14.2 General Duties

The Sponsor's general duties consist of submitting the appropriate regulatory applications, obtaining IRB or Ethics Committee approval prior to shipping the devices, selecting investigators, ensuring proper clinical site monitoring and ensuring study patient informed consent is obtained.

The data management center is responsible for providing the sponsor with quality data that satisfies regulations.

Based on data received from the data management center, the sponsor will prepare written progress reports and a final report. The Sponsor or its designee will coordinate the DSMB, CEC, ECG and QoL Core Laboratories.

14.3 Selection of Investigators

The Sponsor will select qualified investigators, ship devices only to participating investigators, obtain a signed Investigator's Agreement and provide the investigators with the information necessary to conduct the study.

14.4 Study visit compliance

Edwards's implements strict study visit compliance standards as outlined in Section 7.15. Weekly compliance reports are evaluated and communicated to the study investigators and coordinators. Edwards and the PARTNER II Trial Executive Operations Committee reserve the right to temporarily or permanently discontinue enrollment at a study site if compliance standards are not met.

14.5 Monitoring

The Sponsor or its designee, will conduct investigational site monitoring visits to ensure compliance with the protocol and the Investigator's Agreement. The monitor

will ensure that the completed e-CRFs match the source documents, and resolve differences. The sponsor 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.

The Sponsor will review significant new information, including unanticipated adverse events and ensure that such information is provided to the DSMB, CEC, study investigators and to all reviewing IRB/ECs.

Edwards Lifesciences or its designee may perform periodic site and study file audits to evaluate compliance with its own clinical standard operating procedures (SOP) and Good Clinical Practice (GCP) standards.

14.6 Supplemental Applications

As appropriate, the Sponsor will submit changes in the Investigational Plan to the regulatory authority and investigators to obtain IRB re-approval.

14.7 Maintaining Records

The Sponsor, the data management center and CRO (if applicable) will maintain copies of correspondence, all data, device shipment records, adverse device effects and other records related to the clinical trial as appropriate. Investigators or qualified, trained designees will be responsible for maintaining device accountability from the time of receipt of product at the clinical site through use or return of product to Edwards. All investigational devices must be accounted for using the Device Accountability Logs. Investigational devices must be stored according to the conditions set forth for the device on the label in a controlled, locked area. All device shipment records (packing lists, etc.) must be maintained at the site. Device Accountability Logs will be monitored periodically by Edwards and should be faxed in to Edwards on a regular basis. The Sponsor will maintain records related to the signed Investigator Agreements.

14.8 Submitting Reports

The Sponsor will submit all reports required by the appropriate regulatory authorities, including unanticipated adverse device effects, withdrawal of IRB/EC approval, current investigators list, annual progress reports, recall information, final reports and protocol violations.

The data management center investigator or his/her designee will notify the sponsor within 24 hours of any withdrawal of IRB/EC approval or protocol violations.

14.9 Site Record Retention Policy

All core laboratories and clinical sites will maintain study records for two years after marketing approval is obtained or two years after the site is notified that this research protocol has been terminated by the sponsor. Record retention dates will be provided to all parties concerned by the sponsor.

14.10 Informed Consent and IRB

All study patients (or legally authorized representative) must provide written informed consent in accordance with the local clinical site's IRB. A copy of the informed consent form from each center must be forwarded to the Sponsor for review and approval. The Principal Investigator at each site must provide the Sponsor with a copy of the clinical site's IRB approval for the clinical protocol as well as for the informed consent form. Timely approvals for the continuation of the trial as well as the informed consent form at each clinical site must also be forwarded to the Sponsor.

15. 0 Statistical Analysis for the S3 Cohort

Statistical analysis for the S3 Cohort presents a number of unique issues that do not apply to the original cohorts A and B or the registries NR1 – NR6. Those aspects are treated in this section. Items not described in this section will be analyzed according to the methodology of section 7. As with the original cohorts, a more detailed statistical analysis plan will be developed and submitted to the FDA.

15.1 Treatment and Comparator

This is a single arm trial comparing the current treatment group (S3 Cohort) to historical control (SAPIEN) data from the PARTNER I cohorts A and B treatment group representing high risk and inoperable patients. For all data, univariate statistics will be presented for both the current treatment (S3 Cohort) and the combined cohort historical control SAPIEN data without adjustment. Statistical comparisons will be made between the groups through propensity adjusted models; however, unadjusted results will be displayed for descriptive purposes. Details of the propensity modeling will be described below.

The test and control populations are defined as follows:

Test: Prospectively enrolled patients in both inoperable and high-risk patients (S3 Cohort).

Control: Partner I randomized patients whose ITT assignment was the SAPIEN valve, pooled cohorts A and B

Both transapical and transfemoral patients will be included in the Test and Control populations. The primary analysis will be by pooled approaches. Secondary analyses will consider the approaches separately, but these secondary analyses will not be powered.

Transaortic patients will not be included in the analysis population, because there is no comparable group in the PARTNER I trial.

For analysis of PARTNER I data (except echos) the data extract will be the extract dated 15Apr2013. Echos for these historical control patients will be reevaluated by the same core lab used for the S3 Cohort.

Analysis populations

Intent to Treat (ITT) population. The ITT population is defined to include all enrolled subjects in the S3 Cohort who passed all inclusion and exclusion criteria and received treatment assignment from the database, and all ITT randomized PMA patients from the PARTNER I study in the SAPIEN group. Except where otherwise specified, this population will be used for effectiveness endpoint analyses. The

PARTNER I ITT population consists of 527 patients: 179 from cohort B and 348 from cohort A.

Valve Implant population. This population consists of those patients for whom the valve implant process is completed. Except where otherwise specified, this population will be used for all analyses of echocardiographic data including the primary endpoint of Total AR.

- If it is necessary to implant more than one valve (valve-in-valve) the patient will still be in the Valve Implant population.
- If any valve other than the assigned valve is implanted, the patient will not be considered part of the Valve Implant population.
- The PARTNER I valve implant population consists of 496 patients: 170 from cohort B and 326 from cohort A.

15.2 General Statistical Methods

The general statistical methodology is as described in section 7 of this protocol. Changes necessary for the S3 Cohort cohort analysis are described in this section.

15.3 Propensity Modeling

Propensity score methodology will be used to account for the non-randomized nature of the proposed comparisons.

An independent statistician, otherwise uninvolved with the final analysis of this trial and uninvolved in in the analysis of any previous PARTNER data will build the propensity score. This statistician will be blinded to patient level outcome data from both trials.

A logistic regression will be used to model the treatment groups as a function of baseline characteristics. The covariates were chosen based on

- Their suspected relationship to outcomes from the PARTNER I data
- Their possible relationship to the treatment groups (exposure).
- The ability to obtain comparable values from the two trials.

A full list of baseline characteristics to be included in the model is presented in Table 15.1 below. The independent statistician may add to or subtract from the list if doing so will result in a superior propensity model. In particular, covariates with high degrees of correlation may be excluded from the model.

Missing baseline data handling will be discussed below in this section.

After the propensity scores have been created, subjects will be partitioned into quintiles based on their propensity score and irrespective of treatment group. Before proceeding to endpoint analysis, the comparability of the treatment groups with respect to propensity scores and the distribution of the quintiles will be examined.

In order to investigate the comparability of the two groups, balance checking will be performed as follows:

1. Box plots of the propensity scores within each treatment group will be displayed side by side.
2. A table of the number of observations within each of the quintiles by treatment group will be presented.
3. All baseline covariates will be evaluated after propensity adjustment to determine if imbalances still exist. For continuous variables and ordered categorical variables a two-way analysis of variance model will be used. For each of the covariates, the two-way interaction of the treatment and propensity score quintile as well as the treatment comparison after stratification will be checked. A significance level of 0.15 will be used. For categorical variables, a Mantel-Haenszel test will be used at a significance level of 0.15, stratifying by propensity score quintile.
4. The c-statistic from the model will be presented.

The independent statistician will furnish the propensity scores to Edwards, along with appropriate validation of the model and the modeling process.

It is anticipated that echo reading methodology may be different between the original PARTNER I trial and current practice. Accordingly, echo variables for the historical control population for this trial will be reread by the same echo core lab that reads the S3 Cohort echos. Because this new evaluation will eliminate bias, selected baseline echo variables will also be included in the propensity

The variables in the list below have been selected for inclusion in the propensity modeling.

Table 15.1 List of baseline clinical characteristics to be included in the propensity score model.

Variable	Notes
Age	
Sex	
STS Risk Score	
NYHA	
Angina Class	Patients marked as no angina will be considered to be in class 0 for the propensity score development.
BMI	
Native Annular Diameter	Intraoperative TEE measurement
Peripheral Vascular Disease	
Logistic EuroSCORE	
Porcelain Aorta	
High Risk -- Pulmonary Hypertension	
High Risk -- Chest Deformity	
High Risk -- Multiple Previous Interventions	
High Risk -- Chest Radiation	
Renal Insufficiency	Creatinine ≥ 2.0
Peripheral Vascular Disease	
Prior PCI	
Cardiomyopathy	

Variable	Notes
Carotid Disease	
Coronary Artery Disease	
Previous or current smoker	
Hyperlipidemia	
Hypertension	
MI	
Pacemaker	
Peripheral Vascular Disease	
Prior Aortic Valvuloplasty	
Prior CABG	
Aortic valve area	From the reread Echo
Ejection fraction	From the reread Echo
LV Mass	From the reread Echo
Mitral regurgitation	From the reread Echo
Total aortic regurgitation	From the reread Echo

Missing Data in the propensity model

The proportion of missing values at baseline is low in the PARTNER I trial and every effort will be made to ensure this is true for the current trial; however, some missingness does exist. Complete case analysis would not be sufficient, as a few missing values in a number of baseline values would result in a large number of observations being omitted. Accordingly multiple imputation will be used. The following conventions will be followed:

- Imputation will be done within trial, before modeling the treatment groups.
- The initial variable list for the imputation is the same as Table 15.1.
- No outcome variables will be used in the imputation.

- All variables will be converted to numeric variables. Angina and regurgitation will be on a scale of 0 - 4, and NYHA on a scale of 1 - 4. Yes/No variables and sex will be converted to 0-1 variables.

PROC MI will be used to impute values for missing variables. The following conventions will be followed:

- A total of 5 datasets will be created. This number is the SAS default.
- A fixed seed will be used, so that the results can be reproduced. The seed is predefined here as 22675.
- The MCMC method will used.
- After imputation, all Yes/ No variables will be assigned a value of 0 or 1 by rounding to the nearest value.

After the 5 datasets are created, the logistic regression will be run for each imputed dataset. The propensity score for each patient will computed for each of the 5 models as the predicted probability from the model. Then the average score over the 5 models will be calculated for each patient and considered the final propensity score.

The average c-statistic from the five models will also be reported. The c-statistic is not expected to vary widely from model to model, as the extent of missingness is expected to be relatively small.

15.4 Primary endpoints analyses

Propensity quintile Stratified

If the propensity model is deemed adequate per review of the assessments described above, the primary analyses stratified by propensity scores quintiles will be conducted.

Efficacy

For the primary endpoint of total AR classified none/trace versus mild/moderate/severe, a stratified logistic regression model will be used with mild/moderate/severe coded as 1 and none/trace coded 0. The descending option in PROC LOGISTIC will be specified so that the probability of being in the mild/moderate/severe group is being modeled. The logistic regression will be stratified by propensity quintile using the STRATA statement. Treatment will be included as an independent variable coded as 1 if the subject in in the S3 Cohort group and 0 otherwise. The odds ratio and confidence interval for the odds ratio for the effect of treatment will be computed. The upper limit of the confidence interval will be compared to the non-inferiority margin of 1.67, equivalent to a 20% relative reduction as described in the discussion of sample size.

The primary population for this analysis is the valve implant group. The reason for restriction to the valve implant group is that post-baseline echos for other patients contain no information concerning the performance of the valve.

It is certain that by the 30-Day time point there will be missing data. It is reasonable to anticipate 5% deaths at 30 days and there will also be some unevaluable echos, as well as missed visits. The primary analysis will be based on the last available post-procedure echo (30-Day visit or discharge) for each patient. If neither of these post-procedure echos is available the patient will not be included in the primary analysis.

Various sensitivity analyses will be presented as follows:

- A complete case analysis, using only data from the 30 day visit.
- Multiple imputation analysis, where variables observed to be correlated with total AR values will be used in the imputation.

In addition, results will be presented in the ITT population.

Safety

For the primary endpoint of the composite of death, all stroke and major vascular complications, the time to first event (non-hierarchical) will be modeled using the stratified Cox proportional hazards model. The Cox proportional hazards model will be stratified by propensity quintile. Treatment will be included as an independent variable coded as 1 if the subject in in the S3 Cohort group and 0 otherwise. The upper limit of the 95% confidence interval around the hazard ratio for the treatment effect at 1-year will be compared to the non-inferiority margin of 1.2.

Time to the first event will be used for this analysis. Subjects without events who are not followed to 1-year will be censored at their last known time on the study. Only data up to 1-year will be included in the calculation of the hazard ratio. That is, all information after day 365.25 will be censored at day 365.25.

Aside from the propensity adjustment, covariates will not be considered in determining pass or fail for the primary endpoints. Covariate analyses will be presented for sensitivity purposes, following the methodology described in section 7 of this protocol. It should be noted that the chosen endpoint analysis methodology allows for seamless inclusion of covariates, while still using the same statistical methodology and SAS procedures.

Performance Goal Analysis

If the propensity model is not deemed adequate per review of the assessments described above, the primary analysis will be based on PARTNER I and S3 Cohort data without consideration of propensity.

An alternative approach would be to create performance goals for the safety and efficacy endpoints. However, the only reasonable basis for creating a performance goal would be the existing data from the PARTNER I trial; accordingly those data will be used directly for the analysis.

Non-inferiority margins

The non-inferiority margins have been set to be with a relative difference of 20%, which is the value specified by the FDA for cohort A in this protocol.

15.5 Secondary endpoints analyses

All secondary endpoints will be reported both unadjusted and adjusted treatment effects from a model stratified by propensity quintile. These analyses will not be additionally adjusted for any other covariates.

In analyzing the named secondary endpoints for labeling, the propensity adjusted analyses will be used for determining significance, and then the Hochberg correction will be applied.

For continuous variables, a fixed effect ANOVA will be used (PROC GLM in SAS) to determine the stratified treatment effect.

For unordered categorical variables, the Cochran Mantel Haenszel estimates and test statistics will be presented, stratified by propensity quintile.

Time to event variables will be analyzed as described above for the primary safety endpoint using the stratified Cox regression.

The specific secondary endpoints to be considered are those mentioned above in the protocol for cohorts A and B, and the list is not repeated here.

15.6 Sample Size Estimation

The feasibility assumptions for the sample size are based on PARTNER I analysis, PARTNER II Cohort B analysis, and reasonable assumptions as to the S3 Cohort results. The sponsor assumes the risk that the assumptions may not be borne out in the S3 Cohort.

15.6.1 Incorporating the propensity setup into the sample size computation

The sponsor is not aware of any formulas or software that account for the propensity quintile approach. Instead we computed sample size ignoring the propensity matching, and then multiplied by a correction factor.

Table 15.2a shows a potential distribution of patients into propensity quintiles, for a hypothetical trial. This may or may not be the distribution that will be in the S3 Cohort, but it appears reasonable.

Table 15.2a: Hypothetical Propensity Quintile Distribution

Quintile	Control	Test	Total
1	50	150	200
2	75	125	200
3	100	100	200
4	125	75	200
5	150	50	200
Total	500	500	1000

Table 15.2b shows the equivalent-powered sample size, if the enrollment was balanced in each quintile. The computation of the equivalent sizes uses the harmonic mean of the two sizes from table 15.2a.

Table 15.2b: Equivalent balanced sizes

Quintile	Control	Test	Total
1	75	75	150
2	93.75	93.75	187.5
3	100	100	200
4	93.75	93.75	187.5
5	75	75	150
Total	437.5	437.5	875

The difference between 875 and 1000 represents the loss in effective sample size due to the propensity adjustment. The ratio 1000/875 = 1.14 indicates that we would need to add 14% to the sample size computed on the basis of no adjustment.

As mentioned above, the distribution into quintiles in the S3 Cohort is not known at this time, so some higher correction factor is appropriate. We note that the distribution in the paper of Rosenberg and Rubin (1984) is more extreme.

15.7.1 Sample size computation.

Effectiveness endpoint.

- The feasibility assumption for the PARTNER I data is that the proportion of Mild/Moderate/Severe will be 62.72%. As mentioned above, the PARTNER I

echos will be reread, so the actual values for PARTNER I are unknown at this time.

- Since the trial endpoint is non-inferiority, the sample size was computed using the extremely conservative assumption that the rate will be the same in S3 Cohort. In fact, it is anticipated that S3 Cohort should outperform SAPIEN for the primary endpoint due, to the advanced design of the device.

  Extensive simulations were performed to compute the sample size. For the primary effectiveness endpoint, the sample size varies from 200 to 360 patients per trial arm, depending on assumptions concerning the propensity correction and the analysis methodology.

- As a check on the simulations, the sample size was recomputed using PASS 11 software. For an assumed reference event rate of 62.7%, a non-inferiority odds ratio of 1.67, and a power of 90% the software produces a sample size of 328 patients per trial arm.

- The actual S3 Cohort sample size has been set to 500 patients, in order to allow for the various uncertainties in trial design, and for some lost to follow-up.

Safety endpoint.

- The feasibility assumption for the PARTNER I data is that the cumulative composite event rate of all stroke, major vascular complication and mortality at one year is approximately 40.4%.

- Since the trial endpoint is non-inferiority, the sample size was computed using the extremely conservative assumption that the S3 Cohort rate will be the same in SAPIEN. In fact, it is anticipated that S3 Cohort should outperform SAPIEN for the primary endpoint due to the advanced design of the device. The FDA has been furnished data in the PARTNER II B submission showing that SAPIEN XT shows considerable improvement over SAPIEN in both the Vascular complication and Bleeding components of the primary safety endpoint.

- For the primary effectiveness endpoint, the sample size varies from 400 to 800 patients per trial arm, depending on assumptions concerning the propensity correction and the analysis methodology.

- Since the feasibility assumption appears to be highly conservative, the sample size of 500 patients derived for the primary effectiveness endpoint will

be retained. This will provide more than 80% power for the primary safety endpoint analysis.

15.8 Statistical References

References 127, 128 and 129 of section 16.0 – References.

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Appendix A: Training Program

No changes from previous version (protocol version 4.0)

Appendix B: Informed Consent Form

Randomized Cohort A

Randomized Cohort B – Enrollment Closed

Registry NR1, NR2, NR3, NR4, NR5, NR6 – Enrollment Closed

Continued Access Registry NR1, NR2, NR3, NR4, NR5, NR6

Cohort S3

Patient Study ID # PII|_S3_|-|__|__|__|__|-|__|__|__| Patient Initials (First, Mid, Last) |__|__|__|

Patient Information and Study Procedure Informed Consent for Participation in a Clinical Research Study Sponsored by Edwards Lifesciences LLC

The Safety and Effectiveness of the SAPIEN XT™ Transcatheter Heart Valve with NovaFlex and Ascendra delivery systems in Intermediate and High Risk for Aortic Valve Surgery and Patients Who Cannot Undergo Surgery and the SAPIEN 3 Transcatheter Heart Valve with Associated Delivery Systems in High Risk or Inoperable Patients with Severe Symptomatic Aortic Stenosis

RESEARCH PARTICIPANT'S BILL OF RIGHTS

Persons who participate in a medical experiment are entitled to certain rights. These rights include, but are not limited to, the subject's right to:

- be informed of the nature and purpose of the experiment;
- be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized;
- be given a description of any attendant discomforts and risks reasonably to be expected;
- be given an explanation of any benefits to the subject reasonably to be expected, if applicable;
- be given a disclosure of any appropriate alternatives, drugs, or devices that might be advantageous to the subject, and their relative risks and benefits;
- be informed of the avenues of medical treatment, if any available to the subject after the experiment if complications should arise;
- be given an opportunity to ask questions concerning the experiment or the procedures involved;
- be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice;
- be given a copy of the signed and dated consent form; and
- be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

RESPONSIBILITIES OF STUDY PARTICIPANTS

If you decide to participate in this study, your responsibilities will include the following:

- Provide truthful information about your medical history and current conditions.
- Tell the study team about any problems you have during the study.
- Return for the assigned procedure, follow-up visits and tests at the times scheduled.
- Tell the study team if you have been in any other drug or device study during the last 60 days or if you are in a drug or devices study now.
- Keep contact information up to date (address, telephone number, etc.).

Introduction

You are invited to participate in a research study sponsored by Edwards Lifesciences LLC ("Sponsor") that will study the safety and effectiveness of the Edwards SAPIEN 3™ Transcatheter Heart Valve (THV) Model 9600TFX and associated delivery systems:Commander (transfemoral access – through the leg) and Certitude (transapical access – through the side of the chest) or transaortic (through the front of the chest. This investigational (experimental) device is for patients that have severe aortic stenosis (narrowing of the aortic valve resulting in obstructed blood flow) and are either at operable high riskfor standard (traditional) open heart surgery for aortic valve replacement (AVR) or are inoperable (risk is too high for surgery). This investigational (experimental) aortic heart valve (study device) and its delivery system are not yet approved for commercial use by the U.S. Food and Drug Administration (FDA) or any other governmental agency in North America.

Your participation in this research study is voluntary and will be for a minimum of 5 years.

Devices

Patient Study ID # PII|_S3_|-|__|__|__|__|-|__|__|__|__| Patient Initials (First, Mid, Last) |__|__|__|

The Edwards SAPIEN 3™ THV Model 9600TFX study device is a bioprosthetic heart valve. It is an artificial device made to replace your diseased aortic heart valve. Each valve consists of a stent (mesh tube made of metal) to hold the study device in its intended position and valve leaflets (made of biological material derived from cows) to direct the flow of blood in your heart. The THV may be placed transfemorally (through the leg) or transapically (through the side of the chest) or transaortically (through the front of the chest). Transfemorally, the THV is delivered by means of a catheter (small tube) that is placed in an artery (blood vessel) in your leg leading to your aortic heart valve. Transapically and transaortically, the THV is delivered by making an incision in the chest to access the heart directly.

Transfemoral (through the leg) implantation of the study device does not require open heart surgery and is performed in a catheterization laboratory or operating room. The implantation procedure is briefly described in the Procedure section.

Transapical (through the side of the chest) or transaortic (through the front of the chest) implantation of the study device does not require open heart surgery and is performed in the operating room (OR) under general anesthesia. The implantation procedure is briefly described in the Procedure section.

To date, more than 8,000 patients have been enrolled in clinical studies with an Edwards Transcatheter Heart Valve (THV). Some of these patients have died as a result of complications due to the study device and/or the procedure. As a result, there have been changes made to the device and the delivery system. The risks for the study device and the procedure are listed in the Risk section. While the Investigator (research study doctor) performing the procedure may have limited experience with this technology, he or she, has received extensive training by experienced Investigators who have implanted the study device in patients in the United States, Europe and/or Canada, and by the manufacturer of the study device, Edwards Lifesciences LLC.

Purpose
The purpose of this study is to evaluate the safety and effectiveness of the study device in a maximum of 4200 patients in up to 60 hospitals. The S3 Cohort will be evaluated in 300 patients.

You are being considered for this research study to replace your diseased aortic heart valve because your doctors have determined that you are operable high risk or inoperable for standard (traditional) open heart surgery for aortic valve replacement (AVR).

You will be screened (evaluated) for this research study. Based on the results of the screening tests and procedures, it will be determined if you are able to participate in the study. If you are eligible (passed all the screening tests), you will be enrolled into the research study. If the results of the screening tests and procedures show that you are not eligible, you will not be enrolled into the research study.

Methods
To determine your eligibility to participate in this research study, you are being asked to undergo the following screening tests and procedures.

Screening Tests and Baseline Procedures
You will undergo the following routine (not experimental) tests and procedures:

- Review of your medical history
- Physical examination
- Mini-Mental State Examination (questionnaire to assess your mental status)
- National Institutes of Health Stroke Scale (NIHSS) (physical exam and questions)
- Modified Rankin Scale (MRS) (a questionnaire that helps determine your ability to perform activities of daily living and mobility)
- Barthel Index (a questionnaire that helps determine your ability to perform activities of daily living and mobility) may be done

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- Quality of Life questionnaire (a questionnaire that helps determine your quality of life in relation to your health and well-being)
- Transthoracic echocardiogram (TTE: a probe is placed on your chest and images of your heart are recorded). The TTE does not require anesthesia.
- Blood tests (approximately 2-3 teaspoons)
- ECG (a test which measures the electrical activity of your heart)
- Chest x-ray
- Heart catheterization with an x-ray dye (contrast media) to evaluate your heart and the severity of your aortic stenosis
- Thoracic and abdominal catheterization [computed tomography (CT) angiograms] with an x-ray dye (contrast media) to assess your iliac and femoral arteries (blood vessels in your upper legs). Magnetic resonance imaging (MRI) is a special x-ray that will be used as an alternative if you have impaired renal function that does not allow for the usage of x-ray dye (contrast dye).
- [EW1]Frailty Index (test that involves answering a few questions about your ability to perform daily activities, performing a few hand grips, and walking fifteen feet, if you are able.)

There are some risks involved in these procedures (see Potential Risks of Routine Tests and Procedures below).

Potential Risks of Routine Tests and Procedures

Possible complications of the screening assessments may include, but are not limited to:

Arrhythmia (irregular heart beat) or heart murmur
Allergic reaction to anesthesia or to contrast media (x-ray dye)
Anemia (reduced number of red blood cells) or abnormal lab values
Angina (chest pain), arteriovenous fistula (weakening of the vessel wall between the arteries and veins at the access site)
Bleeding or hemorrhage (a rapid loss of blood) requiring transfusion or intervention
Blood Tests: Discomfort, bleeding, bruising or small risk of an infection
Cardiovascular (involving the heart and blood vessels) injury: such as perforation (a hole), tear or dissection (damage) of vessels, heart muscle or valve/valve structures that may require interventionconduction system (the system that controls the heart to contract and pump blood) injury which may require a permanent pacemaker
Death
Embolization (obstruction) including air, calcification (plaque) or thrombus (clot formation)
Exercise intolerance (unable to do exercise that is expected for one's physical condition) or weakness
Fever
Heart failure or heart attack
Hematoma (blood accumulation/bruising) at the access site
Hypertension (high blood pressure) or hypotension (low blood pressure)
Infection including septicemia (infection in the blood), endocarditis (inflammation of the heart) and incisional site infection
Inflammation neurological (brain, spinal cord and nerves) changes: including stroke, transient ischemic attack (mini-strokes), or paralysis
Pain or changes at the access site
Pericardial effusion or cardiac tamponade (bleeding into the heart sac)permanent disabilityrespiratory insufficiency (shortness of breath), pleural effusion (fluid accumulation in the lung) or respiratory failure (inability to breathe requiring a respirator)
Pulmonary edema (fluid in the lungs)
Renal insufficiency (poor kidney function) or renal failure (poor kidney function requiring dialysis) or acute kidney injury (sudden onset of kidney problems)retroperitoneal bleed (bleeding into a space in the abdomen)
Skin injury (painful, disfiguring and long-lasting) due to risk of radiation from some of the tests including the study device procedure
Syncope (fainting or brief loss of consciousness)systemic (body) or peripheral (arms or legs) ischemia (decreased

blood flow) or nerve injury.Chest X-ray: The radiation dose from a single chest x-ray is about the same as the average person receives from background (environmental) radiation in 10 days.

As with any research study, there is also the possibility of side effects not presently known. As the research study progresses, you will be informed of any new study results that may affect your willingness to remain in the research study.

Benefits of Screening Tests and/or Procedures
You may or may not receive any direct benefit from this research study. The potential benefit from undergoing these screening assessments is that you will have undergone a thorough examination of your medical condition and you may have a better understanding of available therapies.

Potential Risks of BAV, Study Implantation Procedure and Study Device
As with any research study, there is a possibility that complications may occur that are not anticipated. The Investigator will speak to you about potential complications and answer your questions.

Other possible risks of the study implantation procedure may include, but are not limited to:

Abnormal lab values (including electrolyte imbalance)
Allergic reaction to antithrombotic therapy, contrast media, anesthesia or device materials
Aortic valve thrombosis/occlusion
Anemia (reduced number of red blood cells)
Aneurysm (widening or bulge of a portion of an artery due to weakness in the wall)
Angina (chest pain)
Arrhythmia (irregular heart beat) or heart murmur including ventricular fibrillation (VF) and ventricular tachycardia (VT)
Arthralgia (joint pain)
Bleeding / Bruising
Cardiogenic shock (heart muscle is unable to supply blood to the body) / pulmonary edema
Cardiovascular injury (involving the heart and/or blood vessels) including perforation or dissection of vessels (damage), ventricle (heart chamber), myocardium (heart muscle) or valvular structures that may require intervention
Conduction system injury (heart doesn't beat effectively) which may require a permanent pacemaker
Embolization (obstruction including air, calcific/thrombotic (plaque) valve material or thrombus (clot formation)
Exercise intolerance or weakness (unable to do exercise that is expected for one's physical condition) (including weakness)
Femoral AV fistula or pseudoaneurysm
Fever
GI symptoms
Headache
Heart failure
Heart murmur
Hematologic dyscrasia (abnormal blood cells)

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Hematoma (blood accumulation or bruising)
Hemorrhage requiring transfusion or intervention (a rapid loss of blood)
Hepatic enzyme changes (changes in liver lab values)
Hypertension (high blood pressure) or hypotension (low blood pressure)
Infection including septicemia and endocarditis (inflammation of the heart)
Inflammation
Ischemia, limb or myocardial (decreased oxygen to the tissues)
Myalgia (muscle pain)
Myocardial infarction (heart attack)
Infection, pain or changes at the access site
Paralysis
Pericardial effusion or cardiac tamponade (bleeding into the heart sac)
Peripheral ischemia (decreased blood flow in arms or legs) or nerve injury
Permanent disability
Pleural effusion (fluid accumulation in the lungs)
Post operative encephalopathy (swelling of the brain)
Pulmonary edema (fluid in the lungs)
Renal insufficiency or renal failure (kidneys do not work well or stop working)
Reoperation (having another operation)
Respiratory insufficiency or respiratory failure (inability to breathe requiring a respirator)
Restenosis (narrowing of the aortic valve)
Retroperitoneal bleed (bleeding into a space in the abdomen)
Shock
Silent cerebral edema
Stroke/transient ischemic attack (mini-strokes), clusters (type of mini stroke) or neurological (brain, spinal cord and nerves) deficit
Syncope (fainting or brief loss of consciousness)
Vasovagal response (lightheaded, nausea, fainting)
Vessel spasm (vessels narrow preventing blood flow)
Vessel thrombosis (blood clot) / occlusion (blockage of vessel)

In a prior clinical investigation, the incidence of strokes or transient ischemic attacks (mini-strokes) were higher in patients who received the study device than in patients who had standard open heart surgery for aortic valve replacement (AVR). At 30 days post operative: 5.5% (study device) versus 2.4% (AVR). At 1 year post operative: 8.3% (study device) versus 4.3% (AVR).

Another possible complication is the inability to place the study device in the correct position in your diseased aortic valve. This may cause three possible outcomes: either the valve will have to be placed in another part of your aorta, (which will not improve your aortic stenosis) the valve will have to be removed using open heart surgery or another valve or valves will be placed in the originally implanted valve.

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Additional risks specifically associated with the use of the study device include, but may not be limited to, the following:

Acute coronary occlusion
Allergic/immunologic reaction to the implant
Aortic annulus dissection/rupture/trauma
Arrhythmia including AV block, Atrial fibrillation/Atrial flutter
Aortic valve insufficiency
Blood loss requiring blood transfusion
Cardiac arrest (heart stops beating)
Cardiac failure or low cardiac output (poor heart function)
Cardiogenic shock (heart does not pump well)
Cognitive impairment
Conduction disturbance including AV block requiring pacemaker
Coronary flow obstruction/transvalvular flow disturbance (a blood clot in the heart vessel which leads to poor blood circulation in the heart)
Device degeneration (device breakdown)
Device embolization (obstruction)
Device explants explants (removal of the device)
Device malfunction requiring intervention/surgery
Device migration or malposition requiring intervention (THV implanted in unintended location)
Device thrombosis (clot formation) requiring intervention
Emergency cardiac (heart) surgery
Endocarditis (infection of the heart)
Hemolysis (disruption of blood cells)
Injury to aortic and/or mitral valve
Mechanical failure of delivery system, and/or accessories
Mediastinitis (swelling between the lungs)
Mediastinal bleeding (bleeding between the lungs)
Non-emergent reoperation (another operation)
Nonstructural dysfunction
Paravalvular or transvalvular leak (blood leakage around or in the valve)
Structural valve deterioration (wear, fracture, calcification, leaflet tear/tearing from the stent posts, leaflet retraction, suture line disruption of components of a prosthetic valve, thickening, stenosis)
Valve deployment in unintended location
Valve regurgitation (blood leakage around the device)
Valve stenosis (narrowing)
Valve thrombosis (blood clot)

Patient Study ID # 2010-12-|__|__|-|__|__|__| Patient Initials (First, Mid, Last) |__|__|__|

Specific risks associated with this research study:

- Blood Tests: Discomfort, bleeding, bruising or small risk of an infection.
- Radiation Exposure:
  This research study includes procedures that will be exposing you to radiation from x-ray procedures. If you receive all of the x-ray procedures (4 chest x-rays, 2 CT scans of the head, x-ray/fluoroscopic guidance of the catheter valve placement) you will receive a total radiation dose of about 50 milliSieverts. A milliSieverts (mSv) is a unit describing an amount of radiation dose to a person. As a comparison, people who work with radiation on a daily basis are allowed to receive a maximum of 50 mSv in one year.
  If you receive the fluoroscopic procedure, the skin area exposed to the x-rays could react to produce an effect similar to sun burn. If a skin reaction occurs at all, it could show up from a few hours to a few days after the procedure, and usually goes away on its own. If you have a skin reaction, you should tell the Investigator immediately and you may be asked to return for a study visit.

As with any research study, there is also the possibility of side effects not presently known.

If you believe you have a research-related complication, you should contact _____at _____.

Potential Benefits of the Research Study Procedures
You may or may not experience any direct benefit from this research study. Potential benefits may include improvement in the symptoms related to your aortic stenosis. Study procedure techniques further include a less invasive procedure, shorter procedure time and less anesthesia than in open heart surgery for aortic valve replacement.

Treatment with the study device may provide both short and long-term relief of your symptoms, improved aortic valve function, and an improvement of your cardiac function that could potentially increase both your life expectancy and improve your quality of life.

While it is possible that you will receive no direct benefit from this research study, but others may benefit in the future from your participation.

What happens next?
Once the screening tests and procedures have been completed, the Investigator will determine whether you are eligible to participate in this research study. If you are eligible, you will be enrolled into the research study. If the results of the screening tests show that you are not eligible, you will not be enrolled into the research study and no further testing or procedures will be done. The Investigator may discuss alternative treatment options available to you.

Alternative Treatments
You have a condition called aortic stenosis, which is a critical narrowing of the aortic valve. Historical treatment options for patients with aortic stenosis are as follows:

- Balloon aortic valvuloplasty (BAV: a procedure to stretch the aortic valve opening)
- Open heart surgery for aortic valve replacement to replace your aortic valve with another commercially available prosthetic valve – either bioprosthetic or mechanical
- Medical management (treatment with medication).
- Newer treatment option for patients with aortic stenosis that are not eligible for open heart surgery for aortic valve replacement: Transcatheter aortic valve replacement with the SAPIEN™ Model 9000TFX, the first device model FDA approved for patients considered high risk or inoperable.

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Enrollment Process
You will be enrolled into the research study if you pass the screening tests and procedures. You will be assigned to receive the SAPIEN 3 THV. You will receive the study device either by transfemoral (through the leg) or by transapical (through an incision in the chest) delivery. The delivery method will be based on your screening tests and the Investigator(s) assessment.

Procedure

What happens during the transfemoral (through the leg) study device procedure?
The Investigator will perform a balloon aortic valvuloplasty (BAV) before implanting the study device. This procedure uses a balloon mounted on a catheter that is inserted through the arteries in your groin leading to your heart to expand (open) your diseased aortic valve.

The study devices are designed for implantation through transfemoral access (a puncture or incision in your groin). Due to the size of the catheter placed in your artery, the Investigator may consult a vascular surgeon to discuss the opening and closure of the artery in your leg. Prior to implantation, the valve will be carefully crimped (compressed) and mounted onto the balloon delivery system by the Sponsor representative or study team designee. It will then be inserted into your groin via a catheter and delivered directly into your diseased aortic valve.

The procedures (BAV and study device implantation) will be performed in a cardiac catheterization laboratory under local and/or general anesthesia using fluoroscopy (x-rays) for visualization. These procedures avoid prolonged, deep anesthesia and open heart surgery which generally requires a longer recovery period than the experimental procedure. The duration of fluoroscopy that you receive will usually fall in the range of 30 minutes.

Employees from the Sponsor that made the valve may be present during the study device implant procedure. A surgical team will be on standby in case of complications.

What happens during the transapical (through the side of the chest) or transaortic (through the front of the chest) study device procedure?
The Investigator will perform a BAV before implanting the study device. This procedure uses a balloon mounted on a catheter that is inserted through the incision in your chest leading to your heart to expand (open) your diseased aortic valve.

The study devices are designed for implantation through transapical or transaortic access (an incision in your chest). The transapical or transaortic approach is performed in a cardiac operating room (OR) under general anesthesia. An incision (thoracotomy) will be made on your left side (transapical) or on the front of your chest (transaortic) so that the Investigator can access the apex (tip of your heart). Prior to implantation, the valve will be carefully crimped (compressed) and mounted onto a balloon delivery catheter by the Sponsor representative or study team designee, using a specially designed crimping (compressing) device. It will then be inserted into your heart through an incision via a balloon catheter, and delivered directly to your diseased aortic valve. The valve will then be expanded to fit across your diseased aortic valve, opening your diseased aortic valve permanently. The incisions in your heart and chest will then be closed.

Employees from the Sponsor that made the valve may be present during the study device implant procedure. A surgical team will be on standby, in case of complications.

What happens after any of the procedures?
After the study device procedure, you may go to the Intensive Care Unit (ICU) for close monitoring. After the open heart surgery, you will go the Intensive Care Unit (ICU) for close post operative monitoring. You may be given blood thinning medications such as: aspirin, clopidogrel (Plavix) or Ticlopidine (Ticlid). Once your Investigator has transferred you to a regular hospital room, you will continue to be closely monitored until you are discharged from the hospital.

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After the procedure, the following tests will be completed:

- Chest x-ray
- Blood tests (approximately 2-3 teaspoons)
- ECG (a test which measures the electrical activity of your heart)
- National Institutes of Health Stroke Scale (NIHSS) (physical exam and questions) may be done
- Modified Rankin Scale (MRS) (a questionnaire that helps determine your ability to perform activities of daily living and mobility)
- Barthel Index (a questionnaire that helps determine your ability to perform activities of daily living and mobility) may be done
- CT or MRI (magnetic resonance imaging) brain scan for any subject with symptoms suggestive of a neurological event and an abnormal NIHSS.

The Investigator may ask you to take Plavix or a similar blood thinner for 6 months after any of these procedures. In addition, you may be prescribed aspirin for the rest of your life. This is recommended for routine stenting of coronary blood vessels and any replacement heart valve.

What happens <u>at the time of discharge from the hospital</u>?
You will undergo the following routine tests and procedures:

- Physical exam
- Blood tests
- National Institutes of Health Stroke Scale (NIHSS) (physical exam and questions)
- Modified Rankin Scale (MRS) (a questionnaire that helps determine your ability to perform activities of daily living and mobility)
- Barthel Index (a questionnaire that helps determine your ability to perform activities of daily living and mobility) may be done
- ECG (a test measures the electrical activity of your heart)
- Chest X-ray
- Transthoracic echocardiogram (TTE: a probe is placed on your chest and images of your heart are recorded). The TTE does not require anesthesia

Follow-up Visits After Any of the Procedures
You will return to the hospital for follow-up evaluations at 30 days, 6 months, 1 Year and then yearly for a minimum of 5 years after the implant procedure. The exams at these visits include:

<u>30 Day Follow-up:</u>

- Physical exam
- Blood tests (approximately 2-3 teaspoons)
- Quality of Life questionnaire
- NIH Stroke Scale test
- Modified Rankin Scale (MRS) test
- Barthel Index (a questionnaire that helps determine your ability to perform activities of daily living and mobility) may be done
- CT or MRI (magnetic resonance imaging) brain scan for any subject with symptoms suggestive of a neurological event and an abnormal NIHSS
- Transthoracic echocardiogram
- ECG
- Chest X-ray. If any changes are identified with the study device, a fluoroscopy (a type of x-ray that shows movement) will be done.
- Six Minute Walk Test (measures how far you can walk in six minutes).

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6 Month Follow-up:

- Physical exam
- NIH Stroke Scale
- Modified Rankin Scale (MRS) (physical exam and questions)
- Barthel Index (a questionnaire that helps determine your ability to perform activities of daily living and mobility) may be done

1 Year Follow-up:

- Physical exam
- Blood tests (amount of approximately 2-3 teaspoons)
- Quality of Life questionnaire
- NIH Stroke Scale
- Modified Rankin Scale (MRS)
- Barthel Index may be done
- CT or MRI brain scan for any subject with symptoms suggestive of a neurological event and an abnormal NIHSS.
- Transthoracic echocardiogram
- ECG
- Chest X-ray. If any changes are identified with the study device, a fluoroscopy (a type of x-ray that shows movement) will be done.
- Six Minute Walk Test.

1 Year Telephone Call

- This call occurs after the last patient enrolled in the study has reached their 1 Year Follow-up visit

2 – 5 Year Follow-up:

- Physical exam
- Blood tests (amount of approximately 2-3 teaspoons)
- Quality of Life questionnaire
- NIH Stroke Scale
- Modified Rankin Scale (MRS)
- Barthel Index may be done
- CT or MRI brain scan for any subject with symptoms suggestive of a neurological event and an abnormal NIHSS may be done
- Transthoracic echocardiogram
- Chest X-ray. If any changes are identified with the study device, a fluoroscopy (a type of x-ray that shows movement) will be done.
- ECG may be done
- Six Minute Walk Test may be done

Telephone Calls

- You may be contacted by telephone in between your study visits to see how you are doing

Unscheduled Study Visit

- If the Investigator has determined that you have received too much radiation exposure you may be asked to return for a skin assessment
- If the you have suffered a neurological injury such as a stroke or a transient ischemic attack (mini-strokes) you may be asked to return for an assessment

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Voluntary Participation and Termination
Your participation in this research study is voluntary and it is your right to refuse to participate or withdraw at any time without penalty or loss of benefits to which you are otherwise entitled. If you decide to withdraw, you must contact the Investigator, Dr. _____, in writing and let him/her know that you are withdrawing from the research study. The mailing address is _____. If you choose to withdraw from the research study, any new information about this research study may not become available to you in a timely manner. Any significant new findings that develop during the course of the research study which may relate to your willingness to continue participation will be provided to you by the Investigator. The Investigator may choose to terminate your participation if you fail to follow the study guidelines or if new information becomes available that may affect your health.

Financial Obligation and Liability
Edwards Lifesciences LLC is the Sponsor and manufacturer of the study device used in this research study. You will not incur any additional costs for the specific tests (blood tests, echocardiogram, angiogram, x-ray, medications) required by the study. You will not be compensated in any way for your participation in this research study. The Sponsor will not compensate you for injury or for any additional expenses incurred due to this research study.

You understand that all forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. In spite of all precautions, you might develop medical complications from participating in this research study. The Sponsor or the hospital will not assume liability for injury directly attributable to this study device, and/or absent negligence on its part. In the event physical injury occurs as a result of participating in this research study, the necessary facilities, emergency treatment and professional medical services will be available to you, just as they are to the general community. You do not waive any liability rights for personal injury by signing this form.

Confidentiality, Anonymity and Authorization
By signing this Consent form you understand that the information derived from this research study may be given to the FDA and to international regulatory agencies which have different privacy laws, as required in the interest of public safety and in accordance with regulations. These regulatory bodies (FDA, for example) may inspect research records and learn your identity. By participating in this research study, you agree to allow representatives from regulatory agencies and the Sponsor to have access to your confidential health, medical records and research information concerning the study device. You will also allow representatives from the Sponsor to photocopy information from your medical records for study purposes. Your medical record number, initials, birth date, implant serial number, and operative and visit dates will be collected by the Sponsor but will not be used to reveal your identity. Except when required by law, you will not be identified by name, address, telephone number, or any other direct personal identifier in the research study records outside of _____ (Institution).

You understand that the Investigators or the Sponsor may use the research study information collected from your participation for publications. Your participation and the information collected during this research study will remain confidential and any research study information that may be published or further researched will not reveal your identity. Your authorization will not expire because this information will be used for research purposes in the future. However, if your information is obtained in the state of California this Authorization will expire in twenty years.

Your echocardiography (ECHO) and ECG evaluations identified by your initials, patient identification number, and date of exam will be read by the ECHO evaluation lab and the ECG evaluation lab respectively, which is under contract with the Sponsor. There may be a possibility that your name may be on the ECHO CD which is held in confidentiality at the lab. No other information about you will be revealed to the evaluation labs. Information from your ECHO evaluation and ECG evaluation will only be used to support product approval applications and publications.

A description of this clinical trial will be available on http://www.Clinicaltrials.gov, as required by U.S Law. This web site will not include information that can identify you. At most, the web site may include a summary of results. You can search this web site at any time.

Patient Study ID # 2010-12-|__|__|-|__|__|__| Patient Initials (First, Mid, Last) |__|__|__|

You understand that the information from this research study will be sent to the Sponsor who is located in the United States. If the research study design or the use of the information is changed, you will be informed and you will be asked to sign another consent form.

While participating in this research study, you will not be allowed to participate in any other research study without approval from the Investigator. This is to protect you from possible injury arising from such events as extra blood tests, x-rays, interaction of research drugs, or similar hazards.

Are you currently participating in any other research study?
☐Yes
☐No

Can your personal physician be informed of your participation in this research study?
☐Yes
☐No

Patient Study ID # 2010-12-|__|__|-|__|__|__| Patient Initials (First, Mid, Last) |__|__|__|

SIGNATURE OF RESEARCH SUBJECT OR LEGAL REPRESENTATIVE

I acknowledge that I have fully read, or have had read to me, the information provided above. I have been given an opportunity to ask questions and all of my questions have been answered to my satisfaction. If I have any additional questions or in the event of a research-related injury, I can contact _____ (name) at _____ (telephone). In the event that I have any questions regarding my rights as a research patient, I may contact _____ (name) at _____ (telephone).

I also acknowledge that I have been given a copy of this signed Consent Form.

BY SIGNING THIS FORM, I WILLINGLY AGREE TO PARTICIPATE IN THE RESEARCH STUDY DESCRIBED.

_____ _____
Name of Subject (Printed) Date

_____
Signature of Subject

_____ _____
Name of Legal Representative (Printed, if applicable) Date

_____
Signature of Legal Representative (Printed, if applicable)

SIGNATURE OF INVESTIGATOR/PERSON OBTAINING CONSENT

I have explained the research study to the patient or his/her legal representative and answered all of his/her questions. I believe that he/she understands the information described in this document and voluntarily consents to participate.

_____ _____
Name of Investigator/Person obtaining Consent (Printed) Date

_____
Signature of Investigator/Person obtaining Consent

SIGNATURE OF WITNESS (If required)

My signature as witnessed certified that the subject or his/her legal representative signed this consent form in my presence as his/her voluntary act and deed.

_____ _____
Date

Name of Witness (Printed)

_____

Signature of Witness

Appendix C: Imaging Core Lab Procedure Manuals

ECHO Core Lab Manual of Operations (C5Research)

ECG Core Lab Protocol (Cardiovascular Research Foundation)

No changes from previous version (protocol version 4.0)

Appendix D: Quality of Life Core Lab Protocol

QOL Core Lab - Mid America Heart Institute (MAHI)

No changes from previous version (protocol version 4.0)

Appendix E: Histopathology Core Lab Protocol

Updated

HISTOPATHOLOGY CORE LAB PROTOCOL

1.0 Purpose

The purpose of the following protocol is to provide the Investigator (clinical site) with procedures for handling and assessing the study valve after explantation. The assessment should include gross examination, identification of the primary failure mode and contributory factors leading to the explant (if possible), photographs and other documentation, and preparation of the explanted valve for shipment to the Sponsor or designated Histopathology Laboratory for further analysis. Also, included is an overview of the procedures to be followed by the Sponsor and/or designated Histopathology Laboratory for gross analysis, as well as macro and micro histopathology analysis. Investigational valves that are removed at any time with an allegation of device malfunction should be returned to the Sponsor for evaluation. All other explants (those not with an allegation of device malfunction) should be sent to the Histopathology Core Lab. Refer to Section 6.0 for Tissue Shipment information.

2.0 Valve Explanation Procedure

Upon autopsy (only), prior to removal of the valve from the heart, obtain *in situ* photographs of the inflow and outflow tracts, valve leaflets, and conduit tissue. Using care, the valve should be excised in a fashion so as to keep the valve and surrounding structure as intact as possible.

For all explants (those obtained at autopsy as described above or through valve replacement surgery following standard surgical practice), once removed the valve should be rinsed of all residual blood by gently agitating in sterile Lactated Ringers solution.

Prior to shipment of the valve to the Sponsor or designated Histopathology Laboratory for further dissection and pathologic analysis, grossly examine the explanted tissue *in toto* and record observations on the explanted valve CRF. Gross photographs will be taken of both inflow and outflow tracks. Observations of stent frame apposition and neointimal incorporation will be documented.

Swab cultures of possibly infected areas should be taken, sent to the appropriate laboratory and documented in the pathology report. If no infection is obvious, then no culture swab is necessary.

3.0 Tissue Dissection Procedure

Once the valve has been explanted, grossly examined, and photographed, the tissue should be sent to the Sponsor or designated Histopathology Laboratory for histological analysis. Place the sample into a specimen cup or equivalent container. The specimen cup should contain 10% buffered formalin solution. On the outside of the container, label the study patient number, valve

serial number, site number, and date of explant. The tissues will be examined at the Sponsor or designated histopathology laboratory to determine the morphology of the tissue/valve, as well as to assess leaflet calcification, and general histopathology. The valve tissues will be stained with H&E, Von Kossa, or other relevant stains and will be reviewed by a certified pathologist.

4.0 Fixation

Explanted study valve samples shall be submitted in 10% formalin.

5.0 Documentation

Please provide the following supporting documents to enable complete explant assessment. The documents should enable the Sponsor to determine explant date, duration of implant, surgical pathology, mediating study patient history, reason for reoperation, gross description, and pathology notes. The documents may be returned with the shipped tissue.

- Operative report dictated at the explant
- Sponsor Case Report Forms
- Pathology report (once available)
- Blood study results (once available)
- Preoperative Echocardiographic Report (Just Prior to Explant)

6.0 ***Tissue Shipment***

Investigational valves that are removed at any time with an allegation of device malfunction should be returned to the Sponsor for evaluation. Contact your sponsor representative for assistance with the return which will include a Complaint Report (completed by the sponsor) and biohazard packaging.

Shipping Address:
Edwards Lifesciences LLC
1212 Alton Pkwy
Irvine, CA 92606
Attention: Returned Goods
CER/RGA#:_____

Investigation valves that are removed for any reason other than an allegation of device malfunction should be sent to the Histopathology Laboratory. Place the specimen container within two, separately sealed biohazard plastic bags. Place the sealed sample in a small non-crushable box. Ship the tissue to the Sponsor's designated Histopathology Laboratory by Federal Express PRIORITY (Sponsor billing number 0900-2768-9) or equivalent shipping service:

Histology Core Laboratory:

Renu Virmani, MD
CV Path Institute, Inc.
19 Firstfield Road
Gaithersburg, MD 20878
Phone: 301-208-3570 ext 114

7.0 Procedure for Evaluation at Sponsor or Designated Histopathology Laboratory

Gross Examination and Photographs
If possible, photographs should be taken at each stage of dissection to better document observations. Assessment of the valve leaflets and commissures will include presence of leaflet fenestrations, tears, thrombus formations and calcified nodules. Photographs will be taken of all suspected abnormalities. The gross examination should include macroscopic assessment of the following:

Mobility and shape of leaflets;

Host tissue overgrowth;

Calcification (leaflet and conduit);

Evidence of infection;

Leaflet wear or degeneration;

Leaflet thickness;

Leaflet fenestrations;

Fibrosis sheathing;

Aneurysm formation;

Valve thrombosis;

Tissue rejection;

Inflammation.

8.0 **Radiographic Analysis**

Additionally, X-rays will be taken of all valve/devices to assess placement and apposition of the stent frame to the host vessel and to identify leaflet calcification. X-rays will be in both transverse and longitudinal planes.

9.0 Dissection and Sampling

A portion of each valve assembly, to include one commissure and one half of each adjacent valve leaflet, will be removed from the assembly and submitted for scanning electron microscopic examination. The portion will be removed by making two longitudinal cuts through the length of the host vessel and metal stent frame. The remaining valve leaflets will be excised away at the point of attachment to the assembly.

Scanning Electron Microscopy

Scanning electron microscopy will be employed to assess degree of intimal incorporation of the metal stent frame, endothelial coverage of the host vessel neointima and valve leaflets. Leaflet surface topology will be assessed and any defects in the surface identified.

10.0 Histopathology Evaluation

Paraffin:

Valve leaflets will be inked on the outflow surfaces to maintain orientation. Serial slices of the leaflets will be made from base to free edge and flat embedded for cross-sectional examination. Hematoxylin and eosin, trichrome, Movat pentachrome, Von Kossa calcium, and Phosphotungstic acid-hematoxylin stains will be performed on all sections

Plastic:

The remaining valve assembly (minus the portion removed for SEM) will be processed and embedded in methylmethacrylate plastic. Transverse sections will be sawed and ground from the area of the superior tip of the first stent strut (proximal end), from the mid portion near the proximal end of the short bar assembly (not to include PET skirt) and from the distal end through the short bar assembly and commissures.

Transmission electron microscopy (TEM)

One half of each valve leaflet from the mid-portion will be reserved for transmission electron microscopy. The section will be of full leaflet thickness, flat embedded in epoxy resin and cross-sectioned. TEM will be employed to assess collagen integrity and calcium deposition.

Explant Shipping Form

Please enter the following information and fax the form to CV Path at (301) 208-3745 24 hours prior to shipment.

Ship to:
TBD

Protocol #: ___PARTNER II 2010-12_____ Subject ID: _____

Sponsor: _____Edwards Lifesciences_____ Device Type: __Sapien XT ™ THV_____

Study Site: _____ Site Principal Investigator: _____

Item Shipped (Serial Number)	**Sender: Print Name / Signature**	**Date Harvested (If available)**	**Shipping Tracking Number**	**Date Sent**

Comments:

Please keep a copy of this form in the subject study file. If possible, please include a copy of this form in the package

Appendix F: NIH Stroke Scale

No changes from previous version (protocol version 4.0)

Refer to Appendix L for NIH Stroke Scale Instructions

Appendix G: Mini Mental State Exam

No changes from previous version (protocol version 4.0)

Appendix H: Six Minute Walk Test

No changes from previous version (protocol version 4.0)

Appendix I: DSMB Charter

No changes from previous version (protocol version 4.0)

Appendix J: Clinical Events Committee (CEC) Charter

Updated

C5Research

Edwards Lifesciences

Cleveland Clinic Center for Clinical Research (C5Research) Clinical Events Committee

Manual of Operations

Version: 3.0 March 12, 2013
Previous Versions: September 13, 2011 and May 17, 2012

The Partner II Trial: Placement of AoRTic Transcatheter Valves Trial
The Safety and Effectiveness of the SAPIEN XT™ Transcatheter Heart Valve with NovaFlex and Ascendra 2 delivery systems (Transfemoral and Transapical) in Intermediate Risk for Aortic Valve Surgery and Patients Who Cannot Undergo Surgery

Reviewed and Approved by:
I have reviewed the Manual of Operations and find the document to be accurate and complete.

Jodi Akin, Vice President, Clinical Affairs, Edwards Lifesciences Corporation — Date

Venu Menon, MD — Date
Medical Director, Clinical Events Committee C5Research, Cleveland Clinic

Martin B. Leon, MD Executive Committee Member — Date

Craig R. Smith, MD Executive Committee Member — Date

Cleveland Clinic Center for Clinical Research (C5Research) Clinical Events Committee

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Reviewed and Approved by:
I have reviewed the Manual of Operations and find the document to be accurate and complete.

Jodi Akin, Vice President, Clinical Affairs, Edwards Lifesciences Corporation — Date

Venu Menon, MD — Date
Medical Director, Clinical Events Committee C5Research, Cleveland Clinic

Martin B. Leon, MD Executive Committee Member — 5/17/13 — Date

Craig R. Smith, MD Executive Committee Member — Date

C5Research

Edwards Lifesciences

Cleveland Clinic Center for Clinical Research (C5Research) Clinical Events Committee

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Reviewed and Approved by:
I have reviewed the Manual of Operations and find the document to be accurate and complete.

Jodi Akin, Vice President, Clinical Affairs, Edwards Lifesciences Corporation — Date 5/15/13

Venu Menon, MD — Date
Medical Director, Clinical Events Committee C5Research, Cleveland Clinic

Martin B. Leon, MD Executive Committee Member — Date

Craig R. Smith, MD Executive Committee Member — Date 05/20/13

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I. Introduction and Goal of the Clinical Event Committee (CEC)

The role of the Clinical Events Committee (referred to in this document as the 'CEC') is to adjudicate the protocol defined clinical events, in a blinded, consistent and unbiased manner throughout the course of the study. The importance of the CEC is to ensure that all events that have been reported are judged uniformly by a single group, using the same definitions as stated in the clinical protocol and in this charter. Given the diversity in the enrolling sites, there will be differences from site to site how each type of event is treated clinically and how it is reported. The aim of the CEC is to eliminate this inherent site difference by using the same criteria to adjudicate every event.

Note: CEC will be blinded to key subject identifiers (name, phone, address, etc) and site and investigator names. Due to the extreme difficulty of blinding the treatment arms (without withholding key clinical information) the CEC will not be blinded to treatment arm. Adjudicators will be internal medicine, cardiologists, neurologists, CT surgery specialists, or vascular specialists. They will not otherwise be involved in the subject's care.

The CEC for this study will be the CEC of the Cleveland Clinic Center for Clinical Research (C5Research), located in Cleveland, Ohio. C5Research is part of the Heart and Vascular Institute at the Cleveland Clinic. The CEC Chairperson oversees the CEC and has ultimate responsibility for the adjudication of all events pre-specified in the clinical study protocol. A CEC Project Manager is responsible for coordinating all aspects of the clinical event review process.

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Clinical Event Committee Location
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II. Scope of Work

The Clinical Events Committee (CEC) was formed to adjudicate prespecified clinical adverse events that occur during the course of the Partner II trial. The CEC is charged with providing a review of and adjudication for all potential clinical events according to established event definitions (see Appendix A: Clinical Event Definitions). The CEC will also assist in the development/review of various data collection forms, development/review of the definitions, and training.

Information on all cases that represent, or are suspected to represent (based on standardized identification criteria), any of the following events will be sent to the CEC:

1) Death (including relationship to study valve/index procedure, throughout follow-up period)
   a) Cardiovascular
   b) Non-cardiovascular
2) Stroke (including relationship to study valve/index procedure & severity, throughout follow-up period)
   a) TIA
   b) Stroke (Hemorrhagic, Ischemic)
3) Bleeding (including relationship to study valve/index procedure, throughout follow-up period)
   a) Life threatening or disabling
   b) Major
   c) Minor or no bleeding
4) Vascular Access & Access Site complications (including relationship to study valve/index procedure, throughout follow-up period)
   a) Major or Minor Vascular Complication (includes ventricular injury and Aortic Root Dissection/Rupture/Perforation)
   b) Sternal wound infection
   c) Other access site infection
5) Myocardial Infarction (including relationship to study valve/index procedure and biomarker analysis, throughout follow-up period)
   a) Clinical Peri-procedure
   b) Spontaneous
6) Acute Kidney Injury (including temporal relationship throughout 2 years)
7) Prosthetic Valve Dysfunction (including relationship to study valve/index procedure, throughout follow-up period)
8) Other (all including relationship to study valve/index procedure, throughout follow-up period unless otherwise noted)
   - Rhythm Disturbance Requiring Permanent Pacemaker
   - Aortic Valve Re-Intervention (not adjudicating relatedness)
   - Endocarditis (not adjudicating relatedness)
   - Coronary Obstruction
   - Rehospitalization or Prolongation of Index Hospitalization (greater than 30 days) due to symptoms of cardiac or valve related decompensation
   - Rehospitalization for Decompensation (Symptoms of Aortic Stenosis) and/or complications of

the valve procedure.

9) Hospitalizations (cardiovascular and those with potential procedure/valve related complications) throughout follow-up period

10) Hemolysis (PII A only)

11) Pericarditis (PII A only)

Members of the CEC will adjudicate each potential event, based on pre-specified definitions, and render an assessment as to whether the case represents a confirmed event (meeting the event definition with all necessary documentation), a non-event (does not meet the event definition and likely represents an alternative or nonevent diagnosis), or lacks sufficient documentation for confirmation of an event.

In addition, the CEC Project Manager (PM) will provide a narrative regarding each event after adjudication of the event is complete.

The PM will also review the discharge summary for hospitalizations (cardiovascular and those with potential procedure/valve related complications) throughout follow-up period and make a determination whether the case needs to be sent for adjudication (if not already done so). If so, the PM will add the unreported event(s) to the CEC dashboard on the e-CRF and notify the Edwards Safety Officer of any source needs.

III. CEC Adjudicators and Responsibilities

1. Qualified adjudicators

Potential events will be adjudicated by qualified physicians who will serve as CEC members. Selection of physician-adjudicators is described in the SOP. The specific composition of the CEC will be provided on a separate signature and delegation log maintained by the CEC. Selection of physician adjudicators who will adjudicate events is based on the following:

The selection of adjudicators (number and specialties) will be dictated by study specific characteristics; these include:

a. Study duration

Estimated event rate and number of endpoints

b. Availability
c. Type of endpoints

Adjudicator Requirements:

a. Ability to adhere to protocol timelines
b. Available for duration of the case review period if duration is expected to be less than 2 years, or at least 1.5 years of case review if duration is expected to exceed 2 years. (If an adjudicator has previously reviewed for a study with similar definitions review duration may be less than 1.5 years)
c. Successful completion of the inservice requirements (study specific)
d. Physicians may not review for studies in which they are the Principal Investigator, Co-Investigator, or in which they have any other direct or indirect involvement (e.g., Steering Committee Member, Data Safety Monitoring Board, Consultant, etc.).
d. They may not be employed by the Sponsor
e. Adjudicators will be internal medicine, cardiologists, neurologists, vascular specialists, or CT surgery specialists.
f. Adjudicators may not participate in the care of a subject that they are reviewing for events.

Adjudicators may be paid for reviews by C5Research. Payments are processed through C5Research Finance and Contracts.

2. Selection process

There will be a defined group of adjudicators, for both Phase I and II reviews. The list of adjudicators will be approved by the CEC Chairperson. They will meet the requirements outlined above. When necessary, new adjudicators will be added to replace or add to the group of initial adjudicators. The new adjudicators will have the same qualifications and meet the same requirements as the initial group.

3. Training

The adjudicators will receive study specific training before starting to review cases, and during the ongoing clinical study, as needed. The training will be conducted by the CEC Chairperson or Associate Chairperson with the assistance of the CEC Project Manager, and will include the following:

a. Overview presentation of the studies and protocol, and TAVR device and procedure as described in the protocol.
b. Clinical events to adjudicate and their definitions
c. Explanation of the clinical event package contents: subject profile (CRF data), adjudication forms, and source documents.
d. Familiarization with adjudication conventions (e.g. adjudication forms completion, overall process, and generating queries)
e. Discussion of adjudication commitment and workload

4. Responsibilities

The Physician Adjudicators of the CEC will be responsible for 1) adjudicating all presented clinical events, 2) communicating whether additional documentation is required for adjudication and 3) providing complete and signed adjudication forms for each potential event reviewed.

IV. Specifics of CEC Operation (see figure 1)

1. Clinical Event Identification

A separate study specific Trigger Document will describe in detail the triggers for event review for this study. Potential events for adjudication may be identified in one or more of the following ways:

a. Events Identified by the Investigator

Subjects will be regularly assessed for AE/SAEs and similar safety signals as described in the protocol. These assessments will typically lead to identification of pre-specified adverse events requiring adjudication. The site will complete the appropriate AE/SAE details form in the e-CRF. Once a site reports the adverse event, the Edwards Partner II team THV Clinical Affairs receives immediate electronic notification about a new AE being reported. These events will have a 3 digit AE ID number.

b. Unreported Events Discovered at a Monitoring Visit

If the site monitor (CRA) discovers an adverse event, during a monitoring visit that has not been previously reported, he/she will instruct the site to report the event properly. In the case where the site declines to report the event, but there are source documents supporting the event, a note to file will be created to document a site's refusal. The Safety Officer will review the event. If the event is, or might be, a pre-specified adverse event requiring adjudication, the Source Documents will be sent to the CEC by Safety..

c. Programmed Triggers

The database will be routinely queried in a blinded fashion for potential events based on reported adverse experience terms. A set of terms (referred to as trigger terms) will be defined for each potential clinical event (see separate document). These trigger terms are designed to identify subjects with adverse events. The identified term may require adjudication or further investigation. Non-reported events will be identified by review of laboratory abnormalities, ECG core lab data, and echo core lab data. All of these triggers will be detailed in a separate "trigger" document. The safety officer will routinely review AE terms that have not been categorized to a drop down list term for potential events requiring adjudication.

If the potential event identified from the silent trigger process has not been previously reported, the Safety Officer will notify the site that a potential clinical event requiring adjudication has been identified by silent trigger and instruct the site to enter the newly discovered event if they are in agreement. In some situations this step may be addressed to the site via the Site CEC Dashboard in the eCRF. If the site declines to do so, the source documents will be sent to the CEC as requested for consideration regardless.

d. Events Identified by an Adjudicator or CEC PM

If an adjudicator or CEC PM identifies a potential event, either in addition to the potential event under review or in lieu of the potential event under review, he/she will make note of this in the comments section of the Event Adjudication Form. The CEC PM will enter the event on the CEC dashboard of the e-CRF and notify Safety Officer via a report if additional source is required. The Safety Office will contact the site to provide source documents (if needed).

Events not reported by the site as "adverse events" will be assigned a 4-6 character AE ID number by the CEC with the first character being a letter that represents the source of the silent trigger as follows. The remaining 3 characters will be a unique number for that event type.
Example:
Site 0001 subject 003: site reports an AE of Myocardial Infarction which is assigned (by e-CRF) AE ID number of 023. This would be 0001-003-A02301.

Site 0002 Subject 004: An abnormal CKMB meeting the trigger criteria is picked up electronically. The site declines to report a Myocardial Infarction. The e-CRF assigns this case as 0002-004-M001.

Site 0014 Subject 024: An abnormal CKMB meeting the trigger criteria is picked up electronically. The site declines to report a Myocardial Infarction. The e-CRF assigns this case as 0014-024-**M001.**

Site 0014 Subject 024: An abnormal troponin meeting the trigger criteria is picked up electronically one year later. The site declines to report a Myocardial Infarction. The e-CRF assigns this case as 0014-024-**M002** (or whatever the next sequential "M" number would be).

2. Specific Procedures at Sites

When an incident constituting an adverse event requiring adjudication has been identified, the investigator (or designee) must complete the appropriate e-CRF forms (Adverse Event Details). In addition, source documents related to the event must be collected, blinded and labeled for submission to Safety and subsequently to the CEC. If the documents are available at the site, they should be immediately forwarded to Sponsor. If they are not available at the site, an attempt should be made by the site to request these within a reasonable time period. If the documents are not available, a justification should be submitted to the Sponsor as soon as possible after site becoming aware that the documents are not available. Blinding should include subject identifiers in addition to site name, location, and PI name. Site personnel are responsible for collecting the appropriate source documents related to potential events, retaining them in their study file and forwarding a copy to Safety Officer. See Appendix B for details about the recommended source documentation for clinical event adjudication packages.

3. Specific Procedures at the Sponsor

The Safety Officer will be responsible for providing C^5 with Clinical Event Packages. Clinical Event Packages consist of a labeled, per-event file that contains, at minimum, required information, as outlined below. Due to the anticipated volume of events a unique ID number (as described above) is assigned. This is to ensure there is no ambiguity over what event is being sent, received or adjudicated through the CEC process. Upon receipt of an Electronic Notification (or any other Notification), THV Safety Team conducts a Sponsor's Assessment review of each AE. Each AE has a unique identification number which links the AE review form with the place in the Medidata and the CEC adjudication. Subsequently, a Safety Officer reviews each subject's file to prepare the cases for the CEC review. If an AE, SAE (or any hospitalization) or other criteria meets a definition of an event designated for adjudication by the CEC as specified in the CEC Charter (or can possibly be related to any endpoint, although reported as "Other"), the source documents will be requested from the site in a timely manner to support the CEC adjudication. Events designated as CEC adjudicatable events are forwarded with source documentation for endpoint adjudication to the CEC coordinator, by Safety as soon as possible after receiving the source documents. The Sponsor will be responsible

for assuring that prior to completion of the trial all subjects have been screened for possible events through the entire duration of study follow-up.

Each Clinical Event Package will consist of the following:

a. Source Document Cover Page
b. Notification of the event type and date of the event to be reviewed (i.e. Myocardial Infarction, Stroke, Death, etc) as well as the "trigger" (i.e. echo core lab, CRF field, etc).

c. Supporting Documentation
   Appendix B outlines the required source documents for each event. The CEC will use the source documentation received in the event review process. The Safety Officer will ensure that all foreign language documentation received from study sites is appropriately translated into English. Copies of both the original language and English translation should be included in the event package.

Supporting Documentation

Sponsor is responsible for collecting recommended supporting documentation from the study site (Appendix B) in a timely manner. Sponsor will contact study sites directly as needed to receive all documentation. A query for outstanding supporting documentation will be sent periodically to the site by Safety, until the SDs are received or the note to file or similar closing the request is obtained. If supporting documentation is permanently unavailable, a supporting narrative will be generated by the site explaining what is known and why the documentation is not available.

Once a clinical event package is complete, Safety Officer will perform a final quality control review to ensure that all personal identification information (such as name, DOB, address, medical record number, site and investigator name and location and all physician names, etc.) is removed, the required documents are present and properly numbered with the unique event number, and the documentation is sufficient to meet the needs of the adjudication committee.

Event Package Distribution to C5Research

A copy of each clinical event package will be submitted to C5Research CEC in an agreed upon manner.

Request for Additional Information

C5Research will contact Safety with requests for additional information if necessary. Safety will forward the query for additional information to the study site within 3 working days of receipt of the query. Safety will continue to follow-up with the site until the requested information or written documentation explaining that the information is permanently unavailable is received.

Once requested information is received and reviewed, the query results will be sent to C5Research CEC.

Tracking of Event Packages

C5Research and Safety will track all clinical event packages using the unique AEID number, from the time of notification/identification until time of final adjudication in their respective tracking database. Intermittently, and at the conclusion of the trial, the safety reporting process for identifying events, the trigger program and the CEC identification process will be reconciled by the CEC Project

Manager and a representative of the Sponsor. This is to ensure that all potential events have been identified and cross referenced between the two surveillance mechanisms.

4. Specific Procedures at EKG and Echo Core Lab

ECG and Echo core labs will make results available for trigger programming on a regular ongoing basis (i.e. will not "batch" reviews). Echo core lab will provide results of core lab review to CEC for adjudication purposes on an as needed basis.

Additionally the echo core lab reports may be requested for the following events:

- Endocarditis
- Prosthetic Valve Dysfunction (Aortic Regurgitation, Aortic Stenosis)
- Aortic Root Rupture

5. Specific Procedures at C5Research (See Figure)

a. Verification and data entry

When an event package is received at C5Research, Key data is entered into the clinical event tracking database referencing the unique event number assigned to the event. The event package is checked for completeness. If the package is incomplete, C5Research will request the outstanding information/documentation from Safety Officer. Requests from the C5Research should be handled and followed up on expeditiously.

b. First Manual Review

First Manual Review will consist of an assessment of the clinical event package by CEC Research Personnel to determine if the source documentation is complete and appropriate for clinical event determination. Cases going to Phase I staff review will have additional header information completed by the CEC PM (i.e. AE ID number and AE term and at times the PI assessment of relationship). If additional source documents are required, a request will be made to the site, through Safety Officer. When the event package is considered complete and appropriate for review, the case is sent for the appropriate review level (Phase I or II).

c. Phase I Review

Cohort A

Phase I review will consist of

1. Two physicians (cardiology fellow, vascular specialist or CT surgery fellow*), independently reviewing the clinical event package. The identities of the two Adjudicators are not known to each other. The results of the independent reviews will be recorded on their respective Adjudication Form.

This type of review will be used for Vascular Access Site/Access Related Complications, Hospitalization for decompensation, Acute Kidney Injury, Bleeding, and Death and MI >30 days after the index procedure.

2. One physician (staff level), reviewing the clinical event package. The results of the review will be recorded on an adjudication form. This type of review will be used for Death and MI < 30 days after the index procedure, coronary obstruction, endocarditis, stroke/TIA, prosthetic valve dysfunction, conduction disturbance requiring PPM, AV re-intervention, , hemolysis and pericarditis.

3. One RN (CEC Project Manager), reviewing the hospitalizations. If no, potential CV events are identified the form will be completed and signed by CEC PM. If a potential CV event is identified and **it has been triggered for review**, the event and its AE number will be noted on the form and the form signed by CEC PM. If a potential CV event is identified that has not been triggered for review, the event will be noted on the review form, and added to the CEC Dashboard in the e-CRF.

* Bleeding and Vascular Access Site/Access Related Complications for subject randomized to surgery will be reviewed by a CT Surgery Fellow and a Cardiology Fellow. For subjects randomized to percutaneous arm bleeding will be reviewed by 2 cardiology fellows and Vascular Access Site/Access Related Complications will be reviewed by a vascular specialist (fellow) and a cardiology fellow.

Cohort B

Phase I review will consist of

1. Two physicians (cardiology fellow or vascular fellow*), independently reviewing the clinical event package. The identities of the two Adjudicators are not known to each other. The results of the independent reviews will be recorded on their respective Adjudication Form. This type of review will be used for Vascular Access Site/Access Related Complications, Hospitalization for decompensation, Acute Kidney Injury, Bleeding, and Death and MI >30 days after the index procedure.
2. One physician (staff level), reviewing the clinical event package. The results of the review will be recorded on an adjudication form. This type of review will be used for Death and MI < 30 days after the index procedure, coronary obstruction, endocarditis, stroke/TIA, prosthetic valve dysfunction, conduction disturbance requiring PPM, AV re-intervention, MV dysfunction, hemolysis and pericarditis.
3. One RN (CEC Project Manager), reviewing the hospitalizations. If no potential CV events, the form will be completed and signed by CEC PM. If a potential CV event is identified and **it has been triggered for review**, the event and its AE number will be noted on the form, the form signed by CEC PM. If a potential CV event is identified that has not been received for review, the event will be entered on the CEC Dashboard in the e-CRF and noted on the review form.

* Vascular Access Site/Access Related Complications will be reviewed by a Vascular Specialty Fellow and a Cardiology Fellow.

d. Second Manual Review

When there is <u>agreement at Phase I (fellows in agreement with each other or staff level adjudicator in agreement with the PI assessment at the time of the review)</u>, the clinical event review is considered complete and the rendered adjudication stands. When there is <u>disagreement</u>, or if one or both adjudicators note insufficient data to make an event determination, after all attempts have been made to secure the missing information, the case is forwarded for Phase II Review (CEC Chairperson, Associate Chairperson, or Specialty Lead).

e. Phase II Review

Phase II review will consist of clinical event package review by one senior staff Cardiologist, Neurologist, or Vascular Specialist (as endpoint appropriate). This physician will adjudicate the case and a CEC Review Form will be completed. Phase II results will be considered final.

Final Adjudication Results are entered in Medidata by the CEC Project Manager and verified by a second CEC Project Manager. In addition, the CEC provides the Sponsor with narratives prepared and updated /per subject describing all adjudicated events. Validations are programmed in Medidata based on the approved data edit check program. If necessary, queries are generated and sent to the CEC Project Manager who follows up with the Physician Adjudicator as needed for resolution. The original paper adjudication forms will be retained by C5Research.

V. CEC Commitment and Workload

Safety should submit clinical event packages as soon as they have collected all available source documents. The documents should be forwarded to the CEC as soon as possible after receiving the source documents. Packages received by C5Research will be distributed for review as soon as they are processed, usually within 24 hours if documentation is complete. CEC adjudicators generally have 10 working days to return their completed adjudication forms.

Clinical event review will occur on a regular and consistent basis throughout the course of the study. At certain times (e.g. interim analysis and/or database lock), it may be necessary to shorten the turnaround time for events to be adjudicated and with the proper advance notice, the CEC will remain flexible to this in order to meet the demands of a particular study.

Another measure put in place to avoid a backlog is that the sites will receive the proper training to ensure they are aware of the importance of reporting events in a timely manner and are aware of what is required when reporting an event. Finally, C5Research will work with Safety on a regular basis to provide the source documents the CEC requires before they can complete the review of an event.

From start-up to study close, there will be consistent communication between the CEC and Sponsor for day-to-day issues related to overall progress and other issues that may arise, such as protocol amendments, study timelines, DMC requests and requirements for expedited clinical event review, etc. To achieve this, teleconferences will occur between the appropriate parties whenever needed.

VI. Quality Assurance

It is the goal of the CEC to provide a high-quality service and to remain consistent in adjudicating clinical events for the entire length of the study. The CEC will conduct all of its operations under Good Clinical Practices (GCP) and based on the CEC SOPs.

The CEC will prepare an Instructions Manual that will detail the conduct of the CEC. Each member of the Committee will follow these written procedures.

In order to ensure accuracy and consistency of the reviews a QA assessment will be performed on all CEC trials to assess intra- and inter-reviewer reliability with respect to adjudicating events consistent with clinical event definitions.

Inter-reviewer assessments for the purpose of accuracy will be performed and managed by the CEC Project Manager responsible for the studies. Details of the assessment process are further detailed in the CEC QA Plan.

Appendix A. Clinical Event Definitions[1] Forms for Each Event Type are in Attachment A.

DEATH:

Cardiovascular Death

Any one of the following criteria:

- Any death due to proximate cardiac disease cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure)
- Unwitnessed death of unknown cause (includes sudden cardiac death)
- All cardiovascular procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure
- Death caused by noncoronary vascular conditions such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, or other vascular disease

Non-Cardiovascular Death

Death is due primarily to an identifiable non-cardiovascular cause or etiology. Specific diagnoses may include respiratory failure, pneumonia, trauma, suicide, or any other non-cardiovascular defined causes (e.g., liver disease, malignancies etc.) not included in the previous categories.

Causality

All deaths will be subcategorized as below (more than one category may apply).

Not related to Study Valve or Index Procedure

Study Valve Related: Death caused by structural valve deterioration, nonstructural dysfunction, valve thrombosis, embolism, bleeding event, operated valvular endocarditis, or death related to reoperation of an operated valve. Sudden, unexplained unexpected deaths of patients with an operated valve are included as valve-related mortality. Death caused by heart failure in patients with advanced myocardial disease and satisfactorily function cardiac valves are not included. Specific cause of valve-related death should be designated and reported.

Index Procedure Related: Death directly related to the index procedure or complications thereof or any death occurring ≤ 30 days of the index procedure will be classified as procedure related.

STROKE/TIA:

Stroke Diagnostic Criteria

Rapid onset of a focal or global neurological deficit with at least one of the following

- change in level of consciousness
- hemiplegia
- hemiparesis
- numbness or sensory loss affecting one side of the body
- dysphasia or aphasia
- hemianopia
- amaurosis fugax
- or other neurological signs or symptoms consistent with stroke

*Duration of a focal or global neurological deficit ≥24 h; **OR** <24 h, if therapeutic intervention(s) were performed (e.g. thrombolytic therapy or intracranial angioplasty); **OR** available neuroimaging documents a new hemorrhage or infarct; **OR** the neurological deficit results in death*
*No other readily identifiable nonstroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences)**

Confirmation of the diagnosis by at least one of the following#:

- Neurology or neurosurgical specialist
- Neuroimaging procedure (MR or CT scan or cerebral angiography)
- Lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage)

Stroke will be further adjudicated as:

- Minor (Non-disabling)— Does not qualify as Major.
- Major (Disabling)—Modified Rankin score ≥2 at either the 30 day or 90 day time period

Stroke will also be further adjudicated as:

- Hemorrhagic
  Hemorrhagic stroke is defined as an acute symptomatic episode of focal or global cerebral or spinal dysfunction caused by a non-traumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage. Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke[2] **or**

- Ischemic
  Ischemic stroke is an acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of the central nervous system tissue **or**

- Undetermined
  Undetermined stroke is defined as a stroke with insufficient information to allow categorization as ischemic or hemorrhagic.

Transient Ischemic Attack (TIA)

- New focal neurological deficit with rapid symptom resolution (usually 1 to 2 h), always within 24 h[‡]
- Neuroimaging without tissue injury

**Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies.*

#If a stroke is reported without evidence of confirmation of the diagnosis by one of these methods, the event may still be considered a stroke on the basis of the clinical presentation alone.

[†]Modified Rankin score assessments should be made by qualified individuals according to a certification process. If there is discordance between the 30 and 90 day Modified Rankin scores, a final determination of major versus minor stroke will be adjudicated by the neurology members of the clinical events committee. If the site does not provide a 30 and/or 90 day MRS at the time of adjudication; the neurology adjudicator will make his/her best assessment using the data provided.

[‡]The diagnosis of a TIA is defined as complete resolution of new neurological symptoms usually within 1-2 h but always within 24 h and also requires a normal neuroimaging study and the absence of any other primary medical cause (hypoglycemia, hypoxia, etc.)

Causality

All Strokes and TIAs will be subcategorized as below by a CV adjudicator (more than one category may apply).

Not related to Study Valve or Index Procedure

Study Valve Related: Stroke or TIA caused by structural valve deterioration, nonstructural dysfunction, valve thrombosis, embolism, bleeding event, operated valvular endocarditis, or stroke related to reoperation of an operated valve.

Index Procedure Related: Stroke/TIA directly related to the index procedure or complications thereof or any stroke/TIA occurring ≤ 30 days of the index procedure will be classified as procedure related.

BLEEDING:

Life-threatening or disabling bleeding

- Fatal bleeding **OR**
- Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular (note 1), or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome **OR**
- Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery **OR**
- Overt (note 2) source of bleeding with drop in hemoglobin of $\geq$5 g/dl or whole blood or packed red blood cells (RBCs) transfusion $\geq$4 U* (note 3)

Major bleeding

Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dl **OR** requiring transfusion of two or three units of whole blood/ RBC

AND

Does not meet criteria of life-threatening or disabling bleeding

Minor or no bleeding

Any bleeding worthy of clinical mention (e.g., access site hematoma) that does not qualify as life-threatening, disabling or major.

**Given 1 U of packed RBC typically will raise blood hemoglobin concentration by 1 g/dl, an estimated decrease in hemoglobin should be calculated with this consideration.*

And

If a Life-Threatening, disabling or Major bleeding event, did the event occur:

- During the index procedure (note 4)
- Within the index hospitalization (but not during the procedure), or
- Post-discharge

Notes:

1. "Intraocular" does not include subconjunctival hemorrhages that may be noted on a physical exam.

2. Overt bleeding may include hematuria, microscopic hematuria, oozing, bloody bandages, occult blood, etc.

3. In general, for purposes of calculating the drop in hemoglobin during the index hospitalization, the hgb value identified on the CRF as "baseline" will be used as the baseline value. After discharge, the hgb value from the most recent (prior) follow-up visit will be considered the baseline value for calculating the drop in hgb.

4. Timing of events and transfusions will be based off of the time the transfusion was started. If a transfusion was not given then the timing should be based off of the time of the first hgb drop (that met the bleeding criteria) was drawn. If no transfusion and no hgb

drop noted, then timing will be from the time of the first diagnostic test or symptom that met the criteria (i.e. time of death in a bleed noted only on autopsy)

Causality

All life threatening and major bleeding complications will be subcategorized as below (more than one category may apply).

Not related to Study Valve (including anticoagulation) or Index Procedure

Study Valve Related: Treatment of valve thrombosis, embolism, operated valvular endocarditis, or related to reoperation of an operated valve.

Index Procedure Related: Directly related to the index procedure or complications thereof or occurring ≤ 30 days of the index procedure will be classified as procedure related.

Related to Anticoagulation: Directly related to subject being anticoagulated (i.e. antiplatelets, warfarin, etc.) for the Study Valve.

VASCULAR ACCESS SITE AND ACCESS RELATED COMPLICATIONS:
This includes Aortic Root Dissection/Perforation/Rupture occurring either during the pre-implant balloon aortic valvuloplasty, or during the transcatheter valve implant. This will be adjudicated through the 5 year follow-up time period.

Major Vascular Complications

- Any thoracic aortic dissection
- Access site or access-related* vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, or compartment syndrome) leading to either death, need for significant blood transfusions (≥4U), unplanned percutaneous or surgical intervention†, or irreversible end-organ damage (e.g., hypogastric artery occlusion causing visceral ischemia or spinal artery injury causing neurological impairment)
- Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage

Minor Vascular Complications

- Access site or access-related* vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm requiring compression or thrombin injection therapy, or hematomas requiring transfusion of ≥2 but, <4U) not requiring unplanned percutaneous or surgical intervention† and not resulting in irreversible end-organ damage.
- Distal embolization treated with embolectomy and/or thrombectomy and not resulting in irreversible end-organ damage.
- Failure of percutaneous access site closure resulting in interventional (e.g. stent-graft) or surgical correction and not associated with death, need for significant blood transfusions (≥4U), or irreversible end-organ damage.

**The 'access site' is defined as any location (arterial or venous) traversed by a guide-wire, a catheter or a sheath [including the left ventricular (LV) apex and the aorta] and 'access related' is defined as any adverse clinical consequence possibly associated with any of the access sites used during the procedure.*

†Many vascular situations require special notice. Femoral vascular access and closure in many centers is routinely achieved using surgical cut-down procedures, and therefore, pre-planned surgical access and/or closure should be considered as part of the procedure and not as a complication. Similarly, uncomplicated non-femoral (e.g., retroperitoneal, iliac, subclavian, or aortic) surgical access for sheath entry (planned or unplanned) is not considered a vascular complication, unless untoward clinical consequences are documented (e.g., bleeding complications). However, interventional or surgical repair for failed percutaneous closure of the arteriotomy site during the index procedure without other clinical sequellae is considered a minor vascular complication. ASD is not considered a complication.

Sternal Wound Infection:

Deep sternal infection involves muscle, bone, and/or mediastinum. Must have one of the following conditions:

- Wound opened with excision of tissue (I&D)
- Positive Culture
- Treatment with antibiotics
- Infection that is contiguous with the sternum on imaging will constitute involvement of the sternum

Other Access Site Infection:
Access Related is defined as any infection possibly associated with any of the access sites used during the procedure. An infection requires intravenous antibiotics for other than prophylaxis, and/or extended hospitalization.

Causality
All vascular access site and access site related complications will be subcategorized as below (more than one category may apply).

Not related to Study Valve or Index Procedure

Study Valve Related: Caused by structural valve deterioration, nonstructural dysfunction, valve thrombosis, embolism, bleeding event, operated valvular endocarditis, or related to reoperation of an operated valve.

Index Procedure Related: Directly related to the index procedure or complications thereof or occurring ≤ 30 days of the index procedure will be classified as procedure related.

MYOCARDIAL INFARCTION:

Peri-procedural MI (≤72 h after the index procedure)

New ischemic symptoms (e.g., chest pain or shortness of breath), ***or*** *new ischemic signs (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes-either elevation >1mm or depression >1mm in two or more contiguous leads, hemodynamic instability, or imaging evidence of new loss of viable myocardium or new wall motion abnormality),* ***AND***
Elevated cardiac biomarkers (preferably CK-MB) within 72 h after the index procedure, consisting of two or more post-procedure samples that are >6 to 8 h apart with a 20% increase in the second sample and a peak value exceeding 10x the 99th percentile URL, or a peak value exceeding 5x the 99th percentile URL with new pathological Q waves in at least 2 contiguous leads.

Spontaneous MI (>72 h after the index procedure)

Any one of the following criteria:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with evidence of myocardial ischemia with at least one of the following:
  - ECG changes indicative of new ischemia [new ST-T changes or new LBBB]
  - New pathological Q waves in at least two contiguous leads
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST-segment elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/ or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- Pathological findings of an acute myocardial infarction.
- Any emergent PCI performed for acute ST-elevation MI.
- Any administration of thrombolytics for acute MI

All Myocardial Infarctions will be subcategorized as below: (more than one category may apply)

Not related to Valve or Index Procedure

Valve Related: MI caused by structural valve deterioration, nonstructural dysfunction, valve thrombosis, embolism, bleeding event, operated valvular endocarditis, or MI related to reoperation of an operated valve.

Procedure Related: MI directly related to the index procedure or complications thereof or any MI occurring ≤ 30 days of the index procedure will be classified as procedure related.

Note: A confirmed coronary embolus, occurring at any time, should be reported as an independent event, if biomarker changes and associated findings fulfill definition criteria.

ACUTE KIDNEY INJURY: (Modified RIFLE Classification)
Change in serum creatinine (up to 30 days) compared with baseline (note 1-5)

Stage 1 Increase in serum creatinine to 150% to 200% (1.5 to 2.0 x increase compared with baseline) or increase of 0.3 mg/dl ($\geq$26.4 mmol/l)

Stage 2 Increase in serum creatinine to 200% to 300% (2.0 to 3.0 x increase compared with baseline) or increase between >0.3 mg/dl (>26.4 mmol/l) and <4.0 mg/dl (<354 mmol/l)

Stage 3* Increase in serum creatinine to $\geq$300% (>3 x increase compared with baseline) or serum creatinine of $\geq$4.0 mg/dl ($\geq$354 mmol/l) with an acute increase of at least 0.5 mg/dl (44 mmol/l)

*Patients receiving renal replacement therapy (i.e. hemodialysis, peritoneal dialysis, or hemofiltration) are considered to meet Stage 3 criteria irrespective of other criteria.

Notes

1. The worse AKI will be adjudicated within 30 days and after 30 days. For up to 6 months, the "baseline" creatinine will be the creatinine done nearest (but prior to) the procedure. The creatinine used to determine the change in creatinine will be the highest value done the closest to, but not after 30 days. In the situation where no baseline and/or follow-up creatinines are done, the adjudicator will indicate "unable to determine" due to creatinine not being done.

2. The discharge creatinine value (from index hospitalization) will be used as the baseline from 6months to one year; and the last normal reading (before an event) from the last available follow-up (one or two year visit) before the event later in the trial.

3. Adjudicator will note if criteria was met prior to and/or after 30 days.

4. The timing of AKI will be based on the date of dialysis (or when not available or note done, the highest creatinine level reported. (If the event is </= 30 days, the date should be </= to 30 days post procedure).

5. In the scenario where the calculation result falls into more than one Stage category, the more severe Stage will be selected.

PROSTHETIC VALVE DYSFUNCTION:
Echo Core Lab will provide a final report of the echocardiogram. The CEC Adjudicator will determine from that report if the "aortic stenosis" or "aortic regurgitation" criteria is met and confirm the potential failure mechanism based on the core lab report. If possible or significant stenosis or moderate or severe regurgitation criteria are met, CEC adjudicator will review for clinical findings.

Aortic Stenosis

*Requires parameters for possible or significant stenosis **AND** clinical findings, symptoms or events indicating impaired cardiovascular or valvular function (e.g., new or worsening congestive heart failure, rehospitalization for worsening symptoms, reoperation or death).*

Prosthetic Aortic Valve Stenosis Criteria*			
Parameter	**Normal**	**Possible Stenosis**	**Significant Stenosis**
Peak Velocity (m/s)†	<3	3-4	>4.0
Mean Gradient (mm Hg)†	<20	20-35	0.35
Doppler velocity index	≥0.30	0.29-0.25	<0.25
Effective orifice area (cm^2)	>1.2	1.2-0.8	<0.80
Contour of the jet velocity through the prosthetic valve	Triangular, early peaking	Triangular to intermediate	Rounded, symmetrical contour
Acceleration time (ms)	<80	80-100	>100
*In conditions of normal or near normal stroke volume (50-70ml). †These parameters are more affected by flow, including concomitant aortic regurgitation.			

Potential Failure Mode will be categorized as below:

- Stent creep
- Pannus
- Calcification
- Support structure deformation (out-of-round configuration), under-expansion, fracture, or trauma (cardio-pulmonary resuscitation, blunt chest trauma)
- Mal-sizing (prosthesis-patient mismatch)
- Endocarditis□
- Prosthetic valve thrombosis[n]
- Native leaflet □rolapsed impeding prosthetic leaflet motion
- Unable to determinate

Aortic Regurgitation

*Requires parameters for moderate or severe regurgitation **AND** clinical findings, symptoms or events indicating impaired cardiovascular or valvular function (e.g., new or worsening congestive heart failure, rehospitalization for worsening symptoms, reoperation or death).*

Prosthetic Aortic Valve Regurgitation Criteria (Central and Paravalvular)

Parameter	Mild	Moderate	Severe
Valve Structure and motion Mechanical or bioprosthetic	Usually normal	Usually abnormal	Usually abnormal
Structural Parameters Left ventricular size	Normal	Normal/Mildly dilated	Dilated
Doppler Parameters (qualitative or semiqualitative) Jet width in central jets (%LVO diameter): color* Jet density: CW Doppler Jet deceleration rate (PHT, ms): CW doppler† LV outflow vs. pulmonary flow: PW Doppler	Narrow (≤25%) Incomplete or faint Slow (>500) Slightly increased	Intermediate (26%-64%) Dense Variable (200-500) Intermediate	Large (≥65%) Dense Steep (<200) Greatly increased
Diastolic flow reversal in the descending aorta PW Doppler Circumferential extent of paraprosthetic AR (%)‡	Absent or brief early diastolic <10	Intermediate 10-20	Prominent, holodiastolic >20
Doppler Parameters (quantitative) Regurgitant volume (ml/beat) Regurgitant fraction (%)	<30 <30	30-59 30-50	>60 >50
*Parameter applicable to central jets and is less accurate in eccentric jets. †Influenced by left ventricular compliance. ‡For paravalvular aortic regurgitation. AR=aortic regurgitation; CW=Continuous Wave; LVO= Left Ventricular Outflow; PW=Pulsed Wave			

Potential Failure Mode will be categorized as below:

- Pannus
- Calcification
- Support structure deformation (out-of-round configuration), recoil, under-expansion, fracture, insufficient radial strength, or trauma (cardiopulmonary resuscitation, blunt chest trauma)
- Endocarditis□
- Prosthetic valve thrombosis[n]
- Malposition (too high, too low)
- Acute malcoaptation
- Leaflet wear, tear/perforation, □rolapsed, or retraction
- Suture breakage or disruption
- Native leaflet □rolapsed impeding prosthetic leaflet motion

□The diagnosis of valve endocarditis is based on one of the following criteria:

- reoperation with evidence of abscess, paravalvular leak, pus or vegetation confirmed as secondary to infection by histological or bacteriological studies;
- autopsy findings of abscess, pus, or vegetation involving a repaired or replaced valve;
- in the absence of reoperation or autopsy, fulfilling the Duke Criteria for endocarditis.[3]

[n]Any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Valve thrombus found at autopsy in a patient whose cause of death was not valve related or found at operation for an unrelated indication should also be reported as valve thrombosis.

Causality
All prosthetic valve dysfunction will be subcategorized as below (more than one category may apply).

Not related to Study Valve or Index Procedure

Study Valve Related: Caused by structural valve deterioration, nonstructural dysfunction, valve thrombosis, embolism, bleeding event, operated valvular endocarditis, or related to reoperation of an operated valve.

Index Procedure Related: Directly related to the index procedure or complications thereof or occurring ≤ 30 days of the index procedure will be classified as procedure related.

OTHER PROSTHETIC VALVE OR PROCEDURE ASSOCIATED COMPLICATIONS:

1. Rhythm Disturbances Requiring Permanent Pacemaker (within 30 days of the index procedure)

Any conduction disorder or bradyarrhythmia that requires a Permanent Pacemaker. The date of event will be based on the date of device implantation.

2. Aortic Valve Re-intervention

Aortic Valve Re-intervention is defined as any operation that repairs, alters or replaces a previously operated valve. Events will be classified as*:*

- Balloon aortic valvuloplasty
- Surgical aortic valve replacement or
- Valve in valve

3. Endocarditis

The diagnosis of prosthetic valve endocarditis is based on one of the following criteria:

- reoperation with evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies
- autopsy findings of abscess, pus, or vegetation involving a repaired or replaced valve

4. Coronary Obstruction (within first 30 days of index procedure)

Mechanical coronary artery obstruction following TAVI or index surgical AVR includes:

- impingement of the coronary ostia by the valve support structure in the setting of suboptimal valve positioning and/or 'small aortic root' anatomy; or
- embolization from calcium, thrombus, air, or endocarditis displacement of native aortic valve leaflets towards the coronary ostia during TAVI ; or
- suture-related kinking or obstruction or cannulation- related obstruction of the coronary ostia associated with surgical AVR.

Note: Determined by imaging studies (coronary angiography, intravascular ultrasound, multi-slice CT angiography, or echocardiography), surgical exploration, or autopsy findings. Cardiac biomarker elevations and ECG changes indicating new ischemia provide corroborative evidence.

Causality

All coronary obstructions will be subcategorized as below (more than one category may apply).

Not related to Study Valve or Index Procedure

Study Valve Related: Caused by structural valve deterioration, nonstructural dysfunction, valve thrombosis, embolism, bleeding event, operated valvular endocarditis, or death related to reoperation of an operated valve.

Index Procedure Related: Directly related to the index procedure or complications thereof or any occurring ≤ 30 days of the index procedure will be classified as procedure related.

5. Re-hospitalization or Prolongation of Index Hospitalization (greater than 30 days) due to symptoms of cardiac or valve-related decompensation (VARC Definition)

Event occurs (or persists beyond) at least 30 days after the index procedure (surgical AVR or TAVI). *

Hospitalization (or prolongation of Index Hospitalization greater than 30 days) for symptoms of valve or cardiac deterioration (e.g. new or worsening heart failure, angina, or syncope, MI, etc.) requiring either a valve procedure (surgery or interventional treatment) or intensification of medical management (new or increased use of inotropes, vasopressors, diuretics, and/or vasodilators).

New or Worsening Heart Failure is defined as an event that meets the following criteria:

Hospitalization AND clinical symptoms of CHF with objective signs including pulmonary edema, hypoperfusion or documented volume overload AND administration of IV diuresis or inotropic therapy, performance of aortic valvuloplasty, institution of mechanical support (IABP or ventilation for pulmonary edema) or hemodialysis for volume overload. Administration of IV therapies in clinic or in the Emergency Department without admission will not qualify as a hospitalization event.

Syncope is defined as an event that meets the following criteria:

Hospitalization AND documented loss of consciousness not related to seizure or tachyarrhythmia. The sudden loss of consciousness should be with loss of postural tone, not related to anesthesia, with spontaneous recovery and believed to be related to a cardiac condition.

Angina is defined as an event that meets the following criteria:

Rehospitalization for angina not related to CAD is defined as: hospitalization AND clear documentation of anginal symptoms AND no clinical evidence that angina is related to CAD or ACS.

All Re-hospitalization or Prolongation of Index Hospitalization (greater than 30 days) due to symptoms of cardiac or valve-related decompensation will be subcategorized as below: (more than one category may apply)

Not related to Study Valve or Index Procedure

Valve Related: Symptoms caused by structural valve deterioration, nonstructural dysfunction, valve thrombosis, embolism, bleeding event, operated valvular endocarditis, or MI related to reoperation of an operated valve.

Procedure Related: Symptoms directly related to the index procedure or complications thereof.

Note: A confirmed coronary embolus, occurring at any time, should be reported as an independent event, if biomarker changes and associated findings fulfill definition criteria.

6. Rehospitalization for symptoms of Aortic Stenosis (AS) and/or Complications of the Valve Procedure (Protocol Definition)

Event occurs (or persists beyond) at least 30 days after the index procedure (surgical AVR or TAVI). *

Rehospitalizations for symptoms of AS includes all rehospitalizations for Symptoms of Cardiac or Valve Related Decompensation such as CHF, syncope, endocarditis, coronary ischemia.

Rehospitalizations for complications include complications directly related to the Index Valve Procedure such as bleeding and vascular complications, stroke/TIA, arrhythmias, and AKI. Does not include complications indirectly related to the procedure or related to the hospitalization such as UTI, dehydration, other hospital acquired infections, GI bleeding, etc. Onset of the complication is generally within 30 days of the procedure.

*All rehospitalizations with the potential for symptoms of cardiac or valve-related decompensation (and/or complications of the procedure) as identified by the site or by CEC PM review of rehospitalizations will be adjudicated regardless if the event occurred more or less than 30 days after the index procedure. The time period (</= or > 30 days after the procedure will be indicated on the adjudication form.
If a subject was re-admitted <30 days after the procedure for these symptoms; but remained hospitalized past the 30 day point the event date will be the date of the readmission; it will be indicated as being ≤30 days after the procedure if the admission date is ≤ 30 days after the index procedure.

Hemolysis (PII A only)
Evidence of Red Blood Cell destruction best explained by hemolysis (LDH >350 u/L and decreased haptoglobin based on site lab normals) and no other explanation for the findings. Microscopic evidence may be considered supportive.

All positively adjudicated events will be subcategorized as below.
1. Possibly Related or Related to the valve (or indeterminate cause)
2. Not related to the valve

Pericarditis (PII A only)
Chest pain, EKG, and/or Echocardiogram findings supportive of pericarditis (inflammation of pericardium and no other explanation for the findings).

All positively adjudicated events will be subcategorized as below.
1. Possibly Related or Related to the Valve
2. Possibly Related or Related to the index procedure (any event within 30 days of the index procedure)
3. Not related to the valve or index procedure

Appendix B: Source Documents Recommended for Clinical Event Adjudication

The site research personnel will collect the appropriate source documentation per event as identified.

Death within index hospitalization

- Admission report for index hospitalization, including history and physical
- Index Procedure Report
- Discharge summary after the index procedure
- Relevant consultations (If findings of each not described in other documents)
    - Always send complete neuro consult if done
- Imaging (CT, X-Ray, MRI, etc)
- Autopsy report (if done)
- Laboratory values and normal ranges
- All echocardiogram reports

Death after discharge from index hospitalization

- Discharge summary and or ER notes if seen in medical facility prior to death
- PI note describing what is known about the circumstances of death (if not hospitalized)
- Last hospitalization summary (if not hospitalized at time of death)
- All relevant consultations (if findings not summarized in discharge summary)
    - Always send complete neuron consult if done
- All imaging done (CT, X-Ray, MRI, etc) (If hospitalized)
- Autopsy report (if done)
- Death certificate **(only if NO other documentation not available).**
- Laboratory values and normal ranges
- All echocardiogram reports

Myocardial Infarction and Coronary Obstruction and Pericarditis

- Index Procedure Report
- Discharge summary after the index procedure
- Consultation (relevant)-always send complete neuro consult if done
- Diagnostic Test Results (X-Ray reports, ultrasounds, etc.). (If findings not described in discharge summary)
- 12 lead ECG's (all, including baseline)
- Laboratory values **and normal ranges** (CK-MB, Troponin I or T, CK)
- Coronary angiography/revascularization reports (if not described in other documents)
- All Echocardiogram reports
- Discharge summary after the event

Stroke/TIA

- Admission report for index hospitalization, including history and physical. (If Stroke occurs after discharge from index procedure, the discharge summary from the index hospitalization is sufficient)
- Index Procedure Report (if stroke occurs during index hospitalization)
- Discharge summary from index procedure

- If rehospitalized, Admission note- ER visit for the event (need details of onset of symptoms, including timing and duration)
- Neurology consultation
- Diagnostic Test Results (CT scan/MRI/angiography)
- Discharge Summary After the Event
- If not hospitalized: need neuron consult (if done, or other outpatient medical records describing the onset of symptoms and duration of symptoms and treatment)
- Make sure all of the Rankin and NIHSS scores are completed in the CRF

Bleeding (within index hospitalization)

- Index Procedure Report
- Discharge summary after the index procedure
- All progress notes describing bleeding site (including bruising and hematomas)
- Repair detailed report (if applicable)
- Transfusion records (need dates of transfusions; need times if on the day of procedure)
- All hemoglobins (including those done during the procedure)
- Discharge Summary
- Relevant Imaging Study results (CT scan, ultrasounds)
- Relevant Diagnostic Tests (endoscopies, colonoscopies, etc)
- Documentation of hemodynamic instability (nursing notes, progress notes, medication records)

Bleeding (after discharge from index hospitalization)

- Index Procedure Report
- Discharge summary after the index procedure
- Admission note- ER visit for the event (if applicable and information is not described in other records)
- Progress notes describing bleeding site (including bruises/hematomas)
- Repair detailed report (if applicable)
- Transfusion records
- All hemoglobins (**make sure discharge hgb value is documented in the CRF)**
- Discharge Summary (if hospitalized)
- Relevant Imaging Study results (CT scan, ultrasounds) if done
- Relevant Diagnostic Tests (endoscopies, colonoscopies, etc) if done
- Documentation of hemodynamic instability (nursing notes, progress notes, medication records)

Acute Kidney Injury

- Renal consultation
- Renal Replacement Therapy records (just need date RRT was initiated)
- Lab results from entire index hospitalization (creatinine) with upper reference limits and units and if rehospitalized with AKI include all of those lab values.
- Discharge Summary from index hospitalization and rehospitalization (if applicable)

Vascular Access Site and Access Related Complications

- Index Procedure Report

- Admission note- ER visit for the event (if rehospitalized) & Discharge summary
- Progress notes describing bleeding site (if not well described in other records)
- Repair detailed report (if applicable)
- Transfusion records
- All hematology labs (hgb/hct with units and upper reference limits)
- Relevant Imaging Study results (CT scan, MRI, ultrasounds) if done
- Documentation of hemodynamic instability (nursing notes, progress notes, medication records)
- Arteriograms
- Relevant consults

Prosthetic Valve Performance

- Index Procedure Report
- Discharge summary after the index procedure
- Admission note- ER visit for the event and discharge summary (if rehospitalized)
- All Echo **core lab** results
- Cardiology Consult records
- All local echo reports
- All daily progress notes (including daily physical exams). If patient obviously exhibited many CV symptoms it may not be necessary to sent all of the daily progress notes, may just send the ones that best describes the most severe symptoms.
- All cardiac surgical/intervention reports

Rhythm Disturbances Requiring PPM

- Discharge summary after the index procedure
- Discharge summary if rehospitalized
- EP Consult records including indication for PPM
- All rhythm strips documenting any arrhythmias (do not need to send ALL rhythm strips, only the ones documenting any arrhythmias, if no arrhythmias were documented a note stating this would be sufficient) **(IF EP CONSULT NOT SENT)**
- Relevant CV procedure reports (i.e. ablations, temporary and permanent pacemaker insertions)

Aortic Valve Re-Intervention

- Index Procedure Report
- Discharge summary after the index procedure
- Admission note- ER visit for the event and discharge summary (if rehospitalized)
- Relevant CV procedure reports (i.e. re-intervention procedure report, ablations, temporary and permanent pacemaker insertions, cardioversions, surgeries or percutaneous interventions)
- Relevant diagnostic reports (i.e. electrophysiology studies, angiography, intravascular ultrasound, CT angiography, echocardiography, surgical explorations)

Endocarditis

- Index Procedure Report
- Discharge summary after the index procedure

- Microbiology
- Relevant Consults (cardiology, infectious disease, etc)
- Medication Administration Records (if antibiotic therapy not described in dc summary)
- Relevant CV procedure reports (i.e. re-operations)
- Relevant diagnostic reports (i.e. CT, TTE, TEE)
- Discharge summary for rehospitalization (or ER visit) if applicable

Re-hospitalization

- Index Procedure Report
- Discharge summary after the index procedure
- Admission note- ER visit for the event and discharge summary (especially presenting symptoms, is not described in other records)
- Lab results (creatinine, cardiac biomarker, hemoglobin, haptoglobin, plasma free hemoglobin)
- Relevant CV Consults (cardiology, hematology, electrophysiology)
- Resuscitation records (if applicable)
- Relevant CV procedure reports (i.e. ablations, temporary and permanent pacemaker insertions, cardioversions, surgeries or percutaneous interventions)
- Relevant CV diagnostic reports (angiography, CV ultrasound, CT angiography, echocardiography, surgical explorations, TTE, TEE)

Re-Hospitalization for Decompensation (CHF) and/or Complications of the Procedure

- All documents described for re-hospitalization and
- All CXR reports
- Medication administration records (if use of IV diuretics and inotropes not described in discharge summary)
- BNP values

Hemolysis

- Index Procedure Report
- Discharge summary after the index procedure
- All Lab results (creatinine, cardiac biomarker, hemoglobin, haptoglobin, plasma free hemoglobin, LDH, Liver Function studies)
- Relevant Consults (cardiology, hematology)
- All echocardiogram reports

Glossary of Terms

Adjudication forms- Forms that are completed separately by each assigned C5Research Adjudicator for each event triggered for review. The adjudicator will complete a paper form and return it to the CEC Research Project Manager, who enters the final results onto either a single paper form or into an eCRF (study dependent).

Case Review Period- The time period from the adjudication of the first event until the adjudication of the final event.

CEC Dashboard- An interactive page in the e-CRF where all of the events that trigger (electronically or are added manually) for adjudication are located. Here the CEC PM confirms which events require adjudication. When the adjudication is complete a field is populated with the date the adjudication was completed.

CEC Site Dashboard- An interactive page in the e-CRF where queries are posted to the site in order to investigate other information reported by the site. The sites are asked to consider whether reported information should be reported as an event that may require adjudication. The site can either confirm the event was already reported (or report the event) or decline to report the event. The CEC PM will review these responses and determine if additional events should be added to the CEC Dashboard.

CEC Project Manager (PM) - The role of the CEC PM is to coordinate the operational aspects of the adjudication process. This includes responsibilities such as quality control of the source documents (assure all personal identification information has been removed, the required documents are present and properly identified, and assure that the documentation is sufficient to meet the needs of the adjudication committee), assists CEC Chairperson in the identification and training of adjudicators, maintains regulatory files, assists study team in the development of start up documents (i.e. event definitions, charter, trigger document, critical field document). The CEC PM will also enter the final adjudication results into the e-CRF form. He/she will assure the QA process is completed and results discussed with the CEC Chairperson or Associate Chairperson. Assist in re-training of adjudicators when required. In conjunction with the Chairperson/Associate Chairperson he/she may re-instruct the adjudicators when necessary if definitions are not being followed as trained. The CEC PM may respond to administrative queries (i.e. Correction to site/subject ID information, event number information, erroneous data entry, date and time of event correction, and other fields that do not effect the adjudication result). Non-administrative queries will be forwarded to an appropriate adjudicator (paper format) for resolution and then responded to in the e-CRF (when applicable) by the CEC PM. He/she will assist data management team in reconciliation of events received and returned. For this study a CEC PM will also complete hospitalization and other designated event type reviews and assign them to the appropriate adjudication category. The PM will also write the narratives.

Components of the trigger program- Components of the trigger program may include the Site Endpoint Forms, AE terms, abnormal lab values, echocardiography core lab values and EKG core lab values.

Critical Field Document- The critical field's document is a listing that identifies fields in the study CRF that are critical to the CEC adjudication and tracking process. Ideally these fields should be query free (although sometimes it is understood this may not be possible) at the time a particular event is adjudicated. In the event that data changes in any of the critical fields the CEC will be notified and a Project Manager or adjudicator (depending on the relevance of the data change) will re-review the event.

First manual review- This term refers to the process of the CEC Research Project Manager reviewing the event package for quality control (i.e. subject identifiers obliterated, sufficient event identifying information, documentation is sufficient to meet the needs of the adjudication committee).

Phase I adjudication- Phase I review consists of two physicians (cardiology, vascular or CT surgery fellows) reviewing the same event independently or one staff level specialist physician, independently reviewing the clinical event package, or one RN (CEC PM) reviewing special events to determine what, if any, additional review is required .

Phase II adjudication- Phase II review consists of clinical event package review by one senior staff Cardiologist, Neurologist, or Vascular Specialist. Phase II adjudication is used when either the cardiology fellows have disagreement with each other or the one staff level specialist has disagreement with the site PI opinion.

Query free- Term used to describe the condition of a CRF field at the time the event package is adjudicated by the CEC. It implies that no known queries are outstanding. It is understood that it is not unusual for queries to that field to arise after the adjudication process for the event in question has started or ended.

Re-Reviews- Re-review is a term used to describe the process of when an event needs to be adjudicated more than one time. Although there can be many reasons, the two most common reasons for re-reviews are changes to critical fields and new source documents become available. The CEC Research Project Manager may re-review the change in information and make the decision whether the information is significant to the event and requires readjudication at the physician level. Each time a case is re-reviewed by the Project Manager or re-adjudicated by the adjudicator the date of the review/adjudication will be reflected on the Adjudication Form.

Second manual review- Second manual review is a term used to describe the process of the CEC Research Project Manager receiving the adjudicated event package back from the adjudicators. She may return the package to the adjudicator in the event of errors in form completion with an explanation of the problem. The Project Manager ensures that the forms were completed as trained and either transcribes them onto a single form or enters into an e-CRF (in the event there is agreement at the Phase I level or it is a Phase II level adjudication).

Site endpoint forms- These are CRF pages that the site is asked to complete when a specific event type has been identified by the investigator. They typically contain information that may not be evident (or may be difficult to obtain) in the source documentation. When the information on the site endpoint form conflicts with the source documents, the source documents take precedence.

Source documents- Source documents are photocopies of the original source describing the reported event circumstances. They may also be lab reports from a central lab, radiology films, etc. The required source documents for each study and event type will be listed in a Source Document Collect Tool available for site reference.

Staff level physicians- A staff level physician refers to a physician adjudicator who has completed his specialty specific training and is board certified in that specialty. Generally they are on staff at the Cleveland Clinic, but qualified adjudicators may be used from other academic/clinical institutions at times.

Subject profile- This is a program generated listing of selected CRF fields that contain event related information. Except for the critical fields the information need not be complete or query free. It is used to guide the adjudicator in the review of the event. Source Documentation will take precedence over information on the profile.

Trigger- A term used to refer to the manner in which an event is identified as needing to be adjudicated. Common methods of triggering cases include site reporting on a trigger and/or event form and programmatically (or manually) scanning AE terms or lab values. A study specific Trigger Document should be prepared for each study.

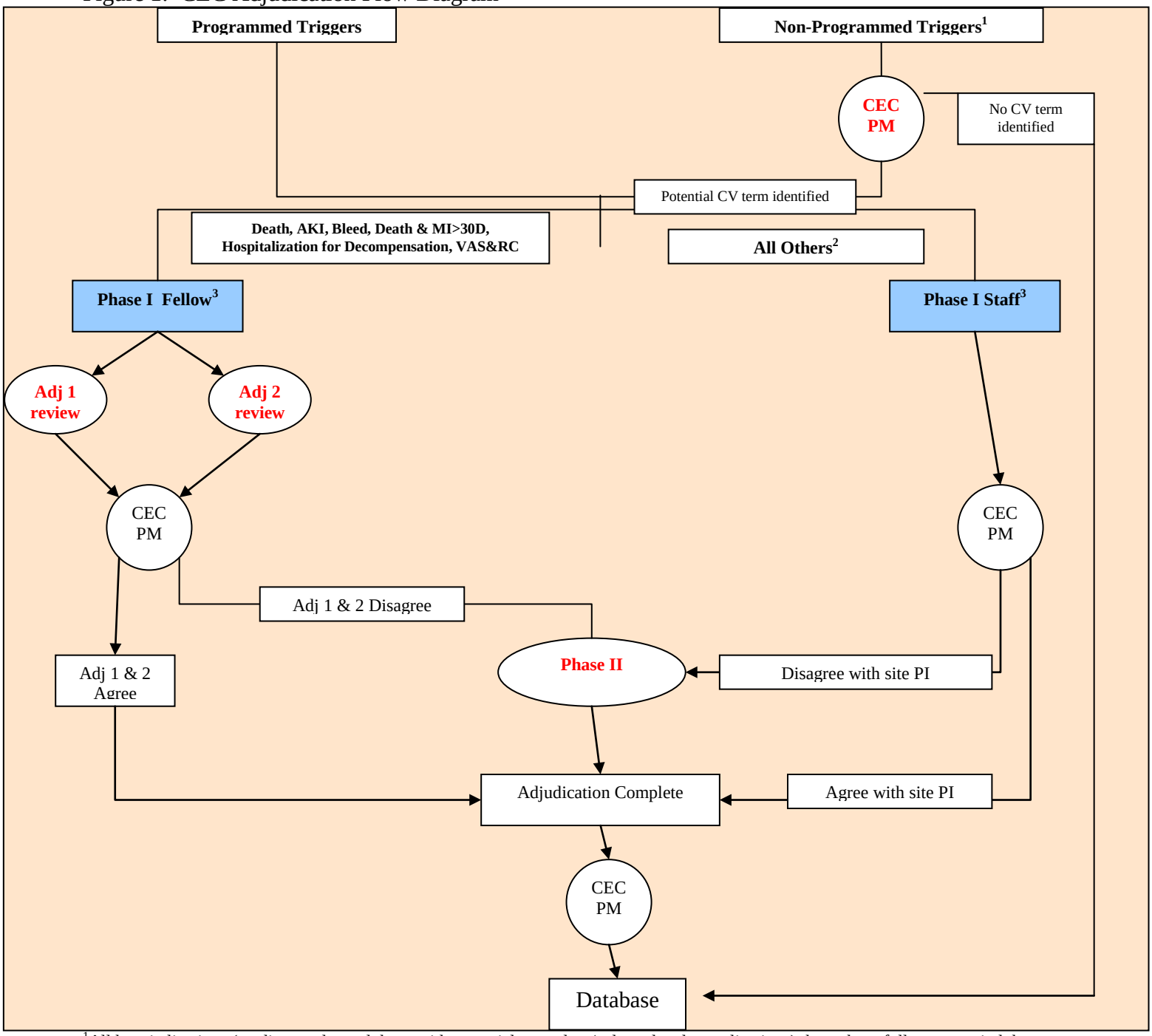
References

1. Leon, Martin B et al. Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation Clinical Trials: A Consensus Report from the Valve Academic Research Consortium. JACC 2011;57:253-269.

2. Hicks, Karen et al. Standardized Definitions for Endpoint Events in Cardiovascular Trials: Draft Recommendations October 20, 2010. http://www.cdisc.org/stuff/contentmgr/files/0/2356ae38ac190ab8ca4ae0b222392b37/misc/cdisc_november_16__2010.pdf

3. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis utilization of specific echocardiographic findings. Duke Endocarditis Service. Am J Med 1994;96:200-9.

Figure 1: CEC Adjudication Flow Diagram



[1]All hospitalizations (cardiovascular and those with potential procedure/valve related complications) throughout follow-up period that did not trigger for a specific endpoint type.
[2]Stroke/TIA, MI≤30days, Prosthetic Valve Dysfunction, Conduction Disturbances requiring PPM, Ao Valve Re-Intervention, MV Dysfunction, Ao Root Rupture/perforation/dissection, Endocarditis, Coronary Obstruction, Death ≤ 30 days after index procedure, and hemolysis and pericarditis (PII A only)
[3]Depending on the event type, the fellow may be cardiology, vascular or CT surgery. Depending on the event type the staff reviewer may be neurologist, cardiologist, or vascular specialist.

Attachment A: CEC Adjudication Forms

Appendix K: The PARTNER II Trial Frailty Index

No changes from previous version (protocol version 4.0)

Appendix L: Assessments for Stroke and Stoke Severity

Modified Rankin Scale

Barthel Index

No changes from previous version (protocol version 4.0)

Appendix M: Case Presentation Template

No changes from previous version (protocol version 4.0)

Appendix N: Case Report Forms

Updated, New format provided.

Form: Inclusion/Exclusion

Date informed consent was signed:	Fixed Unit: (dd MMM yyyy)
Protocol version Subject consented to:	2.5 01 OCT 2011 ☐ 3.0 JAN 2012 ☐ 3.5 APR 2012 ☐ 4.0 AUG 2012 ☐ 4.5 June 2013 ☐
Please indicate if Subject met all inclusion criteria:	Yes ☐ No ☐
Please indicate if Subject met any of the exclusion criteria:	Yes ☐ No ☐

6.000 19MAR2013 Draft 1.0 PROD SRM: All Forms

Form: Inclusion/Exclusion Log

Please indicate:	Inclusion Not Met ☐ Exclusion Met ☐
Criteria Number:	
Reason Met or Not Met:	

Form: Operability Risk Assessment

Please Identify Subject's additional surgical risk factors not included in the STS Risk Score: Check all that apply:	
Liver cirrhosis:	
Porcelain aorta:	
Radiation for treatment of the sternum that precludes an open chest procedure:	
Chest deformities that preclude an open chest procedure:	
Multiple previous interventions in the presence of advanced multi-system dysfunction:	
Pulmonary hypertension:	
Frailty:	
Highly compromised respiratory disease:	
Inoperable pulmonary function:	
Other:	
If Other, specify:	
Evaluating Cardiovascular Surgeon #1	
Name:	
Assessment Date:	Fixed Unit: (dd MMM yyyy)
Check if physical assessment performed:	
Evaluating Cardiovascular Surgeon #2	
Name:	
Assessment Date:	Fixed Unit: (dd MMM yyyy)
Check if physical assessment performed:	
Evaluation Cardiovascular Surgeon #3	
Name:	
Assessment Date:	Fixed Unit: (dd MMM yyyy)
Check if Physical assessment performed:	

6.000 19MAR2013 Draft 1.0 PROD SRM: All Forms

Form: Demographics

Gender:	Male ☐ Female ☐
Race/Ethnicity (check all that apply)	
Hispanic or Latino:	
American Indian or Alaska Native:	
Asian:	
Black or African American:	
Native Hawaiian or Other Pacific Islander:	
White:	
Unknown/Not Reported:	
Date of Birth:	Fixed Unit: (dd MMM yyyy)

6.000 19MAR2013 Draft 1.0 PROD SRM: All Forms

Form: Vital Signs

Date of Measurements:	Fixed Unit: (dd MMM yyyy)
Height:	cm ☐ in ☐
Weight:	kg ☐ lb ☐
Blood Pressure - Systolic:	Fixed Unit: mmHg
Blood Pressure - Diastolic:	Fixed Unit: mmHg
Heart Rate:	Fixed Unit: bpm
BMI (calculated by system):	
BSA (calculated by system):	

Indicate all of the following conditions that currently exist or previously existed.
Please scroll to bottom of form and confirm all applicable conditions are selected.

Condition:	Check all that apply:
	Diabetes type I ☐
	Diabetes type II insulin dependent ☐
	Diabetes type II non insulin dependent ☐
	Previous smoker ☐
	Current smoker ☐
	History of drug abuse ☐
	History of alcohol abuse ☐
	HIV/AIDS ☐
	Pulmonary disease - asthma ☐
	Pulmonary fibrosis ☐
	Anemia ☐
	Hyperthyroid ☐
	Renal insufficiency (Cr greater than or equal to 2.0) ☐
	Dementia ☐
	Thrombocytopenia ☐
	Hypothyroid ☐
	Liver disease (specify mild / moderate / severe) ☐
	Previous cancer (please specify type to the right) ☐
	Current cancer (please specify type to the right) ☐
	Gastro-Intestinal condition (please specify type to the right) ☐
	Coagulopathy (please specify type to the right) ☐
	Current or Previous Immunosuppressive Therapy (please specify type to the right) ☐
	Other (please specify condition(s) to the right) ☐
	None ☐

Indicate all of the following conditions that currently exist or previously existed.
Please scroll to bottom of form and confirm all applicable conditions are selected.

Condition:	Check all that apply:
	Diabetes type I ☐
	Diabetes type II insulin dependent ☐
	Diabetes type II non insulin dependent ☐
	Previous smoker ☐
	Current smoker ☐
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	Dementia ☐
	Thrombocytopenia ☐
	Hypothyroid ☐
	Liver disease (specify mild / moderate / severe) ☐
	Previous cancer (please specify type to the right) ☐
	Current cancer (please specify type to the right) ☐
	Gastro-Intestinal condition (please specify type to the right) ☐
	Coagulopathy (please specify type to the right) ☐
	Current or Previous Immunosuppressive Therapy (please specify type to the right) ☐
	Other (please specify condition(s) to the right) ☐
	None ☐

Indicate all of the following conditions that currently exist or previously existed.
Please scroll to bottom of form and confirm all applicable conditions are selected.

Condition:	Check all that apply:
	Diabetes type I ☐
	Diabetes type II insulin dependent ☐
	Diabetes type II non insulin dependent ☐
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	Dementia ☐
	Thrombocytopenia ☐
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	Current cancer (please specify type to the right) ☐
	Gastro-Intestinal condition (please specify type to the right) ☐
	Coagulopathy (please specify type to the right) ☐
	Current or Previous Immunosuppressive Therapy (please specify type to the right) ☐
	Other (please specify condition(s) to the right) ☐
	None ☐

Indicate all of the following conditions that currently exist or previously existed.
Please scroll to bottom of form and confirm all applicable conditions are selected.

Condition:	Check all that apply:
	Diabetes type I ☐
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	Diabetes type II non insulin dependent ☐
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	Coagulopathy (please specify type to the right) ☐
	Current or Previous Immunosuppressive Therapy (please specify type to the right) ☐
	Other (please specify condition(s) to the right) ☐
	None ☐

Indicate all of the following conditions that currently exist or previously existed.
Please scroll to bottom of form and confirm all applicable conditions are selected.

Condition:	Check all that apply:
	Diabetes type I ☐
	Diabetes type II insulin dependent ☐
	Diabetes type II non insulin dependent ☐
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	Current smoker ■
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	Dementia ☐
	Thrombocytopenia ☐
	Hypothyroid ☐
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	Current cancer (please specify type to the right) ☐
	Gastro-Intestinal condition (please specify type to the right) ☐
	Coagulopathy (please specify type to the right) ☐
	Current or Previous Immunosuppressive Therapy (please specify type to the right) ☐
	Other (please specify condition(s) to the right) ☐
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Indicate all of the following conditions that currently exist or previously existed.
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Condition:	Check all that apply:
	Diabetes type I ☐
	Diabetes type II insulin dependent ☐
	Diabetes type II non insulin dependent ☐
	Previous smoker ☐
	Current smoker ☐
	History of drug abuse ☐
	History of alcohol abuse ☐
	HIV/AIDS ☐
	Pulmonary disease - asthma ☐
	Pulmonary fibrosis ☐
	Anemia ☐
	Hyperthyroid ☐
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	Thrombocytopenia ☐
	Hypothyroid ☐
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	Current cancer (please specify type to the right) ☐
	Gastro-Intestinal condition (please specify type to the right) ☐
	Coagulopathy (please specify type to the right) ☐
	Current or Previous Immunosuppressive Therapy (please specify type to the right) ☐
	Other (please specify condition(s) to the right) ☐
	None ☐

Indicate all of the following conditions that currently exist or previously existed.
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Condition:

- Diabetes type I ☐
- Diabetes type II insulin dependent ☐
- Diabetes type II non insulin dependent ☐
- Previous smoker ☐
- Current smoker ☐
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- History of alcohol abuse ■
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- Pulmonary fibrosis ☐
- Anemia ☐
- Hyperthyroid ☐
- Renal insufficiency (Cr greater than or equal to 2.0) ☐
- Dementia ☐
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- Coagulopathy (please specify type to the right) ☐
- Current or Previous Immunosuppressive Therapy (please specify type to the right) ☐
- Other (please specify condition(s) to the right) ☐
- None ☐

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	Diabetes type I ☐
	Diabetes type II insulin dependent ☐
	Diabetes type II non insulin dependent ☐
	Previous smoker ☐
	Current smoker ☐
	History of drug abuse ☐
	History of alcohol abuse ☐
	HIV/AIDS ■
	Pulmonary disease - asthma ☐
	Pulmonary fibrosis ☐
	Anemia ☐
	Hyperthyroid ☐
	Renal insufficiency (Cr greater than or equal to 2.0) ☐
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	Coagulopathy (please specify type to the right) ☐
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	Other (please specify condition(s) to the right) ☐
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	Coagulopathy (please specify type to the right) ☐
	Current or Previous Immunosuppressive Therapy (please specify type to the right) ☐
	Other (please specify condition(s) to the right) ☐
	None ☐

Indicate all of the following conditions that currently exist or previously existed.
Please scroll to bottom of form and confirm all applicable conditions are selected.

Condition:

- Diabetes type I
- Diabetes type II insulin dependent
- Diabetes type II non insulin dependent
- Previous smoker
- Current smoker
- History of drug abuse
- History of alcohol abuse
- HIV/AIDS
- Pulmonary disease - asthma
- Pulmonary fibrosis
- Anemia
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- Dementia
- Thrombocytopenia
- Hypothyroid
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- Current cancer (please specify type to the right)
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- Coagulopathy (please specify type to the right)
- Current or Previous Immunosuppressive Therapy (please specify type to the right)
- Other (please specify condition(s) to the right)
- None

Check all that apply:

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	Pulmonary disease - asthma ☐
	Pulmonary fibrosis ☐
	Anemia ■
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	Renal insufficiency (Cr greater than or equal to 2.0) ☐
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	Hyperthyroid ☐
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	Current cancer (please specify type to the right) ☐
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	Coagulopathy (please specify type to the right) ☐
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- Other (please specify condition(s) to the right) ☐
- None ☐

Check all that apply:

Indicate all of the following conditions that currently exist or previously existed.
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Condition:

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- None ☐

Check all that apply:

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Condition:

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- Other (please specify condition(s) to the right) ☐
- None ☐

Check all that apply:

Indicate all of the following conditions that currently exist or previously existed.
Please scroll to bottom of form and confirm all applicable conditions are selected.

Condition:

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- Diabetes type II insulin dependent ☐
- Diabetes type II non insulin dependent ☐
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- Current or Previous Immunosuppressive Therapy (please specify type to the right) ☐
- Other (please specify condition(s) to the right) ☐
- None ■

Check all that apply:

Indicate all of the following conditions that currently exist or previously existed.
Please scroll to bottom of form and confirm all applicable conditions are selected.

Condition:	
	Diabetes type I ☐
	Diabetes type II insulin dependent ☐
	Diabetes type II non insulin dependent ☐
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	Previous cancer (please specify type to the right) ☐
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	Current or Previous Immunosuppressive Therapy (please specify type to the right) ☐
	Other (please specify condition(s) to the right) ☐
	None ☐
Check all that apply:	
Please Specify:	

Indicate all of the following conditions that currently exist or previously existed.
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Condition:	
	Diabetes type I ☐
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	Coagulopathy (please specify type to the right) ☐
	Current or Previous Immunosuppressive Therapy (please specify type to the right) ☐
	Other (please specify condition(s) to the right) ☐
	None ☐
Check all that apply:	
Please Specify:	

Indicate all of the following conditions that currently exist or previously existed.
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Condition:	
	Diabetes type I ☐
	Diabetes type II insulin dependent ☐
	Diabetes type II non insulin dependent ☐
	Previous smoker ☐
	Current smoker ☐
	History of drug abuse ☐
	History of alcohol abuse ☐
	HIV/AIDS ☐
	Pulmonary disease - asthma ☐
	Pulmonary fibrosis ☐
	Anemia ☐
	Hyperthyroid ☐
	Renal insufficiency (Cr greater than or equal to 2.0) ☐
	Dementia ☐
	Thrombocytopenia ☐
	Hypothyroid ☐
	Liver disease (specify mild / moderate / severe) ☐
	Previous cancer (please specify type to the right) ☐
	Current cancer (please specify type to the right) ■
	Gastro-Intestinal condition (please specify type to the right) ☐
	Coagulopathy (please specify type to the right) ☐
	Current or Previous Immunosuppressive Therapy (please specify type to the right) ☐
	Other (please specify condition(s) to the right) ☐
	None ☐
Check all that apply:	
Please Specify:	

Indicate all of the following conditions that currently exist or previously existed.
Please scroll to bottom of form and confirm all applicable conditions are selected.

Condition:	
	Diabetes type I ☐
	Diabetes type II insulin dependent ☐
	Diabetes type II non insulin dependent ☐
	Previous smoker ☐
	Current smoker ☐
	History of drug abuse ☐
	History of alcohol abuse ☐
	HIV/AIDS ☐
	Pulmonary disease - asthma ☐
	Pulmonary fibrosis ☐
	Anemia ☐
	Hyperthyroid ☐
	Renal insufficiency (Cr greater than or equal to 2.0) ☐
	Dementia ☐
	Thrombocytopenia ☐
	Hypothyroid ☐
	Liver disease (specify mild / moderate / severe) ☐
	Previous cancer (please specify type to the right) ☐
	Current cancer (please specify type to the right) ☐
	Gastro-Intestinal condition (please specify type to the right) ■
	Coagulopathy (please specify type to the right) ☐
	Current or Previous Immunosuppressive Therapy (please specify type to the right) ☐
	Other (please specify condition(s) to the right) ☐
	None ☐
Check all that apply:	
Please Specify:	

Indicate all of the following conditions that currently exist or previously existed.
Please scroll to bottom of form and confirm all applicable conditions are selected.

Condition:	
	Diabetes type I ☐
	Diabetes type II insulin dependent ☐
	Diabetes type II non insulin dependent ☐
	Previous smoker ☐
	Current smoker ☐
	History of drug abuse ☐
	History of alcohol abuse ☐
	HIV/AIDS ☐
	Pulmonary disease - asthma ☐
	Pulmonary fibrosis ☐
	Anemia ☐
	Hyperthyroid ☐
	Renal insufficiency (Cr greater than or equal to 2.0) ☐
	Dementia ☐
	Thrombocytopenia ☐
	Hypothyroid ☐
	Liver disease (specify mild / moderate / severe) ☐
	Previous cancer (please specify type to the right) ☐
	Current cancer (please specify type to the right) ☐
	Gastro-Intestinal condition (please specify type to the right) ☐
	Coagulopathy (please specify type to the right) ■
	Current or Previous Immunosuppressive Therapy (please specify type to the right) ☐
	Other (please specify condition(s) to the right) ☐
	None ☐
Check all that apply:	
Please Specify:	

Indicate all of the following conditions that currently exist or previously existed.
Please scroll to bottom of form and confirm all applicable conditions are selected.

Condition:	
	Diabetes type I ☐
	Diabetes type II insulin dependent ☐
	Diabetes type II non insulin dependent ☐
	Previous smoker ☐
	Current smoker ☐
	History of drug abuse ☐
	History of alcohol abuse ☐
	HIV/AIDS ☐
	Pulmonary disease - asthma ☐
	Pulmonary fibrosis ☐
	Anemia ☐
	Hyperthyroid ☐
	Renal insufficiency (Cr greater than or equal to 2.0) ☐
	Dementia ☐
	Thrombocytopenia ☐
	Hypothyroid ☐
	Liver disease (specify mild / moderate / severe) ☐
	Previous cancer (please specify type to the right) ☐
	Current cancer (please specify type to the right) ☐
	Gastro-Intestinal condition (please specify type to the right) ☐
	Coagulopathy (please specify type to the right) ☐
	Current or Previous Immunosuppressive Therapy (please specify type to the right) ■
	Other (please specify condition(s) to the right) ☐
	None ☐
Check all that apply:	
Please Specify:	

Indicate all of the following conditions that currently exist or previously existed.
Please scroll to bottom of form and confirm all applicable conditions are selected.

Condition:	
	Diabetes type I ☐
	Diabetes type II insulin dependent ☐
	Diabetes type II non insulin dependent ☐
	Previous smoker ☐
	Current smoker ☐
	History of drug abuse ☐
	History of alcohol abuse ☐
	HIV/AIDS ☐
	Pulmonary disease - asthma ☐
	Pulmonary fibrosis ☐
	Anemia ☐
	Hyperthyroid ☐
	Renal insufficiency (Cr greater than or equal to 2.0) ☐
	Dementia ☐
	Thrombocytopenia ☐
	Hypothyroid ☐
	Liver disease (specify mild / moderate / severe) ☐
	Previous cancer (please specify type to the right) ☐
	Current cancer (please specify type to the right) ☐
	Gastro-Intestinal condition (please specify type to the right) ☐
	Coagulopathy (please specify type to the right) ☐
	Current or Previous Immunosuppressive Therapy (please specify type to the right) ☐
	Other (please specify condition(s) to the right) ■
	None ☐
Check all that apply:	
Please Specify:	

Indicate all of the following conditions that currently exist or previously existed.
Please scroll to bottom of form and confirm all applicable conditions are selected.

Condition:	
	Diabetes type I ☐
	Diabetes type II insulin dependent ☐
	Diabetes type II non insulin dependent ☐
	Previous smoker ☐
	Current smoker ☐
	History of drug abuse ☐
	History of alcohol abuse ☐
	HIV/AIDS ☐
	Pulmonary disease - asthma ☐
	Pulmonary fibrosis ☐
	Anemia ☐
	Hyperthyroid ☐
	Renal insufficiency (Cr greater than or equal to 2.0) ☐
	Dementia ☐
	Thrombocytopenia ☐
	Hypothyroid ☐
	Liver disease (specify mild / moderate / severe) ☐
	Previous cancer (please specify type to the right) ☐
	Current cancer (please specify type to the right) ☐
	Gastro-Intestinal condition (please specify type to the right) ☐
	Coagulopathy (please specify type to the right) ☐
	Current or Previous Immunosuppressive Therapy (please specify type to the right) ☐
	Other (please specify condition(s) to the right) ☐
	None ■
Check all that apply:	
Please Specify:	

Current or Previous COPD:	Yes ☐ No ☐ Unknown ☐
If Yes, FEV-1 value:	Fixed Unit: L _____
If Yes, O_2 dependent:	Yes ☐ No ☐ Unknown ☐

Bleeding History

Current or Previous Bleeding:	Yes ☐ No ☐ Unknown ☐
If Yes, specify type of bleeding (check all that apply):	
Gastro-intestinal:	_____
Genito-urinary:	_____
Pulmonary:	_____
Neurological:	_____
Other:	_____
If Other, specify:	_____
If Yes, date of last known bleed:	Fixed Unit: (dd MMM yyyy) _____

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Form: Cardiac Conditions 1

Indicate all of the following conditions that currently exist or previously existed.

Condition:	Check all that apply:
	Congestive Heart Failure
	Cardiomyopathy
	Marfan's Syndrome
	Coronary Artery Disease
	Hypertension
	Hyperlipidemia
	Dyslipidemia
	Syncope
	Carotid Disease
	Peripheral Vascular Disease
	Endocarditis
	None

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Form: Cardiac Conditions 1

Indicate all of the following conditions that currently exist or previously existed.

Condition:	Check all that apply:
	Congestive Heart Failure ☐
	Cardiomyopathy ■
	Marfan's Syndrome ☐
	Coronary Artery Disease ☐
	Hypertension ☐
	Hyperlipidemia ☐
	Dyslipidemia ☐
	Syncope ☐
	Carotid Disease ☐
	Peripheral Vascular Disease ☐
	Endocarditis ☐
	None ☐

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Form: Cardiac Conditions 1

Indicate all of the following conditions that currently exist or previously existed.

Condition:	Check all that apply:
	Congestive Heart Failure ☐
	Cardiomyopathy ☐
	Marfan's Syndrome ■
	Coronary Artery Disease ☐
	Hypertension ☐
	Hyperlipidemia ☐
	Dyslipidemia ☐
	Syncope ☐
	Carotid Disease ☐
	Peripheral Vascular Disease ☐
	Endocarditis ☐
	None ☐

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Form: Cardiac Conditions 1

Indicate all of the following conditions that currently exist or previously existed.

Condition:	Check all that apply:
	Congestive Heart Failure ☐
	Cardiomyopathy ☐
	Marfan's Syndrome ☐
	Coronary Artery Disease ■
	Hypertension ☐
	Hyperlipidemia ☐
	Dyslipidemia ☐
	Syncope ☐
	Carotid Disease ☐
	Peripheral Vascular Disease ☐
	Endocarditis ☐
	None ☐

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Form: Cardiac Conditions 1

Indicate all of the following conditions that currently exist or previously existed.

Condition:	
	Congestive Heart Failure ☐
	Cardiomyopathy ☐
	Marfan's Syndrome ☐
	Coronary Artery Disease ☐
	Hypertension ■
	Hyperlipidemia ☐
	Dyslipidemia ☐
	Syncope ☐
	Carotid Disease ☐
	Peripheral Vascular Disease ☐
	Endocarditis ☐
	None ☐

Check all that apply:

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Form: Cardiac Conditions 1

Indicate all of the following conditions that currently exist or previously existed.

Condition:	Check all that apply:
	Congestive Heart Failure ☐
	Cardiomyopathy ☐
	Marfan's Syndrome ☐
	Coronary Artery Disease ☐
	Hypertension ☐
	Hyperlipidemia ■
	Dyslipidemia ☐
	Syncope ☐
	Carotid Disease ☐
	Peripheral Vascular Disease ☐
	Endocarditis ☐
	None ☐

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Form: Cardiac Conditions 1

Indicate all of the following conditions that currently exist or previously existed.

Condition:	Check all that apply:
	Congestive Heart Failure ☐
	Cardiomyopathy ☐
	Marfan's Syndrome ☐
	Coronary Artery Disease ☐
	Hypertension ☐
	Hyperlipidemia ☐
	Dyslipidemia ■
	Syncope ☐
	Carotid Disease ☐
	Peripheral Vascular Disease ☐
	Endocarditis ☐
	None ☐

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Form: Cardiac Conditions 1

Indicate all of the following conditions that currently exist or previously existed.

Condition:	Check all that apply:
	Congestive Heart Failure ☐
	Cardiomyopathy ☐
	Marfan's Syndrome ☐
	Coronary Artery Disease ☐
	Hypertension ☐
	Hyperlipidemia ☐
	Dyslipidemia ☐
	Syncope ■
	Carotid Disease ☐
	Peripheral Vascular Disease ☐
	Endocarditis ☐
	None ☐

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Form: Cardiac Conditions 1

Indicate all of the following conditions that currently exist or previously existed.

Condition:	Check all that apply:
	Congestive Heart Failure ☐
	Cardiomyopathy ☐
	Marfan's Syndrome ☐
	Coronary Artery Disease ☐
	Hypertension ☐
	Hyperlipidemia ☐
	Dyslipidemia ☐
	Syncope ☐
	Carotid Disease ■
	Peripheral Vascular Disease ☐
	Endocarditis ☐
	None ☐

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Form: Cardiac Conditions 1

Indicate all of the following conditions that currently exist or previously existed.

Condition:	Check all that apply:
	Congestive Heart Failure ☐
	Cardiomyopathy ☐
	Marfan's Syndrome ☐
	Coronary Artery Disease ☐
	Hypertension ☐
	Hyperlipidemia ☐
	Dyslipidemia ☐
	Syncope ☐
	Carotid Disease ☐
	Peripheral Vascular Disease ■
	Endocarditis ☐
	None ☐

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Form: Cardiac Conditions 1

Indicate all of the following conditions that currently exist or previously existed.

Condition:	
	Congestive Heart Failure ☐
	Cardiomyopathy ☐
	Marfan's Syndrome ☐
	Coronary Artery Disease ☐
	Hypertension ☐
	Hyperlipidemia ☐
	Dyslipidemia ☐
	Syncope ☐
	Carotid Disease ☐
	Peripheral Vascular Disease ☐
	Endocarditis ■
	None ☐

Check all that apply:

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Form: Cardiac Conditions 1

Indicate all of the following conditions that currently exist or previously existed.

Condition:	Check all that apply:
	Congestive Heart Failure ☐
	Cardiomyopathy ☐
	Marfan's Syndrome ☐
	Coronary Artery Disease ☐
	Hypertension ☐
	Hyperlipidemia ☐
	Dyslipidemia ☐
	Syncope ☐
	Carotid Disease ☐
	Peripheral Vascular Disease ☐
	Endocarditis ☐
	None ■

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Form: Cardiac Conditions 2

Indicate all of the following that have occured.	
Intervention/Surgery/Condition:	MI
Check all that apply:	
Date of Most Recent:	
Number Performed/Occurred:	

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Form: Cardiac Conditions 2

Indicate all of the following that have occured.	
Intervention/Surgery/Condition:	CVA
Check all that apply:	
Date of Most Recent:	
Number Performed/Occurred:	

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Form: Cardiac Conditions 2

Indicate all of the following that have occured.	
Intervention/Surgery/Condition:	TIA
Check all that apply:	
Date of Most Recent:	
Number Performed/Occurred:	

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Form: Cardiac Conditions 2

Indicate all of the following that have occured.	
Intervention/Surgery/Condition:	PCI - Drug Eluting Stent
Check all that apply:	
Date of Most Recent:	
Number Performed/Occurred:	

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Form: Cardiac Conditions 2

Indicate all of the following that have occured.	
Intervention/Surgery/Condition:	PCI - Bare Metal Stent
Check all that apply:	
Date of Most Recent:	
Number Performed/Occurred:	

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Form: Cardiac Conditions 2

Indicate all of the following that have occured.	
Intervention/Surgery/Condition:	PCI - Other/Unknown
Check all that apply:	
Date of Most Recent:	
Number Performed/Occurred:	

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Form: Cardiac Conditions 2

Indicate all of the following that have occured.	
Intervention/Surgery/Condition:	CABG Operations
Check all that apply:	
Date of Most Recent:	
Number Performed/Occurred:	

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Form: Cardiac Conditions 2

Indicate all of the following that have occured.	
Intervention/Surgery/Condition:	Prior Sternotomy (Non-CABG)
Check all that apply:	
Date of Most Recent:	
Number Performed/Occurred:	

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Form: Cardiac Conditions 2

Indicate all of the following that have occured.	
Intervention/Surgery/Condition:	Prior Aortic Valvuloplasty
Check all that apply:	
Date of Most Recent:	
Number Performed/Occurred:	

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Form: Cardiac Conditions 2

Indicate all of the following that have occured.	
Intervention/Surgery/Condition:	Prior Mitral Valvuloplasty
Check all that apply:	
Date of Most Recent:	
Number Performed/Occurred:	

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Form: Cardiac Conditions 2

Indicate all of the following that have occured.	
Intervention/Surgery/Condition:	Prior Tricuspid Valvuloplasty
Check all that apply:	
Date of Most Recent:	
Number Performed/Occurred:	

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Form: Cardiac Conditions 2

Indicate all of the following that have occured.	
Intervention/Surgery/Condition:	Peripheral Bypass Graft
Check all that apply:	
Date of Most Recent:	
Number Performed/Occurred:	

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Form: Cardiac Conditions 2

Indicate all of the following that have occured.	
Intervention/Surgery/Condition:	Prior AAA repair
Check all that apply:	
Date of Most Recent:	
Number Performed/Occurred:	

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Form: Cardiac Conditions 2

Indicate all of the following that have occured.	
Intervention/Surgery/Condition:	Prior iliac stent
Check all that apply:	
Date of Most Recent:	
Number Performed/Occurred:	

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Form: Cardiac Conditions 2

Indicate all of the following that have occured.	
Intervention/Surgery/Condition:	Prior femoral stent
Check all that apply:	
Date of Most Recent:	
Number Performed/Occurred:	

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Form: Cardiac Conditions 2

Indicate all of the following that have occured.	
Intervention/Surgery/Condition:	Prior carotid stent
Check all that apply:	
Date of Most Recent:	
Number Performed/Occurred:	

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Form: Cardiac Conditions 2

Indicate all of the following that have occured.	
Intervention/Surgery/Condition:	Prior endovascular repair
Check all that apply:	
Date of Most Recent:	
Number Performed/Occurred:	

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Form: Cardiac Conditions 2

Indicate all of the following that have occured.	
Intervention/Surgery/Condition:	Prior vascular surgery/repair
Check all that apply:	
Date of Most Recent:	
Number Performed/Occurred:	

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Form: Cardiac Conditions 2

Indicate all of the following that have occured.	
Intervention/Surgery/Condition:	None
Check all that apply:	
Date of Most Recent:	
Number Performed/Occurred:	

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Form: Arrhythmia History

Indicate all of the following conditions that currently exist or previously existed and treatments used if applicable.

Condition/Treatment:	Atrial Fibrillation ■
	Atrial Flutter ☐
	Tachyarrhythmia ☐
	Bradyarrhythmia ☐
	Heart Block ☐
	Arrhythmia, other (please specify type to the right) ☐
	Pacemaker - Single chamber ☐
	Pacemaker - Dual chamber ☐
	Pacemaker - Biventricular ☐
	Ablation ☐
	None ☐
Check all that apply:	
Please Specify:	

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Form: Arrhythmia History

Indicate all of the following conditions that currently exist or previously existed and treatments used if applicable.

Condition/Treatment:	
	Atrial Fibrillation ☐
	Atrial Flutter ■
	Tachyarrhythmia ☐
	Bradyarrhythmia ☐
	Heart Block ☐
	Arrhythmia, other (please specify type to the right) ☐
	Pacemaker - Single chamber ☐
	Pacemaker - Dual chamber ☐
	Pacemaker - Biventricular ☐
	Ablation ☐
	None ☐
Check all that apply:	
Please Specify:	

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Form: Arrhythmia History

Indicate all of the following conditions that currently exist or previously existed and treatments used if applicable.

Condition/Treatment:	
	Atrial Fibrillation ☐
	Atrial Flutter ☐
	Tachyarrhythmia ■
	Bradyarrhythmia ☐
	Heart Block ☐
	Arrhythmia, other (please specify type to the right) ☐
	Pacemaker - Single chamber ☐
	Pacemaker - Dual chamber ☐
	Pacemaker - Biventricular ☐
	Ablation ☐
	None ☐
Check all that apply:	
Please Specify:	

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Form: Arrhythmia History

Indicate all of the following conditions that currently exist or previously existed and treatments used if applicable.

Condition/Treatment:	
	Atrial Fibrillation ☐
	Atrial Flutter ☐
	Tachyarrhythmia ☐
	Bradyarrhythmia ■
	Heart Block ☐
	Arrhythmia, other (please specify type to the right) ☐
	Pacemaker - Single chamber ☐
	Pacemaker - Dual chamber ☐
	Pacemaker - Biventricular ☐
	Ablation ☐
	None ☐
Check all that apply:	
Please Specify:	

Form: Arrhythmia History

Indicate all of the following conditions that currently exist or previously existed and treatments used if applicable.

Condition/Treatment:	
	Atrial Fibrillation ☐
	Atrial Flutter ☐
	Tachyarrhythmia ☐
	Bradyarrhythmia ☐
	Heart Block ■
	Arrhythmia, other (please specify type to the right) ☐
	Pacemaker - Single chamber ☐
	Pacemaker - Dual chamber ☐
	Pacemaker - Biventricular ☐
	Ablation ☐
	None ☐
Check all that apply:	
Please Specify:	

6.000 19MAR2013 Draft 1.0 PROD SRM: All Forms

Form: Arrhythmia History

Indicate all of the following conditions that currently exist or previously existed and treatments used if applicable.

Condition/Treatment:	
	Atrial Fibrillation ☐
	Atrial Flutter ☐
	Tachyarrhythmia ☐
	Bradyarrhythmia ☐
	Heart Block ☐
	Arrhythmia, other (please specify type to the right) ■
	Pacemaker - Single chamber ☐
	Pacemaker - Dual chamber ☐
	Pacemaker - Biventricular ☐
	Ablation ☐
	None ☐
Check all that apply:	
Please Specify:	

Form: Arrhythmia History

Indicate all of the following conditions that currently exist or previously existed and treatments used if applicable.

Condition/Treatment:	
	Atrial Fibrillation ☐
	Atrial Flutter ☐
	Tachyarrhythmia ☐
	Bradyarrhythmia ☐
	Heart Block ☐
	Arrhythmia, other (please specify type to the right) ☐
	Pacemaker - Single chamber ■
	Pacemaker - Dual chamber ☐
	Pacemaker - Biventricular ☐
	Ablation ☐
	None ☐
Check all that apply:	
Please Specify:	

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Form: Arrhythmia History

Indicate all of the following conditions that currently exist or previously existed and treatments used if applicable.

Condition/Treatment:	
	Atrial Fibrillation ☐
	Atrial Flutter ☐
	Tachyarrhythmia ☐
	Bradyarrhythmia ☐
	Heart Block ☐
	Arrhythmia, other (please specify type to the right) ☐
	Pacemaker - Single chamber ☐
	Pacemaker - Dual chamber ■
	Pacemaker - Biventricular ☐
	Ablation ☐
	None ☐
Check all that apply:	
Please Specify:	

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Form: Arrhythmia History

Indicate all of the following conditions that currently exist or previously existed and treatments used if applicable.

Condition/Treatment:	
	Atrial Fibrillation ☐
	Atrial Flutter ☐
	Tachyarrhythmia ☐
	Bradyarrhythmia ☐
	Heart Block ☐
	Arrhythmia, other (please specify type to the right) ☐
	Pacemaker - Single chamber ☐
	Pacemaker - Dual chamber ☐
	Pacemaker - Biventricular ■
	Ablation ☐
	None ☐
Check all that apply:	
Please Specify:	

Form: Arrhythmia History

Indicate all of the following conditions that currently exist or previously existed and treatments used if applicable.

Condition/Treatment:	
	Atrial Fibrillation ☐
	Atrial Flutter ☐
	Tachyarrhythmia ☐
	Bradyarrhythmia ☐
	Heart Block ☐
	Arrhythmia, other (please specify type to the right) ☐
	Pacemaker - Single chamber ☐
	Pacemaker - Dual chamber ☐
	Pacemaker - Biventricular ☐
	Ablation ■
	None ☐
Check all that apply:	
Please Specify:	

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Form: Arrhythmia History

Indicate all of the following conditions that currently exist or previously existed and treatments used if applicable.

Condition/Treatment:	
	Atrial Fibrillation ☐
	Atrial Flutter ☐
	Tachyarrhythmia ☐
	Bradyarrhythmia ☐
	Heart Block ☐
	Arrhythmia, other (please specify type to the right) ☐
	Pacemaker - Single chamber ☐
	Pacemaker - Dual chamber ☐
	Pacemaker - Biventricular ☐
	Ablation ☐
	None ■
Check all that apply:	
Please Specify:	

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Form: Barthel Index

Unique AE Number:	
Was Barthel Index performed?	Yes ☐ No ☐
If No, was assessment not done due to medical reason?	Yes ☐ No ☐
Rater Name:	
Date:	Fixed Unit: (dd MMM yyyy)

Activity	
FEEDING:	0 = unable ☐ 5 = needs help cutting, spreading butter, etc., or requires modifed diet ☐ 10 = independent ☐
BATHING:	0 = dependent ☐ 5 = independent (or in shower) ☐
GROOMING:	0 = needs to help with personal care ☐ 5 = independent face/hair/teeth/shaving (implements provided) ☐
DRESSING:	0 = dependent ☐ 5 = needs help but can do about half unaided ☐ 10 = independent (including buttons, zips, laces, etc.) ☐
BOWELS:	0 = incontinent (or needs to be given enemas) ☐ 5 = occasional accident ☐ 10 = continent ☐
BLADDER:	0 = incontinent, or catheterized and unable to manage alone ☐ 5 = occasional accident ☐ 10 = continent ☐
TOILET USE:	0 = dependent ☐ 5 = needs some help, but can do something alone ☐ 10 = independent (on and off, dressing, wiping) ☐

TRANSFERS (BED TO CHAIR AND BACK):	0 = unable, no sitting balance ☐ 5 = major help (one or two people, physical), can sit ☐ 10 = minor help (verbal or physical) ☐ 15 = independent ☐
MOBILITY (ON LEVEL SURFACES):	0 = immobile or < 50 yards ☐ 5 = wheelchair independent, including corners, > 50 yards ☐ 10 = walks with help of one person (verbal or physical) > 50 yards ☐ 15 = independent (but may use any aid; for example, stick) > 50 yards ☐
STAIRS:	0 = unable ☐ 5 = needs help (verbal, physical, carrying aid) ☐ 10 = independent ☐
TOTAL (0-100): (*calculated by the system*)	_____
Timepoint (used to name forms added to AE folder):	_____

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Form: Modified Rankin Scale

Unique AE Number:	
Was MRS performed?	Yes ☐ No ☐
If No, was assessment not done due to medical reason?	Yes ☐ No ☐
Date of Assessment:	Fixed Unit: (dd MMM yyyy)
Description:	No symptoms ☐ No significant disability despite symptoms ☐ Slight disability ☐ Moderate disability ☐ Moderately severe disability ☐ Severe disability ☐
Rankin Score *(Calculated by System):*	
Please indicate who performed the assessment:	Neurology fellow ☐ Certified team member ☐ Neurologist ☐
Timepoint (used for naming the form within AE folder):	

Form: Coronary Artery Stenosis

Please identify major vessel(s) and/or major branch(es) with coronary artery stenosis >50%.	
Vessel / Branch:	RCA
Check all that apply:	
Specify when requested:	

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Form: Coronary Artery Stenosis

Please identify major vessel(s) and/or major branch(es) with coronary artery stenosis >50%.	
Vessel / Branch:	LM
Check all that apply:	
Specify when requested:	

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Form: Coronary Artery Stenosis

Please identify major vessel(s) and/or major branch(es) with coronary artery stenosis >50%.	
Vessel / Branch:	LAD
Check all that apply:	
Specify when requested:	

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Form: Coronary Artery Stenosis

Please identify major vessel(s) and/or major branch(es) with coronary artery stenosis >50%.	
Vessel / Branch:	CX
Check all that apply:	
Specify when requested:	

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Form: Coronary Artery Stenosis

Please identify major vessel(s) and/or major branch(es) with coronary artery stenosis >50%.	
Vessel / Branch:	Grafts (Specify blocked graft)
Check all that apply:	
Specify when requested:	

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Form: Coronary Artery Stenosis

Please identify major vessel(s) and/or major branch(es) with coronary artery stenosis >50%.	
Vessel / Branch:	None
Check all that apply:	
Specify when requested:	

Indicate the number of times Subject was hospitalized for symptoms of aortic stenosis during the last 6 months:*(enter 0 for none)*	
Angina CCS Class: Angina Grading Scale link	None ☐ I ☐ II ☐ III ☐ IV ☐ ND ☐
NYHA Class: NYHA Classification link	I ☐ II ☐ III ☐ IV ☐ ND ☐
Logistic EuroSCORE: EuroSCORE link	Fixed Unit: %
STS Risk Score: STS Risk Score link	
Syntax Score: Syntax Score link	

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Form: Subject Assignment

Subject Assignment:	
Assignment Date:	
Approach Subject was approved for:	TA ☐ TF ☐ TAO ☐
Override Assignment Date:	
Override Comment:	

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Form: Assessments

Indicate if the following were performed:	
Labs:	Yes ☐ No ☐
Frailty Index Assessment:	Yes ☐ No ☐
Mini Mental State Examination (MMSE):	Yes ☐ No ☐
NIH Stroke Scale (NIHSS):	Yes ☐ No ☐
SF-36 Assessment:	Yes ☐ No ☐
If No, was assessment not done due to medical reason?	Yes ☐ No ☐
KCCQ Assessment:	Yes ☐ No ☐
If No, was assessment not done due to medical reason?	Yes ☐ No ☐
EQ-5D Assessment:	Yes ☐ No ☐
If No, was assessment not done due to medical reason?	Yes ☐ No ☐
Chest X-Ray:	Yes ☐ No ☐
12-Lead ECG:	Yes ☐ No ☐
If Yes, date performed:	Fixed Unit: (dd MMM yyyy)
Transthoracic Echocardiogram (TTE):	Yes ☐ No ☐
If Yes, date performed:	Fixed Unit: (dd MMM yyyy)
If Yes, Baseline annulus diameter as measured via TTE:	Fixed Unit: mm

Transesophogeal Echocardiogram (TEE):	Yes ☐ No ☐
If Yes, date performed:	Fixed Unit: (dd MMM yyyy)
Cardiac Catheterization:	Yes ☐ No ☐
If Yes, date performed:	Fixed Unit: (dd MMM yyyy)
6-Minute Walk Test (6MWT):	Yes ☐ No ☐
If No, please indicate main reason for not performing the test:	Angina - chest pain ☐ Hypotension ☐ Hypertension ☐ Non-ambulatory due to medical condition ☐ Respiratory insufficiency - dyspnea ☐ Other medical reason - please specify below ☐ Other non medical reason - please specify below ☐
If Other, specify reason:	
Minimum diameter of access vessel as measured via CT/CT-Angio or MRI:	Fixed Unit: mm
Presence of calcification at level of iliac bifurcation:	Yes ☐ No ☐ Unknown ☐ NA ☐
Presence of aortic aneurysm > 5cm:	Yes ☐ No ☐ Unknown ☐ NA ☐

Form: Lab - Baseline

Date and Time of Blood Draw:	Fixed Unit: (dd MMM yyyy hh:mm)
Complete Blood Count	
WBC:	
Neutrophils:	**%** ☐ 1000/UL ☐
Lymphocytes:	**%** ☐ 1000/UL ☐
Monocytes:	**%** ☐ 1000/UL ☐
Eosinophils:	**%** ☐ 1000/UL ☐
Basophils:	**%** ☐ 1000/UL ☐
RBC:	
HGB:	
HCT:	
Platelets:	
Haptoglobin:	
Plasma Free Hemoglobin:	
Coagulation Profile	
INR:	
Prothrombin Time (PT):	
Partial Thromboplastin Time (PTT):	
Metabolic Panel	
Sodium:	
Potassium:	
Creatinine:	
BUN:	
Liver Panel	
AST:	
ALT:	
Albumin:	
Cardiac Neurohormone	

Indicate B-type natriuretic peptide measured:	B-type natriuretic peptide - BNP ☐ N-terminal B-type natriuretic peptide - NT-BNP ☐ ND ☐
Value of measurement:	**ng/L** ☐ pg/mL ☐

Cardiac Enzymes

CK:	
Date and time of Blood Draw:	Fixed Unit: (dd MMM yyyy hh:mm)
CK-MB:	
Date and Time of Blood Draw:	Fixed Unit: (dd MMM yyyy hh:mm)
Troponin I:	
Date and time of Blood Draw:	Fixed Unit: (dd MMM yyyy hh:mm)
Troponin T:	
Date and time of Blood Draw:	Fixed Unit: (dd MMM yyyy hh:mm)

Date of Assessment:	Fixed Unit: (dd MMM yyyy)
Indicate where assessment was performed:	Inpatient ☐ Outpatient ☐

Katz Activities of Daily Living

Bathing:	Bathes self completely or needs help in bathing only a single part of the body such as the back or genital area or disabled extremity. ☐ Needs help with bathing more than one part of the body or getting in or out of the tub or shower. Requires total bathing. ☐
Dressing:	Gets clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes. ☐ Needs help with dressing self or needs to be completely dressed. ☐
Toileting:	Goes to toilet - gets on and off - arranges clothes - cleans genital area without help. ☐ Needs help transferring to the toilet or cleaning self or uses bedpan or commode. ☐
Transferring:	Moves in and out of bed or chair unassisted. Mechanical transferring aides are acceptable. ☐ Needs help in moving from bed to chair or requires a complete transfer. ☐
Continence:	Exercises complete self control over urination and defecation. ☐ Is partially or totally incontinent of bowel or bladder. ☐
Feeding:	Gets food from plate into mouth without help. Preparation of food may be done by another person. ☐ Needs partial or total help with feeding or requires parenteral feeding. ☐

Form: Frailty Index

Total points: *(Calculated by System)*

Grip Strength

Grasp 1: **kg** ☐
lb ☐

Grasp 2: **kg** ☐
lb ☐

Grasp 3: **kg** ☐
lb ☐

Average Grasp: *(Calculated by System)* Fixed Unit: kg

15-Foot Walk

Seconds:

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Form: MMSE

Date of Assessment:	Fixed Unit: (dd MMM yyyy)
Test:	Copying (0-1)
	Orientation (0-10)
	Registration (0-3)
	Attention - calculation (0-5)
	Recall (0-3)
	Language (0-8)
Score:	
Total MMSE Score: *(calculated by system)*	

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Form: MMSE

Date of Assessment:	Fixed Unit: (dd MMM yyyy)
Test:	Copying (0-1) ☐
	Orientation (0-10) ■
	Registration (0-3) ☐
	Attention - calculation (0-5) ☐
	Recall (0-3) ☐
	Language (0-8) ☐
Score:	
Total MMSE Score: *(calculated by system)*	

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Form: MMSE

Date of Assessment:	Fixed Unit: (dd MMM yyyy)
Test:	Copying (0-1) ☐
	Orientation (0-10) ☐
	Registration (0-3) ■
	Attention - calculation (0-5) ☐
	Recall (0-3) ☐
	Language (0-8) ☐
Score:	
Total MMSE Score: *(calculated by system)*	

6.000 19MAR2013 Draft 1.0 PROD SRM: All Forms
Form: MMSE

Date of Assessment:	Fixed Unit: (dd MMM yyyy)
Test:	Copying (0-1) ☐
	Orientation (0-10) ☐
	Registration (0-3) ☐
	Attention - calculation (0-5) ■
	Recall (0-3) ☐
	Language (0-8) ☐
Score:	
Total MMSE Score: *(calculated by system)*	

6.000 19MAR2013 Draft 1.0 PROD SRM: All Forms
Form: MMSE

Date of Assessment:	Fixed Unit: (dd MMM yyyy)
Test:	Copying (0-1) ☐
	Orientation (0-10) ☐
	Registration (0-3) ☐
	Attention - calculation (0-5) ☐
	Recall (0-3) ■
	Language (0-8) ☐
Score:	
Total MMSE Score: *(calculated by system)*	

6.000 19MAR2013 Draft 1.0 PROD SRM: All Forms
Form: MMSE

Date of Assessment:	Fixed Unit: (dd MMM yyyy)
Test:	Copying (0-1) ☐
	Orientation (0-10) ☐
	Registration (0-3) ☐
	Attention - calculation (0-5) ☐
	Recall (0-3) ☐
	Language (0-8) ■
Score:	
Total MMSE Score: *(calculated by system)*	

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Form: SF-36

Date of Assessment: Fixed Unit: (dd MMM yyyy)

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an X in the one box that best describes your answer.

1. In general, would you say your health is:	Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor ☐
2. Compared to one year ago, how would you rate your health in general now?	Much better now than one year ago ☐ Somewhat better now than one year ago ☐ About the same as one year ago ☐ Somewhat worse now than one year ago ☐ Much worse now than one year ago ☐
3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?	
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports:	Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all ☐
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf:	Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all ☐
c. Lifting or carrying groceries:	Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all ☐
d. Climbing several flights of stairs:	Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all ☐
e. Climbing one flight of stairs:	Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all ☐

f. Bending, kneeling, or stooping:	Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all ☐
g. Walking more than a mile:	Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all ☐
h. Walking several hundred yards:	Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all ☐
i. Walking one hundred yards:	Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all ☐
j. Bathing or dressing yourself:	Yes, limited a lot ☐ Yes, limited a little ☐ No, not limited at all ☐

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

a. Cut down on the amount of time you spent on work or other activities:	All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time ☐
b. Accomplished less than you would like:	All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time ☐
c. Were limited in the kind of work or other activities:	All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time ☐

d. Had difficulty performing the work or other activities (for example, it took extra effort):	All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time ☐

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

a. Cut down on the amount of time you spent on work or other activities:	All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time ☐
b. Accomplished less than you would like:	All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time ☐
c. Did work or other activities less carefully than usual:	All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time ☐
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?	Not at all ☐ Slightly ☐ Moderately ☐ Quite a bit ☐ Extremely ☐
7. How much bodily pain have you had during the past 4 weeks?	None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe ☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all ☐ A little bit ☐ Moderately ☐ Quite a bit ☐ Extremely ☐

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

a. Did you feel full of life?	All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time ☐
b. Have you been very nervous?	All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time ☐
c. Have you felt so down in the dumps that nothing could cheer you up?	All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time ☐
d. Have you felt calm and peaceful?	All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time ☐
e. Did you have a lot of energy?	All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time ☐

f. Have you felt downhearted and depressed?	All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time ☐
g. Did you feel worn out?	All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time ☐
h. Have you been happy?	All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time ☐
i. Did you feel tired?	All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time ☐
10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?	All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time ☐
11. How TRUE or FALSE is each of the following statements for you?	
a. I seem to get sick a little easier than other people:	Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false ☐

b. I am as healthy as anybody I know:	Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false ☐
c. I expect my health to get worse:	Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false ☐
d. My health is excellent:	Definitely true ☐ Mostly true ☐ Don't know ☐ Mostly false ☐ Definitely false ☐
Comments:	_____

Date of Assessment: Fixed Unit: (dd MMM yyyy)

1. Heart failure affects different people in different ways. Some people feel shortness of breath while others feel fatigue. Please indicate how much you have been limited by heart failure (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Dressing yourself	Extremely limited ☐ Quite a bit limited ☐ Moderately limited ☐ Slightly limited ☐ Not at all limited ☐ Limited for other reasons or did not do the activity ☐
Showering/bathing	Extremely limited ☐ Quite a bit limited ☐ Moderately limited ☐ Slightly limited ☐ Not at all limited ☐ Limited for other reasons or did not do the activity ☐
Walking 1 block on level ground	Extremely limited ☐ Quite a bit limited ☐ Moderately limited ☐ Slightly limited ☐ Not at all limited ☐ Limited for other reasons or did not do the activity ☐
Doing yard work, housework, or carrying groceries	Extremely limited ☐ Quite a bit limited ☐ Moderately limited ☐ Slightly limited ☐ Not at all limited ☐ Limited for other reasons or did not do the activity ☐

Climbing a flight of stairs without stopping	Extremely limited ☐ Quite a bit limited ☐ Moderately limited ☐ Slightly limited ☐ Not at all limited ☐ Limited for other reasons or did not do the activity ☐
Hurrying or jogging (as if to catch a bus)	Extremely limited ☐ Quite a bit limited ☐ Moderately limited ☐ Slightly limited ☐ Not at all limited ☐ Limited for other reasons or did not do the activity ☐

2. Compared with 2 weeks ago, have your symptoms of heart failure (shortness of breath, fatigue or ankle swelling) changed?

My symptoms of heart failure have become...	Much worse ☐ Slightly worse ☐ Not changed ☐ Slightly better ☐ Much better ☐ I've had no symptoms over the last 2 weeks ☐

3. Over the past 2 weeks, how many times did you have swelling in your feet, ankles or legs when you woke up in the morning?	Every morning ☐ Three or more times per week - but not everyday ☐ 1-2 times per week ☐ Less than once a week ☐ Never over the past 2 weeks ☐
4. Over the past 2 weeks, how much has the swelling in your feet, ankles or legs bothered you? It has been...	Extremely bothersome ☐ Quite a bit bothersome ☐ Moderately bothersome ☐ Slightly bothersome ☐ Not at all bothersome ☐ I've had no swelling ☐

5. Over the past 2 weeks, on average, how many times has fatigue limited your ability to do what you want?	All of the time ☐ Several times per day ☐ At least once a day ☐ Three of more times per week - but not everyday ☐ 1-2 times per week ☐ Less than once a week ☐ Never over the past 2 weeks ☐
6. Over the past 2 weeks, how much has your fatigue bothered you? It has been...	Quite a bit bothersome ☐ Moderately bothersome ☐ I've had no fatigue ☐ Extremely bothersome ☐ Slightly bothersome ☐ Not at all bothersome ☐
7. Over the past 2 weeks, on average, how many times has shortness of breath limited your ability to do what you wanted?	All of the time ☐ Several times per day ☐ At least once a day ☐ Three of more times per week - but not everyday ☐ 1-2 times per week ☐ Less than once a week ☐ Never over the past 2 weeks ☐
8. Over the past 2 weeks, how much has your shortness of breath bothered you? It has been ...	Quite a bit bothersome ☐ Moderately bothersome ☐ Slightly bothersome ☐ Extremely bothersome ☐ Not at all bothersome ☐ I've had no shortness of breath ☐
9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair with at least 3 pillows to prop you up because of shortness of breath?	Every night ☐ Three or more times per week - but not everyday ☐ 1-2 times per week ☐ Less than once a week ☐ Never over the past 2 weeks ☐

10. Heart failure symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your heart failure gets worse?	Not at all sure ☐ Not very sure ☐ Somewhat sure ☐ Mostly sure ☐ Completely sure ☐
11. How well do you understand what things you are able to do to keep your heart failure symptoms from getting worse? (for example, weighing yourself, eating a low salt diet, etc)?	Do not understand at all ☐ Do not understand very well ☐ Somewhat understand ☐ Mostly understand ☐ Completely understand ☐
12. Over the past 2 weeks, how much has your heart failure limited your enjoyment of life?	It has extremely limited my enjoyment of life ☐ It has limited my enjoyment of life quite a bit ☐ It has moderately limited my enjoyment of life ☐ It has slightly limited my enjoyment of life ☐ It has not limited my enjoyment of life at all ☐
13. If you had to spend the rest of your life with your heart failure the way it is right now, how would you feel about this?	Not at all satisfied ☐ Mostly dissatisfied ☐ Somewhat satisfied ☐ Mostly satisfied ☐ Completely satisfied ☐
14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your heart failure?	I felt that way all the time ☐ I felt that way most of the time ☐ I occasionally felt that way ☐ I rarely felt that way ☐ I never felt that way ☐

15. How much does your heart failure affect your lifestyle? Please indicate how your heart failure may have limited your participation in the following activities over the past 2 weeks.

Hobbies, recreational activities	Severely limited ☐ Limited quite a bit ☐ Moderately limited ☐ Slightly limited ☐ Did not limit at all ☐ Does not apply or did not do for other reasons ☐
Working or doing household chores	Severely limited ☐ Limited quite a bit ☐ Moderately limited ☐ Slightly limited ☐ Did not limit at all ☐ Does not apply or did not do for other reasons ☐
Visiting family or friends out of your home	Severely limited ☐ Limited quite a bit ☐ Moderately limited ☐ Slightly limited ☐ Did not limit at all ☐ Does not apply or did not do for other reasons ☐
Intimate relationships with loved ones	Severely limited ☐ Limited quite a bit ☐ Moderately limited ☐ Slightly limited ☐ Did not limit at all ☐ Does not apply or did not do for other reasons ☐
Comments:	_____

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Form: EQ-5D

Date of Assessment: Fixed Unit: (dd MMM yyyy)

Mobility (Please indicate which statement best describes your own health state today)

1=I have no problems in walking about	1 ☐
2=I have some problems in walking about	2 ☐
3=I am confined to bed	3 ☐

Self-Care (Please indicate which statement best describes your own health state today)

1=I have no problems with self care	1 ☐
2=I have some problems washing or dressing myself	2 ☐
3=I am unable to wash or dress myself	3 ☐

Usual Activities (*e.g. work, study, housework, family or leisure activities*) (Please indicate which statement best describes your own health state today)

1=I have no problems with performing my usual activities	1 ☐
2=I have some problems with performing my usual activities	2 ☐
3=I am unable to perform my usual activities	3 ☐

Pain / Discomfort (Please indicate which statement best describes your own health state today)

1=I have no pain or discomfort	1 ☐
2=I have moderate pain or discomfort	2 ☐
3=I have extreme pain or discomfort	3 ☐

Anxiety / Depression (Please indicate which statement best describes your own health state today)

1=I am not anxious or depressed	1 ☐
2=I am moderately anxious or depressed	2 ☐
3=I am extremely anxious or depressed	3 ☐

Overall state

We would like you to indicate how good or bad your own health is today, in your opinion. The best state you can imagine is 100 and the worst state you can imagine is 0.

Comments:

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Form: Chest X-Ray - Baseline

Date of X-Ray:	Fixed Unit: (dd MMM yyyy)
X-Ray Not Clinically Significant:	
Evidence of Pulmonary Edema:	
Evidence of Cardiomegaly:	
Evidence of Pleural Effusion:	
Evidence of Infiltrate:	
Evidence of Atelectasis:	
Other, specify:	

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Form: 6MWT

Date of Test:	Fixed Unit: (dd MMM yyyy)
Systolic Blood Pressure:	Fixed Unit: mmHg
Diastolic Blood Pressure:	Fixed Unit: mmHg
Indicate if supplemental oxygen was used during the test:	Yes ☐ No ☐
If Yes, oxygen flow:	Fixed Unit: L/min

Baseline/Beginning of Test

Time:	Fixed Unit: (24 Hour Clock)
Heart Rate:	Fixed Unit: bpm
Dyspnea (Borg scale):	0 Nothing at all ☐ 0.5 Very - very slight (just noticeable) ☐ 1 Very slight ☐ 2 Slight (light) ☐ 3 Moderate ☐ 4 Somewhat severe ☐ 5 Severe (heavy) ☐ 6 ☐ 7 Very severe ☐ 8 ☐ 9 ☐ 10 Very - very severe (maximal) ☐

Fatigue (Borg scale):	0 Nothing at all ☐ 0.5 Very - very slight (just noticeable) ☐ 1 Very slight ☐ 2 Slight (light) ☐ 3 Moderate ☐ 4 Somewhat severe ☐ 5 Severe (heavy) ☐ 6 ☐ 7 Very severe ☐ 8 ☐ 9 ☐ 10 Very - very severe (maximal) ☐
SpO2:	Fixed Unit: %

End of Test

Time:	Fixed Unit: (24 Hour Clock)
Heart Rate:	Fixed Unit: bpm
Dyspnea (Borg scale):	0 Nothing at all ☐ 0.5 Very - very slight (just noticeable) ☐ 1 Very slight ☐ 2 Slight (light) ☐ 3 Moderate ☐ 4 Somewhat severe ☐ 5 Severe (heavy) ☐ 6 ☐ 7 Very severe ☐ 8 ☐ 9 ☐ 10 Very - very severe (maximal) ☐

Fatigue (Borg scale):	0 Nothing at all ☐ 0.5 Very - very slight (just noticeable) ☐ 1 Very slight ☐ 2 Slight (light) ☐ 3 Moderate ☐ 4 Somewhat severe ☐ 5 Severe (heavy) ☐ 6 ☐ 7 Very severe ☐ 8 ☐ 9 ☐ 10 Very - very severe (maximal) ☐
SpO2:	Fixed Unit: % _____
Indicate if Subject stopped or paused before 6 minutes:	Yes ☐ No ☐
If Yes, reason:	Angina ☐ Lightheadedness ☐ Hip or leg or calf pain ☐ Dyspnea ☐ Fatigue ☐ Other ☐ Unknown ☐
If Other, specify:	_____
Indicate if Subject had any of the below symptoms at the end of the test:	
Angina:	_____
Lightheadedness:	_____
Hip, leg or calf pain:	_____
Dyspnea:	_____
Fatigue:	_____
Total distance walked in 6 minutes:	**Meters** ☐ Feet ☐

6.000 19MAR2013 Draft 1.0 PROD SRM: All Forms

Form: NIH Stroke Scale

Unique AE Number:

Date of Assessment: Fixed Unit: (dd MMM yyyy)

Assessment performed by:
- Neurology fellow
- Certified team member
- Neurologist

Click here to view the NIH Stroke Scale

Instruction (Enter NM for Not Measurable):
- Level of consciousness (0-1-2-3)
- LOC questions (0-1-2)
- LOC commands (0-1-2)
- Best gaze (0-1-2)
- Visual (0-1-2-3)
- Facial palsy (0-1-2-3)
- Motor arm - Left (0-1-2-3-4)
- Motor arm - Right (0-1-2-3-4)
- Motor leg - Left (0-1-2-3-4)
- Motor leg - Right (0-1-2-3-4)
- Limb ataxia (0-1-2)
- Sensory (0-1-2)
- Best language (0-1-2-3)
- Dysarthria (0-1-2)
- Extinction and inattention (formerly neglect) (0-1-2)

Score:

Total Score *(calculated by system)*:

Comments:

6.000 19MAR2013 Draft 1.0 PROD SRM: All Forms

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- LOC commands (0-1-2) ☐
- Best gaze (0-1-2) ☐
- Visual (0-1-2-3) ☐
- Facial palsy (0-1-2-3) ☐
- Motor arm - Left (0-1-2-3-4) ☐
- Motor arm - Right (0-1-2-3-4) ☐
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- Dysarthria (0-1-2) ☐
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- Best language (0-1-2-3)
- Dysarthria (0-1-2)
- Extinction and inattention (formerly neglect) (0-1-2)

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Comments:

6.000 19MAR2013 Draft 1.0 PROD SRM: All Forms

Form: NIH Stroke Scale

Unique AE Number:	
Date of Assessment:	Fixed Unit: (dd MMM yyyy)
Assessment performed by:	Neurology fellow ☐ Certified team member ☐ Neurologist ☐

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Comments:

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Score:

Total Score *(calculated by system)*:

Comments:

6.000 19MAR2013 Draft 1.0 PROD SRM: All Forms

Form: Procedure 1

Cardiovascular Surgeon Name:	
Interventional Cardiologist Name:	
Indicate if Subject entered the Cath Lab or OR:	Yes ☐ No ☐
If Yes, date and time of entry:	Fixed Unit: (dd MMM yyyy hh:mm)
If Yes, date and time of exit:	Fixed Unit: (dd MMM yyyy hh:mm)
If No, specify reason:	Inclusion/Exclusion ☐ Expired ☐ Withdrawn ☐ Other ☐
If Other, specify:	
Indicate if procedure was started (skin incision):	Yes ☐ No ☐
If No, specify reason:	
If Yes, procedure start date and time (incision):	Fixed Unit: (dd MMM yyyy hh:mm)
If Yes, procedure stop date and time (closure):	Fixed Unit: (dd MMM yyyy hh:mm)
Annular diameter as measured via intra-procedural supra-aortic angiogram or TEE:	Fixed Unit: (mm)
Indicate if pre BAV hemodynamics were done:	Yes ☐ No ☐
Was Subject treated as assigned?	Yes ☐ No ☐
If No, how was Subject treated?	

If Conversion to AVR, specify reason:	Valve dislodged ☐ Ventricular rupture ☐ Annulus rupture ☐ Aortic dissection ☐ Coronary occlusion ☐ Other ☐
If Conversion to AVR reason is Other, specify:	
Additional details explaining why Subject was not treated as assigned:	

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Form: Procedure 2

Indicate type of anesthesia used:	General ☐ Conscious sedation ☐
Anesthesia start time:	Fixed Unit: (24 Hour Clock)
Anesthesia stop time:	Fixed Unit: (24 Hour Clock)
Artery access:	Left Percutaneous ☐ Right Percutaneous ☐ Left Surgical ☐ Right Surgical ☐
Length of skin incision:	**cm** ☐ mm ☐
Indicate time of Edwards sheath insertion:	Fixed Unit: (24 Hour Clock)
Indicate if rapid cardiac pacing was used during BAV:	Yes ☐ No ☐
If Yes, indicate highest pacing rate:	Less than 180bpm ☐ 180-220bpm ☐ Greater than 220bpm ☐
Indicate time of valve deployment:	Fixed Unit: (24 Hour Clock)
Indicate if rapid cardiac pacing was used during valve deployment:	Yes ☐ No ☐
If Yes, indicate highest pacing rate:	Less than 180bpm ☐ 180-220bpm ☐ Greater than 220bpm ☐
Indicate if post dilatation was performed:	Yes ☐ No ☐
If Yes, number performed:	
If Yes, additional fluid used:	Yes ☐ No ☐
Indicate time of Edwards sheath removal:	Fixed Unit: (24 Hour Clock)

Arterial site access:	Percutaneous ☐ Surgical cut-down ☐ Conduit ☐ None ☐
Venous site access:	Percutaneous ☐ Surgical cut-down ☐ Conduit ☐ None ☐
Arterial site closure method (Check all that apply)	
Closure Device:	
Surgical cut-down:	
Manual compression:	
None:	
If Closure Device(s) used, indicate number:	
Venous site closure method (Check all that apply)	
Closure Device:	
Surgical cut-down:	
Manual compression:	
None:	
If Closure Device(s) used, indicate number:	
Adjunctive procedure performed (Check all that apply)	
Endovascular balloon:	
Endovascular stenting:	
None:	
Other:	
If Other, specify:	
Volume of contrast media:	Fixed Unit: mL
Fluoroscopy total time:	Fixed Unit: min
Fluoroscopy Radiation dosage:	
Radiation dosage unit:	Gy ☐ Gy.cm2 ☐
Indicate if Subject received transfusion during the procedure:	Yes ☐ No ☐
If Yes, indicate number of units:	

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Form: Procedure 2

Indicate if Subject required cardiopulmonary bypass:	Yes ☐ No ☐
Indicate if Subject required IABP:	Yes ☐ No ☐
Indicate final position of the functioning transcatheter heart valve:	Acceptable - correct at intended site ☐ Too ventricular ☐ Too aortic ☐ Valve not deployed ☐
Indicate if a valve in valve procedure was performed (THV in THV):	Yes ☐ No ☐
Indicate size of functioning transcatheter heart valve:	23 ☐ 26 ☐ 29 ☐ NA ☐
Indicate total number of transcatheter heart valves deployed during this procedure:	_____
Valve crimped by:	Sponsor ☐ Site ☐ NA ☐
Name of who crimped the valve:	_____
Indicate if concomitant procedure(s) were performed:	Yes ☐ No ☐
If Yes, indicate type below (check all that apply):	
CABG:	_____
If CABG, indicate number performed:	_____
If CABG, indicate location(s) below (check all that apply):	
PROX RCA	_____
MID RCA	_____
DIST RCA	_____
RPDA	_____
RPAV	_____
1st RPL	_____
2nd RPL	_____
3rd RPL	_____
INF. SEPTAL	_____

AC MARG	
LMCA	
PROX LAD	
MID LAD	
DIST LAD	
1st DIAG	
2nd DIAG	
1st SEPTAL	
PROC CX	
MID CX	
1st OB MARG	
2nd OB MARG	
3rd OB MARG	
LAV	
1st LPL	
2nd LPL	
3rd LPL	
LPDA	
RAMUS	
3rd DIAG	
Stent:	
If Stent, indicate number performed:	
If Stent, indicate location(s) below (check all that apply):	
PROX RCA	
MID RCA	
DIST RCA	
RPDA	
RPAV	
1st RPL	
2nd RPL	
3rd RPL	
INF. SEPTAL	
AC MARG	
LMCA	
PROX LAD	
MID LAD	
DIST LAD	
1st DIAG	

2nd DIAG	
1st SEPTAL	
PROC CX	
MID CX	
1st OB MARG	
2nd OB MARG	
3rd OB MARG	
LAV	
1st LPL	
2nd LPL	
3rd LPL	
LPDA	
RAMUS	
3rd DIAG	
PCI:	
Other:	
If Other, specify:	
Indicate if heparin was administered during procedure:	Yes ☐ No ☐
If Yes, amount of heparin administered:	Fixed Unit: IU
If Yes, highest recorded ACT:	Fixed Unit: sec
If No, was a direct anti-thrombin inhibitor or a low molecular weight heparin used during procedure?	Yes ☐ No ☐
Hidden approach field (used to determine fields to show/hide)	

Indicate type of anesthesia used:	General ☐ Conscious sedation ☐
Anesthesia start time:	Fixed Unit: (24 Hour Clock)
Anesthesia stop time:	Fixed Unit: (24 Hour Clock)
Location of skin incision:	Mini Sternotomy ☐ Full Sternotomy ☐
Length of skin incision:	**cm** ☐ mm ☐
Valve Make:	Edwards ☐ Other ☐
If Other, specify:	
Valve Model:	Perimount ☐ Perimount Theon ☐ Perimount Magna ☐ Perimount Magna Ease ☐ Other ☐
If Other, specify:	
Valve Size:	19 ☐ 21 ☐ 23 ☐ 25 ☐ 27 ☐ 29 ☐ Other ☐
If Other, specify:	
Total aortic cross clamp time:	Fixed Unit: min
Total pump time:	Fixed Unit: min
Difficulty weaning from bypass:	Yes ☐ No ☐
If Yes, reason:	

Indicate if a valve in valve procedure was performed (THV in THV):	Yes ☐ No ☐
Indicate if concomitant procedure(s) were performed:	Yes ☐ No ☐
If Yes, indicate type below (check all that apply):	
CABG:	
If CABG, indicate number performed:	
If CABG, indicate location(s) below (check all that apply):	
PROX RCA	
MID RCA	
DIST RCA	
RPDA	
RPAV	
1st RPL	
2nd RPL	
3rd RPL	
INF. SEPTAL	
AC MARG	
LMCA	
PROX LAD	
MID LAD	
DIST LAD	
1st DIAG	
2nd DIAG	
1st SEPTAL	
PROC CX	
MID CX	
1st OB MARG	
2nd OB MARG	
3rd OB MARG	
LAV	
1st LPL	
2nd LPL	
3rd LPL	
LPDA	
RAMUS	
3rd DIAG	

Stent:	
If Stent, indicate number performed:	
If Stent, indicate location(s) below (check all that apply):	
PROX RCA	
MID RCA	
DIST RCA	
RPDA	
RPAV	
1st RPL	
2nd RPL	
3rd RPL	
INF. SEPTAL	
AC MARG	
LMCA	
PROX LAD	
MID LAD	
DIST LAD	
1st DIAG	
2nd DIAG	
1st SEPTAL	
PROC CX	
MID CX	
1st OB MARG	
2nd OB MARG	
3rd OB MARG	
LAV	
1st LPL	
2nd LPL	
3rd LPL	
LPDA	
RAMUS	
3rd DIAG	
PCI:	
Other:	
If Other, specify:	

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Form: Post Procedure

Indicate if a post procedure ECG was performed:	Yes ☐ No ☐
If No, please provide reason:	
If Yes, date and time ECG performed:	Fixed Unit: (dd MMM yyyy hh:mm)
Indicate if post procedure hemodynamics were performed:	Yes ☐ No ☐
NIH Stroke Scale (NIHSS):	Yes ☐ No ☐
If No, was assessment not done due to medical reason?	Yes ☐ No ☐
Indicate which protocol required post procedure lab was performed:	CK - CKMB ☐ Troponin ☐ ND ☐
First Draw CK (within 8 hours after the procedure stop time):	
Date and Time of blood draw:	Fixed Unit: (dd MMM yyyy hh:mm)
Second Draw CK (6 – 8 hours after the first lab draw):	
Date and Time of blood draw:	Fixed Unit: (dd MMM yyyy hh:mm)
Third Draw CK (6 – 8 hours after the second lab draw):	
Date and Time of blood draw:	Fixed Unit: (dd MMM yyyy hh:mm)
First Draw CK-MB (within 8 hours after the procedure stop time):	
Date and Time of blood draw:	Fixed Unit: (dd MMM yyyy hh:mm)
Second Draw CK-MB (6 – 8 hours after the first lab draw):	
Date and Time of blood draw:	Fixed Unit: (dd MMM yyyy hh:mm)

Third Draw CK-MB (6 – 8 hours after the second lab draw):	
Date and Time of blood draw:	Fixed Unit: (dd MMM yyyy hh:mm)
First Draw Troponin (within 8 hours after the procedure stop time):	
Date and Time of blood draw:	Fixed Unit: (dd MMM yyyy hh:mm)
Second Draw Troponin (6 – 8 hours after the first lab draw):	
Date and Time of blood draw:	Fixed Unit: (dd MMM yyyy hh:mm)
Third Draw Troponin (6 – 8 hours after the second lab draw):	
Date and Time of blood draw:	Fixed Unit: (dd MMM yyyy hh:mm)

Mean RA Pressure:	Fixed Unit: mmHg
PA Pressure - Systolic:	Fixed Unit: mmHg
PA Pressure - Diastolic:	Fixed Unit: mmHg
Mean PA Pressure:	Fixed Unit: mmHg
Mean PCWP Pressure:	Fixed Unit: mmHg
LV Pressure - Systolic:	Fixed Unit: mmHg
LV Pressure - End Diastolic:	Fixed Unit: mmHg
Aortic Pressure - Systolic:	Fixed Unit: mmHg
Aortic Pressure - Diastolic:	Fixed Unit: mmHg
Mean Aortic Pressure:	Fixed Unit: mmHg
Mean AV Gradient:	Fixed Unit: mmHg
Peak AV Gradient:	Fixed Unit: mmHg
Aortic Valve Area:	Fixed Unit: cm^2
Cardiac Output:	Fixed Unit: L/min
Cardiac Index:	Fixed Unit: $L/min/m^2$

Total aortic insufficiency/Severity:	None ☐ Trace ☐ Mild ☐ Moderate ☐ Severe ☐ Not evaluable ☐ NA ☐

Mean RA Pressure:	Fixed Unit: mmHg
PA Pressure - Systolic:	Fixed Unit: mmHg
PA Pressure - Diastolic:	Fixed Unit: mmHg
Mean PA Pressure:	Fixed Unit: mmHg
Mean PCWP Pressure:	Fixed Unit: mmHg
LV Pressure - Systolic:	Fixed Unit: mmHg
LV Pressure - End Diastolic:	Fixed Unit: mmHg
Aortic Pressure - Systolic:	Fixed Unit: mmHg
Aortic Pressure - Diastolic:	Fixed Unit: mmHg
Mean Aortic Pressure:	Fixed Unit: mmHg
Mean AV Gradient:	Fixed Unit: mmHg
Peak AV Gradient:	Fixed Unit: mmHg
Aortic Valve Area:	Fixed Unit: cm^2
Cardiac Output:	Fixed Unit: L/min
Cardiac Index:	Fixed Unit: $L/min/m^2$

Coronary Patency Assessed via Supra-Aortic Angiogram

Blood Flow

Left Coronary Ostia:	CABG ☐
	Free Flow ☐
	Partial Flow ☐
	Completely Blocked ☐
	NA ☐
	Not Evaluable ☐
Right Coronary Ostia:	CABG ☐
	Free Flow ☐
	Partial Flow ☐
	Completely Blocked ☐
	NA ☐
	Not Evaluable ☐
TIMI Flow:	Grade 1 ☐
	Grade 2 ☐
	Grade 3 ☐
	NA ☐
	Not Evaluable ☐
Paravalvular Leak/Severity:	None ☐
	Trace ☐
	Mild ☐
	Moderate ☐
	Severe ☐
	Not evaluable ☐
	NA ☐
Central Leak/Severity:	None ☐
	Trace ☐
	Mild ☐
	Moderate ☐
	Severe ☐
	Not evaluable ☐
	NA ☐

Resulting total aortic insufficiency/Severity:	None ☐ Trace ☐ Mild ☐ Moderate ☐ Severe ☐ Not evaluable ☐ NA ☐
Mitral anterior leaflet impingement:	Yes ☐ No ☐ NA ☐ Not evaluated ☐

Date and Time of Blood Draw:	Fixed Unit: (dd MMM yyyy hh:mm)
Complete Blood Count	
WBC:	
Neutrophils:	**%** ☐ 1000/UL ☐
Lymphocytes:	**%** ☐ 1000/UL ☐
Monocytes:	**%** ☐ 1000/UL ☐
Eosinophils:	**%** ☐ 1000/UL ☐
Basophils:	**%** ☐ 1000/UL ☐
RBC:	
HGB:	
HCT:	
Platelets:	
Coagulation Profile	
INR:	
Prothrombin Time (PT):	
Partial Thromboplastin Time (PTT):	
Metabolic Panel	
Sodium:	
Potassium:	
Creatinine:	
BUN:	

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Form: Non Study Devices

Device	Drug Eluting Coronary Stent ■
	Bare Metal Coronary Stent ☐
	Guidewire ☐
	Guide Catheter ☐
	Pacing Wire ☐
	Pulmonary Artery Catheter ☐
	Left Ventricular Assist Device ☐
	Echo Probe ☐
	Balloon ☐
	Valve Prosthesis (Non Investigational) ☐
Number of Devices Used	_____
Manufacturer	_____
Model	_____
Size	_____

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Form: Non Study Devices

Device	Drug Eluting Coronary Stent ☐ Bare Metal Coronary Stent ■ Guidewire ☐ Guide Catheter ☐ Pacing Wire ☐ Pulmonary Artery Catheter ☐ Left Ventricular Assist Device ☐ Echo Probe ☐ Balloon ☐ Valve Prosthesis (Non Investigational) ☐
Number of Devices Used	_____
Manufacturer	_____
Model	_____
Size	_____

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Form: Non Study Devices

Device	Drug Eluting Coronary Stent ☐ Bare Metal Coronary Stent ☐ Guidewire ■ Guide Catheter ☐ Pacing Wire ☐ Pulmonary Artery Catheter ☐ Left Ventricular Assist Device ☐ Echo Probe ☐ Balloon ☐ Valve Prosthesis (Non Investigational) ☐
Number of Devices Used	_____
Manufacturer	_____
Model	_____
Size	_____

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Form: Non Study Devices

Device	Drug Eluting Coronary Stent ☐ Bare Metal Coronary Stent ☐ Guidewire ☐ Guide Catheter ■ Pacing Wire ☐ Pulmonary Artery Catheter ☐ Left Ventricular Assist Device ☐ Echo Probe ☐ Balloon ☐ Valve Prosthesis (Non Investigational) ☐
Number of Devices Used	_____
Manufacturer	_____
Model	_____
Size	_____

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Form: Non Study Devices

Device	Drug Eluting Coronary Stent ☐ Bare Metal Coronary Stent ☐ Guidewire ☐ Guide Catheter ☐ Pacing Wire ■ Pulmonary Artery Catheter ☐ Left Ventricular Assist Device ☐ Echo Probe ☐ Balloon ☐ Valve Prosthesis (Non Investigational) ☐
Number of Devices Used	_____
Manufacturer	_____
Model	_____
Size	_____

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Form: Non Study Devices

Device	Drug Eluting Coronary Stent ☐ Bare Metal Coronary Stent ☐ Guidewire ☐ Guide Catheter ☐ Pacing Wire ☐ Pulmonary Artery Catheter ■ Left Ventricular Assist Device ☐ Echo Probe ☐ Balloon ☐ Valve Prosthesis (Non Investigational) ☐
Number of Devices Used	_____
Manufacturer	_____
Model	_____
Size	_____

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Form: Non Study Devices

Device	Drug Eluting Coronary Stent ☐ Bare Metal Coronary Stent ☐ Guidewire ☐ Guide Catheter ☐ Pacing Wire ☐ Pulmonary Artery Catheter ☐ Left Ventricular Assist Device ■ Echo Probe ☐ Balloon ☐ Valve Prosthesis (Non Investigational) ☐
Number of Devices Used	_____
Manufacturer	_____
Model	_____
Size	_____

Form: Non Study Devices

Device	Drug Eluting Coronary Stent ☐ Bare Metal Coronary Stent ☐ Guidewire ☐ Guide Catheter ☐ Pacing Wire ☐ Pulmonary Artery Catheter ☐ Left Ventricular Assist Device ☐ Echo Probe ■ Balloon ☐ Valve Prosthesis (Non Investigational) ☐
Number of Devices Used	_____
Manufacturer	_____
Model	_____
Size	_____

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Form: Non Study Devices

Device	Drug Eluting Coronary Stent ☐ Bare Metal Coronary Stent ☐ Guidewire ☐ Guide Catheter ☐ Pacing Wire ☐ Pulmonary Artery Catheter ☐ Left Ventricular Assist Device ☐ Echo Probe ☐ Balloon ■ Valve Prosthesis (Non Investigational) ☐
Number of Devices Used	
Manufacturer	
Model	
Size	

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Form: Non Study Devices

Device	Drug Eluting Coronary Stent ☐ Bare Metal Coronary Stent ☐ Guidewire ☐ Guide Catheter ☐ Pacing Wire ☐ Pulmonary Artery Catheter ☐ Left Ventricular Assist Device ☐ Echo Probe ☐ Balloon ☐ Valve Prosthesis (Non Investigational) ■
Number of Devices Used	_____
Manufacturer	_____
Model	_____
Size	_____

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Form: Balloon Catheter

Device Type:	Balloon Catheter
Model #:	9120 BC 20 ☐
	9120 BC 23 ☐
	9350 BC 20 ☐
	9350 BC 23 ☐
	9350 BC 25 ☐
	9100 BAVC ☐
	9100 BCL 23 ☐
	9100 BCL 26 ☐
	NA ☐
Serial/Lot #:	_____
Disposition	Discarded ☐
	Returned ☐
	Used ☐
	Used ViV 1 ☐
	Used ViV 2 ☐
	Used ViV 3 ☐
Comment (If NA):	_____

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Form: Dilator

Device Type:	Dilator
Model #:	9100 DKS 7 ☐
	9100 DKS ☐
	NA ☐
Serial/Lot #:	_____
Disposition	Discarded ☐
	Returned ☐
	Used ☐
	Used ViV 1 ☐
	Used ViV 2 ☐
	Used ViV 3 ☐
Comment (If NA):	_____

Form: Introducer Sheath

Device Type:	Introducer Sheath
Model #:	RetroFlex 9120 S 23 ☐
	RetroFlex 9120 S 26 ☐
	NovaFlex 9350 S 23 ☐
	NovaFlex 9350 S 26 ☐
	NovaFlex+ eSheath 916 ES 23 ☐
	NovaFlex+ eSheath 918 ES 26 ☐
	NovaFlex+ eSheath 920 ES 29 ☐
	Ascendra 9100 IS ☐
	Ascendra2 9320 IS ☐
	Ascendra+ 9350 IS 23 ☐
	Ascendra+ 9350 IS 26 ☐
	Ascendra+ 9350 IS 29 ☐
	NA ☐
	Edwards Expandable Introducer Sheath 9610 ES 14 ☐
	Edwards Expandable Introducer Sheath 9160 ES 23 ☐
	Certitude Introducer Sheath 9620 IS 18 ☐
	Certitude Introducer Sheath 9620 IS 21 ☐
Serial/Lot #:	
Disposition	Discarded ☐
	Returned ☐
	Used ☐
	Used ViV 1 ☐
	Used ViV 2 ☐
	Used ViV 3 ☐
Comment (If NA):	

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Form: Delivery System

Device Type:	Delivery System
Model #:	RetroFlex3 9120 FS 23 ☐
	RetroFlex3 9120 FS 26 ☐
	NovaFlex 9350 FS 23 ☐
	NovaFlex 9350 FS 26 ☐
	NovaFlex+ 9355 FS 23 ☐
	NovaFlex+ 9355 FS 26 ☐
	NovaFlex+ 9355 FS 29 ☐
	Ascendra2 9350 AS 23 ☐
	Ascendra2 9350 AS 26 ☐
	Ascendra+ 9355 AS 23 ☐
	Ascendra+ 9355 AS 26 ☐
	Ascendra+ 9355 AS 29 ☐
	NA ☐
	Edwards Commander Delivery System 9610TF23 ☐
	Edwards Commander Delivery System 9610TF26 ☐
	Edwards Commander Delivery System 9610TF29 ☐
	Edwards Certitude Delivery System 9620TA23 ☐
	Edwards Certitude Delivery System 9620TA26 ☐
	Edwards Certitude Delivery System 9620TA29 ☐

Serial/Lot #	
Disposition	Discarded ☐
	Returned ☐
	Used ☐
	Used ViV 1 ☐
	Used ViV 2 ☐
	Used ViV 3 ☐
Comment (If NA):	

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Form: Crimper

Device Type:	Crimper
Model #:	9100 CR 23 ☐ 9100 CR 26 ☐ 9340 CR 23 ☐ 9340 CR 26 ☐ 9350 CR ☐ NA ☐ 9600 CR ☐
Serial/Lot #:	
Disposition	Discarded ☐ Returned ☐ Used ☐ Used ViV 1 ☐ Used ViV 2 ☐ Used ViV 3 ☐
Comment (If NA):	

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Form: Valve

Device Type:	Valve
Model #:	SAPIEN 9000 TFX 23 ☐ SAPIEN 9000 TFX 26 ☐ SAPIEN XT 9300 TFX 23 ☐ SAPIEN XT 9300 TFX 26 ☐ SAPIEN XT 9300 TFX 29 ☐ NA ☐ SAPIEN 3 9600 TFX 23 ☐ SAPIEN 3 9600 TFX 26 ☐ SAPIEN 3 9600 TFX 29 ☐
Serial/Lot #:	_____
Disposition	Discarded ☐ Returned ☐ Used ☐ Used ViV 1 ☐ Used ViV 2 ☐ Used ViV 3 ☐
Comment (If NA):	_____

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Form: Discharge

Index Hospitalization Admission Date:	Fixed Unit: (dd MMM yyyy)
Index Hospitalization Discharge Date:	Fixed Unit: (dd MMM yyyy)
Indicate where Subject was discharged to:	Rehabilitation unit ☐ Nursing home (permanent) ☐ Home ☐ Another hospital ☐ Extended care ☐ Patient died ☐
Angina CCS Class: Angina Grading Scale link	None ☐ I ☐ II ☐ III ☐ IV ☐ ND ☐
NYHA Class: NYHA Classification link	I ☐ II ☐ III ☐ IV ☐ ND ☐
Weight:	kg ☐ lb ☐
Blood Pressure - Systolic:	Fixed Unit: mmHg
Blood Pressure - Diastolic:	Fixed Unit: mmHg

CHADS Score:	None ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐
Current COPD:	Yes ☐ No ☐ Unknown ☐
If Yes, FEV-1 value:	Fixed Unit: L
If Yes, is subject O_2 dependent?	Yes ☐ No ☐ Unknown ☐

Indicate if the following were performed:

Labs:	Yes ☐ No ☐
NIH Stroke Scale:	Yes ☐ No ☐
If No, was assessment not done due to medical reason?	Yes ☐ No ☐
Chest X-Ray:	Yes ☐ No ☐
12-Lead ECG:	Yes ☐ No ☐
If Yes, date ECG performed:	Fixed Unit: (dd MMM yyyy)
Transthoracic Echocardiogram (TTE):	Yes ☐ No ☐
If Yes, date TTE performed:	Fixed Unit: (dd MMM yyyy)

Please indicate if there were any changes made to medications: *(If Yes, please update the Medication Log form)*	Yes ☐ No ☐

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Form: Lab - Discharge

Date and Time of Blood Draw:	Fixed Unit: (dd MMM yyyy hh:mm)
Complete Blood Count	
WBC:	
Neutrophils:	**%** ☐ 1000/UL ☐
Lymphocytes:	**%** ☐ 1000/UL ☐
Monocytes:	**%** ☐ 1000/UL ☐
Eosinophils:	**%** ☐ 1000/UL ☐
Basophils:	**%** ☐ 1000/UL ☐
RBC:	
HGB:	
HCT:	
Platelets:	
Coagulation Profile	
INR:	
Prothrombin Time (PT):	
Partial Thromboplastin Time (PTT):	
Metabolic Panel	
Sodium:	
Potassium:	
Creatinine:	
BUN:	
Cardiac Neurohormone	
Indicate B-type natriuretic peptide measured:	B-type natriuretic peptide - BNP ☐ N-terminal B-type natriuretic peptide - NT-BNP ☐ ND ☐
Value of measurement:	**ng/L** ☐ pg/mL ☐

Form: Index Hosp Log

Please provide the following information for each ward in which the patient stayed during the Index Hospitalization.

Ward:	General ward ☐ Intensive care unit ☐ Intermediate care ☐
Ward entrance date:	
Ward exit date:	

Form: Radiation Exposure - Discharge

Has the Subject been exposed to any non-protocol required examinations that involve radiation, since screening assessments?:	Yes ☐ No ☐ Unknown ☐
If Yes, check all that apply:	
X-ray Chest:	
Specify number of X-rays:	
X-ray Mammography:	
Specify number:	
X-ray Skull:	
Specify number:	
X-ray Cervical Spine:	
Specify number:	
X-ray Lumbar Spine:	
Specify number:	
X-ray Upper GI:	
Specify number:	
X-ray Abdomen (kidney/bladder):	
Specify number:	
X-ray Barium Enema:	
Specify number:	
X-ray Pelvis:	
Specify number:	
X-ray Hip:	
Specify number:	
X-ray Dental Bitewing/Image:	
Specify number:	
X-ray Extremity (hand/foot):	
Specify number:	
CT Scan - Head:	
Specify number:	
CT Scan - Chest:	
Specify number:	
CT Scan - Abdomen/Pelvis:	
Specify number:	
CT Scan - Extremity:	
Specify number:	
CT Scan - Angiography (Heart):	

Specify number:	
CT Scan - Angiography (Head):	
Specify number:	
CT Scan - Spine:	
Specify number:	
CT Scan - Whole Body:	
Specify number:	
CT Scan - Cardiac:	
Specify number:	
MRI:	
Specify number of MRIs:	
Fluoroscopic Imaging:	
Specify number:	
Other:	
If Other, specify:	
Has the Subject developed an injury related to radiation exposure, since screening assessments? *(If Yes, complete the "Radiation Related Injury" form and "Adverse Event" form):*	Yes ☐ No ☐ Unknown ☐

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Form: Radiation Related Injury

Date of Visit:	
Radiation dose reported:	
Radiation dose unit:	Gy ☐ Gy.cm2 ☐

Radiation Dose Date Range

Start Date:	
Stop Date:	

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Form: Visit Status

Visit Status:	Outpatient ☐
	Inpatient ☐
	Phone ☐
	Letter ☐
	Missed visit ☐
	Other ☐
If Phone, specify from whom and relationship:	_____
If Letter, specify from whom and relationship:	_____

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Form: 30 Day Follow-up

Date of Visit:	Fixed Unit: (dd MMM yyyy)
Weight:	kg ☐ lb ☐
Blood Pressure - Systolic:	Fixed Unit: mmHg
Blood Pressure - Diastolic:	Fixed Unit: mmHg
Heart Rate:	Fixed Unit: bpm
Angina CCS Class: Angina Grading Scale link	None ☐ I ☐ II ☐ III ☐ IV ☐ ND ☐
NYHA Class: NYHA Classification link	I ☐ II ☐ III ☐ IV ☐ ND ☐
Please indicate if subject had a stroke since procedure:	Yes ☐ No ☐
Current COPD:	Yes ☐ No ☐ Unknown ☐
If Yes, FEV-1 value:	Fixed Unit: L
If Yes, is subject O_2 dependent?	Yes ☐ No ☐ Unknown ☐

Indicate if the following were performed:

Labs:	Yes ☐ No ☐

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Form: 30 Day Follow-up

NIH Stroke Scale (NIHSS):	Yes ☐ No ☐
SF-36 Assessment:	Yes ☐ No ☐
If No, was assessment not done due to medical reason?	Yes ☐ No ☐
KCCQ Assessment:	Yes ☐ No ☐
If No, was assessment not done due to medical reason?	Yes ☐ No ☐
EQ-5D Assessment:	Yes ☐ No ☐
If No, was assessment not done due to medical reason?	Yes ☐ No ☐
Chest X-Ray:	Yes ☐ No ☐
If CXR indicates abnormalities due to valve integrity or function, was fluoroscopic imaging performed?	Yes ☐ No ☐
If Yes, Volume of contrast media:	Fixed Unit: ml
If Yes, Fluoroscopy total time:	Fixed Unit: min
If Yes, Radiation dosage:	
Radiation dosage unit:	Gy ☐ Gy.cm2 ☐
12-Lead ECG:	Yes ☐ No ☐
If Yes, date ECG performed:	Fixed Unit: (dd MMM yyyy)
Transthoracic Echocardiogram (TTE):	Yes ☐ No ☐
If Yes, date TTE performed:	Fixed Unit: (dd MMM yyyy)

Please indicate if a 6-Minute Walk Test (6MWT) was performed:	Yes ☐ No ☐
If No, please indicate main reason for not performing the 6MWT:	Angina - chest pain ☐ Hypotension ☐ Hypertension ☐ Non-ambulatory due to medical condition ☐ Respiratory insufficiency - dyspnea ☐ Other medical reason - please specify below ☐ Other non medical reason - please specify below ☐
If Other, please specify reason:	_____
Please indicate if there were any changes made to medications: *(If Yes, please update the Medication Log form)*	Yes ☐ No ☐

Date and Time of Blood Draw:	Fixed Unit: (dd MMM yyyy hh:mm)
Complete Blood Count	
WBC:	
Neutrophils:	**%** ☐ 1000/UL ☐
Lymphocytes:	**%** ☐ 1000/UL ☐
Monocytes:	**%** ☐ 1000/UL ☐
Eosinophils:	**%** ☐ 1000/UL ☐
Basophils:	**%** ☐ 1000/UL ☐
RBC:	
HGB:	
HCT:	
Platelets:	
Haptoglobin:	
Plasma Free Hemoglobin:	
Liver Panel	
Albumin:	
Cardiac Neurohormone	
Indicate B-type natriuretic peptide measured:	B-type natriuretic peptide - BNP ☐ N-terminal B-type natriuretic peptide - NT-BNP ☐ ND ☐
Value of measurement:	**ng/L** ☐ pg/mL ☐

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Form: 6 Month Follow-up

Date of Visit:	Fixed Unit: (dd MMM yyyy)
Weight:	kg ☐ lb ☐
Blood Pressure - Systolic:	Fixed Unit: mmHg
Blood Pressure - Diastolic:	Fixed Unit: mmHg
Heart Rate:	Fixed Unit: bpm
Angina CCS Class: Angina Grading Scale link	None ☐ I ☐ II ☐ III ☐ IV ☐ ND ☐
NYHA Class: NYHA Classification link	I ☐ II ☐ III ☐ IV ☐ ND ☐
Please indicate if subject had a stroke since procedure:	Yes ☐ No ☐
NIH Stroke Scale (NIHSS):	Yes ☐ No ☐
Current COPD:	Yes ☐ No ☐ Unknown ☐
If Yes, FEV-1 value:	Fixed Unit: L
If Yes, is subject O_2 dependent?	Yes ☐ No ☐ Unknown ☐

Please indicate if there were any changes made to medications: *(If Yes, please update the Medication Log form)*	Yes ☐ No ☐

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Form: 1 Year Follow-up

Date of Visit:	Fixed Unit: (dd MMM yyyy)
Angina CCS Class: Angina Grading Scale link	None ☐ I ☐ II ☐ III ☐ IV ☐ ND ☐
NYHA Class: NYHA Classification link	I ☐ II ☐ III ☐ IV ☐ ND ☐
Please indicate if subject had a stroke since procedure:	Yes ☐ No ☐
Weight:	kg ☐ lb ☐
Blood Pressure - Systolic:	Fixed Unit: mmHg
Blood Pressure - Diastolic:	Fixed Unit: mmHg
Heart Rate:	Fixed Unit: bpm
Current COPD:	Yes ☐ No ☐ Unknown ☐
If Yes, FEV-1 value:	Fixed Unit: L
If Yes, is subject O_2 dependent?	Yes ☐ No ☐ Unknown ☐
Indicate if the following were performed:	
Labs:	Yes ☐ No ☐

NIH Stroke Scale (NIHSS):	Yes ☐ No ☐
If No, was assessment not done due to medical reason?	Yes ☐ No ☐
SF-36 Assessment:	Yes ☐ No ☐
If No, was assessment not done due to medical reason?	Yes ☐ No ☐
KCCQ Assessment:	Yes ☐ No ☐
If No, was assessment not done due to medical reason?	Yes ☐ No ☐
EQ-5D Assessment:	Yes ☐ No ☐
If No, was assessment not done due to medical reason?	Yes ☐ No ☐
Chest X-Ray:	Yes ☐ No ☐
If CXR indicates abnormalities due to valve integrity or function, was fluoroscopic imaging performed?	Yes ☐ No ☐
If Yes, Volume of contrast media:	Fixed Unit: mL _____
If Yes, Fluroscopy total time:	Fixed Unit: min _____
If Yes, Radiation dosage:	_____
Radiation dosage unit:	Gy ☐ Gy.cm2 ☐
12-Lead ECG:	Yes ☐ No ☐
If Yes, date ECG performed:	Fixed Unit: (dd MMM yyyy) _____
Transthoracic Echocardiogram (TTE):	Yes ☐ No ☐

If Yes, date TTE performed:	Fixed Unit: (dd MMM yyyy)
Please indicate if a 6-Minute Walk Test (6MWT) was performed:	Yes ☐ No ☐
If No, please indicate main reason for not performing the 6MWT:	Angina - chest pain ☐ Hypotension ☐ Hypertension ☐ Non-ambulatory due to medical condition ☐ Respiratory insufficiency - dyspnea ☐ Other medical reason - please specify below ☐ Other non medical reason - please specify below ☐
If Other, please specify reason:	
Please indicate if there were any changes made to medications: *(If Yes, please update the Medication Log form)*	Yes ☐ No ☐

Date and Time of Blood Draw:	Fixed Unit: (dd MMM yyyy hh:nn)
Complete Blood Count	
WBC:	
Neutrophils:	**%** ☐ 1000/UL ☐
Lymphocytes:	**%** ☐ 1000/UL ☐
Monocytes:	**%** ☐ 1000/UL ☐
Eosinophils:	**%** ☐ 1000/UL ☐
Basophils:	**%** ☐ 1000/UL ☐
RBC:	
HGB:	
HCT:	
Platelets:	
Haptoglobin:	
Plasma Free Hemoglobin:	
Liver Panel	
Albumin:	
Metabolic Panel	
Sodium:	
Potassium:	
Creatinine:	
BUN:	
Cardiac Neurohormone	
Indicate B-type natriuretic peptide measured:	B-type natriuretic peptide - BNP ☐ N-terminal B-type natriuretic peptide - NT-BNP ☐ ND ☐
Value of measurement:	**ng/L** ☐ pg/mL ☐

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Form: 2 Year Follow-up

Date of Visit:	Fixed Unit: (dd MMM yyyy)
Angina CCS Class: Angina Grading Scale link	None ☐ I ☐ II ☐ III ☐ IV ☐ ND ☐
NYHA Class: NYHA Classification link	I ☐ II ☐ III ☐ IV ☐ ND ☐
Please indicate if subject had a stroke since procedure:	Yes ☐ No ☐
Weight:	kg ☐ lb ☐
Blood Pressure - Systolic:	Fixed Unit: mmHg
Blood Pressure - Diastolic:	Fixed Unit: mmHg
Heart Rate:	Fixed Unit: bpm

Indicate if the following were performed:

Labs:	Yes ☐ No ☐
NIH Stroke Scale (NIHSS):	Yes ☐ No ☐
If No, was assessment not done due to medical reason?	Yes ☐ No ☐
SF-36 Assessment:	Yes ☐ No ☐

If No, was assessment not done due to medical reason?	Yes ☐ No ☐
KCCQ Assessment:	Yes ☐ No ☐
If No, was assessment not done due to medical reason?	Yes ☐ No ☐
EQ-5D Assessment:	Yes ☐ No ☐
If No, was assessment not done due to medical reason?	Yes ☐ No ☐
Chest X-Ray:	Yes ☐ No ☐
If CXR indicates abnormalities due to valve integrity or function, was fluoroscopic imaging performed?	Yes ☐ No ☐
If Yes, Volume of contrast media:	Fixed Unit: mL
If Yes, Fluoroscopy total time:	Fixed Unit: min
If Yes, Radiation dosage:	
Radiation dosage unit:	Gy ☐ Gy.cm2 ☐
12-Lead ECG:	Yes ☐ No ☐
If Yes, date ECG performed:	Fixed Unit: (dd MMM yyyy)
Transthoracic Echocardiogram (TTE):	Yes ☐ No ☐
If Yes, date TTE performed:	Fixed Unit: (dd MMM yyyy)
Please indicate if a 6-Minute Walk Test (6MWT) was performed:	Yes ☐ No ☐

If No, please indicate main reason for not performing the 6MWT:	Angina - chest pain ☐ Hypotension ☐ Hypertension ☐ Non-ambulatory due to medical condition ☐ Respiratory insufficiency - dyspnea ☐ Other medical reason - please specify below ☐ Other non medical reason - please specify below ☐
If Other, please specify reason:	_____
Please indicate if there were any changes made to medications: *(If Yes, please update the Medication Log form)*	Yes ☐ No ☐

Date and Time of Blood Draw:	Fixed Unit: (dd MMM yyyy hh:nn)
Complete Blood Count	
WBC:	
Neutrophils:	**%** ☐ 1000/UL ☐
Lymphocytes:	**%** ☐ 1000/UL ☐
Monocytes:	**%** ☐ 1000/UL ☐
Eosinophils:	**%** ☐ 1000/UL ☐
Basophils:	**%** ☐ 1000/UL ☐
RBC:	
HGB:	
HCT:	
Platelets:	
Haptoglobin:	
Plasma Free Hemoglobin:	
Coagulation Profile	
INR:	
Prothrombin Time (PT):	
Partial Thromboplastin Time (PTT):	
Metabolic Panel	
Sodium:	
Potassium:	
Creatinine:	
BUN:	
Liver Panel	
AST:	
ALT:	
Albumin:	
Cardiac Neurohormone	

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Form: Lab - 2 Year

Indicate B-type natriuretic peptide measured:	B-type natriuretic peptide - BNP ☐ N-terminal B-type natriuretic peptide - NT-BNP ☐ ND ☐
Value of measurement:	**ng/L** ☐ pg/mL ☐

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Form: Annual Follow-up

Date of Visit:	Fixed Unit: (dd MMM yyyy)
Angina CCS Class: Angina Grading Scale link	None ☐ I ☐ II ☐ III ☐ IV ☐ ND ☐
NYHA Class: NYHA Classification link	I ☐ II ☐ III ☐ IV ☐ ND ☐
Please indicate if subject had a stroke since procedure:	Yes ☐ No ☐
Weight:	kg ☐ lb ☐
Blood Pressure - Systolic:	Fixed Unit: mmHg
Blood Pressure - Diastolic:	Fixed Unit: mmHg
Indicate B-type natriuretic peptide measured:	B-type natriuretic peptide - BNP ☐ N-terminal B-type natriuretic peptide - NT-BNP ☐ ND ☐
Value of measurement:	**ng/L** ☐ pg/mL ☐
Indicate if the following were performed:	
NIH Stroke Scale (NIHSS):	Yes ☐ No ☐
If No, was assessment not done due to medical reason?	Yes ☐ No ☐
SF-36 Assessment:	Yes ☐ No ☐

If No, was assessment not done due to medical reason?	Yes ☐ No ☐
KCCQ Assessment:	Yes ☐ No ☐
If No, was assessment not done due to medical reason?	Yes ☐ No ☐
EQ-5D Assessment:	Yes ☐ No ☐
If No, was assessment not done due to medical reason?	Yes ☐ No ☐
Chest X-Ray:	Yes ☐ No ☐
If CXR indicates abnormalities due to valve integrity or function, was fluoroscopic imaging performed?	Yes ☐ No ☐
If Yes, Volume of contrast media:	Fixed Unit: mL
If Yes, Fluoroscopy total time:	Fixed Unit: min
If Yes, Radiation dosage:	
Radiation dosage unit:	Gy ☐ Gy.cm2 ☐
Transthoracic Echocardiogram (TTE):	Yes ☐ No ☐
If Yes, date TTE performed:	Fixed Unit: (dd MMM yyyy)
Please indicate if there were any changes made to medications: *(If Yes, please update the Medication Log form)*	Yes ☐ No ☐

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Form: Study Exit Form

Date of Study Exit or Date of Death:	Fixed Unit: (dd MMM yyyy)
Reason for Study Exit	
Subject Completed Study:	
Subject Withdrew Consent to Participate in the Study:	
If Subject Withdrew Consent, Please Specify When:	After treatment ☐
	Before treatment ☐
Subject Lost to Follow-up:	
Death:	
Other, Specify:	

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Form: CEC Site Dashboard

Disclaimer: The items on this list are observations based on data. They are not requirements for reporting events. Events may or may not be reported at the discretion of the site.

Message:

Action:

Event reported ☐

Event not reported ☐

If Event reported, AE ID Number:

Comments:

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Form: Adverse Event

Unique AE Number:	
Event Onset Date:	Fixed Unit: (dd MMM yyyy)
Date Site was made aware of the Event:	Fixed Unit: (dd MMM yyyy)

Event Code:

- ☐ Abnormal lab value
- ☐ Access site and access related vascular injury - Aortic root rupture
- ☐ Access site and access related vascular injury - Areio-venous fistula
- ☐ Access site and access related vascular injury - Compartment syndrome
- ☐ Access site and access related vascular injury - Dissection
- ☐ Access site and access related vascular injury - Distal embolization (noncerebral) from vascular cause resulting in irreversible end-organ damage
- ☐ Access site and access related vascular injury - Distal embolization (noncerebral) from vascular source
- ☐ Access site and access related vascular injury - Hematoma
- ☐ Access site and access related vascular injury - Irreversible nerve injury
- ☐ Access site and access related vascular injury - Perforation
- ☐ Access site and access related vascular injury - Pseudoaneurysm
- ☐ Access site and access related vascular injury - Rupture
- ☐ Access site and access related vascular injury - Stenosis
- ☐ Access site and access related vascular injury - Thoracic aortic dissection
- ☐ Access site and access related vascular injury - Ventricular rupture (Apical rupture)
- ☐ Access site and access related vascular injury - Failure of percutaneous access site closure resulting in intervention
- ☐ Anemia/Hemolytic anemia

- [ ] Anesthesia related complication - Allergic reaction
- [ ] Anesthesia related complication - Anxiety
- [ ] Anesthesia related complication - Aspiration
- [ ] Anesthesia related complication - Confusion
- [ ] Anesthesia related complication - Difficulty urinating
- [ ] Anesthesia related complication - Dysphasia
- [ ] Anesthesia related complication - Memory loss
- [ ] Anesthesia related complication - Panic attack
- [ ] Anesthesia related complication - Other
- [ ] Angina/Cardiac chest pain
- [ ] Aortic insufficiency/Regurgitation non valvular cause
- [ ] Aortic insufficiency/Regurgitation PV leak - Non structural dysfunction
- [ ] Aortic insufficiency/Regurgitation PV leak - Structural dysfunction
- [ ] Arrhythmia/Conduction system injury (defect)
- [ ] Atrial septal defect
- [ ] Bleeding - Hemorrhage
- [ ] Cardiac arrest
- [ ] Cardiac tamponade/Pericardial effusion
- [ ] Cardiogenic shock
- [ ] Coronary flow obstruction/Transvalvular flow disturbance
- [ ] Delirium
- [ ] Device embolization
- [ ] Device migration/malposition requiring intervention
- [ ] Edema

- [ ] Embolization including air/calcific valve material or Thrombus
- [ ] Encephalopathy
- [ ] Exercise intolerance or weakness
- [ ] Gastro Intestinal event - Non-hemorrhagic
- [ ] Genito-Urinary event - Non-hemorrhagic
- [ ] Heart failure/CHF/Low output failure
- [ ] Hemolysis
- [ ] Hypertension
- [ ] Hypotension
- [ ] Infection - Access site infection
- [ ] Infection - Bacteremia
- [ ] Infection - Endocarditis
- [ ] Infection - Mediastinitis
- [ ] Infection - Respiratory infection
- [ ] Infection - Sepsis
- [ ] Infection - Sternal wound infection
- [ ] Infection - Urinary tract infection
- [ ] Infection - Other
- [ ] Ischemia
- [ ] Mental state change (not neurological) - Confusion
- [ ] Mental state change (not neurological) - Dementia
- [ ] Mental state change (not neurological) - Depression
- [ ] MI
- [ ] Miscellaneous - Cancer
- [ ] Miscellaneous - Drug reaction
- [ ] Miscellaneous - Fall
- [ ] Miscellaneous - Suicide
- [ ] Miscellaneous - Other
- [ ] Mitral valve injury or insufficiency
- [ ] Multi organ failure

- [ ] Musculoskeletal - Fracture
- [ ] Musculoskeletal - Pain
- [ ] Neurological - Change in level of consciousness
- [ ] Neurological - Cognitive impairment
- [ ] Neurological - Dysphasia/Aphasia
- [ ] Neurological - Hemianopia (blindness in one half of the visual field)
- [ ] Neurological - Hemiparesis (One sided body weakness)
- [ ] Neurological - Hemiplegia (One side limb weakness)
- [ ] Neurological - Hemorrhagic stroke
- [ ] Neurological - Ischemic stroke
- [ ] Neurological - Other new neurological sign consistent with stroke
- [ ] Neurological - Sensory loss on one side of body
- [ ] Neurological - Syncope
- [ ] Neurological - TIA
- [ ] Neurological - Undetermined stroke
- [ ] Neurological - Other
- [ ] Pericarditis
- [ ] Radiation exposure - Non-skin Injury
- [ ] Radiation exposure - Skin Injury
- [ ] Renal insufficiency or renal failure
- [ ] Respiratory event - Aspiration
- [ ] Respiratory event - Atelectasis
- [ ] Respiratory event - Cough
- [ ] Respiratory event - Dyspnea
- [ ] Respiratory event - Pneumothorax
- [ ] Respiratory event - Pulmonary edema

	Respiratory event - Pulmonary effusion ☐
	Respiratory event - Respiratory failure ☐
	Respiratory event - Other ☐
	Syncope ☐
	Thrombocytopenia ☐
	Unknown cause of death ☐
	Valve stenosis - Restenosis ☐
	Valve thrombosis ☐
	Other ☐
If Event Code is Other, please specify:	_____
If Abnormal Lab Value, please specify value:	Creatinine ☐
	BUN ☐
	Total CK ☐
	Other ☐
	Hct ☐
	Hgb ☐
	RBC ☐
	WBC ☐
	Platelet count ☐
	Prothrombin time (INR) ☐
	PTT ☐
	Thrombocytopenia ☐
	AST ☐
	ALT ☐
	CK-MB ☐
	Troponin I ☐
	Troponin T ☐
Provide a brief description of the event:	_____
Relationship to Device:	None (Not related) ☐
	Possible ☐
	Related ☐
	Unknown (Unable to assess) ☐
	Not applicable (Valve not implanted) ☐

Relationship to Procedure:	None (Not related) ☐ Possible ☐ Related ☐ Unknown (Unable to assess) ☐ Not applicable (Valve not implanted) ☐
Severity:	Mild ☐ Moderate ☐ Severe ☐
Action Taken (Check All That Apply):	
None:	
Medication:	
Transfusion:	
If Transfusion, number of units:	
Hospitalization:	
Admit date:	Fixed Unit: (dd MMM yyyy)
Discharge date:	Fixed Unit: (dd MMM yyyy)
Hospitalization due to symptoms of aortic stenosis, complications of the valve or complications of the valve procedure:	Yes ☐ No ☐
Other:	
If Other, specify:	
Indicate if any of the following were performed to repair, alter or replace the study valve:	
BAV:	
AVR:	
Valve in Valve:	
Outcome:	Ongoing ☐ Resolved ☐ Ongoing at time of death ☐ Temporary disability ☐ Permanent disability ☐ Expiration ☐
AE occurred prior to index procedure:	Yes ☐ No ☐

If Resolved, resolution date:	Fixed Unit: (dd MMM yyyy)
If Expiration, categorical cause of death:	Cardiac ☐ Non-cardiac ☐ Unknown ☐
If Expiration, official cause of death:	
If Expiration, indicate if the study valve was explanted:	Yes ☐ No ☐
If Expiration, indicate if subject was discharged from the Index Hospital prior to expiration: (If Yes, all required Discharge forms must be completed)	Yes ☐ No ☐
Due to Device Malfunction?	Yes ☐ No ☐
Was this event an SAE?	Yes ☐ No ☐
If Yes, provide date Edwards was notified of event:	Fixed Unit: (dd MMM yyyy)
Indicate if event is an EC/IRB reportable event:	Yes ☐ No ☐
If Yes, provide date event was reported to EC/IRB:	Fixed Unit: (dd MMM yyyy)
Was this event an UADE?	Yes ☐ No ☐
If Yes, provide date Edwards was notified of event:	Fixed Unit: (dd MMM yyyy)
If Yes, provide date event reported to EC/IRB:	Fixed Unit: (dd MMM yyyy)
Comments:	

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Form: NIH Stroke Scale Performed Status

Unique AE Number:	
Was NIH Stroke Scale performed?	Yes ☐ No ☐

Corresponding Adverse event number, if applicable:	
In which device did a malfunction occur?	Study valve ☐ Delivery system ☐
If Study Valve, serial #:	
If Delivery system, lot #:	
Malfunction/failure occurred during (check all that apply):	
Procedure prior to valve placement (check all that apply):	
Gaining access:	
Crossing aortic arch:	
Crossing the native aortic valve:	
Other:	
If Other, specify:	
Valve placement (check all that apply):	
Study valve stent fracture:	
Study valve damage:	
Study valve leaflet tear:	
Other:	
If Other, specify:	
If Valve Placement, was the valve retrievable?	Yes ☐ No ☐
If No (the valve was not retrievable), explain:	
If Yes (the valve was retrievable), was the valve returned?	Yes ☐ No ☐
If No (the valve was not returned), explain:	
If Yes (the valve was returned), date returned:	Fixed Unit: (dd MMM yyyy)
Transfemoral delivery system (check all that apply):	
Failure occurred with the delivery system: (complete section below):	
During valve delivery:	
Difficulty inflating balloon during delivery:	
Difficulty removing balloon delivery catheter:	
Other:	
Failure occurred with dilator kit:	
If failure occurred with dilator kit: Specify	
Failure occurred with the introducer sheath set:	

If failure occurred with introducer sheath set: Specify:

Failure occurred with the balloon catheter (complete section below):

Did the failure occur during balloon aortic valvuloplasty? Yes ☐ No ☐

If Yes, was the failure due to: Difficulty inflating balloon ☐ Difficulty removing balloon catheter ☐

Failure occurred with Crimper:

Difficulty crimping:

Failure occurred with Crimper:

Difficulty crimping:

Transapical delivery system (check all that apply):

Failure occurred with the BAVC: (complete section below):

Difficulty inflating balloon:

Difficulty removing balloon catheter:

Other:

If Other, specify:

Failure occurred with Introducer sheath set:

If failure occurred with introducer sheath set: Specify:

Failure occurred with the delivery system (Specify):

Difficulty inflating balloon during delivery:

Difficulty removing balloon delivery catheter:

Other:

If Other, specify:

Failure occurred with Crimper:

Difficulty crimping:

Was another device used? Yes ☐ No ☐ NA ☐

If Yes, specify:

Brief description of malfunction/failure:

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Form: Vascular Complications

Unique AE Number:	
Did the event result into? (Check all that apply)	
Death:	
Transfusion:	
If Transfusion, total number of units transfused:	
Irreversible end organ damage:	
Compression or thrombin injection therapy:	
Failure of percutaneous access site closure resulting in intervention (e.g. stent-graft):	
Failure of percutaneous access site closure resulting in surgical correction:	
Surgical Repair:	
Unplanned use of cardiopulmonary bypass:	
Amputation:	
Embolectomy:	
Thrombectomy:	
Unplanned percutaneous intervention:	
If Unplanned percutaneous intervention, please specify:	
Unplanned surgical intervention:	
If Unplanned surgical intervention, please specify:	
Required Thrombolytic:	
If Required Thrombolytic, please specify:	
None:	
Describe:	
Event Location:	
Location:	Arterial ☐ Venous ☐ NA ☐
Side:	Right ☐ Left ☐ NA ☐
Closure Device Used:	Yes ☐ No ☐ NA ☐
Coagulation Status Closest to Event:	
ACT:	
ACT Date:	Fixed Unit: (dd MMM yyyy)

ACT Time:	Fixed Unit: (24 Hour Clock)
PTT:	Fixed Unit: sec
PTT Date:	Fixed Unit: (dd MMM yyyy)
PTT Time:	Fixed Unit: (24 Hour Clock)
INR:	
INR Date:	Fixed Unit: (dd MMM yyyy)
INR Time:	Fixed Unit: (24 Hour Clock)
Lowest hematology measurements prior to first transfusion:	
ACT:	
ACT Date:	Fixed Unit: (dd MMM yyyy)
ACT Time:	Fixed Unit: (24 Hour Clock)
PTT:	Fixed Unit: sec
PTT Date:	Fixed Unit: (dd MMM yyyy)
PTT Time:	Fixed Unit: (24 Hour Clock)
INR:	
INR Date:	Fixed Unit: (dd MMM yyyy)
INR Time:	Fixed Unit: (24 Hour Clock)

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Form: Infection Event

Unique AE Number:	
Infection (Complete one form per infection)	
Endocarditis (Operated Valvular Endocarditis):	
Positive Blood Culture:	Yes ☐ No ☐
Organism:	
Did the infection occur after the index procedure?	Yes ☐ No ☐
Did the infection result in surgical revision of procedure related incisions?	Yes ☐ No ☐
Antibiotics administered:	Yes ☐ No ☐
Vegetation present:	Yes ☐ No ☐
Access Site Infection (Infection at the Index Procedure Access Site):	
Organism:	
Driveline Related:	Yes ☐ No ☐
Catheter Related:	Yes ☐ No ☐
Antibiotics administered:	Yes ☐ No ☐
Respiratory Infection:	
Organism:	
Antibiotics administered:	Yes ☐ No ☐
Urinary Tract Infection:	
Organism:	
Antibiotics administered:	Yes ☐ No ☐
Sepsis:	
Did the infection result in hemodynamic shock?	Yes ☐ No ☐

Did the infection result in surgical revision of procedure related incisions?	Yes ☐ No ☐
Antibiotics administered:	Yes ☐ No ☐
Bacteremia:	
Organism:	
Driveline related:	Yes ☐ No ☐
Catheter Related:	Yes ☐ No ☐
Antibiotics administered:	Yes ☐ No ☐
Sternal Wound Infection:	
Infection involves:	Muscle ☐ Bone ☐ Mediastinum ☐
Open wound with excision of tissue:	Yes ☐ No ☐
Positive culture:	Yes ☐ No ☐
If Yes, Organism:	
Antibiotics administered:	Yes ☐ No ☐
Other (specify):	

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Form: Myocardial Infarction Event

Unique AE Number:	
Peri-Procedural MI (Beginning = 72 hours of Index procedure):	
New ischemic symptoms (e.g. Chest pain or shortness of breath?):	
New ST segment elevation or depression:	
New-wall motion abnormality:	
If Yes, determined by:	Echo ☐ Nuclear ☐ Angio ☐
New pathological Q wave in 2 contiguous leads:	
Confirmatory Biomarker Evidence	
Are there two or more samples of CK-MB (6-8 hours apart) with 20% increase in second sample and a peak value exceeding 10x the 99th percentile upper reference limit?	
Are there two or more samples of CK-MB (6-8 hours apart) with 20% increase in second sample and a peak value exceeding 5x the 99th percentile upper reference limit?	
CK-MB Reading 1:	
CK-MB Reading 2:	
CK-MB Reading 3:	
Spontaneous MI (>72 hours after the Index procedure):	
Confirmatory Biomarker Evidence	
Is there rise and/or fall of cardiac biomarkers (preferably Troponin) with at least one value above the 99th percentile?	
Troponins:	
Sudden, unexpected cardiac death, involving cardiac arrest, with symptoms suggestive to MI:	
Evidence of fresh thrombus by coronary angiography:	
New ST segment elevation or depression:	
New-wall motion abnormality:	
If Yes, determined by:	Echo ☐ Nuclear ☐ Angio ☐
New pathological Q wave in 2 contiguous leads:	
Pathological findings of an acute MI?	
Echocardiography performed due to this event:	
ECG performed due to this event:	
PCI performed for acute ST elevation:	
Thrombolytic used for acute MI:	

If Yes, specify:

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Form: Neurologic Event

Unique AE Number:	
Diagnostic test to confirm type of injury:	Not Done ☐ CAT Scan ☐ MRI ☐ Cerebral Vessel Angiography ☐ Lumbar Puncture (Spinal Fluid analysis diagnostic of intracranial hemorrhage) ☐ Neurologist or Neurosurgical specialist ☐
Location:	
Cranial nerves/Face:	
Lower extremity:	
Upper extremity:	
Trunk:	
N/A:	
Occurred during index catheterization?	Yes ☐ No ☐ NA ☐
Related to subsequent invasive procedure?	Yes ☐ No ☐ NA ☐
Possibly related to anticoagulation?	Yes ☐ No ☐ NA ☐
Were coagulation results obtained in association with this event?	Yes ☐ No ☐ NA ☐
PTT:	Fixed Unit: sec
PTT Date:	Fixed Unit: (dd MMM yyyy)
PTT Time:	Fixed Unit: (24 Hour Clock)
INR:	
INR Date:	Fixed Unit: (dd MMM yyyy)

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Form: Neurologic Event

INR Time:	Fixed Unit: (24 Hour Clock)
Duration of focal/global neurological deficit:	Greater than or equal to 24 hours ☐ Less than 24 hours ☐
If Less than 24 hours,Thrombolytic drug administered:	Yes ☐ No ☐
If Less than 24 hours, Intracranial Angioplasty performed:	Yes ☐ No ☐
Indicate if brain imaging clearly indicates a new stroke:	Ischemic Stroke ☐ Hemorrhagic Stroke ☐ Undetermined Stroke ☐

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Form: Thromboembolic

Unique AE Number:	_____
Location of Thromboembolism	
Did the thromboembolic event occur after the immediate perioperative period? (When anesthesia induced unconsciousness is completely reversed):	Yes ☐ No ☐
Arterial:	_____
Organ affected:	Brain and/or Eye ☐ Heart ☐ Liver ☐ Kidney ☐ Spleen ☐ Lungs ☐ GI Tract ☐ Extremities ☐
If Extremities, specify:	_____
Confirmed by:	Imaging ☐ Autopsy ☐ Operation ☐
If Imaging, explain:	_____
Were thrombolytic required?	Yes ☐ No ☐
Percutaneous Intervention performed?	Yes ☐ No ☐
Surgical Revascularization:	Yes ☐ No ☐
Venous:	_____
Deep Vein Thrombosis:	Yes ☐ No ☐
Pulmonary Embolism:	Yes ☐ No ☐
Confirmed by:	Pulmonary Angiogram ☐ Ventilation/Perfusion Scan ☐ CT Angiogram ☐ MRI ☐

Thrombolytic Required:	Yes ☐ No ☐
Surgical Intervention Required:	Yes ☐ No ☐

Last labs obtained before initiating event-driven anticoagulation:

Were lab test performed at the enrolling site?	Yes ☐ No ☐ Not Done ☐
PTT:	
PTT Date:	Fixed Unit: (dd MMM yyyy)
PTT Time:	Fixed Unit: (24 Hour Clock)
INR:	
INR Date:	Fixed Unit: (dd MMM yyyy)
INR Time:	Fixed Unit: (24 Hour Clock)
Platelets:	
Platelet Date:	Fixed Unit: (dd MMM yyyy)
Platelet Time:	Fixed Unit: (24 Hour Clock)
Heparin-induced Thrombocytopenia antibody screen:	Positive ☐ Negative ☐ Not Done ☐
Blood culture x3 growth at 7 days:	Yes ☐ No ☐ Not Done ☐

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Form: Renal Insufficiency

Unique AE Number:	
Labs:	
BUN/Cr Ratio:	
N/A:	
Sr Creatinine:	
N/A:	
Did subject require Renal Replacement therapy:	Yes ☐ No ☐
Start Date:	Fixed Unit: (dd MMM yyyy)
End Date:	Fixed Unit: (dd MMM yyyy)
Increase in serum creatinine to 150-200% (1.5-2.0 x increase compared with baseline) or increase of = 0.3 mg/dl (=26.4 μmol/L) **(Stage I)**:	
Increase in serum creatinine to > 200-300% (> 2-3 x increase compared with baseline) **(Stage II)**:	
Increase in serum creatinine to =300% (> 3 x increase compared with baseline) or serum creatinine of = 4.0 mg/d (=354 μmol/L) with an acute increase of at least 0.5 mg/dl (44 μmol/L) **(Stage III):**	

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Form: Bleeding

Unique AE Number:	
Life Threatening or Disabling Bleeding	
Fatal Bleeding:	
Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome:	
Bleeding causing hypovolumic shock or severe hypotension requiring vasopressors or surgery :	
Overt source of bleeding with drop in hemoglobin of greater than or equal to 5g/dl or whole blood of packed red blood cells(RBC) transfusion greater than or equal to 4 units:	
Major Bleeding	
Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dl or requiring transfusion of 2-3 units of whole blood /RBC AND does not meet criteria of life threatening or disabling bleeding:	
Minor Bleeding	
Any bleeding worthy of clinical mention (e.g. access site hematoma) that does not qualify as life threatening, or disabling or major:	
Cause of Bleeding:	
Did the subject require a transfusion?	Yes ☐ No ☐
Total number of units transfused:	
Lowest hematology measurements prior to first transfusion:	
Hgb:	
Hct:	
ACT:	
ACT Date:	Fixed Unit: (dd MMM yyyy)
ACT Time:	Fixed Unit: (24 Hour Clock)
PTT:	
PTT Date:	Fixed Unit: (dd MMM yyyy)
PTT Time:	Fixed Unit: (24 Hour Clock)
INR:	

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Form: Bleeding

INR Date:	Fixed Unit: (dd MMM yyyy)
INR Time:	Fixed Unit: (24 Hour Clock)

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Form: Arrhythmia Event

Unique AE Number:	_____
Type of Arrhythmia:	Atrioventricular block ☐
	Atrial fibrillation ☐
	Atrial flutter ☐
	Vent fibrillation ☐
	Ventricular tachycardia ☐
	Other ☐
If Other, specify:	_____
Status:	Pre-existing ☐
	Not pre-existing ☐
	Worsening ☐
Type of Conduction Defect:	LBBB ☐
	RBBB ☐
	Sick Sinus Syndrome ☐
	Heart Block ☐
ECG performed due to this event: (If Yes, complete the ECG tracking form)	Yes ☐
	No ☐
Arrhythmia requiring Permanent pacemaker:	Yes ☐
	No ☐
Did the subject experience any arrhythmias requiring intervention? (If Yes, complete information below)	Yes ☐
	No ☐
Occurred during study valve implantation procedure:	Yes ☐
	No ☐
If Yes:	Occurred during pre-treatment ☐
	Occurred during perforation of atrial wall ☐
	Occurred during BAV ☐
	Occurred during valve placement ☐
Occurred after study valve implantation procedure:	Yes ☐
	No ☐
If Yes:	<1 Day ☐
	>=1 Day ☐

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Form: Valve Explant

Unique AE Number:	
Explant Date:	Fixed Unit: (dd MMM yyyy)
What was the reason for the valve explant	
Explanted at autopsy (Subject died and autopsy was performed):	
Device explanted due to clinical reason (e.g. Valvular endocarditis, Valve dysfunction):	
If Device explanted due to clinical reason, specify:	
Period:	Intraoperative ☐ Postoperative ☐
Device Received Manufacturer:	
Device Received Size:	Fixed Unit: mm
N/A:	
Macroscopic Findings: Normal Appearance	
Findings:	Leaflet fenestration
Yes/No:	Yes ☐ No ☐
Location:	
Severity:	Mild ☐ Moderate ☐ Severe ☐
Photograph of explant taken:	Yes ☐ No ☐
Was the valve sent to independent histology core lab?	Yes ☐ No ☐
If Yes, date sent:	Fixed Unit: (dd MMM yyyy)
If No, explain:	
Comments:	

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Form: Valve Explant

Unique AE Number:	
Explant Date:	Fixed Unit: (dd MMM yyyy)
What was the reason for the valve explant	
Explanted at autopsy (Subject died and autopsy was performed):	
Device explanted due to clinical reason (e.g. Valvular endocarditis, Valve dysfunction):	
If Device explanted due to clinical reason, specify:	
Period:	Intraoperative ☐ Postoperative ☐
Device Received Manufacturer:	
Device Received Size:	Fixed Unit: mm
N/A:	
Macroscopic Findings: Normal Appearance	
Findings:	Leaftlet tear
Yes/No:	Yes ☐ No ☐
Location:	
Severity:	Mild ☐ Moderate ☐ Severe ☐
Photograph of explant taken:	Yes ☐ No ☐
Was the valve sent to independent histology core lab?	Yes ☐ No ☐
If Yes, date sent:	Fixed Unit: (dd MMM yyyy)
If No, explain:	
Comments:	

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Form: Valve Explant

Unique AE Number:	
Explant Date:	Fixed Unit: (dd MMM yyyy)
What was the reason for the valve explant	
Explanted at autopsy (Subject died and autopsy was performed):	
Device explanted due to clinical reason (e.g. Valvular endocarditis, Valve dysfunction):	
If Device explanted due to clinical reason, specify:	
Period:	Intraoperative ☐ Postoperative ☐
Device Received Manufacturer:	
Device Received Size:	Fixed Unit: mm
N/A:	
Macroscopic Findings: Normal Appearance	
Findings:	Thrombus
Yes/No:	Yes ☐ No ☐
Location:	
Severity:	Mild ☐ Moderate ☐ Severe ☐
Photograph of explant taken:	Yes ☐ No ☐
Was the valve sent to independent histology core lab?	Yes ☐ No ☐
If Yes, date sent:	Fixed Unit: (dd MMM yyyy)
If No, explain:	
Comments:	

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Form: Valve Explant

Unique AE Number:	
Explant Date:	Fixed Unit: (dd MMM yyyy)
What was the reason for the valve explant	
Explanted at autopsy (Subject died and autopsy was performed):	
Device explanted due to clinical reason (e.g. Valvular endocarditis, Valve dysfunction):	
If Device explanted due to clinical reason, specify:	
Period:	Intraoperative ☐ Postoperative ☐
Device Received Manufacturer:	
Device Received Size:	Fixed Unit: mm
N/A:	
Macroscopic Findings: Normal Appearance	
Findings:	Vegetation
Yes/No:	Yes ☐ No ☐
Location:	
Severity:	Mild ☐ Moderate ☐ Severe ☐
Photograph of explant taken:	Yes ☐ No ☐
Was the valve sent to independent histology core lab?	Yes ☐ No ☐
If Yes, date sent:	Fixed Unit: (dd MMM yyyy)
If No, explain:	
Comments:	

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Form: Valve Explant

Unique AE Number:	
Explant Date:	Fixed Unit: (dd MMM yyyy)
What was the reason for the valve explant	
Explanted at autopsy (Subject died and autopsy was performed):	
Device explanted due to clinical reason (e.g. Valvular endocarditis, Valve dysfunction):	
If Device explanted due to clinical reason, specify:	
Period:	Intraoperative ☐
	Postoperative ☐
Device Received Manufacturer:	
Device Received Size:	Fixed Unit: mm
N/A:	
Macroscopic Findings: Normal Appearance	
Findings:	Hemorrhage
Yes/No:	Yes ☐
	No ☐
Location:	
Severity:	Mild ☐
	Moderate ☐
	Severe ☐
Photograph of explant taken:	Yes ☐
	No ☐
Was the valve sent to independent histology core lab?	Yes ☐
	No ☐
If Yes, date sent:	Fixed Unit: (dd MMM yyyy)
If No, explain:	
Comments:	

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Form: Valve Explant

Unique AE Number:	
Explant Date:	Fixed Unit: (dd MMM yyyy)
What was the reason for the valve explant	
Explanted at autopsy (Subject died and autopsy was performed):	
Device explanted due to clinical reason (e.g. Valvular endocarditis, Valve dysfunction):	
If Device explanted due to clinical reason, specify:	
Period:	Intraoperative ☐ Postoperative ☐
Device Received Manufacturer:	
Device Received Size:	Fixed Unit: mm
N/A:	
Macroscopic Findings: Normal Appearance	
Findings:	Ring abscess
Yes/No:	Yes ☐ No ☐
Location:	
Severity:	Mild ☐ Moderate ☐ Severe ☐
Photograph of explant taken:	Yes ☐ No ☐
Was the valve sent to independent histology core lab?	Yes ☐ No ☐
If Yes, date sent:	Fixed Unit: (dd MMM yyyy)
If No, explain:	
Comments:	

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Form: Valve Explant

Unique AE Number:	
Explant Date:	Fixed Unit: (dd MMM yyyy)
What was the reason for the valve explant	
Explanted at autopsy (Subject died and autopsy was performed):	
Device explanted due to clinical reason (e.g. Valvular endocarditis, Valve dysfunction):	
If Device explanted due to clinical reason, specify:	
Period:	Intraoperative ☐ Postoperative ☐
Device Received Manufacturer:	
Device Received Size:	Fixed Unit: mm
N/A:	
Macroscopic Findings: Normal Appearance	
Findings:	Instrument trauma
Yes/No:	Yes ☐ No ☐
Location:	
Severity:	Mild ☐ Moderate ☐ Severe ☐
Photograph of explant taken:	Yes ☐ No ☐
Was the valve sent to independent histology core lab?	Yes ☐ No ☐
If Yes, date sent:	Fixed Unit: (dd MMM yyyy)
If No, explain:	
Comments:	

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Form: Valve Explant

Unique AE Number:	
Explant Date:	Fixed Unit: (dd MMM yyyy)
What was the reason for the valve explant	
Explanted at autopsy (Subject died and autopsy was performed):	
Device explanted due to clinical reason (e.g. Valvular endocarditis, Valve dysfunction):	
If Device explanted due to clinical reason, specify:	
Period:	Intraoperative ☐
	Postoperative ☐
Device Received Manufacturer:	
Device Received Size:	Fixed Unit: mm
N/A:	
Macroscopic Findings: Normal Appearance	
Findings:	Fibrosis
Yes/No:	Yes ☐
	No ☐
Location:	
Severity:	Mild ☐
	Moderate ☐
	Severe ☐
Photograph of explant taken:	Yes ☐
	No ☐
Was the valve sent to independent histology core lab?	Yes ☐
	No ☐
If Yes, date sent:	Fixed Unit: (dd MMM yyyy)
If No, explain:	
Comments:	

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Form: Valve Explant

Unique AE Number:	
Explant Date:	Fixed Unit: (dd MMM yyyy)
What was the reason for the valve explant	
Explanted at autopsy (Subject died and autopsy was performed):	
Device explanted due to clinical reason (e.g. Valvular endocarditis, Valve dysfunction):	
If Device explanted due to clinical reason, specify:	
Period:	Intraoperative ☐ Postoperative ☐
Device Received Manufacturer:	
Device Received Size:	Fixed Unit: mm
N/A:	
Macroscopic Findings: Normal Appearance	
Findings:	Calcification
Yes/No:	Yes ☐ No ☐
Location:	
Severity:	Mild ☐ Moderate ☐ Severe ☐
Photograph of explant taken:	Yes ☐ No ☐
Was the valve sent to independent histology core lab?	Yes ☐ No ☐
If Yes, date sent:	Fixed Unit: (dd MMM yyyy)
If No, explain:	
Comments:	

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Form: CEC Acute Kidney Injury

CEC form number:	_____
Event adjudication:	No event ☐ Event ☐ Insufficient information for determination ☐
If Event, adjudication of date:	_____
If Event, relationship to procedure:	<= 30 days after procedure ☐ > 30 days - <= 1 Year after procedure ☐ > 1 Year - <= 2 Years after procedure ☐ > 2 Years - <= 3 Years after procedure ☐ > 3 Years - <= 4 Years after procedure ☐
If Event, stage:	Stage I ☐ Stage II ☐ Stage III ☐
Comments:	_____
Phase II review:	Source adequate ☐ Source inadequate, best assessment made ☐ Not applicable ☐
Date review completed:	_____

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Form: CEC Aortic Valve Re-Intervention

CEC form number:	
Event adjudication:	No event ☐ Event ☐ Insufficient information for determination ☐
If Event, adjudication of date:	
If Event, type (check all that apply):	
Balloon Aortic Valvuloplasty:	
Surgical AV Replacement:	
Valve in Valve:	
Other:	
If Other, specify:	
Comments:	
Phase II review:	Source adequate ☐ Source inadequate, best assessment made ☐ Not applicable ☐
Date review completed:	

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Form: CEC Bleeding

CEC form number:	_____
Adjudication of event:	No event ☐ Event ☐ Insufficient information for determination ☐
If Event, adjudication of date:	_____
If Event, timing:	During the procedure ☐ Within index hospitalization ☐ Post discharge ☐
If Event, severity:	Life threatening/disabling ☐ Major ☐ Minor ☐
If Event, relationship to study valve or index procedure:	Not related ☐ Possibly related or related ☐ Unable to assess ☐ Not applicable ☐
If Possibly related or related, check all that apply:	
Valve:	_____
Procedure:	_____
Unable to determine:	_____
If Valve, anticoagulation regimen relationship:	Possibly related or related ☐ Not related ☐
Comments:	_____
Phase II review:	Source adequate ☐ Source inadequate, best assessment made ☐ Not applicable ☐
Date review completed:	_____

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Form: CEC Coronary Obstruction

CEC form number:	_____
Event adjudication:	No event ☐ Event ☐ Insufficient information for determination ☐
If Event, adjudication of date:	_____
If Event, relationship to study valve or index procedure:	Not related ☐ Possibly related or related ☐ Unable to assess ☐ Not applicable ☐
If Possibly related or related, check all that apply:	
Valve:	_____
Procedure:	_____
Unable to determine:	_____
Comments:	_____
Phase II review:	Source adequate ☐ Source inadequate, best assessment made ☐ Not applicable ☐
Date review completed:	_____

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Form: CEC Death

CEC form number:	
Adjudicated date of death:	
Adjudicated cause of death category:	Non-CV ☐ CV ☐
If Non-CV, cause of death:	Infectious ☐ Systemic Inflammatory Response Syndrome ☐ Pulmonary ☐ Renal causes ☐ Gastrointestinal ☐ Malignancy ☐ Accidental or trauma ☐ Hemorrhage, not stroke or CV ☐ Suicide ☐ Hepatobiliary ☐ Pancreatic ☐ Non-CV surgery or procedure ☐ Neurologic process that is not a stroke or hemorrhage ☐ Prescription drug error ☐ Other ☐
If Other, specify:	
If CV, cause of death:	Due to proximate cardiac disease cause ☐ Unwitnessed and unknown ☐ Cardiovascular procedure related ☐ Noncoronary vascular condition such as pulmonary embolism ☐ Noncoronary vascular condition such as stroke/ICH ☐
Adjudicated relationship to study valve or index procedure:	Not related ☐ Possibly related or related ☐ Unable to assess ☐ Not applicable ☐
If Possibly related or related, check all that apply:	
Valve:	
Procedure:	

Unable to determine:	
Comments:	
Phase II review:	Source adequate ☐ Source inadequate, best assessment made ☐ Not applicable ☐
Date review completed:	

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Form: CEC Endocarditis

CEC form number:	
Event adjudication:	No event ☐ Event ☐ Insufficient information for determination ☐
If Event, adjudication of date:	
If Event, (check all that apply):	
Study Valve:	
Surgical AVR:	
Transcatheter Heart Valve:	
Non-Study Valve (check all that apply):	
Aortic:	
Mitral:	
Tricuspid:	
Pulmonary:	
Comments:	
Phase II review:	Source adequate ☐ Source inadequate, best assessment made ☐ Not applicable ☐
Date review completed:	

Form: CEC Hemolysis

CEC form number:	_____
Adjudication of event:	No event ☐ Event ☐ Insufficient information for determination ☐
If Event, adjudication of date:	_____
If Event, relationship to study valve:	Not related ☐ Possibly related or related ☐ Unable to assess ☐ Not applicable ☐
Comments:	_____
Phase II review:	Source adequate ☐ Source inadequate, best assessment made ☐ Not applicable ☐
Date review completed:	_____

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Form: CEC Myocardial Infarction

CEC form number:	_____
CKMB Analysis	
CKMB Measurement:	CKMB <= upper reference limits ☐ CKMB >URL- <=3xURL ☐ CKMB >3X URL- <=5XURL ☐ CKMB >5X URL- <=10XURL ☐ CKMB > 10XURL ☐ CKMB data not available ☐
Troponin:	Troponin I ☐ Troponin T ☐
Troponin Measurement:	TN <= URL ☐ TN > URL- <= 3xURL ☐ TN > 3XURL- <= 5XURL ☐ TN > 5XURL- <= 10XURL ☐ TN > 10XURL ☐ TN data not available ☐
Event adjudication:	No event ☐ Event ☐ Insufficient information for determination ☐
If Event, adjudication of date:	_____
If Event, timing:	Peri-procedural ☐ Spontaneous ☐
If Event, type:	1 ☐ 2 ☐ 3 ☐ 4a ☐ 4b ☐ 5 ☐ Uncertain ☐
If Event, relationship to study valve or index procedure:	Not related ☐ Possibly related or related ☐ Unable to assess ☐ Not applicable ☐
If Possibly related or related, check all that apply:	

Valve:	
Procedure:	
Unable to determine:	
Comments:	
Phase II review:	Source adequate ☐ Source inadequate, best assessment made ☐ Not applicable ☐
Date review completed:	

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Form: CEC New/Worsening MV Dysfunction

CEC form number:	_____
Mitral Valve Dysfunction:	No event ☐ Event ☐ Insufficient information for determination ☐
If Event, adjudication of date:	
Agree/Disagree:	Agree ☐ Disagree ☐
If Disagree, adjudication of date:	_____
If Event (mark all that apply)	
New or worsening mitral regurgitation:	_____
New or worsening mitral stenosis:	_____
Disruption: (mark all that apply)	_____
Related to contact with transcatheter valve:	_____
Related to mitral valve endocarditis:	_____
Other:	_____
If Other, specify:	_____
If Event, relationship to study valve or index procedure:	Not related ☐ Possibly related or related ☐ Unable to assess ☐ Not applicable ☐
If Possibly related or related, check all that apply:	
Valve:	_____
Procedure:	_____
Unable to determine:	_____
Comments:	_____
Phase II review:	Source adequate ☐ Source inadequate, best assessment made ☐ Not applicable ☐
Date review completed:	_____

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Form: CEC Pericarditis

CEC form number:	_____
Adjudication of event:	No event ☐ Event ☐ Insufficient information for determination ☐
If Event, adjudication of date:	_____
If Event, relationship to study valve or index procedure:	Not related ☐ Possibly related or related ☐ Unable to assess ☐ Not applicable ☐
If Possibly related or related, check all that apply:	
Valve:	_____
Procedure:	_____
Unable to determine:	_____
Comments:	_____
Phase II review:	Source adequate ☐ Source inadequate, best assessment made ☐ Not applicable ☐
Date review completed:	_____

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Form: CEC Prosthetic Valve Dysfunction

CEC form number:	_____
Event adjudication:	No event ☐ Event ☐ Insufficient information for determination ☐
If Event, adjudication of date:	_____
If Event, choose all that apply:	
Aortic event type:	Aortic Stenosis ☐ Aortic Regurgitation ☐
If Aortic Stenosis, severity:	Possible Aortic Stenosis ☐ Significant Aortic Stenosis ☐
If Aortic Regurgitation, severity:	Moderate Aortic Regurgitation ☐ Severe Aortic Regurgitation ☐
Clinical findings indicating impaired CV or valvular function: (choose all that apply)	
New or worsening CHF:	_____
Rehospitalization for worsening symptoms:	_____
Reoperation:	_____
Death:	_____
Other:	_____
If Other, specify:	_____
If Event, potential failure mode: (mark all that apply)	
Stent Creep:	_____
Pannus:	_____
Calcification:	_____
Support structure deformation, under-expansion, fracture, or trauma:	_____
Mal-sizing:	_____
Endocarditis:	_____
Prosthetic valve thrombosis:	_____
Native leaflet prolapse impeding prosthetic leaflet motion:	_____
Other:	_____
If Other, specify:	_____
Unable to determine:	_____
If Event, relationship to study valve or index procedure:	Possibly related or related ☐ Unable to access ☐ Not applicable ☐
If Possibly related or related, check all that apply:	

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Form: CEC Prosthetic Valve Dysfunction

Valve:	
Procedure:	
Unable to determine:	
Comments:	
Phase II review:	Source adequate ☐ Source inadequate, best assessment made ☐ Not applicable ☐
Date review completed:	

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Form: CEC Re-Hosp/Prolonged Index Hosp for Decompens

CEC form number:	
Symptoms of Cardiac or Valve-Related Decompensation Event Adjudication (symptoms of aortic stenosis) (VARC definition):	No event ☐ Event ☐ Insufficient information for determination ☐
Symptoms of Cardiac or Valve-Related Decompensation Event Adjudication (symptoms of aortic stenosis) (VARC definition) N/A:	
Symptoms of aortic stenosis and/or complications of the valve procedure (Protocol definition):	No event ☐ Event ☐ Insufficient information for determination ☐
If Event, adjudication of date:	
If Event, time period:	<= 30 days post index procedure ☐ > 30 days post index procedure ☐
If Event, cardiac reason for rehospitalization/prolonged hospitalization (check all that apply)	
CHF:	
Coronary Ischemia:	
If Coronary Ischemia, type:	MI ☐ Unstable angina requiring revascularization ☐ Other angina not requiring revascularization ☐ Other ☐ Unable to determine ☐
If Other, specify:	
Arrhythmia:	
Endocarditis:	
Syncope (cardiac related):	
Pericardial Effusion/Cardiac Tamponade:	
Vascular (including access site infection):	
Bleeding:	
Stroke/TIA:	
AKI:	
Ventricle septal perforation:	
Valve embolization/migration:	
Valve thrombosis:	
Other:	
If Other, specify:	

If Event, related to study valve or index procedure:	Not related ☐ Possibly related or related ☐ Unable to assess ☐ Not applicable ☐
If Possibly related or related, check all that apply:	
Valve:	_____
Procedure:	_____
Unable to determine:	_____
Comments:	_____
Phase II review:	Source adequate ☐ Source inadequate, best assessment made ☐ Not applicable ☐
Date review completed:	_____

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Form: CEC Rehospitalization/Prolonged Hospitalization

CEC form number:	
Review:	No potential CV events identified ☐ Potential CV event ☐
Check all that apply:	
Potential event:	Death ☐ Stroke/TIA ☐ Bleeding ☐ Vascular Access Site & Access Related Complications ☐ MI ☐ Acute Kidney Injury ☐ Prosthetic Valve Dysfunction ☐ Conduction Disturbance requiring permanent pacemaker ☐ Aortic Valve Re-Intervention ☐ New or Worsening Mitral Valve Dysfunction ☐ Endocarditis ☐ Coronary Obstruction ☐ Re-Hosp or Prolonged Hosp of Index Hosp for Symptoms of Cardiac or Valve-related Decompensation ☐ Hemolysis ☐ Pericarditis ☐
AE ID Number:	
Comments:	
On dashboard?	Yes ☐ No ☐
Date review completed:	

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Form: CEC Rehospitalization/Prolonged Hospitalization

CEC form number:	
Review:	No potential CV events identified ☐ Potential CV event ☐
Check all that apply:	
Potential event:	Death ☐ Stroke/TIA ■ Bleeding ☐ Vascular Access Site & Access Related Complications ☐ MI ☐ Acute Kidney Injury ☐ Prosthetic Valve Dysfunction ☐ Conduction Disturbance requiring permanent pacemaker ☐ Aortic Valve Re-Intervention ☐ New or Worsening Mitral Valve Dysfunction ☐ Endocarditis ☐ Coronary Obstruction ☐ Re-Hosp or Prolonged Hosp of Index Hosp for Symptoms of Cardiac or Valve-related Decompensation ☐ Hemolysis ☐ Pericarditis ☐
AE ID Number:	
Comments:	
On dashboard?	Yes ☐ No ☐
Date review completed:	

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Form: CEC Rehospitalization/Prolonged Hospitalization

CEC form number:	
Review:	No potential CV events identified ☐ Potential CV event ☐
Check all that apply:	
Potential event:	Death ☐ Stroke/TIA ☐ Bleeding ☐ Vascular Access Site & Access Related Complications ☐ MI ☐ Acute Kidney Injury ☐ Prosthetic Valve Dysfunction ☐ Conduction Disturbance requiring permanent pacemaker ☐ Aortic Valve Re-Intervention ☐ New or Worsening Mitral Valve Dysfunction ☐ Endocarditis ☐ Coronary Obstruction ☐ Re-Hosp or Prolonged Hosp of Index Hosp for Symptoms of Cardiac or Valve-related Decompensation ☐ Hemolysis ☐ Pericarditis ☐
AE ID Number:	
Comments:	
On dashboard?	Yes ☐ No ☐
Date review completed:	

6.000 19MAR2013 Draft 1.0 PROD SRM: All Forms

Form: CEC Rehospitalization/Prolonged Hospitalization

CEC form number:	
Review:	No potential CV events identified ☐ Potential CV event ☐
Check all that apply:	
Potential event:	Death ☐ Stroke/TIA ☐ Bleeding ☐ Vascular Access Site & Access Related Complications ■ MI ☐ Acute Kidney Injury ☐ Prosthetic Valve Dysfunction ☐ Conduction Disturbance requiring permanent pacemaker ☐ Aortic Valve Re-Intervention ☐ New or Worsening Mitral Valve Dysfunction ☐ Endocarditis ☐ Coronary Obstruction ☐ Re-Hosp or Prolonged Hosp of Index Hosp for Symptoms of Cardiac or Valve-related Decompensation ☐ Hemolysis ☐ Pericarditis ☐
AE ID Number:	
Comments:	
On dashboard?	Yes ☐ No ☐
Date review completed:	

6.000 19MAR2013 Draft 1.0 PROD SRM: All Forms

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Check all that apply:	
Potential event:	Death ☐ Stroke/TIA ☐ Bleeding ☐ Vascular Access Site & Access Related Complications ☐ MI ■ Acute Kidney Injury ☐ Prosthetic Valve Dysfunction ☐ Conduction Disturbance requiring permanent pacemaker ☐ Aortic Valve Re-Intervention ☐ New or Worsening Mitral Valve Dysfunction ☐ Endocarditis ☐ Coronary Obstruction ☐ Re-Hosp or Prolonged Hosp of Index Hosp for Symptoms of Cardiac or Valve-related Decompensation ☐ Hemolysis ☐ Pericarditis ☐
AE ID Number:	
Comments:	
On dashboard?	Yes ☐ No ☐
Date review completed:	

6.000 19MAR2013 Draft 1.0 PROD SRM: All Forms

Form: CEC Rehospitalization/Prolonged Hospitalization

CEC form number:	
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	Potential CV event ☐
Check all that apply:	
Potential event:	Death ☐
	Stroke/TIA ☐
	Bleeding ☐
	Vascular Access Site & Access Related Complications ☐
	MI ☐
	Acute Kidney Injury ☐
	Prosthetic Valve Dysfunction ☐
	Conduction Disturbance requiring permanent pacemaker ☐
	Aortic Valve Re-Intervention ☐
	New or Worsening Mitral Valve Dysfunction ☐
	Endocarditis ☐
	Coronary Obstruction ☐
	Re-Hosp or Prolonged Hosp of Index Hosp for Symptoms of Cardiac or Valve-related Decompensation ☐
	Hemolysis ☐
	Pericarditis ☐
AE ID Number:	
Comments:	
On dashboard?	Yes ☐
	No ☐
Date review completed:	

6.000 19MAR2013 Draft 1.0 PROD SRM: All Forms

Form: CEC Rehospitalization/Prolonged Hospitalization

CEC form number:	
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Check all that apply:	
Potential event:	Death ☐ Stroke/TIA ☐ Bleeding ☐ Vascular Access Site & Access Related Complications ☐ MI ☐ Acute Kidney Injury ☐ Prosthetic Valve Dysfunction ■ Conduction Disturbance requiring permanent pacemaker ☐ Aortic Valve Re-Intervention ☐ New or Worsening Mitral Valve Dysfunction ☐ Endocarditis ☐ Coronary Obstruction ☐ Re-Hosp or Prolonged Hosp of Index Hosp for Symptoms of Cardiac or Valve-related Decompensation ☐ Hemolysis ☐ Pericarditis ☐
AE ID Number:	
Comments:	
On dashboard?	Yes ☐ No ☐
Date review completed:	

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	Potential CV event ☐
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Potential event:	Death ☐
	Stroke/TIA ☐
	Bleeding ☐
	Vascular Access Site & Access Related Complications ☐
	MI ☐
	Acute Kidney Injury ☐
	Prosthetic Valve Dysfunction ☐
	Conduction Disturbance requiring permanent pacemaker ■
	Aortic Valve Re-Intervention ☐
	New or Worsening Mitral Valve Dysfunction ☐
	Endocarditis ☐
	Coronary Obstruction ☐
	Re-Hosp or Prolonged Hosp of Index Hosp for Symptoms of Cardiac or Valve-related Decompensation ☐
	Hemolysis ☐
	Pericarditis ☐
AE ID Number:	
Comments:	
On dashboard?	Yes ☐
	No ☐
Date review completed:	

6.000 19MAR2013 Draft 1.0 PROD SRM: All Forms

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CEC form number:	
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Potential event:	Death ☐ Stroke/TIA ☐ Bleeding ☐ Vascular Access Site & Access Related Complications ☐ MI ☐ Acute Kidney Injury ☐ Prosthetic Valve Dysfunction ☐ Conduction Disturbance requiring permanent pacemaker ☐ Aortic Valve Re-Intervention ■ New or Worsening Mitral Valve Dysfunction ☐ Endocarditis ☐ Coronary Obstruction ☐ Re-Hosp or Prolonged Hosp of Index Hosp for Symptoms of Cardiac or Valve-related Decompensation ☐ Hemolysis ☐ Pericarditis ☐
AE ID Number:	
Comments:	
On dashboard?	Yes ☐ No ☐
Date review completed:	

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AE ID Number:	
Comments:	
On dashboard?	Yes ☐ No ☐
Date review completed:	

6.000 19MAR2013 Draft 1.0 PROD SRM: All Forms

Form: CEC Rehospitalization/Prolonged Hospitalization

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Review:	No potential CV events identified ☐
	Potential CV event ☐
Check all that apply:	
Potential event:	Death ☐
	Stroke/TIA ☐
	Bleeding ☐
	Vascular Access Site & Access Related Complications ☐
	MI ☐
	Acute Kidney Injury ☐
	Prosthetic Valve Dysfunction ☐
	Conduction Disturbance requiring permanent pacemaker ☐
	Aortic Valve Re-Intervention ☐
	New or Worsening Mitral Valve Dysfunction ☐
	Endocarditis ■
	Coronary Obstruction ☐
	Re-Hosp or Prolonged Hosp of Index Hosp for Symptoms of Cardiac or Valve-related Decompensation ☐
	Hemolysis ☐
	Pericarditis ☐
AE ID Number:	
Comments:	
On dashboard?	Yes ☐
	No ☐
Date review completed:	

6.000 19MAR2013 Draft 1.0 PROD SRM: All Forms

Form: CEC Rehospitalization/Prolonged Hospitalization

CEC form number:	
Review:	No potential CV events identified ☐
	Potential CV event ☐
Check all that apply:	
Potential event:	Death ☐
	Stroke/TIA ☐
	Bleeding ☐
	Vascular Access Site & Access Related Complications ☐
	MI ☐
	Acute Kidney Injury ☐
	Prosthetic Valve Dysfunction ☐
	Conduction Disturbance requiring permanent pacemaker ☐
	Aortic Valve Re-Intervention ☐
	New or Worsening Mitral Valve Dysfunction ☐
	Endocarditis ☐
	Coronary Obstruction ■
	Re-Hosp or Prolonged Hosp of Index Hosp for Symptoms of Cardiac or Valve-related Decompensation ☐
	Hemolysis ☐
	Pericarditis ☐
AE ID Number:	
Comments:	
On dashboard?	Yes ☐
	No ☐
Date review completed:	

6.000 19MAR2013 Draft 1.0 PROD SRM: All Forms

Form: CEC Rehospitalization/Prolonged Hospitalization

CEC form number:	
Review:	No potential CV events identified ☐
	Potential CV event ☐
Check all that apply:	
Potential event:	Death ☐
	Stroke/TIA ☐
	Bleeding ☐
	Vascular Access Site & Access Related Complications ☐
	MI ☐
	Acute Kidney Injury ☐
	Prosthetic Valve Dysfunction ☐
	Conduction Disturbance requiring permanent pacemaker ☐
	Aortic Valve Re-Intervention ☐
	New or Worsening Mitral Valve Dysfunction ☐
	Endocarditis ☐
	Coronary Obstruction ☐
	Re-Hosp or Prolonged Hosp of Index Hosp for Symptoms of Cardiac or Valve-related Decompensation ■
	Hemolysis ☐
	Pericarditis ☐
AE ID Number:	
Comments:	
On dashboard?	Yes ☐
	No ☐
Date review completed:	

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Form: CEC Rehospitalization/Prolonged Hospitalization

CEC form number:	
Review:	No potential CV events identified ☐ Potential CV event ☐
Check all that apply:	
Potential event:	Death ☐ Stroke/TIA ☐ Bleeding ☐ Vascular Access Site & Access Related Complications ☐ MI ☐ Acute Kidney Injury ☐ Prosthetic Valve Dysfunction ☐ Conduction Disturbance requiring permanent pacemaker ☐ Aortic Valve Re-Intervention ☐ New or Worsening Mitral Valve Dysfunction ☐ Endocarditis ☐ Coronary Obstruction ☐ Re-Hosp or Prolonged Hosp of Index Hosp for Symptoms of Cardiac or Valve-related Decompensation ☐ Hemolysis ■ Pericarditis ☐
AE ID Number:	
Comments:	
On dashboard?	Yes ☐ No ☐
Date review completed:	

6.000 19MAR2013 Draft 1.0 PROD SRM: All Forms

Form: CEC Rehospitalization/Prolonged Hospitalization

CEC form number:	
Review:	No potential CV events identified ☐ Potential CV event ☐
Check all that apply:	
Potential event:	Death ☐ Stroke/TIA ☐ Bleeding ☐ Vascular Access Site & Access Related Complications ☐ MI ☐ Acute Kidney Injury ☐ Prosthetic Valve Dysfunction ☐ Conduction Disturbance requiring permanent pacemaker ☐ Aortic Valve Re-Intervention ☐ New or Worsening Mitral Valve Dysfunction ☐ Endocarditis ☐ Coronary Obstruction ☐ Re-Hosp or Prolonged Hosp of Index Hosp for Symptoms of Cardiac or Valve-related Decompensation ☐ Hemolysis ☐ Pericarditis ■
AE ID Number:	
Comments:	
On dashboard?	Yes ☐ No ☐
Date review completed:	

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Form: CEC Rhythm Disturbance requiring Permanent Pacemaker

CEC form number:	
Conduction Disturbance Requiring Permanent Pacemaker:	No event ☐ Event ☐ Insufficient information for determination ☐
If Event, adjudication of date:	
If Event, timing:	<= 30 days post index valve procedure ☐ > 30 days post index valve procedure ☐
If Event, check all that apply:	
Symptomatic first degree block:	
Second degree heart block:	
Complete heart block:	
Sick Sinus Syndrome:	
Asystole:	
LBBB:	
Other:	
If Other, specify:	
If Event, relationship to study valve or index procedure:	Not related ☐ Possibly related or related ☐ Unable to assess ☐ Not applicable ☐
If Possibly related or related, check all that apply:	
Valve:	
Procedure:	
Unable to determine:	
Comments:	
Phase II review:	Source adequate ☐ Source inadequate, best assessment made ☐ Not applicable ☐
Date review completed:	

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Form: CEC Stroke/TIA

CEC form number:	_____
Adjudication:	No event ☐ Event ☐ Insufficient information for determination ☐
If Event, adjudication of date:	_____
If Event, event type:	TIA ☐ Stroke ☐
If Stroke, stroke type:	Ischemic ☐ Hemorrhagic ☐ Undetermined ☐
Phase II review:	Source adequate ☐ Source inadequate, best assessment made ☐ Not applicable ☐
If TIA or Stroke, relationship of event to study valve or index procedure:	Not related ☐ Possibly related or related ☐ Unable to assess ☐ Not applicable ☐
If Possibly related or related, check all that apply:	
Valve:	_____
Procedure:	_____
Unable to determine:	_____
Phase II review:	Source adequate ☐ Source inadequate, best assessment made ☐ Not applicable ☐
If Stroke, severity:	Minor (non-disabling) ☐ Major (disabling) ☐ Unable to determine ☐

Rankin Score (nearest 90 day post event) per investigator opinion:	0 No symptoms at all ☐ 1 No significant disability despite symptoms ☐ 2 Slight disability ☐ 3 Moderate disability ☐ 4 Moderately severe disability ☐ 5 Severe disability ☐ 6 Dead ☐ Unable to determine ☐
Date of Rankin Score:	_____
Phase II review:	Source adequate ☐ Source inadequate, best assessment made ☐ Not applicable ☐
Comments:	_____
Date review completed:	_____

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Form: CEC Vascular Access Site/Access Related Complications

CEC form number:	_____
Event adjudication:	☐ No event ☐ Event ☐ Insufficient information for determination
If Event, adjudication of date:	_____
If Event, event type:	☐ Major vascular complication ☐ Minor vascular complication ☐ Sternal wound infection ☐ Other access site infection
If Major vascular complication, complication type:	☐ Thoracic aortic dissection ☐ Other access site or access-related vasc. injury ☐ Distal embolization ☐ Aortic root injury
If Minor vascular complication, complication type:	☐ Other access site or access-related vasc. injury ☐ Distal embolization ☐ Failure of percutaneous access site closure
If Other access site infection, select type:	☐ Groin ☐ Other
If Other, specify:	_____
If Aortic root injury, type:	☐ Rupture ☐ Perforation ☐ Dissection
If Aortic root injury, timing:	☐ During pre-implant balloon AO valvuloplasty ☐ During transcatheter valve implant ☐ Other
If Other, specify:	_____
If Event, relationship to study valve or index procedure:	☐ Not related ☐ Possibly related or related ☐ Unable to assess ☐ Not applicable
If Possibly related or related, check all that apply:	

Valve:	
Procedure:	
Unable to determine:	
Comments:	
Phase II review:	Source adequate ☐ Source inadequate, best assessment made ☐ Not applicable ☐
Date review completed:	

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Form: Subject ID

Please enter the Subject's Initials:	
Subject ID:	
Subject Status:	

Medications:

- [ ] None
- [ ] ACE inhibitor - Benazepril (Lotensin)
- [ ] ACE inhibitor - Captopril (Capoten)
- [ ] ACE inhibitor - Enalapril (Vasotec)
- [ ] ACE inhibitor - Fosinopril (Monopril)
- [ ] ACE inhibitor - Lisinopril (Prinivil/Zestril)
- [ ] ACE inhibitor - Moexipril (Univasc)
- [ ] ACE inhibitor - Perindopril (Aceon)
- [ ] ACE inhibitor - Quinapril (Accupril)
- [ ] ACE inhibitor - Trandolapril (Mavik)
- [ ] ACE inhibitor - Ramipril (Altace)
- [ ] ACE inhibitor - Other
- [ ] Alpha-1 Receptor Blocker - Doxazosin (Cardura)
- [ ] Alpha-1 Receptor Blocker - Other
- [ ] Angiotensin II Receptor Blocker (ARB) - Candesartan (Atacand)
- [ ] Angiotensin II Receptor Blocker (ARB) - Eprosartan (Teveten)
- [ ] Angiotensin II Receptor Blocker (ARB) - Irbesartan (Avapro)
- [ ] Angiotensin II Receptor Blocker (ARB) - Losartan (Cozaar)
- [ ] Angiotensin II Receptor Blocker (ARB) - Telmisartan (Micardis)
- [ ] Angiotensin II Receptor Blocker (ARB) - Valsartan (Diovan)
- [ ] Angiotensin II Receptor Blocker (ARB) - Other
- [ ] Antiarrhythmic - Adenosine
- [ ] Antiarrhythmic - Amiodarone (Cordarone)
- [ ] Antiarrhythmic - Disopyramide (Norpace/Rythmodan)

- [ ] Antiarrhythmic - Flecainide (Tambocor)
- [ ] Antiarrhythmic - Ibutilide (Corvert)
- [ ] Antiarrhythmic - Lidocaine (Xylocaine/Xylocard)
- [ ] Antiarrhythmic - Mexiletine (Mexitil)
- [ ] Antiarrhythmic - Phenytoin (Dilantin)
- [ ] Antiarrhythmic - Procainamide (Pronestyl/Procan/Procanbid)
- [ ] Antiarrhythmic - Propafenone (Rythmol)
- [ ] Antiarrhythmic - Quinidine gluconate (Quinidex)
- [ ] Antiarrhythmic - Other
- [ ] Antibiotics
- [ ] Anti-Cholesterol - ezetimibe (Vytorin/Zetia)
- [ ] Anti-Cholesterol - fenofibrate (Tricor/Trilipix/Lipofen)
- [ ] Anti-Cholesterol - Niacin (Niaspan)
- [ ] Anti-Cholesterol - Other
- [ ] Anticoagulant - Coumadin (Warfarin)
- [ ] Anticoagulant - Enoxaparin (Lovenox)
- [ ] Anticoagulant - Fragmin (Dalteparin)
- [ ] Anticoagulant - Heparin (Heparin)
- [ ] Anticoagulant - Pradaxa (Dabigatran)
- [ ] Anticoagulant - Other
- [ ] Antiplatelet - Acetylsalicylic acid (Aspirin/ASA)
- [ ] Antiplatelet - Clopidogrel (Plavix)
- [ ] Antiplatelet - Dipyridamole (Persantine)
- [ ] Antiplatelet - Ticlopidine (Ticlid)
- [ ] Antiplatelet - Tirofiban (Aggrastat)

- [ ] Antiplatelet - Other
- [ ] Antithrombolytic - Alteplase (Activase)
- [ ] Antithrombolytic - ATryn
- [ ] Antithrombolytic - Innohep (Tinzaparin)
- [ ] Antithrombolytic - Reteplase (Retavase)
- [ ] Antithrombolytic - Streptokinase (Streptase)
- [ ] Antithrombolytic - Urokinase (Abbokinase)
- [ ] Antithrombolytic - Other
- [ ] Beta Blocker - Acebutolol (Sectral)
- [ ] Beta Blocker - Betaxolol (Kerlone)
- [ ] Beta Blocker - Bisoprolol (Zebeta)
- [ ] Beta Blocker - Bisoprolol + hydrochlorothiazide (Ziac)
- [ ] Beta Blocker - Carvedilol (Coreg/Dilatrend/Carloc)
- [ ] Beta Blocker - Labetalol (Normodyne/Trandate)
- [ ] Beta Blocker - Metoprolol (Lopressor/Toprol XL)
- [ ] Beta Blocker - Nadolol (Corgard)
- [ ] Beta Blocker - Propranolol (Inderal)
- [ ] Beta Blocker - Sotalol (Betapace)
- [ ] Beta Blocker - Timolol (Blocadren)
- [ ] Beta Blocker- Atenolol (Tenormin)
- [ ] Beta Blocker - Other
- [ ] Ca Channel Blocker - Amlodipine (Norvasc)
- [ ] Ca Channel Blocker - Amlodipine + Benazepril (Lotrel)
- [ ] Ca Channel Blocker - Bepridil (Vascor)
- [ ] Ca Channel Blocker - Diltiazem (Cardizem/Tiazac)

- [ ] Ca Channel Blocker - Felodipine (Plendil)
- [ ] Ca Channel Blocker - Nifedipine (Adalat/Procardia)
- [ ] Ca Channel Blocker - Nimodipine (Nimotop)
- [ ] Ca Channel Blocker - Nisoldipine (Sular)
- [ ] Ca Channel Blocker - Verapamil (Calan/Isoptin/Verelan)
- [ ] Ca Channel Blocker - Other
- [ ] Digoxin - (Digitoxin/Lanoxin)
- [ ] Digoxin - Other
- [ ] Diuretic - Bumetanide (Bumex)
- [ ] Diuretic - Hydrochlorothiazide (Hydrodiuril/Esidrix)
- [ ] Diuretic - Lasix (furosemide)
- [ ] Diuretic - metolazone (Zaroxolyn/Zytanix/Cadila)
- [ ] Diuretic - Spironolactone (Aldactone/Aldactazide)
- [ ] Diuretic - Other
- [ ] Heparin Antagonist - Protamine (Protamine)
- [ ] Heparin Antagonist - Other
- [ ] Immunosuppressive Therapy
- [ ] Nitrate/Vasodilator - Hydralazine (Apresoline)
- [ ] Nitrate/Vasodilator - Isosorbide (Isordil)
- [ ] Nitrate/Vasodilator - Minoxidil (Minoxidil)
- [ ] Nitrate/Vasodilator - Nesiritide (Natrecor)
- [ ] Nitrate/Vasodilator - Nitroglycerin (Nitro-Dur/Nitrostat)
- [ ] Nitrate/Vasodilator - Other
- [ ] Renin Inhibitor - Aliskiren (Rasilez)
- [ ] Renin Inhibitor - Other
- [ ] Statin - Atorvastatin (Lipitor)

	Statin - Fluvastatin(Lescol/Canef/Vastin) ☐
	Statin - Lovastatin (Mevacor) ☐
	Statin - Rosuvastatin (Crestor) ☐
	Statin - Simvastatin (Zocor/Simlup/Simcard/Simvacor) ☐
	Statin - Other ☐
	Vasodilator - Sildenafil (Viagra) ☐
	Vasodilator - Tadalafil (Cialis) ☐
	Vasodilator - Other ☐
Other, specify:	
Start Date:	
End Date:	
Ongoing:	

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Form: Reconsent Log

Indicate if Subject was reconsented:	Yes ☐ No ☐
If No, reason:	Subject refused reconsent ☐ Subject exited study before reconsent ☐
If Yes, Date Subject was reconsented:	_____
If Yes, protocol version reconsented to:	3.0 JAN 2012 ☐ 3.5 APR 2012 ☐ 4.0 AUG 2012 ☐
	4.5 June 2013 ☐

Appendix O: Study Device IFU's

Edwards Transfemoral Balloon Catheter

Instructions for Use

CAUTION: Investigational device. Limited by Federal (or United States) law to investigational use

1.0 Device Description

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

The inflation parameters are as follows:

Table 1: Inflation Parameters

Model	Nominal		
	Balloon Diameter	Inflation Volume	Inflation Pressure
9350BC20	20 mm	16 mL	4 atm (405 kPa)
9350BC23	23 mm	21 mL	4 atm (405 kPa)
9350BC25	25 mm	26 mL	4 atm (405 kPa)

Edwards Transfemoral Balloon Catheter

Black dots indicate position of radiopaque marker bands.

1 – Balloon Inflation Port
2 – Guidewire Lumen Port

Device compatibility specifications are as follows:

Table 2: Device Compatibility

Model	Max. Guidewire Diameter	Min. Edwards Expandable Sheath Set Compatibility
9350BC20	0.035" (0.89 mm)	14 F
9350BC23	0.035" (0.89 mm)	14 F
9350BC25	0.035" (0.89 mm)	16 F

NOTE: For proper volume sizing, the balloon catheter should be used with the inflation device provided by Edwards Lifesciences.

2.0 Indications

The Edwards Transfemoral balloon catheter is indicated for valvuloplasty of a stenotic cardiac valve prior to implantation of the Edwards Transcatheter Heart Valve.

3.0 Contraindications

- Other than standard risks associated with insertion of a cardiovascular catheter, there are no known contraindications for valvuloplasty. The patient's medical condition could affect the successful use of this catheter.

4.0 Warnings

- The device is designed, intended, and distributed for single use only. **Do not resterilize or reuse the device**. There are no data to support the sterility, nonpyrogenicity, and functionality of the device after reprocessing.
- Do not mishandle the balloon catheter or use it if the packaging or any components are not sterile, have been opened or are damaged (i.e. kinked or stretched), or the expiration date has elapsed.

5.0 Precautions

- For special considerations associated with the use of this device prior to transcatheter heart valve implantation, refer to the bioprosthesis instructions for use (IFU).
- Use only appropriate balloon inflation medium. Do not use air or gaseous medium to inflate the balloon.
- The device is not intended for post-dilatation of deployed transcatheter heart valves.
- While exposed within the body, device advancement and retrieval should not be done without the aid of fluoroscopy. Do not advance or retract the device unless the balloon is fully deflated under vacuum.

6.0 Potential Adverse Events

Complications associated with standard catheterization, balloon valvuloplasty, and the use of angiography include, but are not limited to, allergic reaction to anesthesia or to contrast media, injury including perforation or dissection of vessels, thrombus formation, plaque dislodgement and embolization that may result in myocardial infarction, stroke, distal peripheral occlusion and/or death, arrhythmia development, cardiac perforation, conduction system injury, hematoma, infundibulum injury, annular tear or rupture and/or valve leaflet dehiscence, severe valve insufficiency, valve restenosis, valve damage, balloon rupture, balloon separation following balloon rupture, valvular tearing or trauma, thromboembolic events, and infection. Reference the Edwards SAPIEN

3 Transcatheter Heart Valve with the Commander Delivery System Instructions for Use for a full list of potential adverse events.

7.0 Directions for Use

Step	Procedure
1	Prepare vascular access site for catheter insertion and position guidewire using standard techniques.
2	Flush the balloon catheter with heparinized saline. Attach a high pressure 3-way stopcock to the balloon inflation port.
3	Prepare a 20 mLor larger syringe with diluted contrast solution (15:85 contrast to hepranized saline) and attach to the stopcock.
4	Completely fill the inflation device provided by Edwards with diluted contrast solution and attach in the locked position to the stopcock; close the stopcock to the inflation device.
5	Slowly pull vacuum with the syringe repeatedly to remove air, leaving neutral pressure in the system.
6	Close the stopcock to the balloon catheter. Gradually remove contrast medium into the syringe to achieve the appropriate volume (as specified in Table 1: Inflation Parameters) by rotating the knob of the inflation device. Close the stopcock to the syringe and remove the syringe.
7	Advance the balloon catheter over the guidewire, through a sheath, across the aortic valve, and position the balloon markers at the intended site.
8	Fully inflate the balloon with the inflation Device.
9	Completely deflate the balloon, and gently withdraw the balloon catheter and remove from the sheath.

8.0 How Supplied

STERILE: The balloon catheter is supplied sterilized by ethylene oxide.

9.0 Storage

Store in a cool, dry place.

10.0 Device Disposal

Used devices may be handled and disposed of in the same manner as hospital waste and biohazardous materials. There are no special risks related to the disposal of these devices.

Vendor: Do Not Print This Page
For Internal Edwards Lifesciences Use Only

Edwards Lifesciences IRVINE, CA 92614		Title: **IFU, 9350BAV, 20/23/25 mm, IDE**	
Part No.: 157227001 (ECR106767)	Rev: A	Graphics: Heather Bradley	Date:
Rel ID:	Pg.		
First Proofer:	Date:	Second Proofer:	Date:
Full Proof ☒	Proofed Against Redline ☒	Full Proof ☒	Proofed Against Redline ☒

Edwards Lifesciences

Edwards SAPIEN 3 System Transapical and Transaortic

Instructions for Use

CAUTION: Investigational device. Limited by Federal (or United States) law to investigational use.

Implantation of the transcatheter heart valve should be performed only by physicians who have received Edwards Lifesciences training. Implanting physician should be experienced in balloon aortic valvuloplasty.

Product Name	23 mm	26 mm	29 mm
	Model/REF		
Edwards SAPIEN 3 Transcatheter Heart Valve	9600TFX (23 mm)	9600TFX (26 mm)	9600TFX (29 mm)
Edwards Certitude Delivery System	9620TA23	9620TA26	9620TA29
Edwards Certitude Introducer Sheath Set	9620IS18 (18F)		9620IS21 (21F)
Crimper	9600CR		
Ascendra Balloon Aortic Valvuloplasty Catheter	9100BAVC (20 mm)		

1. Device Description

- **Edwards SAPIEN 3 Transcatheter Heart Valve (Figure 1)**

The Edwards SAPIEN 3 transcatheter heart valve (THV) is comprised of a balloon-expandable, radiopaque, cobalt- chromium alloy frame, trileaflet bovine pericardial tissue valve, and polyethylene terephthalate (PET) internal fabric skirt, and a PET outer skirt. The valve is treated according to the Edwards ThermaFix process, and is packaged and terminally sterilized in glutaraldehyde.

- **Crimper (Figure 2)**

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

The THV is intended to be implanted in a native annulus size range comparable to the following transesophageal echocardiography (TEE) measurements:

Native Valve Annulus Size	THV Size
18-22 mm	23 mm
21-25 mm	26 mm
24-28 mm	29 mm

- **Edwards Certitude Delivery System (Figures 3a, 3b, & 3c)**

The Edwards Certitude delivery system includes a handle with a Flex Wheel for articulation of the Balloon Catheter and a Loader. The loader allows for the delivery of the crimped THV through the hemostasis valves of the sheath. Three radiopaque indicators on the catheter shaft define the position on the balloon where the THV should be crimped and also provide visualization of the balloon. The THV is crimped between the two radiopaque shoulders on the distal and proximal ends of the balloon. The central radiopaque marker in the balloon is provided to help with valve positioning. An inflation and guidewire hub is housed in the handle assembly. A 2-piece crimp stopper is also packaged with the delivery system for use with the crimper (see 'Crimper' section for information on these components). The Qualcrimp crimping accessory (packaged with the Edwards Certitude delivery system) is used during crimping of the THV.

- **Edwards Certitude Introducer Sheath Set (Figure 4)**

The Edwards Certitude introducer sheath set is intended for use with the Edwards Certitude delivery system. The introducer sheath has a radiopaque marker for visualization of the sheath tip and non-radiopaque depth markings on the distal end of the body of the sheath. The proximal end of the introducer sheath includes a flush tube and three hemostasis valves. An introducer is supplied with the introducer sheath. The entire introducer is radiopaque.

- **Ascendra Balloon Aortic Valvuloplasty Catheter**

Refer to Ascendra model 9100BAVC instructions for use.

- **Inflation Devices**

An inflation device with a locking mechanism is used during native valve predilation and THV deployment.

NOTE: For proper volume sizing, the Certitude Delivery System and the Ascendra Balloon Aortic Valvuloplasty Catheter should be used with the inflation devices provided by Edwards Lifesciences.

2. Indications

The Edwards SAPIEN 3 THV, Edwards Certitude delivery system and accessories are indicated for use in high risk patients with severe, symptomatic, calcific aortic stenosis with an STS score ≥ 8 or in patients with a surgical mortality or major morbidity ≥ 50% as evaluated by a Heart Team.

3. Contraindications

Use of the Edwards SAPIEN 3 THV with the Edwards Certitude delivery system and accessories is contraindicated in patients with:

- Evidence of intracardiac mass, thrombus, vegetation, active infection, or endocarditis;
- Inability to tolerate anticoagulation/antiplatelet therapy;
- Excessive calcification of aorta at access site (for transaortic approach only)

  Refer to clinical protocol for a full list of study exclusion criteria.

4. Warnings

- The devices are designed, intended, and distributed for single use

only. **Do not resterilize or reuse the devices.** There are no data to support the sterility, nonpyrogenicity, and functionality of the devices after reprocessing.

- Correct sizing of the THV is essential to help prevent paravalvular leak, migration, and/or annular rupture.
- Accelerated deterioration of the THV may occur in patients with altered calcium metabolism.
- Long-term durability has not been established for the THV. Medical follow-up is advised so that THV-related complications can be diagnosed and properly managed.
- The performance of the THV placed into a previously implanted THV has not been evaluated. In the event of a failing THV, conversion to conventional open heart surgery may be required.
- It is recommended that all prosthetic heart valve recipients be prophylactically treated for endocarditis to minimize the possibility of prosthetic valve infection, as described in the protocol.
- Bioprosthetic valve recipients should be maintained on anticoagulant/antiplatelet therapy, except when contraindicated, as determined by their physician, as described in the protocol. This device has not been tested for use without anticoagulation.
- Observation of the pacing lead throughout the procedure is essential to avoid the potential risk of pacing lead perforation.
- Do not add or apply antibiotics to the storage solution, rinse solutions, or to the THV.
- The procedure should be conducted under fluoroscopic guidance. Some fluoroscopically guided procedures are associated with a risk of radiation injury to the skin. These injuries may be painful, disfiguring, and long-lasting.
- Care should be exercised in patients with hypersensitivities to cobalt, nickel, chromium, molybdenum, titanium, manganese, silicon, and/or polymeric materials.

5. Precautions

5.1 Precautions Prior to Use

- Do not use the THV if the tamper evident seal is broken, the storage solution does not completely cover the THV, the temperature indicator has been activated, or the THV is damaged.
- Do not use the delivery system and accessory devices if the packaging sterile barriers and any components have been opened or damaged, cannot be flushed, or the expiration date has elapsed.

5.2 Precautions During Use

- Do not expose the THV to solutions other than the storage solution in which it was shipped and the sterile physiological rinsing and irrigation solutions specified in section 7.2.2.
- Do not allow the leaflet tissue of the THV to become dry. Continuous submersion or irrigation of the THV is required.
- Glutaraldehyde may cause irritation of the skin, eyes, nose and throat. Avoid prolonged or repeated exposure to, or breathing of, the solution. Use only with adequate ventilation. If skin contact occurs, immediately flush the affected area with water; in the event of contact with eyes, seek immediate medical attention. For more information about glutaraldehyde exposure, refer to the Material Safety Data Sheet available from Edwards Lifesciences.
- Do not mishandle the valve tissue during rinsing, mounting, or crimping. If the THV is damaged, it must be replaced.
- Care should be used when handling the devices. Damage may result from kinking or stretching the devices.
- To maintain proper valve leaflet coaptation, do not overinflate the deployment balloon.

5.3 Precautions After Implantation

- Appropriate antibiotic prophylaxis is recommended in patients at risk for prosthetic valve infection and endocarditis.
- THV recipients should be maintained on antiplatelet/anticoagulant therapy, as determined by their physician.

6. Potential Adverse Events

Complications associated with standard cardiac catheterization, balloon valvuloplasty (BAV), and the use of anesthesia include but are not limited to:

- Acute myocardial infarction
- Allergic reaction to antithrombotic therapy or contrast medium or anesthesia
- Anemia
- Aneurysm
- Angina
- Aortic valve thrombosis/occlusion
- Arrhythmias including ventricular fibrillation (VF) and ventricular tachycardia (VT)
- Arteriovenous fistula
- Arthralgia
- Bleeding/bruising
- Cardiogenic shock/pulmonary edema
- Cerebrovascular accident
- Death
- Dissection: aortic or other vessels
- Emboli, distal (air, tissue or thrombotic emboli)
- GI symptoms
- Headache
- Heart failure
- Hematologic dyscrasia
- Hematoma
- Hemorrhage
- Hemorrhagic stroke
- Hepatic enzyme changes
- Hypotension/Hypertension
- Infection and/or pain at access site
- Infection, fever
- Infection, systemic/sepsis
- Ischemia, myocardial
- Limb ischemia
- Myalgia
- Perforation or rupture of cardiac structure
- Perforation or rupture of vessel
- Pericardial effusion/cardiac tamponade
- Peripheral nerve injury/paralysis
- Postoperative encephalopathy
- Pseudoaneurysm
- Renal failure
- Respiratory failure
- Shock
- Silent cerebral ischemia
- Stroke
- Syncope
- Transient ischemic attack (TIA)
- 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 aortic valve replacement and bioprosthetic heart valves include, but may not be limited to, the following:

- Aortic annulus dissection/rupture/trauma
- AV block
- Aortic valve insufficiency
- Injury to aortic and/or mitral valve
- Acute coronary occlusion
- Allergic/immunologic reaction to the implant
- Atrial fibrillation/Atrial flutter
- Blood loss requiring blood transfusion
- Cardiac arrest
- Cognitive impairment
- Conduction disturbance including AV block requiring pacemaker
- Device malfunction requiring intervention/surgery
- Endocarditis
- Hemolysis
- Mediastinitis
- Mediastinal bleeding
- Mitral regurgitation
- Peri-/Paravalvular leak

7. Directions for Use

7.1 Required Equipment

- Cardiac catheterization/hybrid OR suite
- Standard cardiac catheterization lab equipment and supplies, and access to standard heart valve operating room equipment and supplies
- Fluoroscopy (fixed, mobile or semi-mobile fluoroscopy systems appropriate for use in percutaneous coronary interventions)
- Transesophageal or transthoracic echocardiography system
- 18 gauge Seldinger needle (for transaortic)
- 145 cm x 0.035" (0.89 mm) soft guidewire
- 180 cm or 260 cm x 0.035" (0.89 mm) & Exchange length 0.035" (0.89 mm) extra-stiff guidewires
- Pacemaker and pacing leads
- Inflation devices provided by Edwards Lifesciences (x2)
- Edwards Transapical/Transaortic System
    - Edwards SAPIEN 3 THV
    - Edwards Certitude delivery system
    - Edwards Certitude introducer sheath set
    - 20 mm Ascendra balloon aortic valvuloplasty catheter (BAVC) or equivalent
    - Crimper
- Sterile rinsing bowls; sterile physiological saline solution; sterile heparinized saline solution; radiopaque contrast medium (15:85 medium to saline dilution)
- Sterile table for THV and accessories preparation
- 20 mL or larger luer lock syringe
- 50 mL or larger luer lock syringe
- High-pressure 3-way stopcock

7.2 THV Handling and Preparation

Follow sterile technique during device preparation and implantation.

7.2.1 THV Rinsing Procedure

The THV is packaged sterile in a plastic jar with a screw-cap closure and seal. Before opening, carefully examine the jar for evidence of damage (e.g., a cracked jar or lid, leakage, or broken or missing seals).

CAUTION: If the container is found to be damaged, leaking, without adequate sterilant, or missing intact seals, the THV must not be used for implantation.

Step	Procedure
1	Remove the THV/holder assembly from the jar and inspect for any signs of damage. Verify that the serial number on the THV holder and the jar lid match. Record the serial number in the patient information documents.
2	Rinse the THV as follows: **Gently** swirl the THV/holder assembly in 500 mL physiologic saline solution for a minimum of 1 minute. Repeat this process in the second bowl for a minimum of 1 minute. Leave the THV in the second bowl until needed. **CAUTION: Do not allow the THV to come in contact with the rinse bowl or the identification tag. No other objects should be placed in the rinse bowls.**

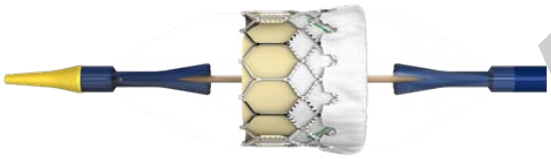
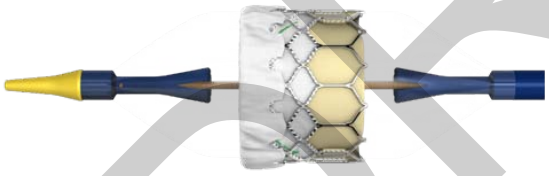
7.2.2 Prepare the System

Step	Procedure
1	Visually inspect all components for damage. Ensure the system is fully unflexed.
2	Prime and flush the introducer and sheath with heparinized saline. Hydrate the length of the introducer and sheath.
3	Advance the introducer fully into the sheath housing.
4	Unscrew the loader cap from the loader and flush the loader cap with heparinized saline.
5	Place the loader cap onto the delivery system with the inside of the cap oriented towards the nose cone.
6	Connect the extension tubing to the delivery system.
7	Partially fill a 50 mL or larger syringe with diluted contrast medium, and connect to the extension tubing.
8	Fill the inflation device with the volume of diluted contrast media indicated in step 11, and connect to the extension tubing.
9	De-air the delivery system and ensure the inflation device is filled with the volume of contrast media indicated in step 11. Leave zero-pressure in the system.
10	Remove fluid from the delivery system balloon to achieve a waist on the balloon by putting slight negative pressure with the inflation device. Ensure the device is locked while maintaining the waist.
11	While maintaining the waist, adjust the inflation device to the inflation volume required to deploy the THV, per the following:

Delivery System	THV	Inflation Volume
Model 9620TA23	23 mm	17 mL
Model 9620TA26	26 mm	23 mL
Model 9620TA29	29 mm	30 mL

12	Remove the 50 mL or larger syringe. **CAUTION: Maintain the inflation device in the locked position until THV deployment.**

7.2.3 Mount and Crimp the THV onto the Delivery System

Step	Procedure
1	Completely submerge the Qualcrimp crimping accessory in a bowl of 100 mL physiological saline solution. Gently compress until fully saturated. Swirl for a minimum of 1 minute. Repeat this process in a second bowl.
2	Rotate the crimper until the aperture is fully opened. Attach the 2-piece Crimp Stopper to the crimper.
3	Remove the THV from the holder and remove the ID tag.
4	Partially crimp the THV in the crimper until it snugly fits inside the Qualcrimp crimping accessory.
5	Place the Qualcrimp crimping accessory over the THV.
6	The orientation of the THV on the delivery system is described below: **Antegrade Transapical Approach:** Inflow (outer skirt) end of the THV towards the **proximal end** of the delivery system.  **Retrograde Transaortic Approach** Inflow (outer skirt) end of the THV towards the **distal end** of the delivery system. 
7	Place the THV and Qualcrimp crimping accessory in the crimper. Insert the delivery system coaxially into the THV.
8	Crimp the THV between the two internal shoulders of the delivery system until it reaches the Qualcrimp stop.
9	Remove the Qualcrimp crimping accessory from the THV/balloon assembly and Qualcrimp stop from the Crimp Stopper, leaving the Final Stop in place. **Note: Ensure that the THV remains centered and coaxial within the two internal shoulders.**
10	Place the THV/balloon assembly back in the crimper aperture, fully crimp the THV until it reaches the Final Stop and hold for 5 seconds.
11	Repeat the full crimp of the THV two times for a total of 3 crimps.
12	Flush the loader with heparinized saline. Immediately advance the loader over the THV until the tapered tip of the delivery system is exposed and the THV is centered in the constrained section of the loader. **CAUTION: To prevent possible leaflet damage, the THV should not remain in the loader over 15 minutes.**
13	Attach the loader cap to the loader and flush through the flush port on the loader. Remove the stylet and flush the guidewire lumen of the delivery system. **CAUTION: Keep the THV hydrated until ready for implantation.** **CAUTION: The physician must verify correct orientation of the THV prior to its implantation; the inflow (outer skirt) end of the THV should be oriented proximally for the antegrade transapical approach and distally for the retrograde transaortic approach.**

7.3 Native Valve Predilation and THV Delivery

Native valve predilation and THV delivery should be performed under general anesthesia with hemodynamic monitoring in a catheterization lab/hybrid operating room with fluoroscopic and echocardiographic imaging capabilities.

The following table shows the minimum required distances from the native valve annulus to the distal tip of the Edwards Certitude sheath to allow the Edwards Certitude delivery system balloon to inflate properly during THV deployment. **These distances do not include sheath insertion depth**, which should be considered during the transaortic approach when selecting the access site on the ascending aorta.

Delivery System	THV	Minimum Required Distance From Sheath Tip to Annulus
Model 9620TA23	23 mm	3.5 cm
Model 9620TA26	26 mm	3.5 cm
Model 9620TA29	29 mm	4.0 cm

Administer heparin to maintain the ACT at ≥ 250 sec.

CAUTION: Use of excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored.

7.3.1 Baseline Parameters

Step	Procedure
1	Advance a 5F (1.67 mm) or 6F (2.0 mm) pigtail catheter into the descending aorta and perform a supra-aortic angiogram with the projection of the native aortic valve perpendicular to the view.
2	Evaluate the distances of the right and left coronary ostia from the aortic annulus in relation to the THV frame height.

7.3.2 Access and Native Valve Predilation

CAUTION: Care should be taken to avoid damage to soft tissue, chordae, aorta, native leaflet or ventricular wall during insertion, positioning and removal of devices.

Transapical Access	
Step	**Procedure**
1	Access the apex through an anterior mini thoracotomy at the 5th or 6th intercostal space. Incise the pericardium to expose the apex of the left ventricle (LV).
2	Attach epicardial pacing leads to left ventricle or insert transvenous pacing leads and secure proximal ends of leads into pacemaker. Set the stimulation parameters, test rapid pacing.

Step	Procedure
3	Place a reinforced double purse string on the LV apex to access the left ventricle.
4	Gain aortic valve access through standard transapical techniques.
5	Insert the tip of the Edwards Certitude introducer sheath assembly or desired introducer sheath for the BAV through the apex of the LV and locate the sheath tip in the LV outflow tract immediately below the aortic valve; withdraw the introducer slowly, keeping the introducer sheath in place. Maintain guidewire position across the aortic valve.
Transaortic Access	
Step	**Procedure**
1	Access the ascending aorta using standard surgical technique (e.g. a partial J-sternotomy or right parasternal mini thoracotomy).
2	Place two reinforced purse string sutures at the intended access site in the ascending aorta. NOTE: The selected access site should be soft by digital palpation.
3	Introduce a pacemaker lead until its distal end is positioned in the right ventricle. Set the stimulation parameters and test pacing.
4	Gain aortic valve access through standard transaortic techniques.
5	Insert the Edwards Certitude introducer sheath, or desired introducer sheath for BAV, into the aorta to approximately 2 cm.

7.3.3 Native Valve Predilation

CAUTION: Care should be taken to avoid damage to soft tissue, chordae, aorta, native leaflet or ventricular wall during insertion, positioning and removal of devices.

Step	Procedure
1	Prepare the BAVC per its instructions for use.
2	Advance the prepared BAVC through the sheath over the guidewire, cross the aortic valve, and position the balloon.
3	Begin predilation: - Begin rapid pacing. Once arterial blood pressure has decreased to 50 mmHg or below, balloon inflation can commence. - Inflate the BAVC as per its instructions for use. - Completely deflate the balloon. Stop rapid pacing.
4	Remove the BAVC, leaving the guidewire in place in the descending aorta if using the transapical approach, or in the ventricle if using the transaortic approach. NOTE: If not using the Edwards Certitude introducer sheath for native valve predilation, remove the sheath used for the valvuloplasty and advance the Edwards Certitude introducer sheath set over the guidewire.

7.3.4 THV Delivery

CAUTION: Care should be taken to avoid damage to soft tissue, chordae, aorta, native leaflet or ventricular wall during insertion, positioning and removal of devices.

Step	Procedure
1	Confirm that the THV is oriented properly and the volume in the inflation device matches the volume indicated in Section 7.2.2, step 11.
2	Advance the THV/balloon assembly with the loader over the guidewire.
3	Engage loader into introducer sheath housing while maintaining a firm grip.
4	Tap on the introducer sheath housing to release air bubbles to the proximal end of the loader. Depress button valve on loader to aspirate the loader.
5	Advance the THV/balloon assembly through the sheath and position within the native aortic valve leaflets. If needed, rotate the flex wheel on the handle to articulate the THV/balloon assembly into position. **CAUTION: To prevent possible leaflet damage, the THV should not remain in the sheath for over 5 minutes.**
6	Ensure that the THV is correctly positioned between the two internal shoulders of the delivery system.
7	Begin THV deployment: - Unlock the inflation device. - Ensure hemodynamic stability is established and begin rapid pacing. Once arterial blood pressure has decreased to 50 mmHg or below, balloon inflation can commence. - Using a slow, controlled inflation, deploy the THV by inflating the balloon with the entire volume in the Inflation device, hold for 3 seconds and confirm that the barrel of the inflation device is empty to ensure complete inflation of the balloon. - Once the THV has been deployed, rapidly deflate the balloon catheter. - When the delivery system balloon has been completely deflated, turn off the pacemaker.
8	If articulation was used, return the delivery system to the straight position. Retract the delivery system and guidewire into the introducer sheath. Remove the loader and delivery system from the sheath. **CAUTION: Patient injury could occur if the delivery system is articulated or not deflated upon removal.**

7.4 Verification of THV Position and Measurements

Step	Procedure
1	Perform a supra-aortic angiogram to evaluate device performance and coronary patency.
2	Measure and record the transvalvular pressure gradients and assess valve competency.
3	Upon satisfactory deployment, remove all devices when the ACT level is appropriate (e.g., reaches < 150 sec).
4	Tie the purse string sutures in place and confirm hemostasis.

8. How Supplied

The THV is supplied sterile and non-pyrogenic, packaged in buffered glutaraldehyde, in a plastic jar to which a tamper evident seal has been applied. Each jar is shipped in a shelf box containing a temperature indicator to detect exposure of the THV to extreme temperature. The shelf box is enclosed in Styrofoam prior to shipping.

The Edwards Certitude delivery system, Edwards Certitude introducer sheath set, Ascendra balloon aortic valvuloplasty catheter and crimper are supplied pouched and sterilized by ethylene oxide.

8.1 Storage

The THV must be stored between 10 °C and 25 °C (50 °F and 77 °F). The delivery system and accessories should be stored in a cool, dry place.

9. MR Safety

Magnetic Resonance (MR) Conditional

Non-clinical testing has demonstrated that the THV (implant) is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 1.5 Tesla (T) or 3.0 Tesla (T).
- Spatial gradient field of 2500 Gauss/cm or less.
- Maximum whole body averaged specific absorption rate (WB-SAR) of 2.0 W/kg for 15 minutes of scanning.
- Normal mode operation, as defined in IEC 60601-2-33, Ed. 2.0, of the MR system.

In non-clinical testing and computer analysis using anatomically correct models of the human anatomy, the implant was determined to produce an estimated *in vivo* temperature rise of less than 2.3 °C for a WB-SAR of 2.0 W/kg for 15 minutes of MR scanning in a 1.5 T whole body coil from a GE Signa MR system. The estimate *in vivo* rise was less than 2.6 °C for a WB-SAR of 2.0 W/kg in a 3.0 T GE Signa HDxt 3T (software version 14\LX\MR) whole body cylindrical bore MR system. These calculations may overestimate the true *in vivo* rise, since the cooling effects of blood are not considered.

The image artifact extends as far as 10 mm from the implant for spin echo images and 30 mm for gradient echo images when scanned in non-clinical testing using a 3.0 T GE Signa HDx MR system (software version 14\LX\MR).

The implant has not been evaluated in MR systems other than 1.5 T or 3.0 T.

10. Patient Information

A patient registration form is included with each THV. After implantation, please complete all requested information. The serial number may be found on the package and on the identification tag attached to the THV. Return the original form to the Edwards Lifesciences address indicated on the form and provide the temporary identification card to the patient prior to discharge.

11. Recovered THV and Device Disposal

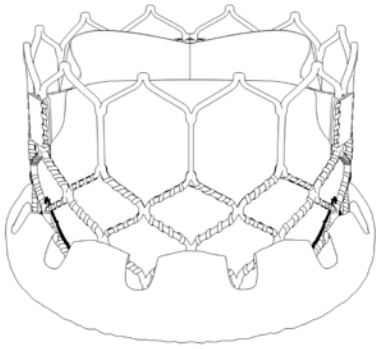
The explanted THV should be placed into a suitable histological fixative such as 10% formalin or 2% glutaraldehyde and returned to the company. Refrigeration is not necessary under these circumstances. Contact Edwards Lifesciences to request an Explant Kit.

The used devices may be disposed of in the same manner that the hospital waste and biohazardous materials are handled. There are no special or unusual risks related to the disposal of the devices.

This product is manufactured and sold under one or more of the following US patents: 5,411,552; 5,931,969; 6,210,957; 6,214,054; 6,547,827; 6,561,970; 6,899,704; 6,908,481; 7,214,344; 7,510,575; 7,530,253; and RE40570 and corresponding foreign patents. Additional patents are pending.

12. Figures

Figure 1. Edwards SAPIEN 3 Transcatheter Heart Valve



Valve Size	Height
23 mm	18 mm
26 mm	20 mm
29 mm	22.5 mm

Figure 2. Crimper and Crimp Stopper

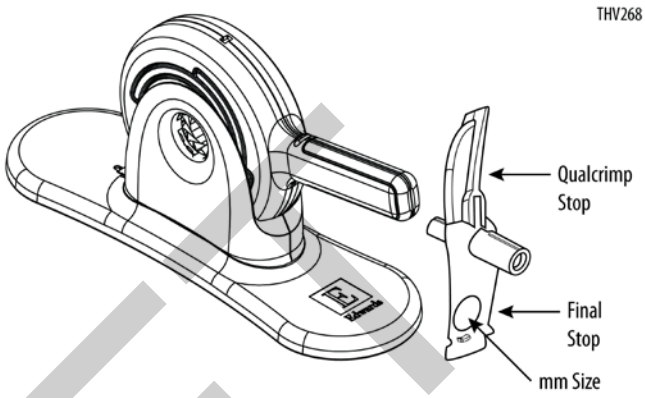


Figure 3a. Edwards Certitude Delivery System

Figure 3b. Qualcrimp Crimping Accessory

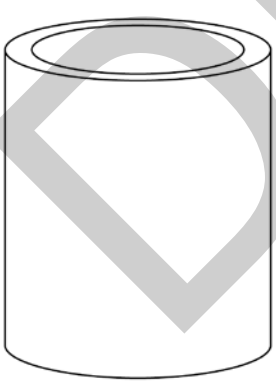
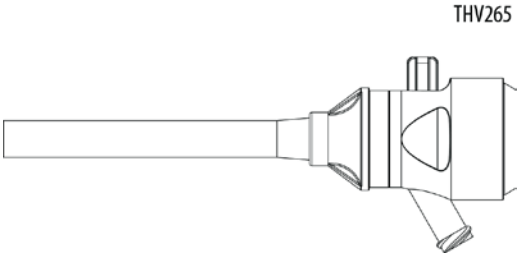
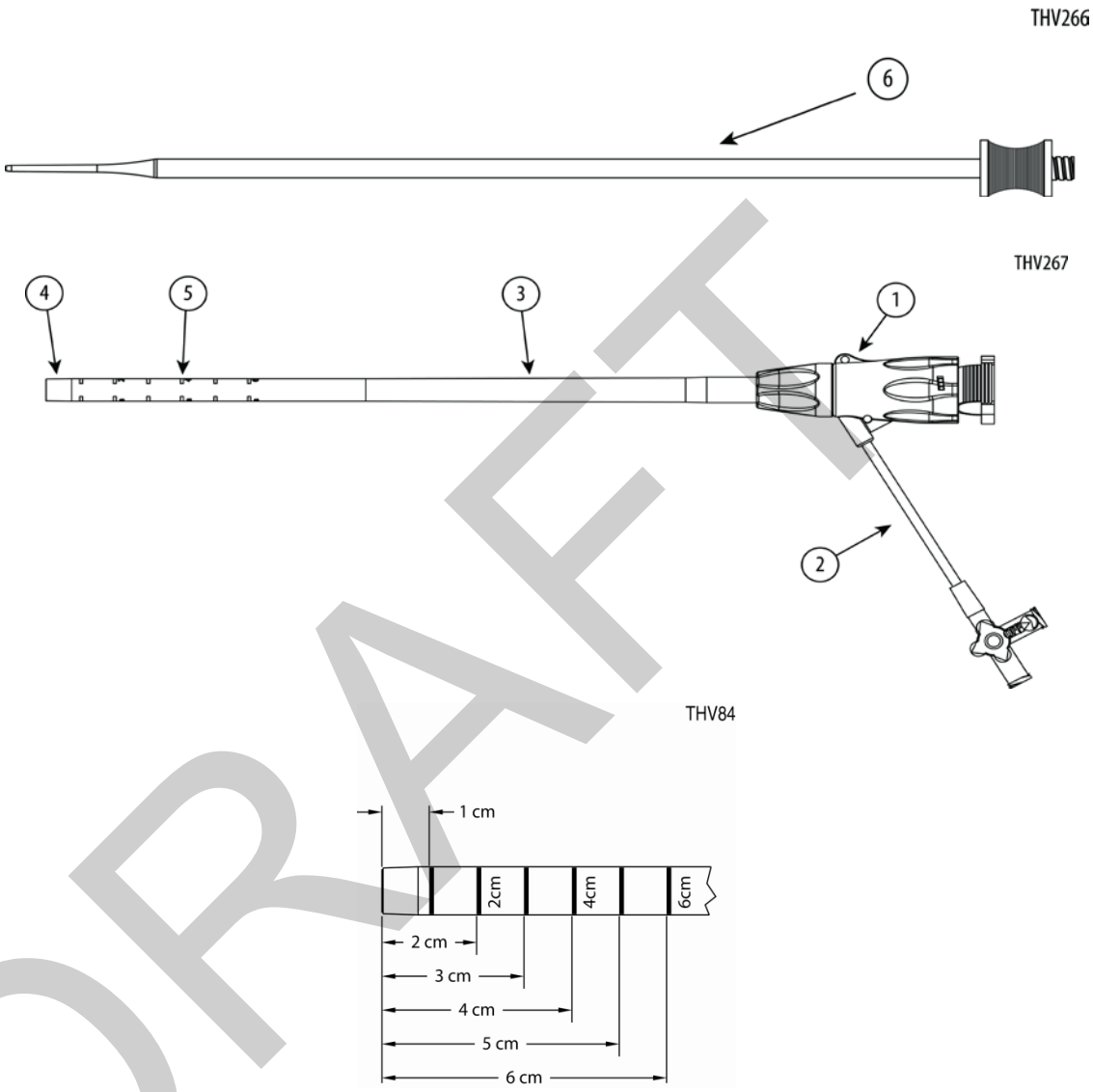


Figure 3c. Loader



1. Housing
2. Flush Tube with Stopcock
3. Sheath
4. Radiopaque Marker
5. Non-Radiopaque Depth Markers
6. Introducer (33 cm working length)

Figure 4. Edwards Certitude Introducer Sheath Set



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Edwards Lifesciences

Edwards SAPIEN 3 System –Transfemoral

Instructions for Use

CAUTION: Investigational device. Limited by Federal (or United States) law to investigational use

Implantation of transcatheter heart valves should be performed by physicians who have received Edwards Lifesciences training. The implanting physician should be experienced in balloon aortic valvuloplasty.

Product Name	23 mm	26 mm	29 mm
	Model/REF		
Edwards SAPIEN 3 Transcatheter Heart Valve	9600TFX (23 mm)	9600TFX (26 mm)	9600TFX (29 mm)
Edwards Commander Delivery System[1]	9610TF23	9610TF26	9610TF29
Edwards Expandable Introducer Sheath Set	9610ES14 or 916ES23		916ES23
Edwards Transfemoral Balloon Catheter	9350BC20	9350BC23	9350BC25
Crimper	9600CR		

[1] Includes a Loader, Qualcrimp Crimping Accessory and a 2-piece Crimp Stopper.

1.0 Device Description

- **Edwards SAPIEN 3 Transcatheter Heart Valve (Figure 1)**

The Edwards SAPIEN 3 transcatheter heart valve (THV) is comprised of a balloon-expandable, radiopaque, cobalt-chromium alloy frame, a trileaflet bovine pericardial tissue valve, a polyethylene terephthalate (PET) internal fabric skirt, and a PET outer skirt. The valve is treated according to the Edwards ThermaFix process, and is packaged and terminally sterilized in glutaraldehyde.

The THV is intended to be implanted in a native annulus size range comparable to the following transesophageal echocardiography (TEE) measurements:

Native Valve Annulus Size	THV Size
18-22 mm	23 mm
21-25 mm	26 mm
24-28 mm	29 mm

- **Edwards Commander Delivery System (Figures 2a and 2b)**

The Edwards Commander Delivery System (Figure 2b) consists of a balloon catheter for deployment of the THV, and a Flex Catheter to aid in valve alignment to the balloon, tracking, and positioning of the THV. The delivery system includes a nose cone to facilitate crossing of the native valve. The handle contains a wheel to control flexing of the Flex Catheter, and a Balloon Lock and Fine Adjustment Wheel to facilitate valve alignment and positioning of the valve within the native annulus. A stylet is included within the guidewire lumen of the delivery system. The Balloon Catheter has radiopaque Valve Alignment Markers defining the working length of the balloon. A central radiopaque marker (Valve Positioning Marker) in the balloon is provided to help with valve positioning. An Accurate Positioning Control (APC) Marker proximal to the balloon indicates the Flex Catheter position during deployment. The Qualcrimp crimping accessory (packaged with the Edwards Commander Delivery System) is used during crimping of the THV (Figure 2a).

The inflation parameters for THV deployment are:

Model	Nominal Balloon Diameter	Nominal Inflation Volume	Rated Burst Pressure (RBP)
9610TF23	23 mm	17 mL	7 atm (709 kPa)
9610TF26	26 mm	23 mL	7 atm (709 kPa)
9610TF29	29 mm	33 mL	7 atm (709 kPa)

- **Edwards Expandable Introducer Sheath Set**

Refer to Edwards Expandable Introducer Sheath Set instructions for use.

- **Edwards Transfemoral Balloon Catheter**

Refer to Edwards Transfemoral Balloon Catheter instructions for use.

- **Crimper (Figure 3)**

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

- **Inflation Devices**

An Inflation device with locking mechanism is used during native valve predilation and THV deployment.

Note: For proper volume sizing, the Commander delivery system and the Edwards transfemoral balloon catheter should be used with the inflation device provided by Edwards Lifesciences.

2.0 Indications

The Edwards SAPIEN 3 THV, Edwards Commander delivery system and accessories are indicated for use in patients with severe, symptomatic, calcific aortic stenosis with a STS score ≥8 or in patients with a surgical mortality or major morbidity ≥ 50% as evaluated by a Heart Team.

3.0 Contraindications

Use of the Edwards SAPIEN 3 THV with the Edwards Commander Delivery System and accessories is contraindicated in patients with:

- Evidence of intracardiac mass, thrombus, vegetation, active infection or endocarditis.
- Inability to tolerate anticoagulation/antiplatelet therapy.
- Femoro-iliac vessels < 5.5 mm for the 23 mm and the 26 mm system and < 6.0 mm for the 29 mm system.

Refer to the clinical protocol for a full list of study exclusion criteria.

4.0 Warnings

- The devices are designed, intended, and distributed for single use only. **Do not resterilize or reuse the devices.** There are no data to support the sterility, nonpyrogenicity, and functionality of the devices after reprocessing.
- Correct sizing of the THV is essential to help prevent paravalvular leak, migration, and/or annular rupture.
- Accelerated deterioration of the THV may occur in patients with an altered calcium metabolism.
- Long-term durability has not been established for the THV. Medical follow-up is advised so that THV-related complications can be diagnosed and properly managed.
- The performance of the THV placed into a previously implanted THV has not been evaluated. In the event of a failing THV, conversion to conventional open heart surgery may be required.
- It is recommended that all prosthetic heart valve recipients be prophylactically treated for endocarditis to minimize the possibility of prosthetic valve infection, as described in the protocol.
- Bioprosthetic valve recipients should be maintained on anticoagulant/antiplatelet therapy, except when contraindicated, as determined by their physician, as described in the protocol. This device has not been tested for use without anticoagulation.
- Observation of the pacing lead throughout the procedure is essential to avoid the potential risk of pacing lead perforation.
- Do not add or apply antibiotics to the storage solution, rinse solutions, or to the THV.
- The procedure should be conducted under fluoroscopic guidance. Some fluoroscopically guided procedures are associated with a risk of radiation injury to the skin. These injuries may be painful, disfiguring, and long-lasting.
- Care should be exercised in patients with hypersensitivities to cobalt, nickel, chromium, molybdenum, titanium, manganese, silicon, and/or polymeric materials.

5.0 Precautions

5.1 Precautions Prior to Use

- Do not use the THV if the tamper evident seal is broken, the storage solution does not completely cover the THV, the temperature indicator has been activated, or the THV is damaged.
- Do not use the delivery system and accessory devices if the packaging sterile barriers and any components have been opened or damaged, cannot be flushed or the expiration date has elapsed.

5.2 Precautions During Use

- Do not expose the THV to solutions other than the storage solution in which it was shipped and the sterile physiological rinsing and irrigation solutions specified in section 7.2.1.
- Do not allow the leaflet tissue of the THV to become dry. Continuous submersion or irrigation of the THV is required.
- Glutaraldehyde may cause irritation of the skin, eyes, nose and throat. Avoid prolonged or repeated exposure to, or breathing of, the solution. Use only with adequate ventilation. If skin contact occurs, immediately flush the affected area with water; in the event of contact with eyes, seek immediate medical attention. For more information about glutaraldehyde exposure, refer to the Material Safety Data Sheet available from Edwards Lifesciences.
- Do not mishandle the valve tissue during rinsing, mounting, or crimping. If the THV is damaged, it must be replaced.
- Care should be used when handling the devices. Damage may result from kinking or stretching the devices.
- To maintain proper valve leaflet coaptation, do not overinflate the deployment balloon.

6.0 Potential Adverse Events

Complications associated with standard cardiac catheterization, balloon valvuloplasty (BAV), and the use of anesthesia include but are not limited to:

- Acute myocardial infarction
- Allergic reaction to antithrombotic therapy or contrast medium or anesthesia
- Anemia
- Aneurysm
- Angina
- Aortic valve thrombosis/occlusion
- Arrhythmias including ventricular fibrillation (VF) and ventricular tachycardia (VT)
- Arteriovenous fistula
- Arthralgia
- Bleeding/bruising
- Cardiogenic shock/pulmonary edema
- Cerebrovascular accident
- Death
- Dissection: aortic or other vessels
- Emboli, distal (air, tissue or thrombotic emboli)
- GI symptoms
- Headache
- Heart failure
- Hematologic dyscrasia
- Hematoma
- Hemorrhage
- Hemorrhagic stroke
- Hepatic enzyme changes
- Hypotension/Hypertension
- Infection and/or pain at access site
- Infection, fever
- Infection, systemic/sepsis
- Ischemia, myocardial
- Limb ischemia
- Myalgia
- Perforation or rupture of cardiac structure
- Perforation or rupture of vessel
- Pericardial effusion/cardiac tamponade
- Peripheral nerve injury/paralysis
- Postoperative encephalopathy
- Pseudoaneurysm
- Renal failure
- Respiratory failure
- Shock
- Silent cerebral ischemia
- Stroke
- Syncope
- Transient ischemic attack (TIA)
- 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 aortic valve replacement and bioprosthetic heart valves include, but may not be limited to, the following:

- Aortic annulus dissection/rupture/trauma
- AV block
- Aortic valve insufficiency
- Injury to aortic and/or mitral valve
- Acute coronary occlusion
- Allergic/immunologic reaction to the implant
- Atrial fibrillation/Atrial flutter
- Blood loss requiring blood transfusion
- Cardiac arrest
- Cognitive impairment
- Conduction disturbance including AV block requiring pacemaker
- Device malfunction requiring intervention/surgery
- Endocarditis
- Hemolysis
- Mediastinitis
- Mediastinal bleeding
- Mitral regurgitation
- Peri-/Paravalvular leak.

7.0 Directions for Use

7.1 Required Equipment

- Standard cardiac catheterization lab equipment
- Fluoroscopy (fixed, mobile or semi-mobile fluoroscopy systems appropriate for use in percutaneous coronary interventions)
- Transesophageal or transthoracic echocardiography capabilities
- Exchange length 0.035 inch (0.89 mm) extra-stiff guidewire
- Pacemaker (PM) and pacing lead
- Inflation Devices provided by Edwards Lifesciences (x2)
- SAPIEN 3 Transfemoral System
  - Edwards SAPIEN 3 THV
  - Edwards Commander Delivery System
  - Edwards Expandable Introducer Sheath Set
  - Edwards Transfemoral Balloon catheter or equivalent
  - Crimper
- Sterile rinsing bowls; sterile physiological saline solution; sterile heparinized saline solution, and diluted radiopaque contrast medium (15:85 medium to saline dilution)
- Sterile table for THV and device preparation
- 20 cc syringe or larger
- 50 cc syringe or larger
- High-pressure 3-way stopcock (x2)

7.2 THV Handling and Preparation

Follow sterile technique during device preparation and implantation.

7.2.1 THV Rinsing Procedure

The THV is packaged sterile in a plastic jar with a screw-cap closure and seal. Before opening, carefully examine the jar for evidence of damage (e.g., a cracked jar or lid, leakage, or broken or missing seals).

CAUTION: If the container is found to be damaged, leaking, without adequate sterilant, or missing intact seals, the THV must not be used for implantation.

Step	Procedure
1	Remove the THV/holder assembly from the jar and inspect for any signs of damage. Verify that the serial number on the THV holder and the jar lid match. Record the serial number in the patient information documents..
2	Rinse the THV as follows: **Gently** swirl the THV/holder assembly in 500 mL physiological saline solution for a minimum of 1 minute. Repeat this process in the second bowl for a minimum of 1 minute. Leave the THV in the second bowl until needed. **CAUTION: Do not allow the THV to come in contact with the rinse bowl or the identification tag. No other objects should be placed in the rinse bowls.**

7.2.2 Prepare the System

Step	Procedure
1	Visually inspect all the components for damage. Ensure the delivery system is fully unflexed and the balloon catheter is fully advanced in the flex catheter.
2	Flush the delivery system with heparinized saline through the flush port.
3	Remove the distal balloon cover from the delivery system. Remove the stylet from the distal end of the guidewire lumen and set aside.
4	Flush the guidewire lumen with heparinized saline. Insert the stylet back into the guidewire lumen. **Note:** Failure to replace the stylet in the guidewire lumen may result in damage to the lumen during the THV crimping process.
5	Place the delivery system into the Default Position (end of strain relief is aligned between the two white markers on the balloon shaft) and make sure that the flex catheter tip is covered by the proximal balloon cover.
6	Unscrew the loader cap from the loader and flush the loader cap with heparinized saline.
7	Place the loader cap onto the delivery system with the inside of the cap oriented towards the distal tip. Fully advance the balloon catheter in the flex catheter. Peel off the proximal balloon cover over the blue section of the balloon shaft.
8	Attach a 3-way stopcock to the balloon inflation port. Fill a 50 cc or larger syringe with 15-20 mL of diluted contrast medium and attach to the 3-way stopcock.
9	Fill the inflation device with excess volume of diluted contrast medium relative to the indicated inflation volume. Lock and attach to the 3-way stopcock. Close stopcock to the inflation device.
10	Pull vacuum with the syringe to remove air. Slowly release the plunger to ensure that the contrast medium enters the lumen of the delivery system. Repeat until all air bubbles are removed from the system. Leave zero-pressure in the system. Close stopcock to the delivery system.

Step	Procedure
11	Rotate the knob of the Inflation device to remove the contrast medium into the syringe and achieve the appropriate volume required to deploy the THV. Close the stopcock to the syringe and remove syringe.
12	Verify that the inflation volume in the inflation device is correct. **CAUTION: Maintain the inflation device in the locked position until THV deployment.**

7.2.3 Mount and Crimp the THV on the Delivery System

Step	Procedure
1	Completely submerge the Qualcrimp crimping accessory in a bowl of 100 mL physiological saline. Gently compress until fully saturated. Swirl for a minimum of 1 minute. Repeat this process in a second bowl.
2	Remove the THV from the holder and remove the ID tag.
3	Rotate the crimper handle until the aperture is fully open. Attach the 2-piece Crimp Stopper to the base of the crimper and click into place.
4	Partially crimp the THV in the crimper until it snugly fits inside the Qualcrimp crimping accessory.
5	Place the Qualcrimp crimping accessory over the THV orienting the skirt of the Qualcrimp towards the inflow (outer skirt) end of the THV.
6	Place the THV and Qualcrimp crimping accessory in crimper aperture. Insert the delivery system coaxially within the THV 2-3 mm distal to the blue balloon shaft (in the Valve Crimp Section) of the delivery system with the inflow of the THV towards the distal end of the delivery system.
7	Center the balloon shaft coaxially within the THV. Crimp the THV until it reaches the Qualcrimp Stop.
8	Remove the Qualcrimp from the THV and Qualcrimp Stop from the Crimp Stopper, leaving the Final Stop in place.
9	Center the THV within the crimper aperture. Fully crimp the THV until it reaches the Final Stop and hold for 5 seconds. Repeat this crimp step two (2) more times for a total of 3 crimps. **NOTE: Ensure that the Valve Crimp Section is coaxial within the THV.**
10	Pull the balloon shaft and engage the Balloon Lock so the delivery system is in Default Position.
11	Flush the loader with heparinized saline. Immediately advance the THV into the loader until the nose cone of the delivery system is exposed. **CAUTION: To prevent possible leaflet damage, the THV should not remain fully crimped and/or in the loader for over 15 minutes.**
12	Attach the loader cap to the loader, re-flush the Flex Catheter and close the stopcock to the delivery system. Remove the stylet and flush the guidewire lumen of the delivery system. **CAUTION: Keep THV hydrated until ready for implantation.** **CAUTION: The physician must verify correct orientation of the THV prior to its implantation; the inflow (outer skirt end) of the THV should be oriented distally towards the nose cone.**

7.3 Native Valve Predilation and THV Delivery

Native valve predilation and THV delivery should be performed under local and/or general anesthesia with hemodynamic monitoring in a catheterization lab/hybrid operating room with fluoroscopic and echocardiographic imaging capabilities.

Administer heparin to maintain the ACT at ≥ 250 sec.

CAUTION: Use of excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored.

7.3.1 Baseline Parameters

Step	Procedure
1	Perform a supra-aortic angiogram with the projection of the native aortic valve perpendicular to the view.
2	Evaluate the distance of the left and right coronary ostia from the aortic annulus in relation to the THV frame height.
3	Introduce a pacemaker (PM) lead until its distal end is positioned in the right ventricle.
4	Set the stimulation parameters, and test pacing.

7.3.2 Native Valve Predilation

Refer to Edwards Transfemoral Balloon Catheter Instructions for Use.

7.3.3 THV Delivery

Step	Procedure
1	Prepare the Edwards Expandable Introducer Sheath Set per its instructions for use.
2	If necessary, predilate the femoro-iliac vessel.
3	Introduce the sheath per its instructions for use.
4	Insert the loader assembly into the sheath until the loader stops.
5	Advance the delivery system until the THV exits the sheath. Retract the loader to the proximal end of the delivery system. **CAUTION: The THV should not be advanced through the sheath if the sheath tip is not past the aortic bifurcation.** **CAUTION: To prevent possible leaflet damage, the THV should not remain in the sheath for over 5 minutes.**

Step	Procedure
6	In the descending aorta, initiate valve alignment by disengaging the Balloon Lock and pulling back the balloon catheter. Continue pulling back the balloon catheter until the THV passes over the center Valve Positioning Marker. Engage the Balloon Lock. Utilize the Fine Adjustment Wheel to position the THV between the Valve Alignment Markers. **NOTE: Do not turn the Fine Adjustment Wheel if the Balloon Lock is not engaged.** **WARNING: Do not position the THV past the distal Valve Alignment Marker. This will prevent proper THV deployment.** **CAUTION: Maintain guidewire position in the left ventricle during valve alignment.**
7	Utilize the Flex wheel to traverse the aortic arch and cross the native valve. **NOTE: Verify the Edwards logo is facing up.** **NOTE: The delivery system articulates in a direction opposite from the flush port.**
8	If additional working length is needed, remove the loader by unscrewing the loader cap and peeling the loader tubing from the delivery system.
9	Disengage the Balloon Lock and retract the tip of the Flex Catheter to the center of the APC Marker. Engage the Balloon Lock.
10	Position the THV with respect to the native valve.
11	As necessary, utilize the Flex wheel to adjust the co-axiality of the THV and the Fine Adjustment Wheel to adjust the position of the THV.
12	Before deployment, ensure that the THV is correctly positioned between the Valve Alignment Markers and the Flex Catheter tip is over the APC Marker.
13	Begin THV deployment: • Unlock the inflation device. • Ensure hemodynamic stability is established and begin rapid pacing; once arterial blood pressure has decreased to 50 mmHg or below, balloon inflation can commence. • Using slow controlled inflation, deploy the THV with the entire volume in the inflation device, hold for 3 seconds and confirm that the barrel of the inflation device is empty to ensure complete inflation of the balloon. • Deflate the balloon. When the balloon catheter has been completely deflated turn off the pacemaker.

7.3.4 System Removal

Step	Procedure
1	Unflex the delivery system while traversing the aortic arch. Verify that the Flex Catheter tip is locked over the APC Marker and remove the delivery system from the sheath. **CAUTION: Patient injury could occur if the delivery system is not unflexed prior to removal.**

7.4 Verification of Prosthetic Valve Position and Measurements

Measure and record hemodynamic parameters.

Step	Procedure
1	Perform a supra aortic angiogram to evaluate device performance and coronary patency.
2	Measure and record the transvalvular pressure gradients.
3	Remove all devices when the ACT level is appropriate (e.g., reaches < 150 sec). Refer to the introducer sheath instructions for use for device removal.
4	Close the access site.

8.0 How Supplied

The THV is supplied sterile and nonpyrogenic packaged in buffered glutaraldehyde, in a plastic jar to which a tamper evident seal has been applied. Each jar is shipped in a shelf box containing a temperature indicator to detect exposure of the THV to extreme temperature. The shelf box is enclosed in Styrofoam prior to shipping.

The delivery system and accessories are supplied pouched and sterilized by ethylene oxide.

8.1 Storage

The THV must be stored at 10 °C - 25 °C (50 °F - 77 °F). The delivery system and accessories should be stored in a cool, dry place.

9.0 MR Safety

MR Conditional

Non-clinical testing has demonstrated that the THV (implant) is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 1.5 Tesla (T) or 3.0 Tesla (T).
- Spatial gradient field of 2500 Gauss/cm or less.
- Maximum whole body averaged specific absorption rate (WB-SAR) of 2.0 W/kg for 15 minutes of scanning.
- Normal mode operation, as defined in IEC 60601-2-33 Ed.2.0, of the MR system.

In non-clinical testing and computer analysis using anatomically correct models of the human anatomy, the implant was determined to produce an estimated *in vivo* temperature rise less than 2.3 °C for a WB-SAR of 2.0 W/kg for 15 minutes of MR scanning in a 1.5 T whole body coil from a GE Signa MR system. The estimated *in vivo* temperature rise was less than 2.6 °C for a WB-SAR of 2.0 W/kg in a 3.0 T GE Signa HDxt 3T (software version 14\LX\MR) whole body cylindrical bore MR system. These calculations may overestimate the true *in vivo* temperature rise, since the cooling effects of blood are not considered.

The image artifact extends as far as 10 mm from the implant for spin echo images and 30 mm for gradient echo images when scanned in non-clinical testing using a 3.0 T GE Signa HDx MR system (software version 14\LX\MR).

The implant has not been evaluated in MR systems other than 1.5 T or 3.0 T.

10.0 Patient Information

A patient registration form is provided with each THV. After implantation, please complete all requested information. The serial number may be found on the package and on the identification tag attached to the THV. Return the original form to the Edwards Lifesciences address indicated on the form and provide the temporary identification card to the patient prior to discharge.

11.0 Recovered THV and Device Disposal

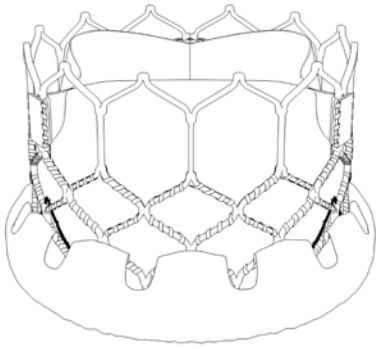
The explanted THV should be placed into a suitable histological fixative such as 10% formalin or 2% glutaraldehyde and returned to the company. Refrigeration is not necessary under these circumstances. Contact Edwards Lifesciences to request an Explant Kit.

Used devices may be handled and disposed of in the same manner as hospital waste and biohazardous materials. There are no special risks related to the disposal of these devices.

These products are manufactured and sold under one or more of the following US patent(s): US Patent No. 5,411,552; 5,931,969; 6,210,957; 6,214,054; 6,547,827; 6,561,970; 6,908,481; 7,214,344; 7,530,253; 7,585,321; 7,780,723; 7,846,203; 8,057,540; and RE40570 and corresponding foreign patents. Additional patents are pending.

12.0 Figures

Figure 1. Edwards SAPIEN 3 Transcatheter Heart Valve



Valve Size	Valve Height (mm)
23 mm	18
26 mm	20
29 mm	22.5

Figure 2a. Qualcrimp Crimping Accessory

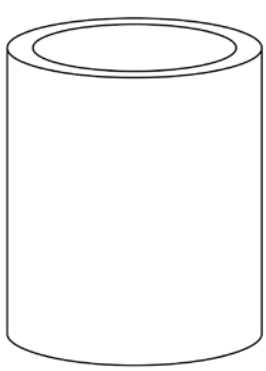


Figure 2b. Edwards Commander Delivery System

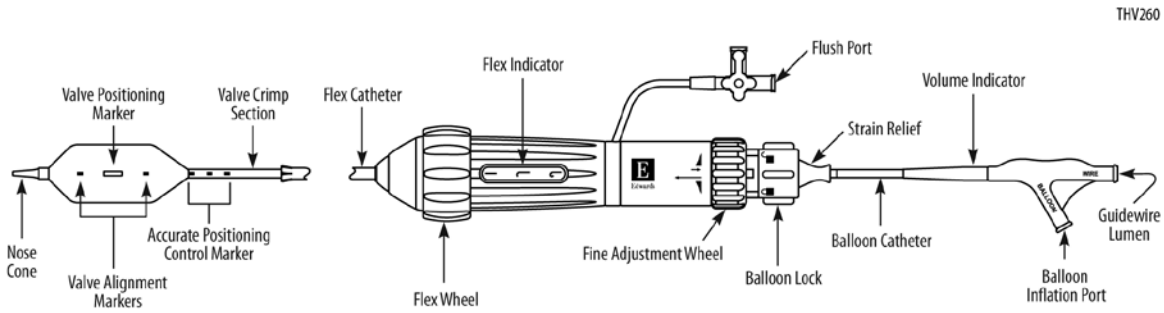
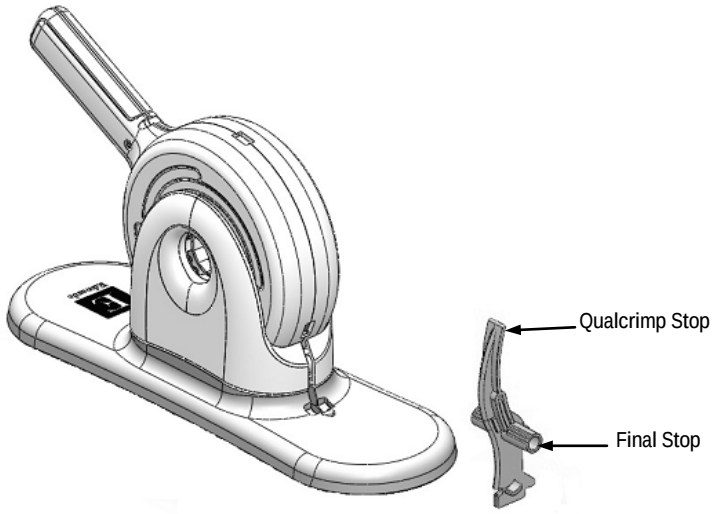


Figure 3. Crimper and 2-piece Crimp Stopper



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Edwards Lifesciences IRVINE, CA 92614		Title: **IFU, 23/26/29 S3 Commander IDE**			
Part No.: **157461001**	Rev: A	Graphics: Heather Bradley		Date:	
Rel ID: ECN	Pg. 9 of 9				
First Proofer:	Date:		Second Proofer:		Date:
Full Proof ☒	Proofed Against Redline ☒		Full Proof ☒	Proofed Against Redline ☒	

Appendix P: Fluoroscopic Imaging Guidelines

No changes from previous version (protocol version 4.0)

Appendix Q: 1201 JVIR Dose Reporting

No changes from previous version (protocol version 4.0)

Appendix R: Transcatheter Heart Valve Surgical Aortic Bioprosthetic Valve

No changes from previous version (protocol version 4.0)