Edwards Lifesciences
Transcatheter Heart Valves

THE PARTNER TRIAL: Placement of AoRTic TraNscathetER Valves Trial
VERSION 2.0

Edwards SAPIEN™ Transcatheter Heart Valve

Pivotal Trial #2006-06-US
US IDE PIVOTAL TRIAL

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This protocol was developed in collaboration with the following individuals who have either participated in the REVIVAL Trial (Cribier-Edwards Valve IDE Feasibility Study), plan to participate in the PARTNER Pivotal Trial or have relevant expertise in the field. The protocol was developed through careful planning and review of the historical literature, feasibility data and insights from clinical practice.

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INVESTIGATIONAL PLAN SUMMARY

Title: **THE PARTNER TRIAL "P**lacement of **A**o**Rt**ic **T**ra**N**scathet**ER"** Valves Trial" (US) [Edwards Study # 2006-06-US]

Design: A prospective, randomized-controlled, multi-center pivotal trial evaluating the safety and effectiveness of the Edwards SAPIEN™ Transcatheter Heart Valve (formerly known as the Cribier-Edwards Aortic Bioprosthesis), via transfemoral and transapical delivery, in a stratified population of high risk patients. An initial stratification based on operability for aortic valve replacement surgery (AVR) is followed by determination of vascular access for transfemoral delivery. Those not meeting criteria for transfemoral delivery are candidates for transapical delivery. Patients who are considered high surgical risk and eligible for transfemoral access will be stratified into Cohort A and randomized to treatment (transfemoral AVR) or control (surgical AVR). Patients who are considered high risk and not eligible for transfemoral access will be stratified into Cohort A and randomized to treatment (transapical AVR) or control (surgical AVR). Those patients who are considered non-surgical candidates are stratified into Cohort B and randomized to treatment (transfemoral AVR) or control (medical management). Those who are non-operable and assigned to Cohort B but are not eligible for transfemoral delivery will not be eligible for randomization into the trial.

Cohort A – High risk surgery patients undergoing transcatheter aortic valve implantation (treatment) via transfemoral or transapical delivery vs. surgical aortic valve replacement (control).

Cohort B – Non-surgical patients undergoing transcatheter aortic valve implantation (treatment) via transfemoral delivery vs. best medical management (control).

Purpose: The purpose of this trial is to determine the safety and effectiveness of the device and delivery systems (transfemoral and transapical) in high risk, symptomatic patients with severe aortic stenosis.

Enrollment: At least 1040 subjects, including a minimum of 690 patients in the high risk surgery cohort (Cohort A) and

350 patients in the best medical therapy cohort (Cohort B). The enrollment in Cohort A may expand to a maximum of 750 patients, if needed, to meet separate minima for each approach in Cohort A and the transfemoral approach for Cohort B.

This trial is powered separately for the two cohorts, and Edwards intends to submit separately for each cohort, even if the other cohort has not reached its minimum.

For Cohort A there will be a minimum of 690 randomized patients and a maximum of 750 randomized patients. Within these limits there will be a minimum of 450 transfemoral eligible patients and 200 transapical eligible patients. These minimum approach enrollments deliberately add up to less than 690 to avoid artificial enrollment caps in one of the approaches. If both minima are met before the 690 total is reached, enrollment will continue in both approaches to 690. If one minimum is not met when the 690 total has been reached, enrollment will continue in both approaches until both minima are met, or until 750 patients have been randomized.

Additionally, there will be 2 roll-in patients with successful delivery of the Edwards SAPIEN Transcatheter Heart Valve to its intended location per delivery approach per new clinical site [excluding sites participating in REVIVAL II trial (Edwards study 2005-01-PHV)]. These patients will not be included in the total enrollment population nor the data analysis.

Follow up:

Subjects will undergo clinical follow-up at discharge or 7 days, whichever comes first, 30 days, 6 months, 12 months, and annually thereafter to a minimum of 5 years post procedure.

The analysis close for PMA submission is based on completion of one year follow-up for Cohort A. For Cohort B the analysis close date is the later of the date of one-year follow-up on all patients and 150 deaths.

Clinical Sites:

Up to 30 sites total including up to 5 sites outside of the United States.

Study Duration:

Initial enrollment: April, 2007

Last enrollment for Pivotal Trial:
Approximately September 2009, depending on exact enrollment rate and initial enrollment date.

Primary Endpoints:

Cohort A: Test (transfemoral or transapical) vs. surgical control
Endpoint: Freedom from death at one year (non-inferiority)

Cohort B: Test (transfemoral) vs. non-surgical best medical therapy control
Endpoint: Freedom from death, over the duration of the trial (superiority)

Secondary Endpoints:

Cohort A:

1) Separate analyses of the primary endpoint in the transapical and transfemoral groups.
2) Functional improvement from baseline as measured per a) NYHA functional classification, b) effective orifice area (EOA) and c) six minute walk test at 30 days, six months and one year
3) Freedom from MACCE and expanded safety composite events at 30 days, 6 and 12 months

   MACCE definition includes death, MI, stroke and renal failure.
   Expanded safety composite event includes death, MI, stroke, aortic valve reintervention, recurrent hospitalization and procedure access complications (unplanned surgical vascular conduit, unplanned vascular grafting intervention, repair of thoracic or abdominal aorta, or access wound infection).
4) Evidence of prosthetic valve dysfunction (hemolysis, infection, thrombosis, severe paravalvular leak, or migration) at 30 days, 6 and 12 months
5) Length of index hospital stay
6) Total hospital days from the index procedure to one year post procedure.
7) Improved Quality of Life (QOL) from baseline at 30 days, 6 and 12 months
8) Improved valve function demonstrated by a responder analysis showing the percentage of patients in each treatment group who have a greater than 50% improvement in AVA at 30 days, 6 and 12 months.

Cohort B:

1) Composite of survival, recurrent hospitalization and NYHA using the Finkelstein-Schoenfeld methodology (Powered secondary endpoint)

2) Functional improvement from baseline as measured per a) NYHA functional classification, b) effective orifice area (EOA) and c) six minute walk test at 30 days, six months and one year
3) Freedom from MACCE and expanded safety composite events at 30 days, 6 and 12 months

   MACCE definition includes death, MI, stroke and renal failure.
   Expanded safety composite event includes death, MI, stroke, aortic valve reintervention, recurrent hospitalization and procedure access complications (unplanned surgical vascular conduit, unplanned vascular grafting intervention, repair of thoracic or abdominal aorta, or access wound infection).
4) Total hospital days from the index procedure or randomization into control arm for medical management patients to one year post procedure or randomization.
5) Improved Quality of Life (QOL) from baseline at 30 days, 6 and 12 months
6) Improved valve function demonstrated by a responder analysis showing the percentage of patients in each treatment group who have a greater than 50% improvement in AVA at 30 days, six months and one year

Additional Safety Variables:

Additional safety variables will be collected and analyzed at 30 days, 6 and 12 months (section 4.3).

Additional Efficacy Variables:

Additional efficacy variables will be collected and analyzed at index hospitalization, 30 days, 6 and 12 months (section 4.4).

Primary Analytical Subset: Intent-to-treat for the effectiveness endpoints. As-treated for the adverse events analyses.

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1 Background and Introduction

1.1 Aortic Valve Stenosis as a Clinical Problem and its Traditional Management

Prolonged average life expectancy has resulted in an aging population and consequently, in an increase in the number of patients requiring aortic valve replacement (AVR). Severe aortic stenosis (AS) represents the most common indication for AVR [1].

The main causes of acquired AS include rheumatic heart disease and senile degenerative calcification. Rheumatic AS, uncommon in the United States, involves both progressive fibrosis of the valve leaflets with varying degrees of commissural fusion, often with retraction of the leaflet edges and, in certain cases, calcification. Senile degenerative calcific AS, common in the United States and typically occurring in individuals > 65 years of age, 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 very 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 the onset of symptoms to the 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 degree 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 [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].

Table 1 describes criteria for determining the severity of AS, as defined by the 2006 published practice guidelines of the joint ACC/AHA Task Force [4, 6]:

Table 1. Criteria for Determining Severity of Aortic Stenosis

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

Aortic valve replacement (AVR) is the only effective treatment in adults with severe symptomatic aortic stenosis (ACC) and is considered to be a Class I indication. Apart from symptomatic relief, the operation improves long-term survival [7]. In multiple reported series, one, three and five year survival were extraordinarily disparate in operated versus non-operated patients [8]. In 2006, Charlson, Legedza et al., [1] reported that in a series of 124 patients studied, 49 (39.5%) had aortic valve replacement (AVR) surgery. In a logistic regression analysis adjusting for gender, comorbidity and baseline functional status, those patients aged < 80 years were significantly more likely to have surgery than older patients. Surgery was associated with a large reduction in mortality in all age groups. At one-year follow up, 87.8% of all patients (87.5% of those who were at least 80 years old) who had undergone surgery were alive, while only 54.7% (49.1% of those who were at least 80 years old) who did not receive surgery were alive.

Alternative Therapies:

Alternatives for patients deemed to be at excessive risk for surgery, or non-operable (non-surgical) include temporary relief using a percutaneous technique called balloon aortic valvuloplasty (BAV) or medical therapy (no obstruction-relieving intervention) for the inoperable patient. In patients with congenital, non-calcified AS, both BAV and surgery may be applied successfully. However, for acquired degenerative AS, AVR surgery is the treatment of choice.

The overall rate of operative mortality for AVR surgery ranges from 2 to 8% in most centers, with an STS National Database average of 4% [8-10]. However, the operative risk is much higher (4% to 29.6%) for patients with comorbid conditions such as emergency operations [11], elderly patients [11, 12], patients with advanced New York Heart Association (NYHA) functional classification of heart failure [11-13], and patients requiring concomitant coronary artery bypass surgery [12] and/or severely reduced preoperative left ventricular (LV) systolic function [11-17]. The latter represents the most powerful predictor of adverse surgical prognosis. In a study by Korfer *et al.* [11] the mortality rate was doubled in patients with reduced LV function (12.8%) compared to those with normal LV function (6.1%). The combination of severely reduced LV systolic function and prior myocardial infarction results in an especially unfavorable operative risk, with an associated mortality rate of 45% [16].

Table 2 provides a review of the literature of operative mortality in selected high risk series.

Table 2. Review of Literature of Operative Mortality After AVR Surgery - High Risk Series

Paper	N=	Operative mortality	Comorbidities
[18] (Ambler)	32,839	6.4%	All comers
[19] Bloomstein et al.	180	16.7%	70 /80 yr. old pts.
		23.2%	BSA < 1.82m^2
		8.1%	BSA > 1.82m^2
		8.9%	CPB <100min
		10.2%	CPB> 100-124min
		29.6%	CPB >124min
[20] Collart et al.	115	8.5%	Mean age 82.3yrs
[21] Collart et al.	200	7%	Mean age 83 yrs, EuroSCORE 9.1
[22] Collart et al.	215	8.8%	Mean age 83 yrs; mean additive EuroSCORE was 9.5%, mean logistic EuroSCORE was 15.1%
[23] Craver et al.	601	9.1%	>80 yrs
[24] Edwards et al.	49,073	4%	STS Database
		7.64%	Previous cardiac surgery
		17.07%	Dialysis
		10.09%	3 vessel disease
		7.03%	PVD
[25] Rankin et al.	409,904	9.4%	>70yrs
		11.3%	Re-op
		8.4%	Female
		5.5%, 6.4%, 8.1%, 10.5%	1, 2, 3, 4 comorbidities
		5.4%	Isolated aortic (overall)
[26] Nowicki et al.	5793	6.8%	Females
		8.9%	Diabetes
		7.9%	Hx CHF
		5.3%, 11.4%	NYHA Class III/IV
		9.4%	BSA < 1.7
		12.8%, 4.6%	Serum Cr. >1.3, less than 1.3
[27] Jamieson et al.	86,580	5.3% 8.5% 14.5%	Age 70-79, Age 80-89, Age 90-99
[15] Sundt	133	11%	Age > 80 yrs

Even in this complicated setting, AVR surgery still has a survival benefit compared to no intervention/medical therapy [28], [29]; however, post-operative recovery including complications and prolonged hospitalization may be high.

Therapeutic options for patients with such high risk profiles are limited. BAV has been studied for the treatment of calcific aortic stenosis in patients with severe coronary artery disease, reduced left ventricular function or significant medical comorbidities. When applied in this setting, BAV results in a temporary improvement of valvular function and relief of symptoms resulting from a small increase in aortic valve area (typically <1.0 cm^2). However, unlike AVR surgery, BAV does not provide a definitive durable treatment in these patients. Even after successful BAV, the underlying pathology persists; valve leaflets remain thickened, calcified and deformed. Additionally, in a large proportion of cases, BAV results simply in stretching of the valve leaflets rather than any long-term morphologic change in valve orifice area [30]. Restenosis is common, particularly in patients with unicuspid valves or with valves affected by severe dysplasia (>60% at 6 months, virtually 100% at 2 years). The procedure has high rates of related complications and mortality. In one multicenter registry [28], the procedural mortality was 3% and 30-day mortality 14%. Rates of serious complications (free myocardial wall perforation, myocardial infarction, and severe aortic regurgitation) are also high (6-10%) [17-23].

O'Neill *et al.* [31] reported the predictors of long-term survival after percutaneous aortic valvuloplasty on a series of 198 patients with a median follow-up of 7 months (range 0-18.8 months). Of these patients, 81 had repeat valvuloplasty or valve replacement and 117 patients died. At one year, the survival rate was 64% and the event-free survival rate (absence of death, repeat valvuloplasty or valve replacement) was 43%. One year cumulative survival for patients with a final valve area of <=0.5 cm^2 was 44% compared with 63% for patients with a valve area of >0.5 cm^2 (p=0.2). In 2007, Shareghi et al. [32] described their experience in 104 inoperable aortic stenosis patients who underwent valuloplasty and were followed for a mean of 3 ± 2 years. The 1-, 2- and 3-year mortality rates were 44%, 62%, and 71%, respectively. Seventeen patients (21%) underwent repeat BAV procedures and had long-term mortality similar to those undergoing a single BAV procedure. Hence, the incentives to develop minimally invasive aortic valve replacement that would mitigate or lessen the morbidities associated with traditional AVR have heightened in recent years. The advancements in transcatheter therapeutics, including stent devices and delivery catheters have led to the innovation of transcatheter AVR.

There is now a substantial body of literature describing conceptual ideas for transcatheter based aortic valve replacement, delivered both transapically and transfemorally. These publications include conceptual development, in vivo validation and clinical feasibility studies [33-36, 46-47]. The earliest publications reference animal trials performed in Europe by H.R. Andersen in 1992 [33]. These animals were implanted with a porcine bioprosthesis attached to a wire-based stent frame and delivered on a large diameter balloon. These acute experiments demonstrated effective hemodynamic function after successful deployment. Since these early experiences in vivo, more recent reports have been published describing the implantation of prosthetic aortic valves of various designs by catheter-delivered techniques in animals and in man [34-37]. Early experience using an antegrade transcatheter demonstrated feasibility of transcatheter aortic valve implantation and while demonstrating clear benefit in some patients, complications were prohibitive for broad applicability (Webb, Cribier). This led to the development of alternative delivery approaches (retrograde approach via transfemoral artery and, the transapical approach via minithoracotomy. Both approaches have been demonstrated to be reasonably safe and effective in feasibility studies.

The underlying assumptions of this study proposal is that transcatheter aortic valve replacement (Edwards SAPIEN™ THV delivered transfemorally or transapically) in patients with documented high operative risk (predicted operative mortality ≥15%) will result in mortality rates that are non-inferior to conventional aortic valve replacement and superior to medically managed patients in non-operable (non-surgical) patients. Given the increased risk of mortality and morbidity of AVR surgery for such patients, and the poor long-term effectiveness of BAV, there has been an interest in the development of less invasive aortic heart valve replacement for many decades. While both approaches are considered to be less invasive than surgery, the retrograde transfemoral approach is presumed to be less invasive possibly due to lack of thoracotomy incision. It is presumed therefore that the clinical approach would be to assess first for transfemoral access and for patients not eligible for transfemoral cannulation, the transapical approach would then be applied. The proposed trial is designed accordingly.

1.2 Background- Percutaneous Heart Valve Implantation

1.2.1 Historical Overview

Hufnagel *et al.* [38] in the 1950s, prior to the advent of extra-corporeal circulation, developed a technique for surgical implantation of a ball-valve aortic prosthesis in the descending aorta, just beyond the origin of the left subclavian artery. The technique provided a reduction of regurgitant blood flow in cases of chronic aortic regurgitation and lead to an improvement of symptoms and LV systolic function at short and at long term follow-up intervals (13 to 23 years) [39].

It is only recently that percutaneous/transcatheter implantation of a prosthetic aortic valve has been proposed as an alternative in managing subjects with AS [40-42]. The principle challenge of treating AS with a transcatheter-delivered heart valve has been resection of the aortic valve stenosis. It is the advent of tubular stent technology that has allowed the conceptual approach of balloon dilatation with simultaneous stented valve deployment across the native stenotic annulus. The tubular stent must withstand the strong recoil of the dilated segment and fibrotic annulus to provide and maintain an effective valve orifice area sufficient to improve hemodynamic function.

Given the increased risk of mortality and morbidity of AVR surgery for high risk subjects, and the poor long-term patency of BAV, there has been an interest in the development of a percutaneously delivered aortic heart valve for many decades. Despite a preponderance of conceptual ideas, publications have primarily referenced animal trials performed in Europe by H.R. Anderson in 1992 [33]. These animals were implanted with a porcine bioprosthesis attached to a wire-based stent frame and delivered on a large diameter balloon. These acute experiments demonstrated effective hemodynamic function after successful deployment. Several other reports have been published describing the implantation of prosthetic aortic valves of various designs by catheter-delivered techniques in animals [34-37] including valve harvested from bovine jugular vein and mounted in a stent [36].

The first successful percutaneous aortic stent valve implantation in a human was performed by Cribier et al, using the antegrade approach, in April 2002. The patient had critical aortic stenosis and was deemed inoperable for surgical valve replacement. The valve performed well after percutaneous implantation but the patient died of complications from peripheral arterial disease [40]. Further experience with antegrade approach proved it to be a limited delivery system due to the technical complexities and risks. Paniagua el al described the first retrograde transcatheter implantation of an aortic valve prosthesis[43]. Webb and colleagues refined the retrograde approach and in 2006, he reported the results from 18 patients who underwent the procedure as they were deemed to be excessive surgical risk due to their comorbidities. Implantation was successful in 14 patients and aortic valve area increased from 0.6±0.2 to 1.6±0.4 cm^2. Mortality at 30 days was 11% in this group with a mean age of 82 years. Iliac arterial injury, which occurred in the first two patients, did not recur with improvement in screening and access site management [42]. In a follow-up publication in 2007 on 50 patients, he reported an improvement in procedural success from 76% in the first 25 patients to 96% in the second 25 (p=0.10) and a decrease in 30-day mortality from 16% to 8% (p=0.67). Successful valve implantation was associated with an increase in echocardiographic valve area from 0.6±0.2 to 1.7±0.4 cm^2 [44]. As an alternative to the retrograde transfemoral approach, the transapical approach was developed to address

the need for those patients with diseased peripheral vascular anatomy not conducive to the large profile transfemoral delivery system. In 2007, Lichtenstein el al described the initial experience with the transapical approach in 7 patients who were deemed excessive surgical risk due to their comorbidities. There were no intraprocedural deaths and 30-day mortality was 14%. The valve area increased from 0.7±0.3 to 1.8±0.7 cm^2 at 30 days. There were no valve related complications at follow-up. Walter et al described their experience from 59 patients with high operative risk. Good valve positioning was noted in 55 patients (93.2%) with 4 (6.8%) being converted to conventional sternotomy. Neither coronary artery obstruction nor migration of the prosthesis was observed, and all valves had good hemodynamic function. The average logistic EuroSCORE predicted risk of mortality was 27±14% but the observed in-hospital mortality was 13.6% [45]. The initial experience shows this approach to be a viable alternative for patients not considered to be candidates for surgical valve replacement or transcatheter valve replacement via the transfemoral approach [46, 47].

1.2.2 Clinical Experience

Preclinical testing (bench and animal studies) has been conducted to support initiation of the clinical investigation outlined in this protocol. The study device includes the Edwards SAPIEN™ Transcatheter Heart Valve (previously known as the Cribier-Edwards Aortic Bioprosthesis, renamed December 2006) and its delivery systems.

Feasibility clinical studies have been conducted with both the transfemoral and transapical delivery system approaches. As of October 2007, 494 patients worldwide have been implanted with the Edwards SAPIEN™ THV (Transcatheter Heart Valve), formerly known as the Cribier-Edwards Aortic Bioprosthesis. Valve performance has been consistent in all feasibility studies regardless of method of delivery. There are now implants out over 3 years and long term follow-up will be ongoing.

The chart on the following page outlines the entire worldwide experience with the Edwards SAPIEN™ THV as of October 2007 with the early antegrade transfemoral delivery (abandoned), retrograde transfemoral delivery (RetroFlex) and transapical delivery (Ascendra):

Chart 1: Worldwide Experience with the Edwards SAPIEN™ THV (as of October 2007)

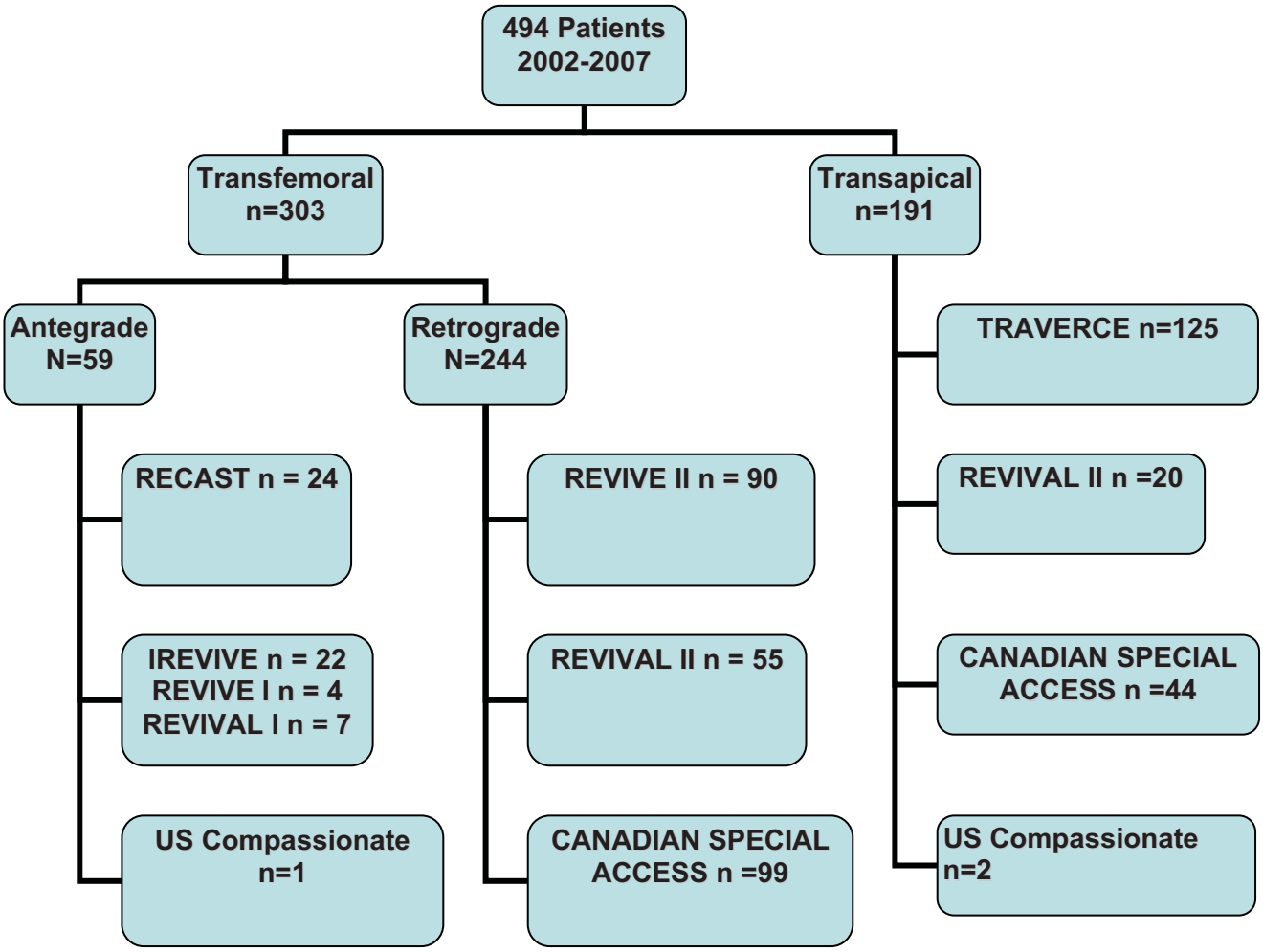


Table 3 provides a brief overview of the worldwide experience with the current (model 9000TFX) and prior (models 9000 and 9000MIS) versions of the Edwards SAPIEN Transcatheter Heart Valve and the transfemoral and transapical delivery systems. All data presented represent information available to Edwards as of October 2007. The data were presented in October 2007 at the Transcatheter Cardiovascular Therapeutics medical conference. Additional implants have occurred which are not reflected in the table below due to ongoing data collection/data entry. An update will be provided in the next IDE Annual Report (January 2008).

Table 3. Worldwide Clinical Experience with Transfemoral and Transapical Delivery of the Edwards SAPIEN™ Transcatheter Heart Valve (as of October 2007)

Trial	Number of Subjects Enrolled	Number of Subjects Receiving Valve	Survival at 1 month % (n)	Survival at 6 month % (n)	Survival at one year % (n)
I-REVIVE*	22**	17	67.2% (14)	33.6% (7)	28.0% (6)
RECAST*	24***	20	71.9% (17)	46.2% (9)	40.4% (6)
REVIVAL-I*	7	7	57.1% (4)	28.5% (2)	28.5% (2)
REVIVAL-II transfemoral	55	47	92.7% (51)	83.1% (39)	73.8% (19)
REVIVE-II	90	80	84.0% (64)	77.8% (26)	73.0%(10)
REVIVAL-II transapical	20	19	90.0%(18)	62.9% (6)	NA
TRAVERCE	125	116	87.0% (87)	69.2% (43)	63.5% (14)
TOTAL	**343**	**306**			
Compassionate Use	**Number of Subjects**	**Number of Subjects Receiving Valve**	**Surviving with Valve**		
I-REVIVE	6	6	0		
REVIVAL-I	1	1	1		
REVIVAL-II	2	2	2		
Canada Special Access (transfemoral & transapical)	99 TF 44 TA	NA	--		

Note: Edwards SAPIEN™ Transcatheter Heart Valve previously known as the Cribier-Edwards Aortic Bioprosthesis, renamed December 2006

*There are no new enrollments into this study and therefore the data were not updated
**One patient did not receive the valve and is lost to follow-up
*** One patient withdrew consent prior to procedure. That patient is not included in any analyses.
Note: The table excludes one compassionate use case involving implantation in the pulmonary artery position.
The proportions presented are the Kaplan-Meier numbers, and the counts are the patients at risk at exactly 1 month, 6 months, or 12 months.

1.3 Defining the Patient Population

1.3.1 Defining the "High Risk Surgical Patient"

There are several scorecard assessment tools to assess operative risk in cardiac surgery patients (STS Risk Score, Ambler, Logistic EuroSCORE, New York State Cardiac Surgery Database) [18, 24, 48]. The STS Risk Score System, Ambler[18] and recently the New York State Cardiac Surgery Database (Hannon et al, in press) have been validated for isolated AVR. Notably, the currently available validated risk score

systems by definition have not captured the “non-operable” patients. Understandably, assessing predicted operative mortality in these patients is currently best assessed by surgeon opinion. Hence in the absence of single tool available to quantify the total predicted risk for the targeted study population, the judgment of cardiac surgeons and co-principal investigators in addition to validated tool such as the STS Risk Score will be required for screening.

In the REVIVAL II Feasibility IDE, operative risk was assessed by the STS Risk Score System, the Logistic EuroSCORE System and by surgeon assessment. In this study, the mean STS score was 12.8 and mean Logistic EuroSCORE was 33.8. All patients were evaluated by a cardiac surgeon and deemed high risk and appropriate for the study as required in the study guidelines. The patients who did not meet the proposed risk score criteria (because scores were lower) were deemed eligible due to high risk comorbidities such as porcelain aorta, chest wall radiation, chest wall deformity and COPD, which are not captured in either the EuroSCORE or the STS scoring systems. These comorbidities have been documented in the baseline data per study protocol. In five patients who did not meet the EuroSCORE criteria of 20%, the following risk factors deemed the patients inoperable: porcelain aorta (n=2), radiation therapy of the sternum and porcelain aorta (n=1), radiation therapy to the sternum (n=1), and severe COPD (n=1).

To assure that patients are of high enough risk to justify the investigation, an STS score of 10 has been selected as the minimum risk score. This score represents patients in less than the top decile of risk in the STS National Registry Database*. The following data ensures that this score represents the extreme end of risk in the currently available surgical population in the US.

Table 4. STS Risk Deciles (Isolated AVR)

Decile Risk	<.10	>.10	>.20
% Cohort	92.01	7.99	1.88
Eligible pts.	12,725	1106	260

* 2005 STS Database Statistics

For the purposes of the pivotal trial, the STS Risk Score has been selected as the primary screening tool and the following primary entry criteria for risk assessment is proposed:
Candidates for this study must meet **all** of the following inclusion criteria:

Patients must have co-morbidities such that the surgeon and cardiologist Co-PIs agreed predicted risk of operative mortality is ≥15% and/or a minimum STS score of 10. A candidate who does not meet the STS score criteria of ≥10 can be included in the study if a peer review by at least two surgeon 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 in the study case report form as well as in the patient medical record.

1.3.2 Defining the "Non-operable (non-surgical) Patient"

Patients who are high risk but are not eligible for the surgical randomization arm due to prohibitive medical or anatomical conditions will be eligible for the best medical management randomization arm. These medical and anatomical conditions include highly compromised respiratory disease, severe immunosuppressive diseases, "true" porcelain aorta, chest wall radiation or deformity and multiple previous interventions in the presence of advanced multi-system dysfunction. Most of these characteristics are not included in the STS or other risk assessment systems (often such patients will score less than an STS of 10). Therefore, the evaluation of "non-operable" will be established by assessment of two cardiac surgeons along with the medical assessment of the cardiologist.

1.4 Conclusion

The next natural step in the development and progression of this intervention and associated technologies for aortic valve replacement is to further evaluate the safety and efficacy of the Edwards SAPIEN Transcatheter Heart Valve and the delivery systems in a pivotal randomized-controlled clinical trial. In order to maximize the risk-benefit for potential treatment subjects, only adult patients who are severely symptomatic and at very high risk for in-hospital mortality following AVR surgery or who have limited options for symptom and function improving intervention will be enrolled.

Most patients in this late disease stage who receive palliative balloon valvuloplasty restenose with acute recurrence of symptoms within 6 months. Because of the severity of the disease and the lack of alternatives to BAV, repeat BAV procedures are being performed with results that provide improved survival rates up to 3 years [49]. Additionally in a small feasibility study a combination of BAV and radiation therapy in extremely elderly patients (mean age 89 ± 4 years) has been undertaken. Unfortunately these additional therapies still have a very high mortality rate over time, with patients receiving repeat BAV attaining a 33% survival at 3 years. Based on extensive bench testing, animal experiments, and more importantly, initial clinical data, treatment of these patients with a transcatheter-delivered heart valve in a well controlled study may provide both short and long-term relief of their symptoms, improved hemodynamic function, and a gradual, consistent improvement of their cardiac function resulting in both increased survival and improved quality of life. Availability of the transcatheter-delivered heart valve for these patients is only made possible by recent advances in engineering blending state of the art balloon expandable stent technology and a durable bioprosthetic valve.

The results of the REVIVAL II Feasibility Trial which have included both transfemoral and transapical delivery of the transcatheter heart valve are encouraging. Reasonable safety and effectiveness has been demonstrated and the study population clearly defined. A pivotal trial is the next logical step for evaluating the device and the delivery systems as compared to standard of care therapy for the selected population in a controlled study.

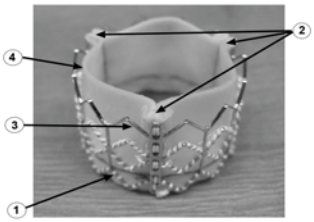
2 General Overview of the Study Valve Technology

The Edwards SAPIEN™ transcatheter heart valve (THV, or "study valve") is a catheter-delivered heart valve that combines a balloon expandable stent and bioprosthetic valve technology. The bioprosthesis, available in two sizes (23 mm and 26 mm), is designed for implantation via transcatheter access in patients with severe calcific aortic stenosis (AS), who require aortic valve replacement (AVR), but who are not good candidates for open-chest surgery due to extremely high operative risk or co-morbid conditions. Transcatheter delivery of the study valve is done via transfemoral and transapical cannulation.

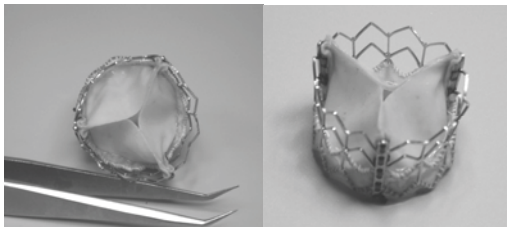
Implantation of the study valve is preceded by dilatation of the stenotic native aortic valve by means of balloon aortic valvuloplasty (BAV). Predilatation tests the expansion capacity of the native valve and prepares the annulus for implantation of the study valve. Prior to implantation, the study valve is carefully mounted and crimped onto a balloon delivery catheter using a specially designed crimping device. The study valve/balloon assembly is inserted either A) into the femoral artery (retrograde approach) and delivered to the site of the native stenotic aortic valve using the components of the RetroFlex™ delivery system, or B) in the left ventricular apex (antegrade approach) using the components of the Ascendra™ delivery system. The study valve is positioned and deployed across the stenotic native valve. The balloon delivery system is 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.

2.1 Edwards SAPIEN™ Transcatheter Heart Valve

The Edwards SAPIEN™ transcatheter heart valve (bioprosthesis; Figure 1) 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. 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.



1. PET Cuff
2. Commissures (in the valve) and Supporting bars (in the frame)
3. Stent (Frame)
4. A unidirectional valve



Study Valve

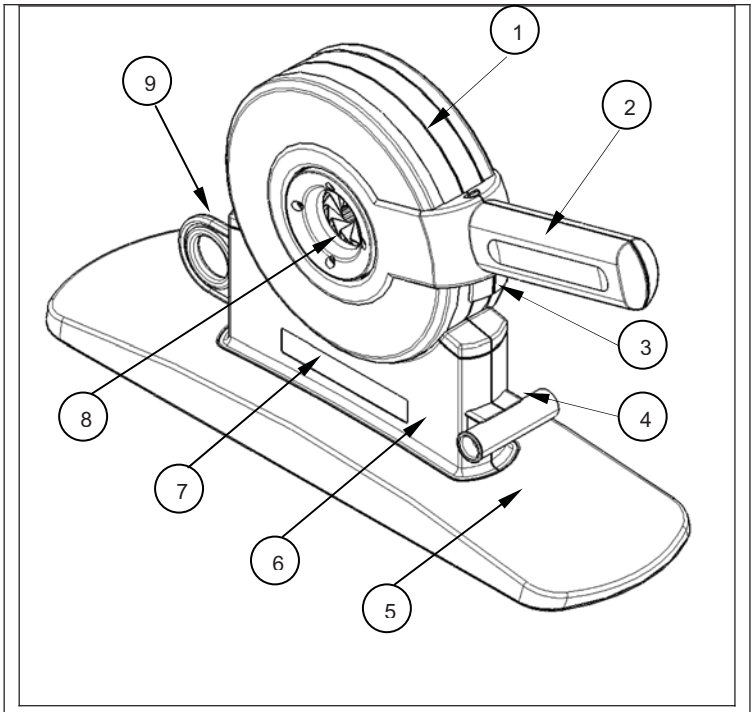
Study valve crimped on delivery balloon

Figure 1. Edwards SAPIEN™ Transcatheter Heart Valve (Study Valve)

2.2 Crimper

The crimper (Models 9100CR23 and 9100CR26) is a single-use non-patient contacting, compression device (Figure 2) that symmetrically reduces the overall diameter of the bioprosthesis from its expanded size to its collapsed (mounted) size, effectively mounting the bioprosthesis to its delivery balloon catheter. The crimper is comprised of a housing and a compression mechanism (creating the aperture). The aperture is closed by means of a handle located on the housing. The crimper is equipped with two measuring gauges:

- A crimp gauge to verify that the bioprosthesis/balloon assembly has been suitably collapsed.
- A balloon gauge to verify the bioprosthesis/balloon assembly catheter diameter when inflated.



1 - Housing
2 - Handle
3 - Stopper
4 - Crimp Gauge
5 – Base
6 - Stand
7 – ID Label
8 – Aperture
9 - Balloon Gauge

Figure 2. Crimper

2.3 RetroFlex™ Delivery System

The RetroFlex delivery system is used for transfemoral (retrograde) delivery of the Edwards SAPIEN transcatheter heart valve (study valve, or bioprosthesis).

The RetroFlex delivery system consists of the following:

- RetroFlex™ catheter or RetroFlex II™ catheter
- RetroFlex™ introducer sheath set (sheath, introducer[s], and loader)
- RetroFlex™ dilator kit
- RetroFlex™ balloon catheter

RetroFlex Catheter

The RetroFlex catheter (model 9100FC; Figure 3a) is used to advance the bioprosthesis (Edwards SAPIEN transcatheter heart valve) through the RetroFlex sheath over a guidewire and to track the bioprosthesis over the aortic arch. It is also used to aid in crossing, and positioning the bioprosthesis within the native valve. The catheter has a shaft made of a stainless steel braid covered in a medical grade plastic with a softer durometer distal section that can flex from 0 to 120 degrees to help deliver the bioprosthesis. The handle of the catheter provides a rotational grip for flexing the distal end as well as a hemostasis seal.

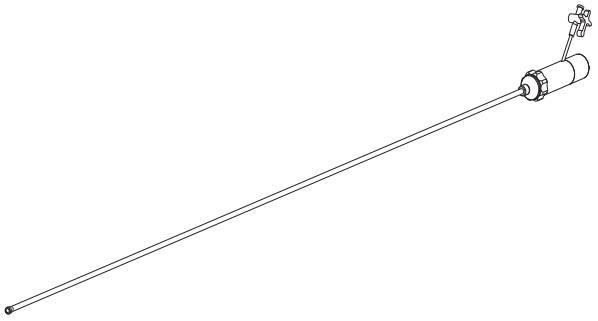


Figure 3a. RetroFlex Catheter

RetroFlex II Catheter

The RetroFlex II catheter (models 9100HDSLT23 and 9100HDSLT26; Figure 3b) is used to deliver and deploy the appropriate size Edwards SAPIEN transcatheter heart valve (bioprosthesis). The RetroFlex II catheter is used to advance the bioprosthesis through the RetroFlex sheath over a guidewire and track it over the aortic arch. It is also used to aid in crossing, and positioning the bioprosthesis within the native valve. The catheter has a shaft made of a stainless steel braid covered in a medical grade plastic with a softer durometer distal section that can flex from 0 to 120 degrees to help deliver the bioprosthesis. The handle of the catheter provides a rotational grip for flexing the distal end as well as a hemostasis seal. There is a tapered nose cone tip at the distal end of the RetroFlex II catheter which allows the system to cross the native valve easily. The

nose is advanced or pulled back over the distal portion of the balloon by a knob on the proximal end of the handle. The RetroFlex II catheter also incorporates a balloon catheter which expands the bioprosthesis with a controlled volume of saline/contrast.

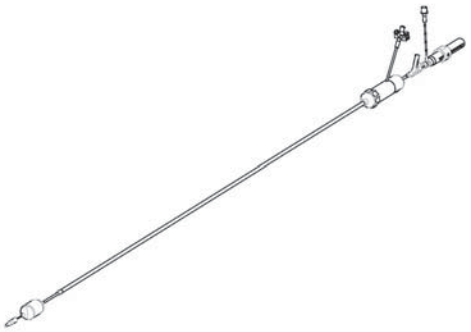


Figure 3b. RetroFlex II Catheter

RetroFlex Introducer Sheath Set

The RetroFlex sheath set (models 9100SL23, and 9100SL26) includes an introducer[s] with a hydrophilic coating and a long soft tip to facilitate introduction into the vessel and improved trackability (Figure 4), a sheath with three seal valve (Figure 5) that provides hemostasis, and a loader with a cap (Figure 6) is available to introduce the bioprosthesis (Edwards SAPIEN transcatheter heart valve) through the sheath valves while providing hemostasis.

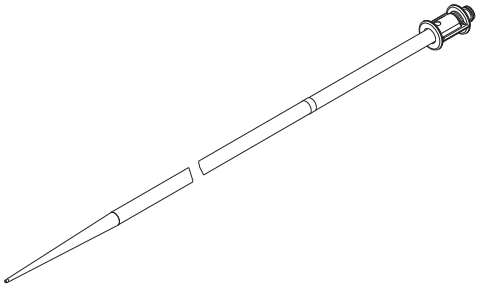


Figure 4. Introducer

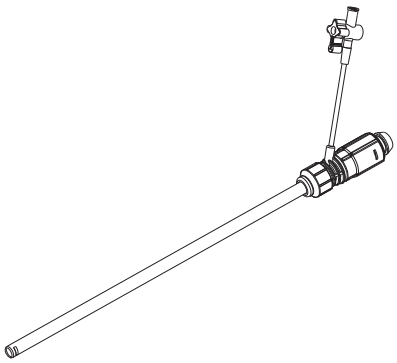


Figure 5. Sheath

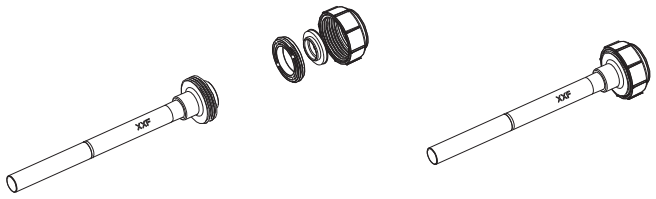


Figure 6. Loader

RetroFlex Dilator Kit

The RetroFlex dilator kit (model 9100DKS [4 dilators] and model 9100DKS7 [7 dilators]) consists of dilators that are used during the catheterization procedure to gradually dilate the femoral artery to accommodate the RetroFlex sheath for bioprosthesis implantation.

Figure 7. RetroFlex Dilator

RetroFlex Balloon Catheter

The RetroFlex balloon catheter (Figure 8) is available as models 9100BC20, 9100BC23 and 9100BC26. Model 9100BC20 (or any 20 mm commercially available balloon valvuloplasty catheter [BVC]) can be used to predilate the native annulus to ease crossing with the 23 mm bioprosthesis; and model 9100BC23 (or any 23 mm commercially available BVC) can be used to predilate the native annulus to ease crossing with the 26 mm bioprosthesis. Model 9100BC23 and model 9100BC26 are used in association with the RetroFlex catheter (model 9100FC) for transfemoral delivery and deployment of the 23 mm or 26 mm bioprosthesis, respectively. The balloon catheter is advanced through the introducer sheath by the RetroFlex catheter and through the arterial system to the native aortic valve. The balloon expands the native aortic valve and/or the bioprosthesis with a controlled volume of saline/contrast. Two outer radiopaque markers indicate the dilating section of the balloon and aid in balloon placement. Two inner radiopaque markers are used to indicate the location of the bioprosthesis on the balloon and aid in positioning of the bioprosthesis in the native valve. The balloon catheter shaft has a braided multi-durometer outer-shaft. Rapid inflation and deflation of the balloon is achieved through the 130 cm coaxial shaft design.

Figure 8. RetroFlex Balloon Catheter

2.4 Ascendra™ Delivery System

The Ascendra delivery system is used for transapical (antegrade) delivery of the Edwards SAPIEN transcatheter heart valve (study valve, or bioprosthesis).

The Ascendra delivery system consists of the following:

- Edwards MIS introducer sheath set
- Ascendra introducer sheath set
- Ascendra balloon aortic valvuloplasty catheter
- Ascendra balloon catheter

Edwards MIS and Ascendra Introducer Sheath Set

The introducer sheath set (models 9100MISIS and 9100IS; Figure 9) 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 side port and three hemostasis valves. A dilator is supplied with the introducer sheath. The dilator has a radiopaque marker at the distal end where the taper begins.

1. Housing
2. Side Port with Stopcock
3. 33F (11.0 mm) or 26F (8.6 mm) Sheath
4. Radiopaque Marker
5. Non-Radiopaque Depth Markers
6. 33F (11.0 mm) or 26F (8.6 mm) Dilator

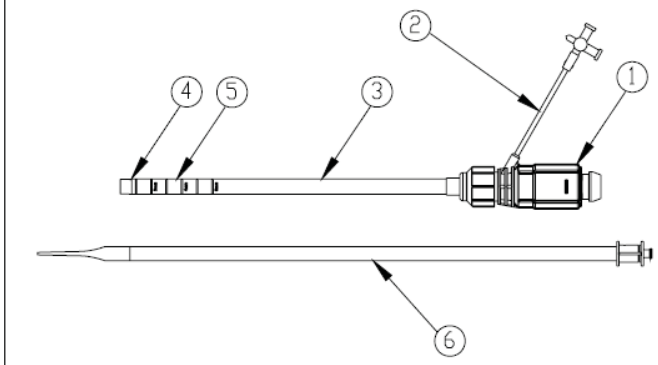


Figure 9. Edwards MIS Introducer Sheath Set or the Ascendra Introducer Sheath Set

Ascendra Balloon Aortic Valvuloplasty Catheter

The Ascendra balloon aortic valvuloplasty catheter (model 9100BAVC) is a coaxial designed catheter with a distal inflatable balloon. Two radiopaque marker bands indicate the dilating section of the balloon and aid in balloon placement. The proximal end of the catheter has a a standard “Y” connector for balloon inflation and a guidewire lumen. An optional balloon extension tubing is provided for user preference. The balloon is inflated by injecting diluted contrast medium solution through the luer port (marked “BALLOON”) on the “Y” connector.

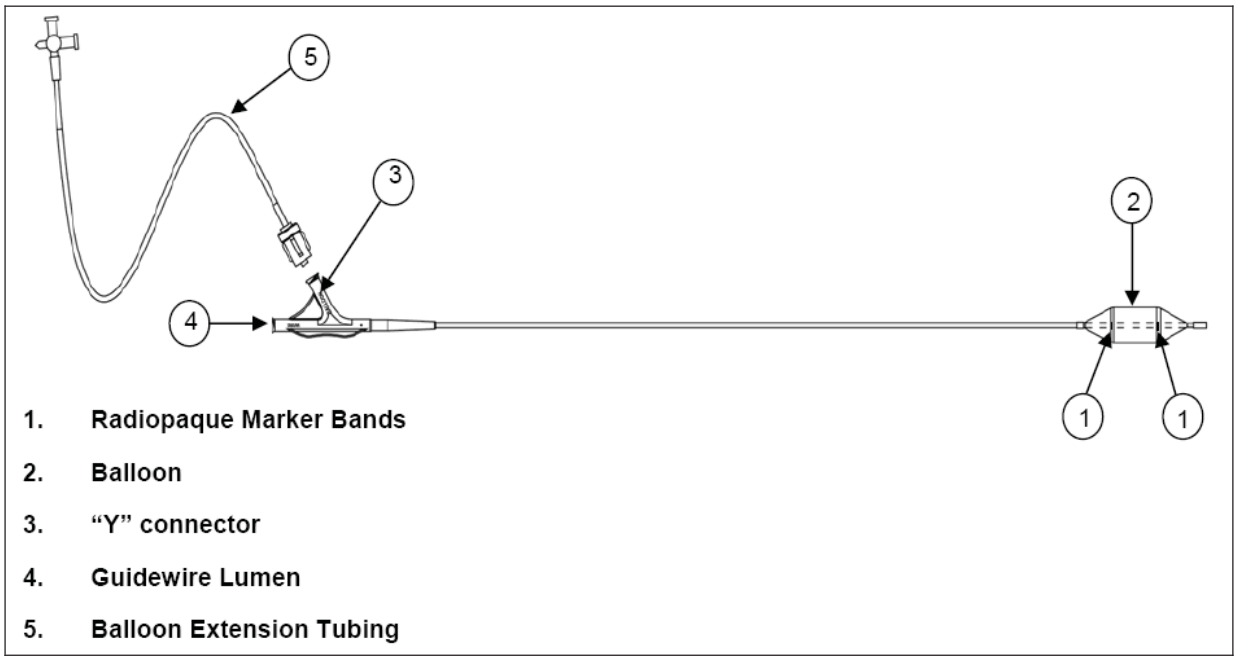


Figure 10. Ascendra Balloon Aortic Valvuloplaty Catheter

Ascendra Balloon Catheter

The Ascendra balloon catheter system (models 9100BCL23 and 9100BCL26; Figure 11) consists of a balloon catheter and a loader. Two radiopaque markers on the balloon serve as indicators for bioprosthesis placement during crimping, as well as visualization of the balloon. The catheter has a deflecting mechanism to steer the balloon. The loader allows for the delivery of the crimped bioprosthesis through the hemostasis valves.

1. Balloon with Radiopaque Markers
2. Pusher Tip
3. Washers, Seal, and Loader Cap
4. Pusher Y-Fitting
5. Proximal Pusher Nut
6. Deflecting Mechanism
7. Balloon Inflation "Y"
8. Balloon Extension Tubing with Stopcock
9. 26F (8.6 mm) Loader

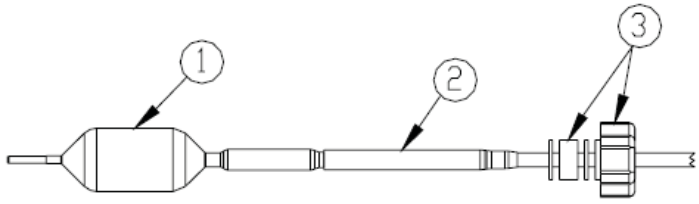


Figure 18a

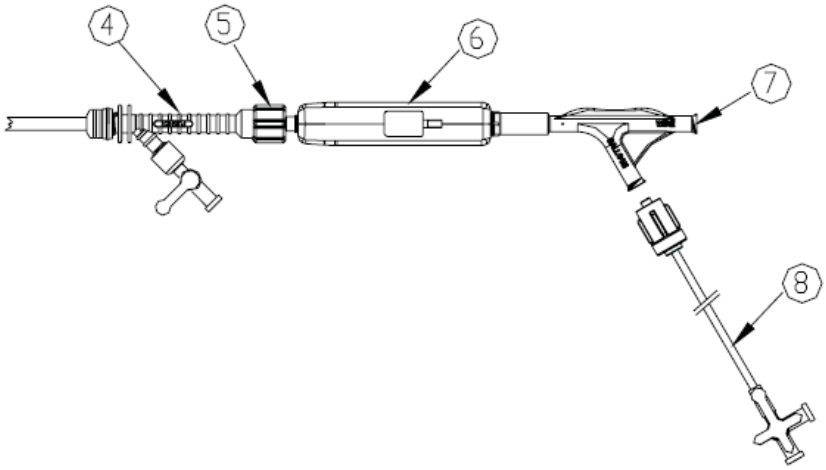


Figure 18b

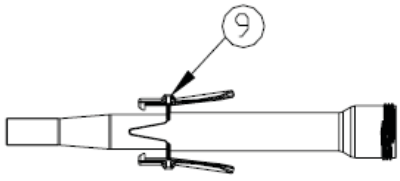


Figure 18c

Figure 11. Ascendra Balloon Catheter

3 Benefits and Risks

3.1 Benefits

There are no guaranteed benefits from participation in this study.

Implantation of the transcatheter heart valve in the subcoronary position may result in one or more of the following: improved valvular function, acute alleviation of symptoms related to aortic stenosis, improved morbidity and mortality.

Additionally, information gained from the conduct of this study may be of benefit to other people with the same medical condition in the future. The long-term results of using the study valve are not known at the present time. Alternative treatments include palliative medical therapy, aortic balloon valvuloplasty and surgical replacement of the aortic valve.

3.2 Risks

The potential risks associated with BAV and the use of the study valve can be grouped into two categories. First, there are the potential risks associated with the overall procedure including standard cardiac catheterization for the transfemoral access, surgical access for the transapical delivery, balloon valvuloplasty, and the potential risks of local and/or general anesthesia. Second, there are the additional potential risks uniquely associated with the use of the study valve.

The first set of risks includes, but is not limited to, the following:

- death;
- cardiovascular or vascular injury, such as perforation or damage (dissection) of vessels, myocardium or valvular structures that may require intervention;
- myocardial infarction;
- stroke/ transient ischemic attack;
- embolization: air, calcification or thrombus;
- hemorrhage requiring transfusion or intervention;
- hematoma;
- hypertension/hypotension;
- renal failure;
- renal insufficiency;
- allergic dye reaction;
- anesthesia reactions;
- arrhythmia;
- conduction system injury, which may require a permanent pacemaker;
- fever;
- infection including endocarditis, incisional site infection/inflammation and septicemia;
- pericardial effusion/cardiac tamponade;
- systemic peripheral ischemia/nerve injury; and
- AV fistula.

In addition to the risks listed above, additional potential risks specifically associated with the use of the study valve include, but may not be limited to, the following:

- bleeding;
- device explant;
- device migration or malposition requiring intervention;
- device thrombosis requiring intervention;
- emergency cardiac surgery;
- endocarditis;
- hemolysis;
- hemolytic anemia;
- non-emergent reoperation;
- nonstructural dysfunction;
- paravalvular leak;
- structural valve deterioration;
- valve stenosis;
- valvular thrombosis;
- injury at the site of venous, arterial or ventricular access requiring surgical repair.

All efforts will be made to minimize these risks by selecting investigators and study sites who meet the following criteria:

- interventional cardiologists (transfemoral operators) are experienced and skilled in percutaneous, structural heart interventions (BAV).

- cardiovascular surgeons performing procedures must be board certified (or equivalent) and have performed at least 100 high risk AVR operations as well as maintain an average a minimum of 30 aortic valve operations per year. Each surgeon performing the procedures in this study should provide a statement that their operative mortality results meet an observed/expected ratio of 1 or better per their institution's preferred, validated quality benchmarking system for valve surgery, (STS, or other). Additionally, the study Co-PIs will assess and determine site and investigator eligibility.

- strong interdepartmental collaboration between cardiac surgery and interventional cardiology operators and a team that has been trained in the use of the study valve (See Appendix A for details on the training program). In addition, study investigators will sign a survey verifying that they meet the criteria.

- procedure setting to include either a hybrid catheterization/operating room suite and/or a fixed C-arm angiography imaging capability in the operative suite. Imaging is an essential requirement for site selection.

4 Study Objectives and Endpoints

4.1 Primary Objectives

The purpose of this trial is to determine the safety and effectiveness of the Edwards SAPIEN™ Transcatheter Heart Valve and delivery systems (transfemoral and transapical) in high risk symptomatic patients with severe aortic stenosis: a) patients with high surgical risk for aortic valve replacement who are candidates for the transfemoral approach, b) patients with high surgical risk who do not meet vascular access criteria for transfemoral delivery and are thus transapical candidates, and c) non- surgical patients who are candidates for the transfemoral approach. Those who are non-operable but are not eligible for transfemoral delivery will not be eligible for randomization into the trial.

The primary study endpoints are defined as follows:

Primary Endpoints:

Cohort A: Test (transfemoral or transapical) vs. surgical control
Endpoint: Freedom from death at one year (non-inferiority)

Cohort B: Test (transfemoral) vs. non-surgical best medical therapy control
Endpoint: Freedom from death, over the duration of the trial (superiority)

4.2 Secondary Objectives

The secondary study endpoints are defined as follows:

Secondary Endpoints: Cohort A:

1) Separate analyses of the primary endpoint in the transapical and transfemoral groups.
2) Functional improvement from baseline as measured per a) NYHA functional classification, b) effective orifice area (EOA) and c) six minute walk test at 30 days, six months and one year
3) Freedom from MACCE and expanded safety composite events at 30 days, 6 and 12 months.
   MACCE definition includes death, MI, stroke and renal failure.
   Expanded safety composite event includes death, MI, stroke, aortic valve reintervention, recurrent hospitalization and procedure access complications (unplanned surgical vascular conduit, unplanned vascular grafting intervention, repair of thoracic or abdominal aorta, or access wound infection).
4) Evidence of prosthetic valve dysfunction (hemolysis, infection, thrombosis, severe paravalvular leak or migration) at 30 days, 6 and 12 months

5) Length of index hospital stay
6) Total hospital days from the index procedure to one year post procedure.
7) Improved Quality of Life (QOL) from baseline at 30 days, 6 and 12 months
8) Improved valve function demonstrated by a responder analysis showing the percentage of patients in each treatment group who have a greater than 50% improvement in AVA at 30 days, 6 and 12 months

Cohort B:

1) Composite of survival, recurrent hospitalization and NYHA using the Finkelstein-Schoenfeld methodology (Powered secondary endpoint)
2) Functional improvement from baseline as measured per a) NYHA functional classification, b) effective orifice area (EOA) and c) six minute walk test at 30 days, six months and one year
3) Freedom from MACCE and expanded safety composite events at 30 days, 6 and 12 months. MACCE definition includes death, MI, stroke and renal failure.
   Expanded safety composite event includes death, MI, stroke, aortic valve reintervention, recurrent hospitalization and procedure access complications (unplanned surgical vascular conduit, unplanned vascular grafting intervention, repair of thoracic or abdominal aorta, or access wound infection).
4) Total hospital days from the index procedure or randomization into control arm for medical management patients to one year post procedure or randomization.
5) Improved Quality of Life (QOL) from baseline at 30 days, 6 and 12 months
6) Improved valve function demonstrated by a responder analysis showing the percentage of patients in each treatment group who have a greater than 50% improvement in AVA at 30 days, six months and one year

4.3 Additional Safety Endpoint Collection

In addition to the above primary and secondary study endpoints, the data for endpoints listed below will be collected, analyzed and reported:

Event	Reporting Interval
Annular dissection	30 days or hospital discharge, whichever is longer, 6 and 12 months
Aortic dissection	30 days or hospital discharge, whichever is longer, 6 and 12 months
Structural valve deterioration	30 days or hospital discharge, whichever is longer, 6 and 12 months
Nonstructural dysfunction (includes paravalvular leak)	30 days or hospital discharge, whichever is longer, 6 and 12 months
Valve thrombosis	30 days or hospital discharge, whichever is longer`, 6 and 12 months
Embolism	30 days or hospital discharge, whichever is longer, 6 and 12 months
Bleeding event	30 days or hospital discharge, whichever is longer, 6 and 12 months
Operated valvular endocarditis	30 days or hospital discharge, whichever is longer, 6 and 12 months
Conduction defects	30 days or hospital discharge, whichever is longer, 6 and 12 months
Ventricular injury	30 days or hospital discharge, whichever is longer, 6 and 12 months
Valve migration	30 days or hospital discharge, whichever is longer, 6 and 12 months
Hemolysis	30 days or hospital discharge, whichever is longer, 6 and 12 months
Vascular and access-related complications	30 days or hospital discharge, whichever is longer, 6 and 12 months
Mitral valve compromise	30 days or hospital discharge, whichever is longer, 6 and 12 months

4.4 Additional Efficacy Endpoints

In addition to the above primary and secondary study endpoints, the data for endpoints listed below will be collected, analyzed and reported:

Endpoint	Reporting Interval
Device Success	Index hospitalization
Procedure Success	30 days
Cost and Cost-Effectiveness	Index hospitalization and 12 months

5 Study Design

This is a prospective, stratified, then randomized-controlled, multi-center pivotal trial evaluating the safety and effectiveness of the Edwards SAPIEN™ Transcatheter Heart Valve in the following patient populations versus separate controls:

Cohort A High risk surgery patients undergoing transcatheter aortic valve implantation (treatment) via transfemoral or transapical delivery vs. surgical AVR (control)

Cohort B Non-surgical patients undergoing transcatheter aortic valve implantation (treatment) via transfemoral delivery vs. best medical management (control). Those who are non-operable and assigned to Cohort B but are not eligible for transfemoral delivery will not be eligible for randomization into the trial.

This pivotal trial will include at least 1040 subjects at up to 30 sites, including up to five sites outside the US. The study is powered to effectively analyze each stratification cohort against its own control as well as to ensure ample power to evaluate safety and effectiveness of the transfemoral and transapical delivery methods.

Table 6 in Section 5.12 and Appendix B (Study Flow Chart) provide general information on the study design. Primary analysis will be used to demonstrate study success and support device approval for the US, Japan and other countries as applicable.

Trial Endpoint Analysis

Trial analysis will generally consist of comparisons of Test vs. Control. The endpoints for the two trial cohorts are separate, and data from the trial cohorts will not be pooled for the endpoint analysis.

Specific details of endpoint analysis are given in the Statistical Analysis section of this protocol.

5.1 Sample Size Computation

The sample size is based on the primary effectiveness and safety test.

The size is computed separately for the two patient cohorts, and is based on obtaining at least 85% power for each cohort when analyzed separately. The size is also based on randomization ratios of 1:1 between the trial arms.

Cohort A:

The feasibility assumptions for one year mortality are**:**

Patient Group		Mortality at 12 Months
Transfemoral	Test	25%
	Control	30%
Transapical	Test	35%
	Control	35%
Combined (based on 65% transfemoral	Test	29%
	Control	32%

For the transfemoral Test arm, the 25% assumption comes from the latest analysis of the REVIVAL II trial. Based on data as of October 7, 2007, the Kaplan-Meier mortality in for the transfemoral implants is 26.2% at 1 year, with a standard error of 6.3%. This value is consistent with other feasibility studies (REVIVE and Canadian Special Access). Based on the fact the some of the early deaths may not recur as a result of lessons learned, the 25% mortality figure has been assumed.

Based on REVIVAL II data as of October 7, 2007, the Kaplan-Meier mortality for the transapical implants is 37.1% at 1 year, with a standard error of 11.3%. This value is consistent with, but slightly higher than, other feasibility studies (TRAVERCE and Canadian Special Access). As some of the early deaths may not recur as a result of lessons learned, a mortality figure of 35% has been assumed.

The feasibility assumption for the transfemoral Control arm comes from the observed 30-death rate of 7.3% in the REVIVAL II transfemoral patients and the 13.1 mean STS score in these same patients. To the extent that the STS score is predictive of mortality in this high risk group, there should be at least a 5% improvement from Control to Test.

For the transapical Control arm the STS comparison again favors the Test arm, but the situation is not so clear because of the smaller sample size. Accordingly for sample size purposes the same mortality figure is assumed in the transapical Control arm as in the transapical Test arm.

Rationale for the selection of non-inferiority margin can be found in section 7.7.1.

Because little or no censored data is anticipated in analyzing the primary effectiveness endpoint, the formula of Makuch and Simon [50] for the pure proportion analysis is used. This formula is

$$n = \frac{(\pi_T(1-\pi_T)+\pi_C(1-\pi_C))(z_\alpha + z_\beta)^2}{(\pi_T - \pi_C - \Delta)^2},$$

where n is the sample size per trial arm, π_T is the mortality rate in the Test arm, π_C is the mortality rate in the Control arm, and z_α and z_β are the percentiles of the standard normal distribution.

The final sample size for the primary analysis is based on a combined assumption as shown in the table above. The proposed sample size will give approximately 90% power

for the combined endpoint. Since the actual transfemoral/transapical split is a random variable, the power is also impacted by the split. However, this dependence is not severe.

If the transapical survival is truly better than transfemoral, the power will go up. If the transapical difference reaches the same 5% assumed for the transfemoral, the power will be over 95%.

It should be noted that these powers for the combined analysis ignore the impact of a potential interaction. A simulation, based on the feasibility assumptions, indicates that the probability of a statistically significant interaction (at the 0.05-level) is at least 10%. The interaction issue is further addressed in the statistical analysis section.

The minimum specified sample size of 450 transfemoral eligible patients will also give a power of 90% for the transfemoral subgroup. The interaction is irrelevant for this subgroup analysis.

Cohort B:

The feasibility assumptions for one year mortality are**:**

Patient Group	Mortality at 12 Months
Test Arm	25%
Control Arm	37.5%

The feasibility assumption for the Test arm is also from the REVIVAL trial. The feasibility assumption for Cohort B is taken from Charlson, Legedza, et al. [8] where the death rate for such patients is 45%; the 37.5% figure in our table is conservative.

For use of the sample size software, we also assume that the death rates follow a constant hazard distribution, and that trial enrollment is at a constant rate over 18 months, with additional follow-up of 1 year, and a lost to follow-up rate of 0.10 per year. Based on all these assumptions and $\alpha = 0.05$, the sample size of 175 per trial arm will give a power of 84%, as computed by nQuery Advisor 6.0 software. If the lost to follow-up can be managed in the trial, the power reaches the 85% goal specified above.

The sample size software also indicates that the power is based on a total of 148 deaths in the combined trial arms. In order to protect against deviation from the enrollment assumptions, an additional criterion of 150 deaths has been placed on determining the analysis close date for Cohort B.

It remains to consider the power of the secondary endpoint that uses the Finkelstein-Schoenfeld methodology. The first patient comparison in this test is survival; the increase in power over the survival test comes from the additional comparisons based on recurrent hospitalization and NYHA evaluation. Based on the assumptions outlined below, we estimate that the power for the Finkelstein-Schoenfeld test will be at least 95%. Because the test is not considered in standard sample size software, these values are obtained by simulation.

For the one year rehospitalization, the assumption is that reoperation will occur on the basis of a constant hazard model, with the hazard rate 12% per year for the Test arm and 20% per year for the Control arm.

- The 12% rate in the Test arm is approximately what was observed in the Revive and Revival trials; however, the definitions are not identical and this must be considered an educated guess only.

- The 20% rate in the Control arm is loosely based on a number of different papers, although none considers the exact information needed for this trial. The paper of Otto [28], indicates that 64% of patients were rehospitalized in a 3-year study. Other literatures support the same general rate assumptions, although some are higher and some lower.

- The constant hazard model has been chosen because it is simplest, and we have no specific information to suggest what model might be better.

- For simulation purposes it was assumed that the rehospitalization and survival distributions are independent. This independence cannot be strictly true, since many deaths will be preceded by rehospitalization. However, most of these rehospitalizations will be irrelevant in the Finkelstein-Schoenfeld analysis, since death is considered first in comparing pairs of patients. In any event, there are no data to assume a specific dependence pattern.

For one-year NYHA, the assumptions are:

- For the test arm, the proportion of patients in NYHA classes (I, II, III, and IV) is (30%, 45%, 15%, 5%) respectively. The missing 5% is to account for missing data. These figures are based on the Revive and Revival trials.

- For the control arm, the proportion of patients in NYHA classes (I, II, III, and IV) is (15%, 30%, 45%, 5%) respectively. The missing 5% is to account for missing data. We do not have directly relevant feasibility data. The Otto paper does report somewhat better NYHA values, but we feel those are unlikely to be reproduced in our patient group.

- For simulation purposes it was assumed that the NYHA distribution was independent of both the rehospitalization and survival distributions. This independence cannot be strictly true, since many deaths or rehospitalizations will be preceded by raised NYHA. However, the NYHA values are not of major importance for patients who die or are rehospitalized. In any event, there are no data to assume a specific dependence pattern.

- The assumptions used in the simulation are definitely not solid gold, but they represent reasonable assumptions based on limited feasibility data. In any event, the final trial analysis is based on observed data rather than these assumptions. The sponsor accepts the risk that the assumptions were unduly optimistic.

Notes:

a) For the purposes of completion of training which includes 2 proctored procedures (there is a need to allow for scheduling of proctors), there will be 2 roll-in patients with successful delivery of the Edwards SAPIEN Transcatheter Heart Valve to its intended location per delivery approach per new clinical site [excluding sites participating in REVIVAL II trial (Edwards study 2005-01-PHV)]. These patients will not be included in the total enrollment population nor the data analysis.

b) 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.

5.1.1 Enrollment Close

Total enrollment for the trial is a minimum of 1040 patients, subject to further clarification below. When the sponsor has been notified that the necessary number of patients has been enrolled, the sites will be notified to discontinue enrollment. However, all consented patients will still be allowed to receive the treatment for their trial arm. This may result in a small number of additional patients in the trial. All such patients will be included in trial analysis.

Some sites may also be notified to stop enrollment in one or both cohorts due to the 15% limitation mentioned in section 5.1, note b.

The enrollment in Cohort A will be from 690 to 750 randomized patients, with a minimum of 450 transfemoral eligible patients and 200 transapical eligible patients. Enrollment will continue past 690 if needed to meet both minima. If 750 patients do not meet both minima, the FDA will be contacted to determine the further course of action.

The rationale for the approach minima given above is to avoid biasing the physician's assignment decision between transfemoral and transapical. Clinicians have consistently advised that determination of transfemoral eligibility cannot be performed with mathematical precision; instead there is a considerable gray area where a knowledgeable physician might decide in either direction. If physicians were forced to meet precise targets within the 690 there would be no way to avoid such bias.

The enrollment in Cohort B will be 350 randomized patients.

5.2 Subject Selection Criteria

This is a stratified study of patients at high risk for surgery. All subjects who meet the study eligibility requirements will be stratified into cohorts for operability, followed by stratification based on vascular access. Those not meeting vascular criteria for transfemoral delivery are candidates for transapical approach.

Patients who are considered high surgical risk and eligible for transfemoral access will be stratified into Cohort A and randomized to treatment (transfemoral AVR) or control (surgical AVR). Patients who are considered high risk and not eligible for transfemoral access will be stratified into Cohort A and randomized to treatment (transapical AVR) or control (surgical AVR). Those patients who are considered non-surgical candidates are

stratified into Cohort B and randomized to treatment (transfemoral AVR) or control (medical management). Those who are non-operable and assigned to Cohort B but are not eligible for transfemoral delivery will not be eligible for randomization into the trial.

Candidates for this study must meet **all** of the following Inclusion/Exclusion criteria:

5.2.1 Inclusion Criteria

Cohort A:

All candidates for Cohort A of this study must meet **all** of the following Inclusion criteria:

1. Patients must have co-morbidities such that the surgeon and cardiologist Co-PIs concur that the predicted risk of operative mortality is ≥15% and/or a minimum STS score of 10. A candidate who does not meet the STS score criteria of ≥10 can be included in the study if a peer review by at least two surgeon 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 in the study case report form as well as in the patient medical record.
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 or an initial aortic valve area (AVA) of < 0.8 cm^2 (indexed EOA < 0.5 cm^2/m^2). (Qualifying AVA baseline measurement must be within 30 days of study valve implantation procedure).
3. Patient is symptomatic from his/her aortic valve stenosis, as demonstrated by NYHA Functional Class II or greater.
4. The subject or the subject'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 subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits.

Cohort B

All candidates for Cohort B of this study must meet # 2, 3, 4, 5 of the above criteria, ***and***

6. The subject, after formal consults by a cardiologist and two cardiovascular surgeons agree 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 should exceed 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 these patients.

5.2.2 Exclusion Criteria

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

1. Evidence of an acute myocardial infarction ≤ 1month 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 bicuspid valve, or is non-calcified.

3. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).

4. Any therapeutic invasive cardiac procedure performed within 30 days of the index procedure, (or 6 months if the procedure was a drug eluting coronary stent implantation).

5. Pre-existing prosthetic heart valve in any position, prosthetic ring, or severe (greater than 3+) mitral insufficiency.

6. Blood dyscrasias as defined: leukopenia (WBC<3000 mm^3), acute anemia (Hb< 9 mg%), thrombocytopenia (platelet count <50,000 cells/mm^3), history of bleeding diathesis or coagulopathy.

7. Untreated clinically significant coronary artery disease requiring revascularization.

8. Hemodynamic instability requiring inotropic support or mechanical heart assistance.

9. Need for emergency surgery for any reason.

10. Hypertrophic cardiomyopathy with or without obstruction (HOCM).

11. Severe ventricular dysfunction with LVEF <20.

12. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.

13. Active peptic ulcer or upper GI bleeding within the prior 3 months.

14. A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media, which cannot be adequately pre-medicated.

15. Native aortic annulus size < 16mm or > 24mm per the baseline echocardiogram as estimated by the left ventricular outflow tract (LVOT).

16. Patient has been offered surgery but has refused surgery.

17. Recent (within 6 months) cerebrovascular accident (CVA) or a transient ischemic attack (TIA).

18. Renal insufficiency (creatinine > 3.0) and/or end stage renal disease requiring chronic dialysis.

19. Life expectancy < 12 months due to non-cardiac co-morbid conditions.

20. Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5cm or greater; 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 (applicable for transfemoral patients only).

21. Iliofemoral vessel characteristics that would preclude safe placement of 22F or 24F introducer sheath such as severe obstructive calcification, severe tortuosity or vessels size less than 7 mm in diameter (applicable for transfemoral patients only).

22. 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].

5.3 Subject Screening

The screening phase of the trial is designed to meet three objectives:
1) determine subject eligibility, 2) determine surgical risk for stratification into the high risk Cohort A or inoperable Cohort B, and 3) evaluate vascular access characteristics to determine eligibility for transfemoral delivery; those not meeting the criteria for transfemoral delivery are candidates for transapical delivery.

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 in section 5.5. The screening of patients in both departments will be coordinated by one study coordinator who will be a member of the Institution's research team assigned to the trial. The study coordinator will be responsible for ensuring and reporting subject screening for study eligibility. A screening log will be provided to study sites to maintain a cumulative log of all the screened patients and patients enrolled. Reasons for meeting study criteria, but failure to enroll will be captured on the screening/enrollment log and will be monitored in the trial. This screening/enrollment log will be completed and faxed or emailed by the site study coordinator to Edwards Lifesciences on a weekly basis. Summaries of patient enrollment data along with patient screening and enrollment logs will be reviewed periodically by the study executive committee, co-PIs and DSMB to monitor for appropriate stratification between Cohort A and Cohort B.

Surgical risk profiles will be evaluated by the STS Risk Score Calculator. Additional assessments regarding the patient's "operability" will be assessed by the surgeon investigator (this will be further discussed in the "Patient Enrollment"). To ensure consistency of risk score assessment and documentation, the *STS Risk Score Calculator* is available on line at www.STS.org. A candidate who does not meet the STS

score criteria of ≥10 can be included in the study if a peer review by at least two surgeon investigators (not including the enrolling surgeon) concludes and documents that the patient's predicted risk of operative mortality is ≥15%.

5.4 Informed Consent

All potential subjects must be consented prior to the screening assessments as well as the study procedures. Once the Investigator has determined the subject's eligibility for the study through the screening process, the background of the proposed study and the benefits and risks of the study and procedures must be explained to the subject. The subject (or the subject's legal representative) must sign the Institution's Ethics Committee (EC) approved informed consent forms (Appendix C) prior to participation as described below in section 5.5. Failure to provide informed consents renders the subject ineligible for the study.

5.5 Enrollment

Prior to patient enrollment, potential study patients will require screening tests determining study eligibility. Accordingly, a Screening Informed Consent form will be required prior to completing the screening tests as follows:

Apart form a medical history evaluation, physical examination, blood work analysis, NYHA classification assessment, either transthoracic or transesophageal echocardiography assessment, all candidates shall have the following assessments:

1) A NIHSS exam will be performed prior to enrollment. Patients with abnormal findings and who have had a CT or MRI confirmed stroke (within 6 months), will not be eligible for enrollment. Additionally, a CT or MRI brain scan will be performed for any subject with an abnormal result on the stroke scale at baseline whether or not they have a documented stroke OR any subject that has had a stroke in the past 6-12 months that did not receive a post stroke image or there is no record of an image IF there is an abnormal change in the NIH stroke scale.

2) A screening thoracic and abdominal aortograms or thoracic and abdominal CT angiograms with complete visualization of both iliacs and femorals to the aorta will be performed. In the situation where patients have compromised renal function that precludes contrast media, MR imaging may be used as an alternative. These studies will determine vascular access eligibility and will be confirmed by a vascular interventionalist.

3) Left and right heart catheterization will be done to assess the severity of aortic stenosis and severity of coronary artery disease if applicable.

All subjects who meet the study eligibility requirements will be stratified into cohorts for operability, followed by stratification based on vascular access. Patients who are considered high surgical risk and eligible for transfemoral access will be stratified into Cohort A and randomized to treatment (transfemoral AVR) or control (surgical AVR). Patients who are considered high risk and not eligible for transfemoral access will be stratified into Cohort A and randomized to treatment (transapical AVR) or control (surgical AVR). Those patients who are considered non-surgical candidates are stratified into Cohort B and randomized to treatment (transfemoral AVR) or control

(medical management). Those who are non-operable and assigned to Cohort B but are not eligible for transfemoral delivery will not be eligible for randomization into the trial. Patients who are stratified as high risk surgery but refuse surgery may not be enrolled in the trial. Once the patient understands their cohort assignment, the patients will then be required to sign a separate Study Procedure Informed Consent form. Subjects will be considered enrolled into the study after completion of all four of the following steps:

- Signed Screening Informed Consent is obtained.
- Based on the screening assessments it is determined that the subject meets all of the inclusion and none of the exclusion criteria.
- The trial cohort has been determined, and understood by the patient.
- Signed Study Procedure Informed Consent is obtained.

5.6 Randomization

After the patient is enrolled into the trial they will undergo randomization to treatment versus control.

- The high risk surgical patients will be randomized against surgery on a 1:1 basis.
- The non-surgical cohort will be randomized against medical therapy on a 1:1 basis.

All other baseline assessments, apart from those stated above will be performed after the patient is enrolled and randomized.

Subjects will be randomized according to a computer-generated randomization scheme. Randomization will be blocked separately at each clinical site, and separately in the two trial cohorts. The sites will not be informed of the precise block sizes.

For purposes of analysis, intent to treat is established at the moment of patient randomization.

5.7 Subject Withdrawal

All living subjects are required to complete clinical follow-up. Subjects will be exempt from follow-up only if they withdraw their consent. A study subject that has been withdrawn from the study will not be replaced.

5.8 Prior to Study Procedures

5.8.1 Baseline Assessments

Informed consent will be obtained from all subjects who are potential trial candidates prior to commencement of study related procedures. All medications (long-acting nitrates, diuretics, cardiac glycosides, etc.) will be continued at their chronic prescribed dosages.

The following baseline data will be collected for all subjects prior to procedure or the medical management commencement (see Table 6 in Section 5.12).

1) Physical assessment and patient interview; Medical history and pertinent physical examination [includes vital signs and all major systems findings, including weight, height and body surface area (BSA); BSA will be calculated from height and weight by use of the formula by Dubois and Dubois (BSA = 0.007184 × weight [kg]$^{0.425}$ × height [m]$^{0.725}$)];
2) Current medications;
3) CCS status of angina;
4) NYHA status of congestive heart failure (assessed by non-implanting physician);
5) History of syncope not related to AV block;
6) Number of hospitalizations for symptoms of aortic stenosis for the last 6 months;
7) Baseline Quality of Life Survey(s);
8) Baseline NIHSS Stroke Scale and Mini-Mental State Exam (AppendixH). Baseline neurological assessment should include a careful neurological exam including cranial nerves, peripheral assessment of motor and sensory, and cerebellar function performed by a physician or physician assistant or nurse practitioner.
9) STS Risk Score
10) Logistic EuroSCORE
11) Six Minute Walk Test
Patient who exhibit any of the following criteria will be exempt from the Six Minute Walk test:

1) postural hypotension, 2) postural change in heart rate, arrhythmia, 3) resting systolic pressure less than 95mmHg, 4) non-ambulatory due to PVD, neuromuscular or severely arthritic disease, 5) COPD with 02 desaturation on ambulation, or oxygen dependent, or 6) unstable angina

Clinical Laboratory Tests

12) CBC with differential and platelet count (≤ 2 weeks before procedure);
13) Complete metabolic panel (≤ 2 weeks before procedure);
14) Liver panel
15) Albumin
16) B-type natriuretic peptide (BNP)
17) Plasma free hemoglobin (if possible);
18) Haptoglobin and reticulocytes (if possible)
19) Troponins or cardiac enzymes (CK/CK-MBs) ≤ 24 hours before the procedure or at the time of access, but before the procedure;
20) PTT or PT/INR if applicable

Non-Invasive Studies

21) Standard 12-lead ECG (an ECG performed ≤ 48 hours prior to the procedure may be used as the baseline ECG)
22) Comprehensive transthoracic or transesophageal 2D echocardiogram, including assessment of aortic valve gradients (mean and peak), areas, indices, degree of regurgitation, cardiac output and cardiac index, left ventricle systolic function (global and segmental); (less than 30 days before the procedure or randomization to medical management)
23) Chest X-ray examination
24) CT or MRI brain scan for any subject with an abnormal result on the stroke scale at baseline whether or not they have a documented stroke OR any subject that has

had a stroke in the past 6-12 months that did not receive a post stroke image or there is no record of an image IF there is an abnormal change in the NIH scale.

Invasive Studies

25) All candidates should have screening thoracic and abdominal aortograms or thoracic and abdominal CT angiograms with complete visualization of both iliacs and femorals to the aorta. In the situation where patients have compromised renal function that precludes contrast media, MR imaging may be used as an alternative.
26) All candidates should have left and right heart catheterization to assess the severity of aortic stenosis and severity of coronary artery disease if applicable.

5.9 Procedure Assessments

The following data are to be collected pre and post implant:

27) Aortic systolic/diastolic pressure, Mean aortic pressure, Mean AV gradient, Peak AV gradient
28) Simultaneous Aortic and LV pressure measurements for valve area calculation
29) RA pressure, PA systolic/diastolic pressure, Mean PA pressure, PCWP pressure, Cardiac output and Cardiac index
30) A supra-aortic angiogram for valve performance and coronary patency.

5.10 Device Preparation

A detailed description of device preparation and required equipment is supplied in the Instructions for Use, Appendix I.

5.11 Procedure Notes

Patients who are randomized to Cohort A (control arm) will be implanted with a commercially available Carpentier-Edwards® pericardial aortic bioprosthesis.

5.11.1 Arteriotomy for Retrograde Approach

A consultation with a cardiovascular or vascular surgeon is required for the determination of the appropriateness of the femoral artery access for the procedure as well as arteriotomy creation and closure.

5.11.2 Recommended Antiplatelet/Anticoagulation Regimen

At the Investigator's discretion, it is recommended that all patients receive aspirin (75-100 mg daily) and clopidogrel (300 mg loading dose if patient is not currently taking clopidogrel, and then 75 mg. daily) prior to procedure. Ticlopidine may be used instead of clopidogrel at the Investigator's discretion. The ACT should be monitored and recorded on source documentation during the procedure and adjusted to keep the patient's ACT$\geq$250 sec. The sheaths may be removed when ACTs reach <150 sec after implantation of the study valve (for non-surgical closure).

Table 5. Summary of Recommended Concomitant Medical Therapy

Medication	Pre-Procedure	During Catheterization	Post-Procedure	30 -Day Follow-up	6-M Follow-up
IV Heparin	PRN	5000 IU Bolus, then as needed to achieve/maintain ACT≥250 sec.			
Aspirin	75-100 mg QD		75-100 mg QD	75-100 mg QD	75-100 mg QD for life
Clopidogrel*	300 mg po (if not on long-term therapy)	75 mg po QD	75 mg po QD	75 mg po QD for 6 M100	

* Ticlopidine may be used instead of clopidogrel at the Investigator's discretion.

5.11.3 Antibiotic Prophylaxis

It is recommended that all heart valve recipients be prophylactically treated for endocarditis per the recommendations of the American Heart Association [51].

5.11.4 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.

5.11.5 Radiation Skin Dose Calculation

A skin dose dosimeter will be placed at the area of the thyroid in all patients. Data on total radiation exposure, as well as total procedural fluoroscopy time will be collected on the case report forms.

5.12 Post-Procedure

Subjects will be continuously monitored clinically, hemodynamically, and electrocardiographically during catheterization for all local and systemic side-effects. After completion of the procedure, all subjects will be monitored in the catheterization laboratory or operating room for at least 15 minutes with special attention to hemodynamic condition and cardiac rhythm.

Subsequent monitoring will be continued in the ICU. On day 1 (up to 36 hours post procedure), a chest x-ray will be taken to define the patient's initial valve implantation position and blood draws will be performed to monitor the patient's cardiac enzymes. See Table 6, Subject Schedule of Events.

Table 6: Subject Schedule of Events

	Baseline	During procedure	Day 1 (Up to 36 hrs post procedure)	Discharge / 7 D Follow Up[i]	30 D Follow Up	6 M Follow Up	12 M Follow Up	Annual Follow Up ≥5 Y	Telephone Follow-up 1 Y Post Last Patient Enrolled[ii]
Physical assessment and Patient interview									
Informed Consent	X								
History	X								
Physical Exam	X			X	X	X	X	X	
CCS Angina	X			X	X	X	X	X	
NYHA Class	X			X	X	X	X	X	
Current Medications	X	X		X	X	X	X	X	
Event Assessment		X		X	X	X	X	X	X[iii]
NIH Stroke Score Assessment	X			X	X	X	X	X	
Mini Mental State Exam	X								
Risk Score Assessments: STS Risk Score and Logistic EuroSCORE	X								
Six Minute Walk Test	X				X	X	X		
Lab Measurements									

	Baseline	During procedure	Day 1 (Up to 36 hrs post procedure)	Discharge / 7 D Follow Up[i]	30 D Follow Up	6 M Follow Up	12 M Follow Up	Annual Follow Up ≥5 Y	Telephone Follow-up 1 Y Post Last Patient Enrolled[ii]
CBC with Differential and Platelet Count	X				X	X	X		
Troponins or CK, CK-MB	X		X						
Complete Metabolic Panel	X					X	X		
Liver Panel	X								
Albumin	X								
BNP	X			X	X	X	X	X	
PTT or PT/INR if applicable	X				X	X	X		
Plasma Free Hemoglobin & Haptaglobin[iv]	X				X	X	X		
Non-Invasive Tests									
ECG	X			X	X	X	X		
Chest X-ray	X		X	X	X	X	X		
Echocardiogram – TTE or TEE[v]	X			X	X	X	X	X	
Invasive Tests									
Abdominal Aortogram	X[vi]								
Aortic arch angiogram	X[vi]	X							

	Baseline	During procedure	Day 1 (Up to 36 hrs post procedure)	Discharge / 7 D Follow Up[i]	30 D Follow Up	6 M Follow Up	12 M Follow Up	Annual Follow Up ≥5 Y	Telephone Follow-up 1 Y Post Last Patient Enrolled[ii]
Economics and Quality of Life Measures									
Kansas City Cardiomyopathy	**X**				**X**	**X**	**X**		
EuroQOL	**X**				**X**	**X**	**X**		
SF-12	**X**				**X**	**X**	**X**		

[i] Discharge/7 Day follow-up is required for patients undergoing the test therapy, surgical intervention (Cohort A, control arm) or Cohort B, control arm patients who are hospitalized for treatment. Day zero is the date of randomization for Cohort B, control arm patients.
[ii] See section 5.12.1. *Follow-up Procedures*
[iii] The additional telephone follow-up will be performed for the purposes of determining patient survival and hospitalization post last follow-up only.
[iv] If possible
[v] TEE will be performed if TTE examination is inadequate. TEE will be accepted in place of TTE if performed for other reasons.
[vi] All candidates should have screening thoracic and abdominal aortograms or thoracic and abdominal CT angiograms with complete visualization of both iliacs and femorals to the aorta.

5.12.1 Follow-up Procedures

Follow-up procedures will be conducted at the intervals specified in Table 6. 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 is collected at scheduled follow-ups as well as at unscheduled visits, including the echocardiogram, ECG and the Quality of Life questionnaires, will 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 discharge, 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 subject. 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 subject'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) days, 6 months (180 days ± 14 days), 12 months (365 ± 30 days), and annually (anniversary date ± 45 days) for a minimum of 5 years. At 30-days, 6 and 12 months, the following examinations will be conducted: Physical Exam, CCS Angina, NYHA Class, Current Medications, Event Assessment, the NIHSS, 6-minute walk test (if eligible), CBC with differential, Complete Metabolic Panel (at 6 and 12 months), B-type natriuretic peptide (BNP), PTT or PT/INR if applicable, Plasma Free Hemoglobin & Haptaglobin, ECG, Chest XRay, Echocardiogram, The Kansas City Cardiomyopathy Assessment, EuroQOL and SF-12. Annual follow-up visits for up to five years thereafter will include Physical Exam, CCS Angina, NYHA Class, Current Medications, Event Assessment, the NIHSS and echocardiogram. Patients in the control arms will be followed annually for a minimum of five years, patients in the treatment arms will be followed through their lifetime via phone interviews.

The actual timing of the 30-day visit depends on the cohort and trial arm.

- For Cohort B Control patients, the 30-day time period starts at randomization.
- For all other patients, the 30-day time period starts on the date of the implant procedure. If the implant procedure never occurs for a patient, then the 30-day visit will never occur for that patient.

For 6-month and later visits, the time period starts at randomization for all patients.

At one year (365 days – 395 days) past enrollment of the last patient, an additional telephone follow-up will be performed for all patients for the purposes of determining patient survival and hospitalization post last follow-up only. The reason for this additional follow-up is that the exact one year survival information is needed for

evaluating the Cohort A primary endpoint, and the latest possible survival information is needed for evaluating the Cohort B primary endpoint.

5.13 Assurance of thorough follow-up (Medical Management Group)

The clinical research coordinator will contact the patients after discharge. Documented measures will be taken to ensure and track that the medical therapy group has the same number of contacts with the medical personnel as do the Cohort A patients over the course of the first year.

6 Endpoint Data Collection

6.1 ECG

All ECGs will be sent to the ECG Core Lab (see Appendix D) 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

The pre-procedure transthoracic or transesophageal echocardiograms (TTE or TEE) will be performed to assess risk factors and eligibility. Post procedure TTE will be performed at the intervals specified in Table 6. If post procedure TTE is not adequate, TEE will also be performed. All echocardiograms will be independently analyzed by the Echocardiographic Core Lab (see Appendix D). 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, and 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 Economics and Quality of Life Sub-Study

Costs directly related to the procedure as well as costs for 6 months and I year after procedure will be collected beginning with each patient's index hospitalization and continuing through any subsequent hospitalizations during the follow-up period. Quality of life will also be measured through standard survey(s). The protocol describing this plan and the analysis to be used is located in Appendix E.

6.4 Six Minute Walk Test

A six minute walk test per the American Thoracic Society Guidelines (2002) (Appendix J), will be performed unless the patient is exempt due to any of the following conditions: (postural hypotension, postural arrhythmia, resting systolic pressure less than 95mmHg, non-ambulatory due to arthritis, neuromuscular disease or PVD, COPD with O_2 desaturation upon ambulation or oxygen dependent, unstable angina) will not undergo the test, but the reasons for not performing the test must be completed on the six minute walk test case report form.

6.5 Clinical Follow-up

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

6.6 Histopathology Studies

Histopathology studies of explanted valves, including those removed during AVR surgery 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). Only those investigational valves that are removed during the THV procedure will be returned to the Sponsor for evaluation. Appendix F 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 are to 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).

7 Statistical Analysis

7.1 Visit Windows

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 5.12.1 of the 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.

7.2 Patient groups

7.2.1 Trial cohorts

As defined above in this protocol, there are two trial cohorts, Cohort A "high risk surgery" patients and Cohort B "excessive risk for surgery (non-surgical)" patients. Patients are assigned to one of these cohorts before randomization. Unless otherwise specified, the two cohorts will not be pooled for analyses.

All analyses for Cohort A will be presented for the combined transapical/transfemoral approaches, and for the approaches separately. Analyses will also compare the two approaches wherever statistically meaningful.

7.2.2 Trial arms

Test arm:

Patients randomized to the Test arm will receive the valve implant using the transfemoral or transapical approach in the high risk surgery cohort, and the transfemoral approach in the non-surgical cohort.

Control arm:

Patients randomized to the Control arm in the high risk surgery cohort will undergo surgical AVR. Patients randomized to the Control arm in the non-surgical cohort will receive best medical therapy.

7.2.3 Analysis populations

Intent to treat (ITT) population:

Intent to treat (ITT) will be defined at the moment the randomization is performed. For the primary endpoint analysis in this trial, patients will be followed with their ITT arm. In analyses referring to a specific number of days, the randomization day will be considered day 0.

As-treated population:

This population is based on the treatment actually received. This population will be used for the adverse event analyses.

Test arm – Cohort A:

This population consists of the Cohort A patients randomized to the Test arm for whom the study valve implant procedure is begun, and the day of implant is considered day 0 for these patients. The definition of "procedure is begun" is "the time the study catheter is placed in the patient in the catheterization laboratory."

If a Test patient in Cohort A is assigned to the transfemoral approach, and it is determined during further access evaluation that the transapical approach is needed, that patient will be considered a transapical patient for as treated analyses of implant subgroups. This will not impact the combined Cohort A analysis.

Test arm –Cohort B:

This population consists of the Cohort B patients randomized to the Test arm for which the study valve implant procedure is begun, and the day of implant is considered day 0 for these patients. The definition of "procedure is begun" is "the time the study catheter is placed in the patient in the catheterization laboratory."

Control arm – Cohort A:

This population consists of the Cohort A patients randomized to the Control arm for whom the valve implant procedure is begun, together with Cohort A patients randomized to the Test arm who receive an open aortic valve replacement instead of the Test valve. The day of implant is considered day 0 for these patients. The definition of "procedure is begun" is "the induction of general anesthesia for the open operation."

Control arm – Cohort B:

This population consists of two groups:

- The Cohort B patients randomized to the Control arm.
- Other Cohort B patients who did not receive a valve implant.

Not included:

A Cohort A patient who does not receive either the test valve or an open aortic valve replacement will not be included in the as-treated analysis. If there are any such patients, a separate report will be made of their adverse experience.

Valve implant population

The valve implant population will be defined as the subset of the as treated population consisting of those patients (Test or Control) for whom the valve is implanted and remains in position.

Crossovers:

Trial analysis does not allow for crossover from one assignment group to another. However, it is inevitable that some patients will not receive the randomized treatment, generally for sound medical reasons. Such situations do not impact the ITT analysis.

The as-treated population will reflect the treatment actually received.

7.2.4 Analysis close date

The analysis close date for Cohort A is at the completion of one-year follow-up on the cohort. The primary endpoint is based on the exact one-year time point for each patient, and event. For other analyses all available data will be used.

The analysis close date for Cohort B is the later of two dates:

- The completion of one-year follow-up on the cohort.
- A total of 150 deaths in the combined trial arms.

The reason for the second criterion is in order to preserve power in case the actual enrollment deviates from the feasibility assumptions. This additional criterion does not in any manner depend on endpoint evaluation, and accordingly, no alpha correction is appropriate.

7.3 Primary and Secondary Endpoints

7.3.1 Primary Endpoint (effectiveness and safety)

The primary effectiveness and safety endpoint for Cohort A is freedom from all cause mortality at exactly day 365, analyzed in the ITT population.

The test will be performed as a one-sided non-inferiority test, using the non-inferiority margin $\Delta = 0.075$. The acceptance criterion for the test is that the freedom from death in the Test arm be not inferior to the freedom from death in the Control arm. Covariates will not be included in analysis of the primary endpoint.

The methodology for performing this non-inferiority test is described in section 7.7.1. *Non-inferiority Testing.*

The primary effectiveness and safety endpoint for Cohort B is freedom from all cause mortality over the duration of the trial. The trial arms will be compared using the log-rank test, as a two-sided test. The acceptance criterion for the test is that the freedom from death in the Test arm be significantly higher than the freedom from

death in the Control arm. For the purpose of this analysis, the latest available data will be used for each patient. These data will cover a period longer than one year for many patients in the trial, and the sample size has been based on including all such data.

The study will be deemed a success for each cohort if the primary endpoint for that cohort is met. It is acknowledged that reviewing agencies will also consider the secondary endpoints in making produce approval decisions.

7.3.1a Interaction analysis

In order to analyze interaction, a logistic regression model will be fit for death at one year. The model will include an intercept term, an approach term, a trial arm term, and an approach*trial arm interaction term.

If the interaction term is not statistically significant, the approaches will be deemed poolable for purposes of the primary analysis. Statistical significance will be judged at alpha = 0.10, using the Wald statistic[1].

If the interaction term is statistically significant, Edwards accepts that reviewers may place additional reliance on the subgroup analyses. Since the trial is powered for the combined analysis, Edwards also accepts that in analyzing the subgroups reviewers may place additional reliance on the various secondary analyses.

Even though this protocol calls for a special telephone follow-up for purposes of one-year survival analysis, it is realistic that there will be some patients lost to follow-up. For endpoint analysis purposes these patients are handled by Kaplan-Meier. But there is no direct way to include these patients in the logistic analysis.

Instead all lost patients will be excluded from the interaction analysis. The Rita 3 paper also points out that including the log time term made negligible difference to the results.

As an additional analysis of the interaction term a multiple imputation will be presented.

7.3.2 Secondary endpoints

The secondary endpoints listed in this section will be evaluated in the ITT population, or the as treated population, whichever is appropriate for the endpoint. For clarity each endpoint will contain a statement as to the population used.

Powered secondary endpoint for Cohort B (ITT population).

The powered secondary endpoint for Cohort B is based on a combination of the all cause mortality, time to first recurrent hospitalization, and NYHA, using the method of Finklestein and Schoenfeld [52]. More specifically, for each pair of patients (call them patients *i* and *j*), we define a score u_{ij} in the following manner:

[1] The sponsor believes that the normal statistical standard of alpha = 0.05 is the most appropriate. The larger value has been included at the request of the FDA.

(1) If patient *i* is known to have lived longer than patient *j*, then u_{ij} = 1 (if patient *j* is known to have lived longer, then u_{ij} = -1). This determination would happen if death dates are available for both patients, or if one patient was censored at a later time than the death time for the other.

(2) Time to first recurrent hospitalization: If it is not known which patient has lived longer, then compare the time to first recurrent hospitalization using the same methodology as for survival. If patient *i* is known to have a longer time to first rehospitalization than patient *j*, then u_{ij} = 1; (if patient *j* known to have a longer time, then u_{ij} = -1).

(3) NYHA: If the comparison is still unresolved, then compare NYHA score at the last time interval post-surgery at which both patients have data. If patient *i* has a lower NYHA than patient *j*, then u_{ij} = 1; if patient *i* has a higher NYHA than patient *j*, then u_{ij} = -1. If the values are equal, then u_{ij} will remain 0, in which case the 0 value will be used in the subsequent analysis.

In all cases, $u_{ij} = -u_{ji}$.

Note that the score looks first for a difference in survival. If there is no difference in survival, then the score looks for improvement in the one of the other measures. The final test statistic is based on the sum of the scores for patients in the treatment group. If we let D_i = 1 for patients in the test group and let D_i = 0 for patients in the control group, we define the statistic using the score described above:

$$T = \sum_{i=1}^{n} U_i D_i$$

where $U_i = \sum_{i \neq j} u_{ij}$ .Values for *T* greater than zero indicate superiority of the test arm as the mean of the test statistic is 0 under the null hypothesis of no difference between treatment and control). Finkelstein and Schoenfeld [52] derive the variance for this statistic:

$$V = \frac{n_T (n - n_T)}{n(n-1)} \sum_{i=1}^{n} U_i^2$$

where n_T is the number of patients in the test arm. Superiority of the test group may be tested by comparing $T/V^{1/2}$ to the upper 97.5th percentile of the standard normal distribution.

It should be noted that no imputation is made in the above analyses for missing or unevaluable NYHA data.

In keeping with the longitudinal nature of the test, as described by Finkelstein and Schoenfeld [52], the values for two patients must be obtained at the same time point if a comparison is to be made.

1. As a secondary analysis, the primary endpoint for Cohort A will be analyzed separately in the two approaches. Per trial design, this analysis does not have the same power as for the primary analysis in the combined approaches. Interaction will not be an issue in this analysis.

In addition, all analyses for Cohort A will be performed in the combined group, and in the separate approach subgroups.

2. Improved functional status per NYHA (Classification) at 30 days, 6 and 12 months, in the ITT population.

For both Cohorts A and B the percentage of patients in each NYHA classification at each time point will be reported by trial arm.

To test for a difference in NYHA between one year and baseline for the test group in Cohort A, NYHA will be treated as a continuous variable and the paired sample t-test will be used. The analysis for this endpoint will be based on complete case data. However, multiple imputation and a worst rank analysis will also be presented as sensitivity analyses.

To test the difference in NYHA between trial arms in Cohort B, the method of Lachin (1999) will be used. This method proposes that all patients with one-year NYHA data available be ranked according to NYHA, while patients that expire before one year are ranked in order of time of death below all patients that survive to one year. The difference in stochastic ordering between the trial arms can then be tested via a Wilcoxon signed-rank test. A key feature of this approach is that all patients that expire before one year receive a lower rank than patients that survive to one year. This methodology addresses the fact that a sizeable proportion of patients are expected to expire before reaching the one year visit, and the missing NYHA classifications for these expired patients cannot be considered missing at random (i.e. these observations are informatively missing) unless it is assumed that survival is entirely unrelated to NYHA classification. As NYHA is a measure of heart disease severity, this assumption is tantamount to supposing that the reason the one year NYHA classifications are missing (death) is unrelated to a decline in heart function patients expiring prior to one year. As this trial involves only patients with advanced heart disease, this assumption is not tenable. The method proposed is therefore thought to be more appropriate than the complete case and multiple imputation analyses as both these analyses require the assumption that all missing observations are missing at random, including those observations missing due to patient expiration.

To address the possibility of missing NYHA at one year for patients that are not known to be deceased, we propose an approach presented in McMahon and Harrell (2001). Under this approach, patients that are not known to be deceased but with missing NYHA at one year will be ranked above all deceased patients and tied with all surviving patients. McMahon and Harrell (2001) point out that this method is appropriate under the assumption that observations that are missing for reasons other than death are missing at random. As a sensitivity analysis, a second approach proposed by McMahon and Harrell (2001) will be presented which is appropriate when such observations are missing for reasons associated with disease progression (see Section 7.7.7 for details).

Additional quantitative assessment of functional status will be captured in the QOL surveys at 30 days, 6 and 12 months.

3. Freedom from MACCE and expanded safety composite events at 30 Days, 6 and 12 months, in the as treated population.

The Kaplan-Meier methodology described in section 7.7.1 will be used to compare freedom from MACCE and expanded safety composite events across trial arms at 30 days, 6 and 12 months.

4. Evidence of prosthetic valve dysfunction, in the as treated population.

The components of this endpoint are adverse events, and the analysis specified for adverse events will be used.

5. Length of index hospital stay, in the ITT population.

Length of index hospital stay will be compared between ITT trial arms in Cohort A. It is anticipated that this variable will be heavily right skewed, and the Wilcoxon rank sum test will be used.

6. Total first year hospital days, in the ITT population.

Total hospital days from randomization to one year post randomization will be compared between 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 to compare the trial arms.

- Measuring from the randomization date will ensure a common time interval for all patients, which will simplify the interpretation of the statistical results. If the patient is already hospitalized for the index procedure on the randomization date, then starting on the randomization date and starting at the beginning of the index procedure hospitalization will be the same.

- Valve implantation can be delayed for some patients, for various medical reasons. If one were to measure this endpoint from the index procedure two statistical problems would result. First, there would be no way to account for the time period before the index hospitalization, which might include other hospitalizations. (The patient might even die before the index hospitalization.) Second, starting the clock later than randomization would extend the evaluation period past 1 year, and appropriate follow-up data would not be available until the patient returned for the 2 year visit.

7. Improved QOL, in the ITT population.

The quality of life (QOL) instruments will be analyzed using the scoring algorithms distributed by the vendors of the instruments.

For each Test, patient the 30 Day, 6 and 12 month QOL will be compared against the preoperative QOL. The acceptance criterion is that the 30 Day and 6 and 12-month QOL be improved from baseline. For this purpose QOL will be treated as a continuous variable and the paired sample t-test will be used.

QOL will also be compared across trial arms via a regression model adjusted for patient baseline QOL. This model will account for repeated measures via an unstructured covariance matrix. The difference between arms will be tested statistically using a test of the appropriate model coefficients.

8. Effective orifice area (EOA) at 30 days, 6 and 12 months, in the as treated population. If the implanted valve is explanted, patients will not be evaluated at time points after the explant.

For each Test patient in Cohort A the follow-up EOA will be compared against the preoperative EOA. For this purpose the paired sample t-test will be used. An additional analysis will be to compare the proportion of patients who experience a 50% or greater increase in EOA. A further analysis will consider as a success a patient who either achieves an EOA increase of 100%, or who reaches an EOA of > 1.5 cm^2; the proportion of successes will be compared between trial groups. In both analyses, only complete case data will be used.

EOA will be compared across trial arms via a regression model adjusted for patient baseline EOA. This model will account for repeated measures via an unstructured covariance matrix. The difference between arms will tested be statistically using a test of the appropriate model coefficients.

A still further analysis will consider as a success a patient who reaches one of the EOA targets described below, based on native annulus size as evaluated by the preimplant echo. For an annulus size <= 21 mm, the target would be an EOA of 1.0 cm^2. For an annulus size > 21 mm, the target would be 1.4 cm^2. This would allow for comparison against the recently approved St. Jude Medical Biocor® Valve, where more than half of the patients reached these targets, based on St. Jude Medical Biocor® Valve labeling.

9. Six Minute walk.

For each Test 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 [53]*, 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. Patient response over time will be tested at each time point based on a repeated measures logistic regression model. An appropriate covariance matrix will be selected to account for repeated measures on each patient. This model will be adjusted by patient baseline six minute walk test. 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 have missing data at baseline or at a given follow-up time for reasons other than death will be accounted for via the imputation techniques presented in Section (7.7.7).

Additionally, the six minute walk distance at six months will be compared across trial arms via the method of Lachin (1999). This method proposes that all patients with 6MWT data available at a given time point be ranked according to 6MWT, while patients that expire before one year are ranked in order of time of death below all patients that survive to one year. The difference in stochastic ordering between the trial arms at each point can then be tested via a Wilcoxon test. More specifically, the null and alternative hypotheses for a given follow up time T are:

$$H_0: G_C(x) = G_T(x) \text{ and } K_C(t) = K_T(t) \text{ for } t \le T$$
$$H_A: G_C(x) < G_T(x) \text{ and } K_C(t) \le K_T(t) \text{ for } t \le T$$
$$\text{or}$$
$$G_C(x) \ge G_T(x) \text{ and } K_C(t) < K_T(t) \text{ for } t \le T.$$

$G_C(x)$ and $G_T(x)$ denote the distribution of 6MWT for patients surviving to time T in the control and test groups, respectively. $K_C(t)$ and $K_T(t)$ denote the distribution of survival times for the control and test arms, respectively. Lachin (1999) also presents a multivariate test that investigates the overall difference between the trial arms over all time points.

The Lachin (1999) methodology addresses the fact that a sizeable proportion of patients are expected to expire before reaching all follow up visits and the missing 6MWT for these expired patients cannot be considered missing at random (i.e. these observations are informatively missing). To account for patients with missing 6MWT at one year *for reasons other than death*, we propose an approach presented in McMahon and Harrell (2001). Under this approach, these patients will be ranked above all deceased patients and tied with all surviving patients. McMahon and Harrell (2001) note that this method is appropriate under the assumption that observations that are missing for reasons other than death are missing at random. As a sensitivity analysis, a second approach proposed by McMahon and Harrell (2001) will be presented which is appropriate when such observations are missing for reasons associated with disease progression (see Section 7.7.7 for details).

7.3.3 Multiplicity Adjustment

The protocol contains a large number of secondary endpoints and additional analysis. The trial sponsor acknowledges that all of these analyses may be considered by reviewing agencies as part of the product approval evaluation. The multiplicity discussions in this section refer to the specific secondary endpoints identified by the trial sponsor as most important for labeling.

The powered secondary endpoint for Cohort B is not part of this multiplicity adjustment, because it is intended that this endpoint would be passed.

Multiplicity adjustment will apply to a specific list of secondary endpoints within each cohort. Only the p-values of these secondary comparisons will be considered for labeling claims.

For these specified secondary endpoints, the data analysis will be done using Hochberg's procedure, as implemented in SAS PROC MULTEST. Hochberg's method is described in the online documentation furnished with SAS, version 9 [54].

The rationale for using Hochberg's method is because the secondary endpoints are expected to all work in the same direction. Schulz and Grimes [55] 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 [56], and is described in the FDA approved labeling for the InSync® ICD [57].

In order to describe the specific methodology of the Hochberg method, suppose that there are *n* secondary 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*.
- The method of analyses for all of these tests calls for two-tailed *p*-values. The term "meet statistical significance" above means that the *p*-value is less than the target, and that the difference is in the direction that favors the test device. Effectively these become one-tailed tests at half the *p*-value.

The chosen endpoints are:

For Cohort A there are 4 endpoints for this purpose:

1. Effective orifice area (EOA) at 1 year, compared between trial arms.
2. Total hospital days through 1year, compared between trial arms.
3. NYHA improvement, compared between baseline and 1 year in the Test arm.
4. EOA at 1 year, compared between baseline and 1 year in the Test arm.

The Cohort A analysis will be performed in the combined approaches.

For Cohort B there are 4 endpoints for this purpose:

1. EOA at 1 year, compared between trial arms.
2. Total hospital days through 1 year, compared between trial arms.
3. NYHA at 1 year, compared between trial arms.
4. Aortic regurgitation at 1 year, compared between trial arms.

The methods for testing each of these endpoints are described in Section 7.3.2.

As requested by the FDA, a formal hypothesis test formulation of each of these

specific endpoints is given below. The actual *p*-value used to determine statistical significance for each test is determined by Hochberg method, as described above.

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 imputations, are described elsewhere in this protocol.

EOA: [Cohort A #1 and Cohort B#1]

H_0: $EOA_{Test} = EOA_{Control}$.

H_1: $EOA_{Test} \neq EOA_{Control}$.

The test will be evaluated as a two-tailed test, using repeated measures in order to accommodate all follow-up data through the 1 year visit. This will be a complete case analysis, without any imputation for missing data.

Hospital days to one year: [Cohort A #2 and Cohort B #2]

H_0: Test arm hospital days distribution = Control arm hospital days distribution.

H_1: Test arm hospital days distribution $\neq$ Control arm hospital days distribution.

The test will be evaluated as a two-tailed test, using the Wilcoxon rank-sum test. Only time points through one year will be considered in this analysis. The actual number of hospital days will be used for patients who die before one year.

NHYA: [Cohort A #3] Test arm only

H_0: $NYHA_{Baseline} = NYHA_{1\ Year}$.

H_1: $NYHA_{Baseline} \neq NYHA_{1\ Year}$.

The test will be evaluated as a two-tailed test, using the paired-sample t-test. This will be a complete case analysis, without any imputation for missing data.

NHYA: [Cohort B #3]

H_0: $NYHA_{Test} = NYHA_{Control}$.

H_1: $NYHA_{Test} \neq NYHA_{Control}$.

The test will be evaluated as a two-tailed test, using the Lachin methodology described above.

EOA: [Cohort A #4] Test arm only

H_0: $EOA_{Baseline} = EOA_{1\ Year}$.

H_1: $EOA_{Baseline} \neq EOA_{1\ Year}$.

The test will be evaluated as a two-tailed test, using the paired-sample t-test. This will be a complete case analysis, without any imputation for missing data. Only the one-year data will be used in this analysis.

Aortic regurgitation: [Cohort B#4]

H_0: $Regurgitation_{Test} = Regurgitation_{Control}$.

H_1: $Regurgitation_{Test} \neq Regurgitation_{Control}$.

For this test, aortic regurgitation will be considered as a continuous variable, as opposed to dichotomization. The test will be evaluated as a two-tailed test, using repeated measures in order to accommodate all follow-up data through the 1 year visit. This will be a complete case analysis, without any imputation for missing data.

7.4 Additional Safety Variables

All adverse events, including the additional safety variables, will be analyzed using the as-treated trial arms. Events occurring prior to implant will not be included. The primary purpose of this restriction is to ensure that the Test arm data do not include denominator information from the time before implant. Any bias introduced by this choice will work against the device.

Adverse events to be analyzed will include the specific adverse events gathered on the CRFs. Composite analyses will include MACCE, expanded safety composite events, device related events, and serious AE's. Analysis will also include the additional safety endpoints described in this protocol.

Where AE's are adjudicated by the CEC, the adjudicated classifications will be used in preference to the original investigator classifications.

Within each trial cohort, data will be stratified into: the control group, and the transfemoral or transapical test group. Within each trial cohort, comparisons will be made as described below.

- Perioperative adverse events will be analyzed as a proportion of patients experiencing the event. Test and Control will be compared within each trial cohort. 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 within each trial cohort.

- The time to first adverse event will be analyzed as a time dependent variable. Test and Control will be compared within each trial cohort. This analysis will be performed for each event type.

7.5 Additional Efficacy Variables

7.5.1 Device Success and Procedure Success

Device Success will be analyzed as a binary variable. These analyses will be presented for the test arms separately in each trial cohort. There will be no comparison against the control. The same analysis will be used for procedure success.

For aortic regurgitation, the proportion of patients achieving regurgitation of 3+ or less will be presented for each time point; a similar proportion will be presented for patients achieving aortic regurgitation of 2+ or less. Additionally, tables and graphs will be presented showing the trends of aortic regurgitation over time. These analyses will be presented for the test arms separately in each trial cohort. There will be no comparison against the control.

7.5.2 Cost and Cost Effectiveness

Medical care costs will be analyzed and compared between trial arms. No imputation will be made for additional costs that might have been accumulated by patients who die during the trial. It is anticipated that cost data will be difficult to collect and difficult to compare among different centers. The data will simply be presented as they are available.

7.6 Additional Analyses

7.6.1 Hemodynamic valve function

Summary statistics for peak gradient, mean gradient, effective orifice area (EOA), EOA index, performance index, cardiac output, cardiac index, and valvular regurgitation will be presented for the valve implant population at each time point at which echocardiograms are specified in the protocol. The statistics will be separately presented for two groups: Test and Control patients in trial Cohort A, and Test patients in trial Cohort B. Values from the two test cohorts will be pooled.

7.6.2 Blood Laboratory data

Blood laboratory data will be reported as the percent of patients with results within the normal ranges at each time interval. 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.

7.6.3 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. Generally, these analyses will be performed in the valve implant population only.

- 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 first event.

- 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 procedure 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 trial cohort to which each patient belongs.

- ROC curves will be presented for prediction of 30-day mortality, using both STS score and logistic EuroSCORE as predictors. For this purpose, the exact area under the ROC curve will be computed, rather than the approximate area produced by SAS PROC LOGISTIC. Statistical significance of the ROC area will be tested using bootstrap methodology.

Use of the ROC score in this manner does not depend on prior validation of the predictors; in fact, computation the ROC area – there called the c-index – is one of the key statistical tests used to validate new predictive scores. The paper of Edwards et al [28] presents this area for the STS score.

Methods of statistically analyzing ROC scores are presented in chapters 4 and 5 of Pepe; the textbook contains no suggestion that there has been any prior validation of the predictors used to compute the ROC scores.

Since the purpose of these 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.

7.6.4 Center comparisons

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

7.7 General Statistical Methodology

7.7.1 Non-inferiority Testing

Non-inferiority tests at a point in time are based on the approach described by Com-Nougue et al. [58]; the test is defined in the same form by Freitag [59].

The test is performed at a point in time *T,* using the Kaplan-Meier estimates for freedom from the endpoint being evaluated, and the Greenwood standard errors for these estimates. A 95% one-sided lower confidence limit will be computed for the difference (Test – Control). The Test arm will be judged not inferior to the Control if the lower confidence limit is greater than $-\Delta$, where Δ is the predetermined non-inferiority margin.

Using the notation of Com-Nougue, let $S_T(T)$ denote the freedom from endpoint for the Test arm at the analysis close time *T*, and let $S_C(T)$ denote the freedom from endpoint for Control at *T*. The hypothesis test is

$$H_0: \; S_T(T) - S_C(T) \leq -\Delta$$

$$H_A: \; S_T(T) - S_C(T) > -\Delta$$

Following the standard non-inferiority testing methodology, this test will be evaluated as a one-sided test at $\alpha = 0.05$.

The test statistic is

$$\frac{\hat{S}_T(T) - \hat{S}_C(T) + \Delta}{\sqrt{\hat{V}[\hat{S}_T(T)] + \hat{V}[\hat{S}_C(T)]}}$$

In the test statistic, $\hat{S}_T(T)$ and $\hat{S}_C(T)$ are the survivals estimated by the Kaplan-Meier algorithm, and $\hat{V}[\hat{S}_T(T)]$ and $\hat{V}[\hat{S}_C(T)]$ are the variances estimated by Greenwood's formula.

The null hypothesis will be rejected, and non-inferiority concluded, if the test statistic is greater than 1.645.

In addition to formal analysis of non-inferiority endpoints, the Kaplan-Meier curves will be presented for each group in the analysis, and a 95% two-sided confidence interval for the difference of the curves will be shown.

Non-inferiority methodology note:

- In analysis of the primary endpoint, there will be little or no censored data. The only censoring would be due to lost to follow-up or withdrawal from the trial.

  It is possible that there will be no censored data at all in evaluating the primary endpoint. In such a case the Kaplan-Meier estimators are pure proportions, and the Greenwood variance is the standard variance for an estimated proportion. The non-inferiority test described in this section is then the same as the standard non-inferiority test for the difference of proportions. This test and a sample size formula are given by Makuch and Simon (1978).

  The Kaplan-Meier formulation has been chosen in order to incorporate data from those few, if any, patients whose data are censored.

For analyses other than all cause mortality, patients will be censored at the death date. Use of Kaplan-Meier methodology is vital for these analyses.

- Another method that is sometimes used is proportional hazards regression. Non-inferiority is based on a confidence interval for the estimated constant hazard ratio. However in this trial the hazard ratio will not be constant. In the high risk surgery cohort, the early risk of death is anticipated to be higher in the Control arm, and the risk will be approximately the same after the perioperative period. In the excessive risk for surgery cohort, the early risk of death is anticipated to be higher in the Test arm, because of the implant procedure, but the risk would be higher in the Control arm thereafter. Accordingly the constant hazard ratio approach would not be appropriate for the primary endpoint. For consistency, the point in time approach will be used for other non-inferiority analyses.

- Where these analyses are performed at the nominal 12-month follow-up point, some patients will have completed their 12-month follow-up prior to 365 days. If needed to evaluate the primary endpoint, there will be a special telephone follow-up for these patients to determine survival at 365 days; a telephone follow-up is adequate to determine this particular data point. It should be noted that this situation will not arise for the 30-day endpoint, since all living patients will have later data.

Choice of Δ

The issue remains as to how Δ should be chosen. As a reference, Section 6.6 of the standard textbook by Wellek [60] discusses non-inferiority testing for survivor functions. The book suggests that a liberal choice of the non-inferiority margin is Δ = 0.20, and a strict choice is Δ = 0.10. At the request of the FDA the even stricter value 0.075 will be used.

7.7.2 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. The log-rank statistic will be used for any comparison among groups.

The precise formulation of the log-rank test as a hypothesis test is given in terms of the hazard functions $\lambda(t)$ for the two trial arms.

$$H_0: \ \lambda_T(T) = \lambda_C(T) \ \text{ for all T}$$

$$H_A: \ \lambda_T(T) \neq \lambda_C(T) \ \text{ for some T}$$

The acceptance criterion for the primary endpoint of Cohort B is that statistical significance be achieved as a two-sided test, and that the difference favors the test arm, as defined by the log-rank statistic. The actual formula for the log-rank statistic is omitted here because it is contained in standard textbooks on survival analysis, such as Kalbfleisch and Prentice, section 1.5 [61].

As already mentioned in section 7.3.1, all available data will be used in performing log-rank tests. For the primary endpoint in Cohort B, this specifically means that the data for each patient will extend to the evaluation date; for all but the last few patients the time involved will be greater than one year, and the sample size has been based on including all such data.

Confidence limits for these graphs will be based on the Greenwood standard error, computed using the logit transformation.

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, their logarithms, and the Wald p-value will be presented.

Where appropriate, time-dependent variables will be analyzed using a constant hazard model. Confidence limits will be computed using Cox's approximate (2 statistic, as recommended by Grunkemeier and Anderson [62]. 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 or the death date. For the special case of the primary endpoint at one year, there may be a special telephone follow-up to determine survival at the precise time point used in the analysis.

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.

7.7.3 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 observed, comparisons will also be performed using the Wilcoxon rank-sum test.

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

7.7.4 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.

7.7.5 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 [63].

7.7.6 Exact tests

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.

7.7.7 Missing Data Imputation

Missing variables will not be imputed for planned analyses, except where otherwise specified.

Even where imputations are specified, a complete case analysis will also be presented. This is because the complete case analysis is the most common method in cardiovascular literature.

Wherever imputations are performed, the imputation algorithms will make no reference to the specific trial arm of the patient, thus ensuring no analysis bias between trial arms. The imputations specified below are the planned imputations; others may be performed when specifically requested by reviewing agencies.

NYHA:

As a sensitivity analysis for the difference in NYHA between trial arms, patients that are not known to be deceased but with missing NYHA at one year will be ranked above all deceased patients, below all surviving patients above the median, and tied with all surviving patients below the median. This method is proposed in McMahon and Harrell (2001) as a variation on a method presented in Brown (1999). McMahon and Harrell (2001) point out that this method is appropriate when such observations are missing for reasons associated with disease progression.

Length of index hospital stay:

Patients who die before discharge will be imputed to have a hospital stay of the longest length of hospital stay from the alive discharged patients from the same treatment arm in the same cohort for this analysis. An additional analysis will be performed using just the actual hospitalized days, without any additional days being imputed for patients who die.

Six-minute walk

As a sensitivity analysis for the difference in 6MWT between trial arms, patients that are not known to be deceased but with missing 6MWT at one year will be ranked above all deceased patients, below all surviving patients above the median, and tied with all surviving patients below the median. As noted above, this method is proposed in McMahon and Harrell (2001) and is appropriate when such observations are missing for reasons associated with disease progression.

Sensitivity Analyses

Sensitivity analyses for missing outcomes in the ITT population for all variables will be performed. First, we shall perform a worst-case analysis where the worst observed value for the outcome at a given time point in the treatment arm will be imputed for any missing outcome in the treatment arm at that time point. Conversely, the best observed value for the outcome at a given time point in the control arm will be imputed for any missing outcome in the control arm at that time point. Secondly, multiple imputation will also be used to perform a sensitivity analysis. Finally, the available case analysis will also be presented for all outcomes.

While sensitivity analyses will be performed as described above, the primary evaluation analysis for all outcome variables will still be performed as described in the earlier part of this chapter. The additional analyses as described above will be provided for sensitivity purposes only.

7.7.8 Periodic Analyses

Periodic analyses will be performed during the trial as required by the appropriate regulatory authorities and the DSMB. These analyses will include review of screening criteria to ensure appropriate stratification to Cohort A and Cohort B.

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.

7.7.9 Data from Other Trials

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

To the extent required by regulatory authorities, data from other sources will be presented in an appendix.

7.7.10 Miscellaneous

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

Unless otherwise specified, the precise form of each algorithm will be the default of SAS®, using the latest release generally available at the time of analysis. This will be version 9.1 or later.

8 Definitions

Term	Definition	Reference/Justification
Adverse Event (AE)	An adverse event is any "untoward medical occurrence in a study subject" which does not necessarily have to have a causal relationship with study 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.	ISO 14155-1:2003
Serious Adverse Event (SAE)	*Adverse Event* that: a) led to a death, b) led to a serious deterioration in the health of a subject 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. c) led to fetal distress, fetal death or a congenital abnormality or birth defect. Any major or clinically significant adverse event occurring during and after the study valve implantation or BAV procedure: Death; Life-threatening adverse event; Inpatient hospitalization or prolongation of existing hospitalization; Persistent or significant disability/incapacity; Medically significant event (includes laboratory abnormalities). Medically significant events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the	ISO 14155-1:2003

Term	Definition	Reference/Justification
	outcomes listed in the definition above. The following is not considered an SAE: • Hospitalization for diagnostic or elective surgical procedures for a pre-existing condition	
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 14155-1:2003
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 14155-1:2003
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
Major Adverse Cardiac And Cerebro-Vascular Events (MACCE)	MACCE definition includes death, MI, stroke and renal failure.	FDA
Expanded Safety Composite	Expanded safety composite event includes death, MI, stroke, aortic valve reintervention, recurrent hospitalization and procedure access complications (unplanned surgical vascular conduit, unplanned vascular grafting intervention, repair of thoracic or abdominal aorta, or access wound infection).	FDA
Annular Dissection	Disruption or tear of the valve annulus extending to the aorta caused by mechanical injury from oversizing a balloon or the valve device itself	STS

Term	Definition	Reference/Justification
Aortic Dissection	Aortic dissection defined as Type A or B dissections that require surgical or percutaneous intervention.	FDA
Aortic Stenosis	Aortic stenosis is classified as "severe" when the following are present: • Jet velocity greater than 4.0 m/s • Mean gradient greater than 40mmHg • Valve area less than 1.0 cm^2 • Valve area index less than 0.6cm^2/m^2	ACC/AHA p. e14, e18
Bleeding Event	Any episode of major internal or external bleeding that causes death, hospitalization or permanent injury (e.g., vision loss) or necessitates transfusion of greater than 3 units PRBCs or pericardiocentesis procedure. The complication *bleeding event* applies to all patients whether or not they are taking anticoagulants or antiplatelet drugs, since bleeding events can occur in patients who are not receiving anticoagulants. Embolic stroke complicated by bleeding is classified as a neurologic event under *embolism* and is not included as a separate bleeding event. Hemorrhage that requires 2 or more units of transfusion within the index procedure shall be reported as serious adverse events. (FDA)	STS FDA
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	Canadian Cardiovascular Society

Term	Definition	Reference/Justification
	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.	
CABG	Coronary artery bypass surgery.	
Cerebrovascular Accident (CVA):	*See "Embolism"*	*STS/AATS*
Conversion To Bypass	Conversion to cardiopulmonary bypass is defined when patient is cannulated and heparinized	FDA
Death **(See Also "Sudden Death" And "Valve-Related Death")**	In general deaths will be classified as cardiac or non-cardiac and procedure/valve-related. *Cardiac death* is defined as all deaths resulting from cardiac causes. This category includes valve-related deaths (including sudden unexplained deaths) and non-valve related cardiac deaths (e.g., congestive heart failure, acute myocardial infarction, documented fatal arrhythmias.) *Non-cardiac death* is defined as a death not due to cardiac causes (as defined above). *Procedure-related death*: Deaths directly related to the procedure or complications thereof or any death occurring ≤ 30 days of the procedure will be classified as procedure-related. *Valve-related death*: Death caused by structural valve deterioration, nonstructural dysfunction, valve thrombosis, embolism, bleeding event,	STS/AATS

Term	Definition	Reference/Justification
	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. Deaths caused by heart failure in patients with advanced myocardial disease and satisfactorily functioning cardiac valves are not included. Specific causes of valve-related deaths should be designated and reported. *Sudden death:* Sudden, unexpected, unexplained death. The cause of these deaths is unknown and the relationship to an operated valve is also unknown. Therefore, these deaths should be reported as a separate category of valve-related mortality if the cause cannot be determined by clinical data or autopsy.	
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).	
Device Success	Successful delivery and deployment of the device and retrieval of the delivery catheter resulting in an aortic valve area greater than 0.9cm^2 with <3+ aortic regurgitation in the earliest evaluable echocardiogram and only one valve is implanted in the correct anatomical position.	FDA
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	STS

Term	Definition	Reference/Justification
	reversed). A *neurologic event* includes any new, temporary or permanent focal or global neurologic deficit. A *transient ischemic attack (TIA)* is a fully reversible neurologic event that lasts less than 24 hours and if an imaging study is performed, shows no evidence of infarction. A *stroke* or *permanent neurologic event* lasts $\geq$ 24 hours, or lasts < 24 hours with a brain imaging study showing infarction. Patients who do not awaken or who awaken after operation with a new stroke are excluded in tabulations of valve-related morbidity. Psychomotor deficits should be classified as adverse events if they are newly noted post baseline. A 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.	
Emergent Bypass Surgery	Emergent bypass surgery is defined as urgent or emergent coronary bypass surgery < 30 days of the index treatment.	FDA
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	STS Definition of Cardiac Surgery Status

Term	Definition	Reference/Justification
	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: a) Not elective status b) Not emergent status c) Procedure required during same hospitalization in order to minimize chance of further clinical deterioration d) Worsening, sudden chest pain, CHF, acute myocardial infarction (AMI), anatomy, IABP, unstable angina (USA) 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.	
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. Suggested reference: Duke Criteria for Infective Endocarditis	STS Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings: Duke Endocarditis Service. Am J Med. 96:200-209, 1994

Term	Definition	Reference/Justification
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
Hemodynamic Collapse	Hemodynamic collapse is defined when the systolic blood pressure drops below 40mmHg or when there is electromechanical dissociation.	
Hemolysis	• Plasma Hgb >40 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 serial hemoglobin, serum LDH, haptoglobin, serum bilirubin and/or urine bilirubin levels	FDA
Hemorrhage	See "Bleeding event" Events which are excluded are: those due to liver disease, myocardial infarction, or systemic infection. Reported as major or minor as defined below: Major: Requires intervention. Minor: Does not require intervention.	STS/AATS
Hemorrhagic Vascular Complication	Vascular complications include the following: 1. Hematoma at access site >5 cm 2. False aneurysm 3. Arterio-venous fistula 4. Retroperitoneal bleeding 5. Peripheral ischemia/nerve injury 6. Any transfusion required will be reported as a vascular complication unless for a clinical indication clearly other than catheterization complication. 7. Vascular surgical repair	
Infection	Known infection requiring intravenous antibiotics for other than prophylaxis,	

Term	Definition	Reference/Justification
	and/or extended hospitalization.	
Mitral Valve Compromise	Mitral valve compromise defined as mitral injury producing a 1+ increase in mitral regurgitation (MR).	FDA
Myocardial Infarction	Any of the following criteria will meet the definition of MI: 1) Any Acute MI demonstrated by autopsy 2) Any emergent PCI performed for acute ST-elevation myocardial infarction 3) Any administration of thrombolytics for acute myocardial infarction 4) Clinical Periprocedural MI (up through 7 complete days post index procedure): a) Periprocedural Q-wave MI: Development of new pathologic Q waves in 2 or more contiguous leads with elevation of CK-MB or CK in absence of CK-MB data. New Q waves in the absence of symptoms or elevated markers will NOT be considered an MI. b) Periprocedural Non-Q-wave MI: Documented signs or symptoms of ischemia and/or new ischemic changes on ECG **AND** CK-MB elevation > 10 X ULN. In the absence of CK-MB data, CK should be used. In the absence of CK-MB data, CK can be used with the same > 10 X ULN criteria. 5) Clinical Non-procedural MI a) Q-wave MI: Development of new pathologic Q waves in 2 or more contiguous leads with elevation of CK, CK-MB or Troponin in clinical setting with signs or symptoms of myocardial ischemia. b) Non-Q-wave MI: Elevation of CK > 2 times ULN with elevation of CK-MB or Troponin in clinical setting with signs or symptoms of myocardial	

Term	Definition	Reference/Justification
	ischemia.	
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
New York Heart Association Classification (NYHA Class)	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")	Leakage due to a separation of the prosthetic valve from the annulus. Any evidence of leakage of blood around the device. Diagnosis of paravalvular leak may be obtained from echo; however definitive diagnosis is obtained at reoperation, explant, or autopsy.	STS/AATS, FDA

Term	Definition	Reference/Justification
	Primary paravalvular leak 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 Paravalvular leaks (≥ 2+) not requiring reintervention or having no clinical consequence for the patient will be classified as **Adverse Events**. All major paravalvular leaks will be classified as **Serious Adverse Events**.	
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
Peripheral Thromboembolic Event	See "Embolism"	STS/AATS
Pre-Existing Condition	A pre-existing condition is one that is present at the start of study treatment.	
Procedure Success	Device success and no occurrence of in-hospital or 30 day (± 7 days), whichever is longer, MACCE and <3+ AI	FDA
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	FDA

Term	Definition	Reference/Justification
	the annulus and the prosthetic valve, or the need for more than one Edwards SAPIEN 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.	
Recurrent Hospitalization	Rehospitalization for symptoms of heart failure, angina or syncope due to aortic valve disease requiring aortic valve intervention or intensified medical management, hospitalization for complications from the procedure, such as infection, renal failure, etc.	
Renal Failure	Patient requires chronic dialysis for greater than 30 days	
Renal Insufficiency	Creatinine level above 3.5	FDA
Reintervention	Any intervention that repairs, alters or replaces a previously operated valve.	STS/AATS
Sternal Wound Infection	Deep sternal infection involving muscle, bone, and/or mediastinum Must have one of the following: 1) Wound opened with excision of tissue (I&D) 2) Positive culture 3) Treatment with antibiotics. Infection that is contiguous with the sternum on imaging will constitute involvement of the sternum.	STS/AATS
Stroke	A neurological deficit lasting $\geq$ 24 hours, or lasting < 24 hours with a brain imaging study showing infarction	STS/AATS
Structural Valvular Deterioration (SVD)	Any change in valve function (a decrease of one NYHA functional class or more) of an operated valve resulting from an intrinsic abnormality of the valve that causes stenosis or regurgitation. Structural valve deterioration includes operated valve dysfunction or deterioration *exclusive of infection or thrombosis* as determined by reoperation, autopsy or clinical	STS/AATS

Term	Definition	Reference/Justification
	investigation. The term structural deterioration refers to changes intrinsic to the valve, such as wear, fracture, poppet escape, calcification, leaflet tear, stent creep and suture line disruption of components (e.g. leaflets, chordae) of an operated valve.	
Sudden Death (See Also "Death")	Sudden, unexpected, unexplained death. The cause of these deaths is unknown and the relationship to an operated valve is also unknown. Therefore, these deaths should be reported as a separate category of valve-related mortality if the cause cannot be determined by clinical data or autopsy.	STS/AATS
Thromboembolic Event	See "embolism"	STS/AATS
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
Transient Ischemic Attack (TIA)	See "embolism"	STS/AATS
Traumatic Cardiac Microangiopathic Hemolytic Anemia	The intravascular fragmentation of red blood cells characterized by low hemoglobin 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	

Term	Definition	Reference/Justification
	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.	
Valve-Related Mortality (See Also "Death")	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. Deaths caused by heart failure in patients with advanced myocardial disease and satisfactorily functioning cardiac valves are not included. Specific causes of valve-related deaths should be designated and reported.	STS/AATS

9 Study Committees

9.1 Executive Operations Committee

The Executive Operations Committee will be responsible for the day-to-day administrative management of the trial. This committee will meet periodically by teleconference to monitor subject enrollment, clinical site progress, and protocol compliance. This committee will be 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 will be comprised of 6 study investigators (3 cardiovascular surgeons, and 3 interventional cardiologists), an independent clinical cardiologist, QOL Medical Advisor, Echocardiography Expert and sponsor representative.

Cardiovascular Surgeons	Craig Smith, MD Columbia University Medical Center, New York
	Frederich Mohr, MD Universität Leipzig, Hertzzentrum, Germany
	Michael Mack, MD Medical City Dallas Hospital, Texas
	Tirone David, MD Toronto General Hospital, Toronto, Canada
Interventional Cardiologists	Martin Leon, MD Columbia University Medical Center, New York
	John Webb, MD St. Paul Hospital, Vancouver, Canada
	Murat Tuzcu, MD The Cleveland Clinic Foundation, Ohio
Independent Cardiologist	Robert Bonow, MD Northwestern Medical Center, Illinois
Quality of Life PI	David Cohen, MD MidAmerica Medical Center, Missouri
Echocardiologist	Pamela Douglas, MD Duke University Medical Center, North Carolina
Sponsor	Jodi J. Akin, RN, MSN Edwards Lifesciences Vice President, Clinical Affairs Heart Valve Therapies, Global
Advisors	Stuart Pocock, PhD University of London, United Kingdom

Mitch Krucoff, MD
Duke University Medical Center, North Carolina

9.2 Steering Committee

The Steering Committee consists of members of the Executive Operations Committee and all clinical site principal investigators.

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 clinical care of the study subjects. 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 Edwards Lifesciences and Duke Cardiovascular Research Institute (DCRI). DCRI will contract with the potential members.

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 Events 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 DCRI SOPs and applicable regulatory guidelines.

The DSMB committee will review all safety data from the PARTNER (US) Trial 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 and regulatory authorities, 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, MACCEs, expanded safety composite 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 Events Committee

The Clinical Events Committee (CEC) will be responsible for adjudicating endpoint related events reported during the trial. The CEC (under the direction of the CRO) will include both invasive and non-invasive cardiologists, 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. CEC members are independent from the investigational sites.

At the onset of the study, the CEC, under the Medical Director of CRO, will detail explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical event. These rules will be submitted to the Executive Operations Committee for final approval. 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. 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) will not be submitted until the final data lock for panel review. Any requests for substudies must be submitted to the Co-Chairman for formal review. Any substudies that would increase the potential risk to the patient will not be considered.

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

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, Investigators are free to publish or present their own clinical study data subject to review by Edwards Lifesciences 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 and will require the review and approval of Edwards Lifesciences. If 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.

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. The publication of results from any single center experience within the trial is strongly discouraged until one year following the trial's termination, in order to allow for preparation and publication of the multi-center results. Such analyses, as well as other proposed investigations by members of the Steering Committee, will require the approval of the Executive Operations Committee. We anticipate many secondary manuscripts with principal authorship drawn from members of the Steering Committee. For purposes of timely abstract presentation and publication, such secondary publications will be delegated to the appropriate principal authors, and final analyses and manuscript review for all multi-center data will require the approval of the Executive Operations Committee.

Edwards Lifesciences will provide statistical support for the publication process. Authors may also request the services of an independent statistician.

10 Administrative Responsibilities

10.1 Institutional Review Board (IRB)/Ethics Committee (EC) Information

This protocol and the informed consent must be reviewed and approved by the appropriate IRB/EC 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/EC before the change is implemented.

10.1.1 Reviewing Institutions

Up to 30 institutions in the US and up to five institutions outside the US will participate in the trial.

10.1.2 Institutional Review Board/EC Approval Letter

Institutional Review Board (IRB)/Ethics Committee (EC) 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/EC approval letter addressed to the investigator must be submitted to Edwards Lifesciences certifying trial approval. Investigators are responsible for submitting and obtaining initial and continuing review (at intervals not greater than once a year) of the trial by their IRB/EC.

10.1.3 Patient Informed Consent

Informed consent is mandatory and must be obtained from all patients (or their legal guardian) prior to their participation in this trial.

The Patient Informed Consent Form is included in Appendix C. Any modifications to the Patient Informed Consent Form must be approved by Edwards Lifesciences, FDA and, as necessary, by the IRB/EC.

A copy of the IRB/EC approved Patient 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 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 will be available for printing on the website. An e-mail notification will be sent to Edwards Lifesciences, the data management center, and CRO, when enrollment data is 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 study manager. The eCRFs should be completed at the first earliest opportunity.

10.3.2 Data Reporting

The investigator, or an individual designated by him/her, 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 (CRFs or database to be completed within 10 days of procedure or follow-up events) 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, MACCE, expanded safety composite events, 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
- IRB/EC approval letter, including informed consent

- IRB/EC membership list
- Correspondence relating to the trial
- CVs for all investigators and research coordinator
- Site personnel signature list
- 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, serious adverse events, MACCE and/or expanded safety composite events

Edwards Lifesciences requests that the investigator retain copies of procedure reports, procedure nursing notes and the results of any interventional procedures that occurs post 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 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 (US) Trial, the principal investigator must submit a final written report to Edwards Lifesciences and the IRB/EC as required by the regulations. The report must be submitted within 3 months of completion or termination of the trial. The investigator's final report will include:

- Introduction: A brief description of the rationale and objectives of the trial.
- Methods: A description of the methods employed and any deviations from the investigational plan.
- Trial Population: A statement of the number of patients evaluated; of the number of dropouts and reasons for them; and description of the initial nature and severity of medical conditions for which the patients were evaluated.
- Results and Discussions: A clinical assessment of the effect of the investigational treatment on the medical condition of the patients and a description of complications reported with an

indication of their relationship to the investigational treatment.

- Conclusion: A summary statement of the principal investigator's opinion of the effectiveness of the investigational treatment in the patients enrolled at his/her investigational site.

10.6 Labeling: Instructions for Use

The Instructions for Use for use of the study device with the transfemoral and transapical delivery systems are included in Appendix G. The Instructions for Use for other approved devices are not included, but are packaged with each device by the 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 holds the right to hold enrollment in sites deemed to have excessive protocol compliance issues.

11 Adverse Event Reporting

At each evaluation, the investigator will determine whether any adverse events (AEs) have occurred. For the purpose of this protocol, an adverse event is any undesirable medical occurrence in a subject. This definition does not depend on a causal relationship with the device or the protocol requirements.

Adverse events may be volunteered by patients, elicited from questioning by Investigator or designee, or collected via observation by the Investigator. The Investigator 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.

In addition, patients will be instructed to contact the investigator, and/or study coordinator if any significant adverse events (e.g., MACCE and/or expanded safety composite events) occur between study evaluation visits.

AE Reporting Period:
Adverse events (AEs) are reported beginning from randomization date until subject 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.
- Remote: The temporal sequence between device or procedure and the event is such that the relationship is unlikely
- Possible: 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 subject's condition.

- Probable or Definite: 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.

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 subject 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;
- Leads to fetal distress, fetal death or a congenital abnormality or birth defect.

All Serious Adverse Events (SAE) must be reported to Edwards Lifesciences within 24 hours of the Investigator becoming aware of the event. At the time of initial notification, the following minimal information must be provided:

- Identifiable patient: subject number
- Identifiable reporter: study site
- Adverse event
- Causal relationship to device and procedure

In addition, all MACCE and expanded safety composite events are considered to be serious and also need to be reported to sponsor within 24 hours of the Investigator becoming aware of the event. The AE Forms of the CRF must be completed within 7 working days of awareness for all SAEs, MACCE and expanded safety composite events. The site will provide to Edwards Lifesciences (or designee) a copy of supporting documentation (such as hospital record, laboratory results, autopsy results) of all SAEs, MACCE and expanded safety composite events.

Anticipated Adverse Events

Anticipated adverse events are AEs that have been identified as possible adverse events related to the investigational device, or procedure. The anticipated events in this study are outlined in Section 3.2.

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 subjects.

All UADEs must be reported to Edwards Lifesciences within 24 hours of the Investigator becoming aware 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 (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 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 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. If a patient is unable to return to the clinic, 3 separate telephone calls should be made to attempt to bring the patient back into the clinic or obtain safety 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 subject. 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.

12 Study Data Reporting and Processing

12.1 Study Data Collection

The final set of electronic case report forms (e-CRFs) is designed to accommodate the specific features of the study design. Modification of e-CRFs will only be made if deemed necessary by the Executive Operations and Steering Committees.

The following is a list of e-CRFs to be submitted by the investigator or designee:

- Patient Enrollment CRF
- Baseline CRFs
- CRFs through Discharge
- Clinical Follow-up CRFs
- Adverse Event CRFs (this e-CRF includes the type of adverse events)
- Study Exit CRF
- Protocol Deviation CRF

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 7.

Table 7. Responsibilities for Submitting Other Data

Type of Data	Prepared by Investigator For
EQoL Forms: Baseline, 30 Day, 6 and 12 Month	EQoL Core Lab
Echocardiograms: Baseline, Discharge, 30 Day, 3, 6, 12, and Annually thereafter to 5 Years Post Procedure, and Other	Echocardiography Core Lab
ECGs: Enrollment, 48 Hours Pre-Procedure, Discharge, 30 Day, 3, 6 and 12 Month, and Other	ECG Core Lab
Explanted Valves	Histology Core Lab
Supporting documentation of any serious adverse event, MACCE or expanded safety composite events	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 e-CRFs will be automatically available to the study coordinator as new patients are enrolled in the study. Due to this reason a data form inventory process is not needed.

All clinical sites will be monitored periodically by the sponsor 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 for a period of one month. 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 Committee.

12.3 Communication

During the initial phases of the protocol, weekly or biweekly teleconference calls between CRO, the data management center, the sponsor monitor, and each clinical site will be conducted to resolve problems concerning the protocol and data collection. If problems cannot be resolved immediately, an appropriate expert will be consulted, and an updated version of the Manual of Operations will be generated reflecting the solution. Problems may be elevated to the Executive Committee as necessary.

12.4 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.

12.5 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 (subject 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 mistakes.

Specific components of this process include:

12.5.1 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.

12.5.2 Data Cleaning

All e-CRFs will be subjected to initial inspection for omitted data, gross data inconsistencies, and deviations. The resolution of data inconsistencies will be done using electronic tracking and will be resolved by the clinical site.

12.5.3 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.

12.5.4 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 or source documentation errors are discovered during the site visit, additional queries will be generated and will have to be addressed by the clinical site.

12.5.5 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.

12.5.6 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, subjects' 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.

12.6 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 Training

The training of appropriate clinical site personnel will be the responsibility of the Sponsor (see Appendix A). To ensure proper device usage, uniform data collection, and protocol compliance, the Sponsor will present a formal training session to study site personnel 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.

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14 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 will 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 subject 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 CRO will coordinate the DSMB, CEC, ECG and EQoL 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 Monitoring

The sponsor, or its designee, will conduct investigational site monitoring to ensure that all investigators are in 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.

14.5 Supplemental Applications

As appropriate, the sponsor will submit changes in the Investigational Plan to the regulatory authority and investigators to obtain IRB/EC re-approval.

14.6 Maintaining Records

The sponsor, the data management center and CRO will maintain copies of correspondence, all data, device shipment records, adverse device effects and other records related to the clinical trial as appropriate.

The sponsor will maintain records related to the signed Investigator Agreements.

14.7 Submitting Reports

The sponsor will submit all reports required by the appropriate regulatory authority as identified in this section of the regulation. This includes 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 will notify the sponsor within 24 hours of any withdrawal of IRB/EC approval or protocol violations.

14.8 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.

14.9 Informed Consent and IRB/Ethics Committees

All subjects must provide written informed consent in accordance with the local clinical site's IRB or Ethics Committee (EC). A copy of the 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/EC approval for the 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.

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Appendix A: Training Program

Title: Edwards Lifesciences Physician Training Plan

Date: November 2007 (Rev. 9)

Purpose: The purpose of this plan is to document and standardize the procedure and requirements for physician training for transcatheter heart valve (THV) implantation.

Scope: This plan applies to the physician training for the PARTNER clinical studies for both the transfemoral and transapical implant procedures.

* Note: This training plan will be revised as necessary to include physician feedback.

Physician training includes:

Written materials
In addition to the materials provided through the clinical trial (Clinical Investigator Brochure, Study Binder, and Instructions for Use), the Investigator is provided with a 'Training Manual', instructions on how to access the training web site, and a copy of the metrics printout from the Medical Simulation Corporation (MSC) simulator.

Training web site
A password protected web site is available to the study Investigators. This training web site has patient clinical selection suggestions, procedural steps, potential complications and methods for prevention, the pacing protocol, access site angiograms and technique suggestions and links to the current Instructions for Use, STS web site and EuroSCORE information.

Simulated valve implant procedures
Hands-on training will be conducted using the MSC Simantha™ simulator. The Investigator is first given a demonstration of the study valve and all specialty ancillary equipment. The Investigator then simulates two procedures to obtain a feel for the steps of the procedure and how all the equipment works together. This training exercise provides a mechanism for practicing procedural steps including use of the delivery system, balloon inflation, pacing protocol, and valve placement.

Didactic presentation and case review
A presentation is given to the Investigator that includes patient selection, the steps of the procedure with in-depth discussion on the more challenging aspects (e.g., valve placement within the calcific native aortic valve), troubleshooting techniques, and challenging situations such as difficult anatomy (e.g., tortuous iliacs). This presentation includes a review of cases including angiograms and echocardiograms of previous procedures.

Observing cases
Prior to being proctored, each Investigator is required to attend a minimum of one live THV implantation procedure performed by an experienced implanter and/or with an experienced implanter in attendance (proctoring).

Proctoring
Prior to the proctoring session, the Investigator will provide the proctor or Edwards designee with patient information (H&P, lab work, echo and any relevant angiograms) to review for discussion and planning purposes. The Investigator and scrub team will be proctored by an experienced physician on a minimum of two valve implantation procedures. These are to be performed at the Investigator's institution with his staff. If the proctor or Investigator is not satisfied that these two procedures provide sufficient preparation, then subsequent proctoring sessions may be added as needed.

Proctor Credentialing
An implanting cardiologist/surgeon is considered a proctor only after having completed a minimum of eight procedures.

Transfemoral access site assessment
For any Investigator who does not have experience with peripheral vascular procedures, to avoid the potential for access site complications, it is highly recommended that the Investigator have a vascular surgeon, peripheral trained cardiologist, or radiologist assist and/or instruct him in assessing patients for retrograde access.

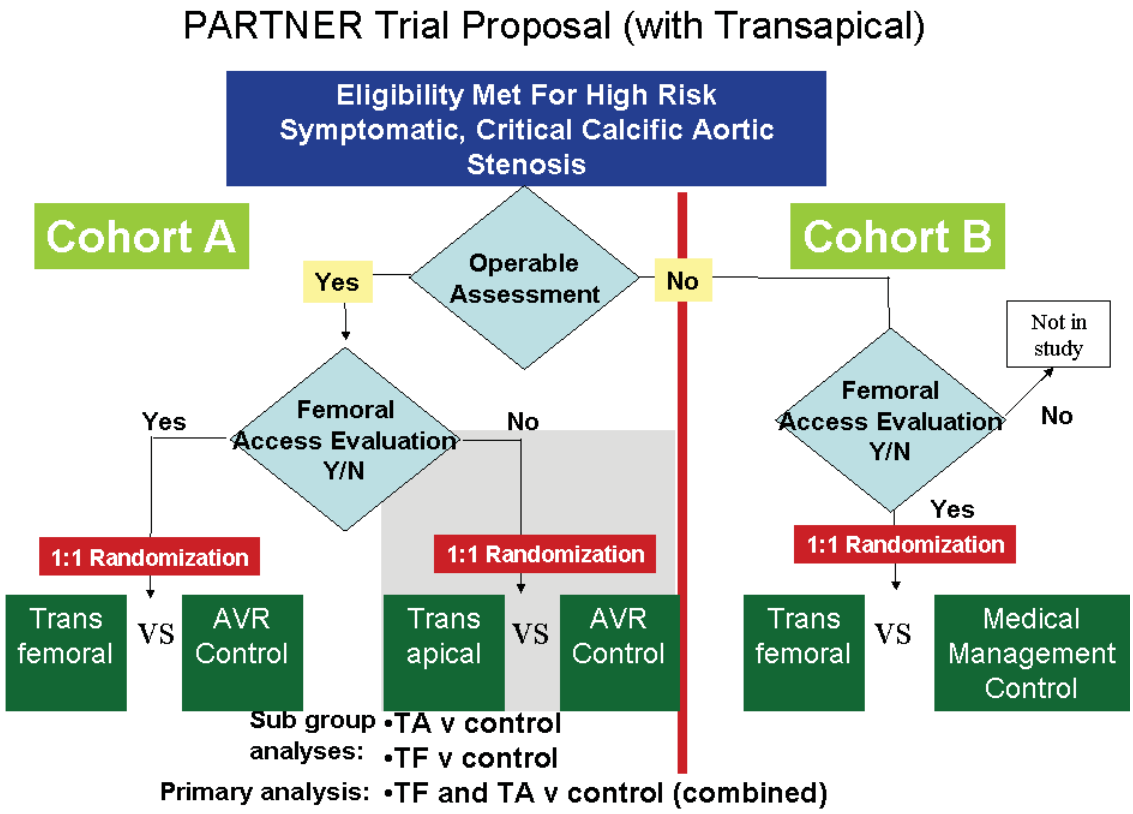
Valve preparation and crimping
An Edwards Representative that has been trained on the device preparation and crimping procedure will be in attendance at all implant procedures. They are responsible for the appropriate preparation of the THV delivery system and valve. The Investigator will be responsible for checking the placement and orientation of the valve on the balloon catheter prior to implantation.

Follow-up procedural support
An Edwards Lifesciences representative will attend all procedures to answer device and procedural questions.

Investigator meetings
Follow up Investigator meetings are held to discuss the valve implant procedure and what each site has learned. This meetings are held on an annual basis; e.g., during the TCT meeting or PCR. It is critical that all Investigators attend.

Documentation
Each step of the training program will be documented on the appropriate Training Forms (i.e., checked-off, dated and signed) by an Edwards Lifesciences representative as training is completed. Original training records are maintained by Edwards Lifesciences.

Appendix B: Study Flow Chart



Appendix C: Sample Informed Consent Forms

Patient Study ID # 2006-06-US-|__|-|__|__|__|-|__|__| Patient Initials (First, Mid, Last) |__|__|__|Site #|__|__|__|

Patient Information and Screening Informed Consent for Participation in a Clinical Research Study Sponsored by Edwards Lifesciences LLC

The Edwards SAPIEN™ Transcatheter Heart Valve, Model 9000TFX
***The PARTNER (US) Trial: P**lacement of **A**o**R**tic **T**ra**N**scathet**ER** Valves* **Trial**
Transfemoral Approach

Introduction

You are being asked to participate in a research study sponsored by Edwards Lifesciences LLC ("Sponsor") that will evaluate the safety and effectiveness of the Edwards SAPIEN™ Transcatheter Heart Valve (THV), Model 9000TFX in subjects who are determined to be at a high risk for conventional open-chest surgery. This is an investigational device (new heart valve repair mechanism for human use, not yet approved for commercial use).

This first generation investigational device is intended to treat subjects who are at high risk for the traditional operation for aortic valve replacement (AVR) surgery. You are being asked to participate because it has been determined that you have severe aortic stenosis (narrowing of the aortic valve resulting in the obstructed passage of blood) and you may benefit from this new aortic valve replacement system. Your involvement in this study will be for a minimum of 5 years. It is anticipated that the research study will be complete in approximately 5 to 7 years. Your participation in this research study is voluntary.

Background and Purpose

The goal of this study is to assess the safety and effectiveness of transcatheter (delivered through the blood vessels) implantation of a bioprosthetic (composed of biological and man-made materials) aortic valve (THV) in a minimum of 1040 subjects and up to 30 hospitals total including up to 5 sites outside of the United States.

You are being considered for this research study because your doctors have decided that, due to your medical condition, you are a high risk candidate for conventional (standard) open-heart surgery to replace your diseased aortic heart valve and that you may benefit from the alternative aortic valve replacement method offered by the THV replacement system. The standard medical treatments generally available to non-surgical patients with aortic stenosis may temporarily alleviate some of your symptoms, but will not cure your aortic stenosis permanently. In order to determine your eligibility to participate in this research study, you are being asked to undergo the following screening assessments.

Screening Assessments

You will undergo routine evaluation including; medical history evaluation, a physical exam, a transthoracic echocardiogram (a probe is placed on your chest and images of your heart are recorded) or a transesophageal echocardiogram (a probe is placed down the throat into the food pipe and images of your heart are recorded) and blood work. You will also undergo NIH Stroke Scale testing (physical exam and questions) to assess your neurological status prior to the procedure. If you have suffered a stroke in the last 6-12 months and do not have any images documenting the stroke and there is an abnormal results in the NIH stroke scale testing or if the NIH stroke scale testing shows abnormal results you will need to undergo a brain CT scan (x-ray) for documentation purposes. Additionally, you will receive a left and right heart catheterization (angiogram) with an x-ray dye (contrast media) to assess

your heart, and the severity of your aortic stenosis. You will also have screening thoracic and abdominal images of the aorta (aortograms) or thoracic and abdominal catheterization (CT angiograms) with an x-ray dye (contrast media) to assess your iliac and femoral arteries. MR imaging will be used as an alternative if you have compromised renal function that does not allow for the usage of x-ray dye (contrast dye). These procedures are not experimental. The transthoracic echocardiogram does not require any anesthesia. The transesophageal echocardiogram requires either a local or a general anesthesia. There are some risks involved in these procedures (see Risks section).

What happens next?

The screening procedures will determine whether you are eligible for participating in this research study. If you are eligible, you and the study investigator will discuss the treatment options available to you. Based on these assessments the study investigator will place you in one of two groups of people: These will include either the non-surgical group or the high risk surgery group.

Once you and the study investigator have agreed on which population fits best for you, you will be asked to sign a separate Study Procedure Informed Consent form which describes the research study in greater detail and then you will be randomized to either the control treatment (best medical management for the non-surgical subject group and surgical aortic valve replacement for the high risk surgery group) or the experimental treatment (undergoing transcatheter aortic valve implantation). The randomization method is like “pulling a number out of a hat”. You will have an equal chance of receiving either the control treatment or the experimental treatment.

Alternative Treatments

You have a condition termed aortic stenosis, which is a critical narrowing of the aortic valve. The general treatment options for patients with aortic stenosis are as follows:

- Balloon aortic valvuloplasty (BAV) (a procedure to stretch the aortic valve opening)
- Surgical aortic valve replacement (traditional open-chest surgery to replace your aortic valve with another commercially available prosthetic valve – either bioprosthetic or mechanical)
- Medical management (pharmacological treatment)

The preferred treatment of severe aortic stenosis is aortic valve replacement surgery. However, you are not considered an optimal candidate for surgery because of the high-risk of your condition.

Risks

Possible complications of the screening assessments may include, but are not limited to:

- death;
- cardiovascular or vascular injury, such as perforation or damage (dissection) of vessels, heart muscle or valve/valve structures that may require intervention;
- myocardial infarction (heart attack);
- stroke/ transient ischemic attack;

- embolization: air, calcification or thrombus;
- hemorrhage (bleeding) requiring transfusion or intervention;
- hematoma;
- hypertension (high blood pressure) / hypotension (low blood pressure);
- renal failure;
- renal insufficiency;
- allergic dye reaction;
- anesthesia reactions.
- arrhythmia;
- conduction system injury, which may require a permanent pacemaker;
- fever;
- infection including endocarditis (inflammation of the heart), incisional site infection/inflammation and septicemia (infection in blood);
- pericardial effusion/cardiac tamponade (bleeding into the heart sac);
- systemic peripheral ischemia/nerve injury; and
- AV fistula.

CT scan risks are similar to those of conventional x-rays. During the CT scan you are briefly exposed to radiation. There is always a slight chance of cancer from radiation. However, the benefit of an accurate diagnosis far outweighs the risk. The effective radiation dose from this procedure is about the same as the average person receives from background radiation in 8 months.

When a blood sample is taken there is a small risk for bruising, discomfort, bleeding, or infection.

The Institutional Review Board (IRB)/Ethics Committee (EC) and the FDA have reviewed and approved the study.

If you believe you have a research related complication, you understand that you should contact _____at _____.

You agree ____, You decline _____ to have your personal physician informed of your participation in this study.

Benefits

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 have a better understanding of the available therapies for your condition. If upon completion of these assessments you are determined to be eligible for participating in this clinical trial and you chose to do so, there may be an improvement in the symptoms related to your aortic stenosis, but it is not certain that these procedures will be of benefit to you. The benefits of these techniques include potentially a less invasive procedure, shorter procedure time, and less anesthesia than in an open-heart surgical procedure.

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Voluntary Participation and Termination

You understand that 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 study 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, you understand that any new information about the Edwards SAPIEN™ THV may not become available to you on a timely basis. Any significant new findings that develop during the research study which may relate to your willingness to continue participation will be provided to you by the study investigator. The study investigator may choose to terminate your participation, if you fail to follow the study guidelines, or in view of new information, at any time during the study.

Financial Obligation and Liability

Edwards Lifesciences LLC is the Sponsor and manufacturer of the investigational 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 understand that you will not be compensated in any way for your participation in this research study. You also understand that the Sponsor will not compensate you for injury or for any additional expenses incurred because of 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. You understand that the Sponsor or the hospital will not assume liability for injury directly attributable to this investigational 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 further understand that you do not waive any liability rights for personal injury by signing this form.

Confidentiality, Anonymity and Authorization

By signing this Consent you understand that the information derived from this research study may be given to the, FDA in the United States, 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, of this study, to have access to your confidential health, medical records and research information concerning the investigational device. You will also allow representatives from the Sponsor, of this study, 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 physicians involved in the research study or the study Sponsor, , may use the research study information collected from your participation for publications on the results of the use of this investigational device. 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 California, USA this Authorization will expire in twenty years.

Your echocardiography 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. 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.

Another portion of this research study contains a health economics review that will be done to assess the costs of the study investigational device for the treatment of critical aortic stenosis. As part of the research study, you will be asked to sign a Medical Billing Release Form. This form will be used by the Economic and Qualify of Life Assessment Group of the Harvard Clinical Research Institute (HCRI) to collect hospital bills from the patient accounting department at any hospital to which you are admitted, from the time of your enrollment in the research study through the entire study period. If you are eligible for Medicare or Medicare Plus Choice insurance coverage, you will also be asked to provide your Medicare Beneficiary number to the study personnel. This information will be kept strictly confidential and be used solely to assess the medical expenses which occur as a direct result of participating in the research study and to ensure that hospitals receive the appropriate reimbursement when providing this service.

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 to be changed, you will be informed and you will be asked again for your consent.

While participating in this research study, you will not be allowed to participate in any other research study without approval from the study 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.

Experimental Subject'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;

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- 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.

Patient Study ID # 2006-06-US-|__|-|__|__|__|-|__|__| Patient Initials (First, Mid, Last) |__|__|__|Site #|__|__|__|

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 subject, I may contact _____(name) at _____(telephone).

I also acknowledge that I have been given a copy of this Consent Form.
BY SIGNING THIS FORM, I WILLINGLY AGREE TO PARTICIPATE IN THE RESEARCH STUDY DESCRIBED.

_____	_____	_____
Name of Subject (Printed)	Date	Time

_____
Signature of Subject

_____	_____	_____
Name of Legal Representative (Printed, if applicable)	Date	Time

_____
Signature of Legal Representative (Printed, if applicable)

SIGNATURE OF INVESTIGATOR

I have explained the research study to the subject 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 (Printed)	Date	Time

_____	_____
Signature of Investigator	Hospital

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.

_____	_____	_____
Name of Witness (Printed)	Date	Time

_____
Signature of Witness

Edwards

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Patient Information and Study Procedure Informed Consent for Participation in a Clinical Research Study Sponsored by Edwards Lifesciences LLC

The Edwards SAPIEN™ Transcatheter Heart Valve, Model 9000TFX
The PARTNER (US) Trial: P*lacement of* ***A****oR****T****ra****N****scathet****ER*** *Valves* ***Trial***
Transfemoral Approach

Introduction

You are being asked to participate in a research study sponsored by Edwards Lifesciences LLC ("Sponsor") that will evaluate the safety and effectiveness of the Edwards SAPIEN™ Transcatheter Heart Valve (THV), Model 9000TFX in subjects who are determined to be at a high risk for conventional open-chest surgery. This is an investigational device (new heart valve repair mechanism for human use, not yet approved for commercial use).

This first generation investigational device is intended to treat subjects who are at high risk for the traditional operation for aortic valve replacement (AVR) surgery. You are being asked to participate because it has been determined that you have severe aortic stenosis (narrowing of the aortic valve resulting in the obstructed passage of blood) and you may benefit from this new aortic valve replacement system. Your involvement in this study will be for a minimum of 5 years. It is anticipated that the research study will be complete in approximately 5 to 7 years. Your participation in this research study is voluntary.

Background and Purpose

The goal of this study is to assess the safety and effectiveness of transcatheter (delivered through the blood vessels) implantation of a bioprosthetic (composed of biological and man-made materials) aortic valve (THV) in a minimum of 1040 subjects and up to 30 hospitals total including up to 5 sites outside of the United States.

You are being considered for this research study because your doctors have decided that, due to your medical condition, you are a high risk candidate for conventional (standard) open-heart surgery to replace your diseased aortic heart valve and that you may benefit from the alternative aortic valve replacement method offered by the THV replacement system. The standard medical treatments generally available to non-surgical patients with aortic stenosis may temporarily alleviate some of your symptoms, but will not cure your aortic stenosis permanently.

This research study will be separated into two different groups of people: The first group will be high risk surgical subject group (Group A) and the second group will be a non-surgical subject group (Group B). The high risk surgical subject group, group A, means that, based on the opinion of a cardiothoracic surgeon and a cardiologist, you have a greater than or equal to 15% risk of death if you were to have your valve replaced through a traditional open-chest surgical procedure. Non-surgical subject group (best medical management group), group B, means that, based on the opinion of two cardiothoracic surgeons and a cardiologist, you have a greater than or equal to 50% risk of death or serious, irreversible morbidity if you were to have your valve replaced through a traditional open-chest surgical procedure. Your physician believes that this level of risk rules you out for a traditional open-chest surgical replacement of your valve.

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The high risk surgical subject group (Group A) will then be divided into three smaller groups. One group will receive the transcatheter procedure through the artery (blood vessel) in the leg (this is the transfemoral group). Another group will receive the transcatheter procedure through an incision in the chest (this is the transapical group). The third group will undergo conventional (open-chest) aortic valve replacement therapy.

Based on the results of your screening tests, you have been assigned to the following group:

☐ High Risk Surgical Subject Group (Group A)

☐ Non-Surgical Subject Group (Best Medical Management Group, Group B)

The Edwards SAPIEN™ THV, Model 9000TFX (formerly known as the Cribier-Edwards™ Aortic Bioprosthesis, Model 9000TFX), "investigational device", is a prosthetic heart valve, meaning that it is an artificial device, made to replace your diseased aortic heart valve. The valve consists of a stent (made of stainless steel) to hold the device in its intended position and valve leaflets (made of biological material derived from cows) to direct the flow of blood in your heart (prior versions of the device, the Cribier-Edwards™ Aortic Bioprosthesis, Model 9000 and Model 9000MIS, used valve leaflets made of material derived from horses). The implantation of the valve does not require open-heart surgery and can be done in a catheterization laboratory (as used for balloon angioplasty procedures) for the transfemoral approach (through the leg). The implantation procedure is briefly described in the Procedure section.

The Transcatheter Heart Valve device has limited human experience. Feasibility clinical studies have been conducted with both the transfemoral and transapical delivery system approaches. As of October 2007, 494 subjects worldwide have been implanted with either the THV or prior version of the Cribier-Edwards Aortic Bioprosthesis in the US, Europe or Canada either under other feasibility studies or on a compassionate basis. Some of these subjects have died as a result of complications due to the study device and/or procedure. The compassionate use cases involved subjects who were faced with imminent death, were not candidates for surgery and had multiple additional diseases (e.g. severe heart failure, cancer, kidney failure, pulmonary diseases). There have been improvements since the initial procedures. The risks for the procedure are listed in the Risk section. The study investigator performing the procedure has limited experience performing this procedure, but has received training by other study investigators who have implanted the investigational device in subjects in United States, Europe and/or Canada, and by the manufacturer of the investigational device.

Procedure

If you agree to be enrolled in this research study, you may or may not receive the investigational device (Edwards SAPIEN™ THV, Model 9000TFX). The decision whether to receive the investigational device will be left to chance, through a randomization scheme.

Each group (high risk surgery group and the non-surgical group) at your hospital will be randomized to either receive the investigational device or not. If you are randomized to receive the investigational device, the study investigator will determine if the investigational device will be inserted through the blood vessel in your leg or through an incision in your chest. If you are not randomized to receive the investigational device, you will be treated according to the study investigator's determination of the appropriate therapy for the group that you have been assigned to. If you are assigned to the high

surgical risk subject group, group A, you will be treated with conventional (open-chest) aortic valve replacement surgery. If you are assigned to the non-surgical subject group, group B, you will be treated with non-surgical means such as balloon aortic valvuloplasty (a procedure to stretch the aortic valve opening) and/or taking medication and limiting activities for the rest of your life.

What happens before the procedure?
You will undergo routine evaluation including; a physical exam, ECG (a recording of the electrical activity of your heart) and chest x-ray. You will also undergo a Mini-Mental State Exam (questionnaire) to assess your neurological status and a 6-minute walk test prior to the procedure. You will not need to take the test if you meet any of the following conditions: presence of palpitations or low blood pressure associated with changing position, unable to walk due to arthritis, neuromuscular disease, chronic pulmonary medical condition or presence of chest discomfort at effort.

The PARTNER US trial will also include a quality of life assessment, for which, the research study coordinator will have you or your legal representative complete a questionnaire called a Quality of Life Survey during your enrollment in the research study. You will also be asked to sign a Patient Address Form, which will be kept in strict confidence by the Economic and Quality of Life Assessment Group (EQOL) at the Harvard Clinical Research Institute (HCRI). In the event that you miss your appointment or are unable to complete the forms at the time of the visit, this form will be used by the EQOL Group to contact you or your legal representative via mail or telephone. The survey, or person administering it, will ask you to answer questions about your general health, and symptoms that you may or may not have (i.e. chest pain, shortness of breath, sleep problems, etc). All of your responses to the survey questions will remain completely confidential and you may also choose not to answer any question. The schedule of contact will be before the procedure, 30 days, 6 months, and 12 months after your research study treatment.

How am I assigned to a treatment group?

You have been determined to be eligible for participate in this research study. If you agree to be enrolled into this research study, you will be randomized to either the control treatment (surgical aortic valve replacement for the high risk surgical subject population or the best medical management for the non-surgical subject population based on your group assignment) or the experimental treatment (undergoing transcatheter aortic valve implantation). The randomization method is like “pulling a number out of a hat”. You will have an equal chance of receiving either the control treatment or the experimental treatment.

If I receive the experimental treatment, what happens during the procedure?
Your doctor will perform a Balloon Aortic Valvuloplasty (BAV) before implanting the experimental valve. BAV is a procedure to stretch the aortic valve opening. This procedure uses a balloon mounted on a catheter that is inserted through the arteries in your groin and into your heart to expand open your stenotic aortic valve – similar to a coronary angioplasty balloon, but larger and is used to temporarily reduce aortic stenosis.

The investigational device is designed for implantation through a transfemoral access (through a balloon catheter inserted through a small puncture in your groin to access the arteries leading from your thigh

directly to your heart) or through a transapical access (through an incision in your chest to access the heart directly).

If you are selected for the experimental treatment:
Due to the large size of the catheter being placed in your artery, the study investigator may request a consultation with a vascular surgeon to discuss the plan to open and close the artery in your leg prior to and/or following your procedure. The vascular surgeon has specific expertise in this type of procedure. Prior to implantation, the valve will be carefully crimped (compressed) and mounted onto a balloon delivery catheter by the interventional team, using a specially designed crimping device. It will then be inserted into your heart through a catheter, and delivered directly to your stenotic aortic valve. The valve will then be balloon-expanded to fit across your stenotic aortic valve, holding it open permanently. This procedure is designed to improve your heart function, without requiring removal of your native stenotic aortic valve.

The procedures (BAV and valve implantation) will be performed in a cardiac catheterization laboratory under local and/or general anesthesia, using fluoroscopy (x-rays) for visualization. The intent of these procedures is to avoid prolonged and deep anesthesia and open-heart surgery which requires a long recovery period. The duration of fluoroscopy that you receive will usually not be more than 20 minutes, the normal duration that occurs with an angiogram procedure in the cardiac catheterization laboratory.

The transapical (surgical) approach is performed in a cardiac operating room (OR) under general anesthesia. A small incision (thoracotomy) will be made on your left side so that the study investigator can access the apex, or tip, of your heart. Prior to implantation, the valve will be carefully crimped (compressed) and mounted onto a balloon delivery catheter by the surgical team, using a specially designed crimping device. It will then be inserted into your heart through a catheter, and delivered directly to your stenotic aortic valve. The valve will then be balloon-expanded to fit across your stenotic aortic valve, holding it open permanently. This procedure is designed to improve your heart function, without requiring the removal of your native stenotic aortic valve.

What happens after the procedure?
After the procedure you will go to the Intensive Care Unit (ICU) for close monitoring. You will be given blood thinning medications; aspirin, and clopidogrel (Plavix).

While in the hospital, the following procedures will be completed:
- A physical exam (just prior to discharge or at 7 days, whichever comes first)
- Chest x-ray (Day 1 post procedure and just prior to discharge or at 7 days, whichever comes first),
- Urine analysis
- Blood work (Day 1 post procedure. The total blood sample will be about 2-3 teaspoons)
- ECG (to be performed daily)
- Transthoracic (TTE) or transesophageal (TEE) echocardiogram - to be performed just prior to discharge or at 7 days, whichever comes first. A TTE does not require anesthesia. A probe is placed on your chest and images of your heart are recorded. A TEE requires either a local or a general anesthesia. In this procedure a probe is placed down the throat into the food pipe and images of your heart are recorded
- NIH Stroke Scale testing (physical exam and questions)

- CT brain scan (as needed)

You will remain in the ICU until the study investigator feels you can be transferred to a regular hospital room, where you will continue to be monitored, until you are discharged from the hospital.

The study investigator may ask you to continue taking Clopidogrel or similar blood thinner for 6 months post-procedure, and aspirin for life (as is recommended for routine stenting of coronary blood vessels and any replacement heart valve).

You will return to the hospital for follow-up evaluations at 30 days, 6 months, 12 months, and then yearly for a minimum of 5 years after the implant procedure. The exams at these visits include:

- A physical exam
- Blood work (study specific at 30-days, 6 and 12 month and annual follow-up visits for five years and according to hospital standard or medication regimen)
- Transthoracic (external) or transesophageal (internal) echocardiogram (ultrasound of your heart)
- ECG (at 30 days, 6 and 12 month follow-up visits only)
- Chest X-ray (at 30 days, 6 and 12month follow-up visit only)
- Completion of a Quality of Life questionnaires (at 30-days, 6 and 12 months follow-up visits only)
- NIH Stroke Scale testing (at 30-days, 6 and 12 months follow-up visits and annually thereafter for a minimum of 5 years)
- 6-minute walk test, if eligible (at 30 days, 6 and 12 month follow-up visits only)

In order to assess your medical condition, phone interviews will be conducted throughout your lifetime.

What happens if I am assigned to the control group instead of the treatment group?
If you are randomized to the control group, you will receive the appropriate therapy for the group you have been assigned to, either traditional open-chest aortic valve surgery (for high risk surgical subject population, group A, or best medical management (for non-surgical subject population, group B):

Best Medical Management (Group B)

If you receive medical management, you will be treated with either BAV (procedure to stretch the aortic valve opening) and/or medications appropriate to your general condition for the rest of your life or both. Medications may include, but are not limited to blood thinners, diuretics (“water pills”), beta-blockers, and blood pressure medications.

Risks associated with medical management are dependent on the specific drug therapies your doctor chooses to give you. Risks associated with the BAV procedure are as described below in the Risk section. One of the main risks of medical management is death, since the underlying disease (aortic stenosis) is not being treated; instead the drug therapy is considered palliative (meaning it is just designed to make you more comfortable).

Traditional Open-Chest Aortic Valve Surgery (Group A)

If you receive traditional aortic valve surgery, you will undergo open-heart surgery in a cardiac operating room (OR) under general anesthesia. An incision (sternotomy) will be made down the center of your chest so that the surgeon can access the heart. The study investigator will stop your heart from beating and remove your natural aortic valve. The study investigator will then sew in a new valve made from bovine (cow) pericardium (the sac that contains the heart). The study investigator will use a commercially available (not an experimental valve) Edwards aortic valve.

You will be placed on cardiopulmonary bypass (the "heart-lung machine") during your procedure. This will remove the blood from your body through tubes, send it to a machine which adds oxygen back into the blood, and then returns it to the body. Risks associated with cardiopulmonary bypass include stroke and infection at the incision in the groin. Every precaution will be taken to avoid these risks, including minimizing the time on bypass.

Other risks associated with traditional aortic valve replacement include, but are not limited to, death during or after the surgery, valve dysfunction, stroke, bleeding events or hemorrhages, the need for another operation, and infection. The study investigator will explain the entire procedure to you, including all the risks and the steps he will take to minimize those risks.

Even though you may not have received the experimental valve, the following exams will be conducted day 1 post procedure and just prior to discharge or at 7 days whichever comes first (If you are in the best medical management (Cohort B) and will not be treated in the hospital, a 7-day follow-up is not required):

- A physical exam (just prior to discharge or at 7 days whichever comes first)
- Blood work (Day 1 post procedure and according to hospital standard or medication regimen)
- ECG (just prior to discharge or at 7 days whichever comes first)
- Chest X-ray (Day 1 post procedure, just prior to discharge or at 7 days, whichever comes first)
- Transthoracic (external) or transesophageal (internal) echocardiogram (ultrasound of your heart) (just prior to discharge or at 7-days whichever comes first)
- NIH Stroke Scale testing (just prior to discharge or at 7-days whichever comes first)

Even though you may not have received the experimental valve, you will return to the hospital for follow-up evaluations at 30 days, 6 months, 12 months, and then yearly for a minimum of 5 years after the implant procedure. The exams include:

- A physical exam
- Blood work (at 30-days, 6 and 12 month and annual follow-up visits for five years and according to hospital standard or medication regimen)
- Transthoracic (external) or transesophageal (internal) echocardiogram (ultrasound of your heart) (at 30-days, 6 and 12 months follow-up visits and annually thereafter for a minimum of 5 years)
- ECG (at 30 days, 6 and 12 months follow-up visits only)
- Chest X-ray (at 30 days, 6-month and 12-month follow-up visit only)
- Completion of a Quality of Life questionnaires (at 30-days, 6 and 12 months follow-up visits only)
- NIH Stroke Scale testing (at 30-days, 6 and 12 months follow-up visits and annually thereafter for a minimum of 5 years)

- 6-minute walk test, if eligible (at 30-days, 6 and 12 month follow-up visits only)

Your continued participation in the study is important even if you do not receive the experimental product. This helps to establish a baseline of results which the experimental treatment can be compared against.

Alternative Treatments
You have a condition termed aortic stenosis, which is a critical narrowing of the aortic valve. The general treatment options for patients with aortic stenosis are as follows:

- Balloon aortic valvuloplasty (BAV) (a procedure to stretch the aortic valve opening)
- Surgical aortic valve replacement (traditional open-chest surgery to replace your aortic valve with another commercially available prosthetic valve – either bioprosthetic or mechanical)
- Medical management (pharmacological treatment)

The preferred treatment of severe aortic stenosis is aortic valve replacement surgery. However, you are not considered an optimal candidate for surgery because of the high-risk of your condition.

Risks
If you are assigned to the control therapy, the risks are as outlined previously. If you are assigned to receive the experimental treatment for your aortic stenosis, you will be implanted with the investigational device. As with any research study, there is a possibility that complications could develop that are not anticipated. The study investigator will discuss these complications and the appropriate alternative procedures in detail with you before your procedure.

The investigational device is an experimental valve and has not received approval from the U.S. Food and Drug Administration (FDA), or any other governmental agency in North America, for the treatment of aortic stenosis or any disease of the aortic valve. The transfemoral (through the groin) approach with the device has received CE Mark for commercial use in Europe. As such, the safety and/or effectiveness of the investigational device are currently unknown compared to conventional aortic valve replacement.

The implantation of the investigational device includes BAV as an initial step in the valve implantation process. Consequently, there are many risks that are common to both treatment options. However, the implantation of the investigational device includes additional procedural steps, beyond those required for BAV alone, and includes the permanent implantation of an experimental prosthetic heart valve. The corresponding additional risks (complications that either can potentially occur with only the investigational device, or can potentially occur at a clinically significant rate greater than with BAV) are also provided for your consideration. Some complications for the investigational device will also be expected for other approved bioprosthetic (composed of biological and man-made materials) heart valves (if you were to undergo surgery).

Another possible complication is the inability to place the valve in the correct position across your diseased aortic valve. This may result in two possible outcomes; either the valve will have to be placed in another part of your aorta, (which will not improve your aortic stenosis) or, the valve will have to be removed using an open-chest operation.

The major risks associated with BAV alone include; bleeding from the groin artery requiring surgery

(2%), stroke (<2%), heart attack (<2%). Any of these may result in death (<2%). Standard medical therapy does not modify the underlying obstruction and is associated with approximately 50% mortality in two years.

For transfemoral cases if the need should arise, a standby surgical team will be available for consultation and to determine if you are a candidate for emergency cardiac surgery. If the surgical team determines that you can be operated on, it will be in an emergency situation and this will further increase your surgical risk.
Other possible complications of the valve implantation procedure may include, but are not limited to:

- death;
- cardiovascular or vascular injury, such as perforation or damage (dissection) of vessels, heart muscle or valve/valve structures that may require intervention;
- myocardial infarction (heart attack);
- stroke/ transient ischemic attack;
- embolization: air, calcification or thrombus;
- hemorrhage (bleeding) requiring transfusion or intervention;
- hematoma;
- hypertension (high blood pressure) / hypotension (low blood pressure);
- renal failure;
- renal insufficiency;
- allergic dye reaction;
- anesthesia reactions.
- arrhythmia;
- conduction system injury, which may require a permanent pacemaker;
- fever;
- infection including endocarditis (inflammation of the heart), incisional site infection/inflammation and septicemia (infection in blood);
- pericardial effusion/cardiac tamponade (bleeding into the heart sac);
- systemic peripheral ischemia/nerve injury; and
- AV fistula.

In addition to the risks listed above, additional potential risks specifically associated with the use of the investigational device include, but may not be limited to, the following:

- bleeding;
- device explant;
- device migration or malposition (THV implanted in unintended location) requiring intervention;
- device thrombosis requiring intervention;
- emergency cardiac surgery;
- endocarditis (inflammation of the heart);
- hemolysis (disruption of blood cells);
- hemolytic anemia (not enough red blood cells);
- non-emergent reoperation;

- nonstructural dysfunction;
- paravalvular leak (blood leakage around the device);
- structural valve deterioration (structural failure of the THV);
- valve stenosis;
- valvular thrombosis;
- vascular (vessel) injury at the site of venous, arterial or ventricular access requiring surgical repair.

The radiation dose from a single chest x-ray is about the same as the average person receives from background radiation in 10 days. When a blood sample is taken there is a small risk for bruising, discomfort, bleeding, or infection.

The Institutional Review Board (IRB)/Ethics Committee (EC) and the FDA have reviewed and approved the study.

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 study.

If you believe you have a research related complication, you understand that you should contact _____at _____.

You agree ____, You decline _____ to have your personal physician informed of your participation in this study.

Benefits

You may or may not receive any direct benefit from this research study. The potential benefit may be improvement in the symptoms related to your aortic stenosis, but it is not certain that these procedures will be of benefit to you. The benefits of these techniques include potentially a less invasive procedure, shorter procedure time, and less anesthesia than in an open-heart surgical procedure.

Balloon aortic valvuloplasty is a less invasive (than surgical valve replacement) option that can provide short-term palliation (relief) of symptoms.

Treatment with the investigational device may provide both short and long-term relief of your symptoms, good aortic valve function, and an improvement of your cardiac function that could potentially increase both your life expectancy and improve your quality of life.

It is possible that you will receive no direct benefit from this research study, but others may benefit in the future from your participation. If you should die from a cardiac related cause, or if a cardiac cause can not be excluded during or after the procedure, your physician will request autopsy permission from your relatives, legal representative or others as appropriate.

Voluntary Participation and Termination

You understand that 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 study investigator, Dr. _____, in writing and let

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him/her know that you are withdrawing from the research study. The mailing address is _____. If you choose to withdraw from the research study, you understand that any new information about the Edwards SAPIEN™ THV may not become available to you on a timely basis. Any significant new findings that develop during the research study which may relate to your willingness to continue participation will be provided to you by the study investigator. The study investigator may choose to terminate your participation, if you fail to follow the study guidelines, or in view of new information, at any time during the study.

Financial Obligation and Liability
Edwards Lifesciences LLC is the Sponsor and manufacturer of the investigational 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 understand that you will not be compensated in any way for your participation in this research study. You also understand that the Sponsor will not compensate you for injury or for any additional expenses incurred because of 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. You understand that the Sponsor or the hospital will not assume liability for injury directly attributable to this investigation 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 further understand that you do not waive any liability rights for personal injury by signing this form.

Confidentiality, Anonymity and Authorization
By signing this Consent you understand that the information derived from this research study may be given to the, FDA in the United States, 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, of this study, to have access to your confidential health , medical records and research information concerning the investigational device. You will also allow representatives from the Sponsor of this study, 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 physicians involved in the research study or the Sponsor may use the research study information collected from your participation for publications on the results of the use of this investigational device. 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 California, USA this Authorization will expire in twenty years.

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Your echocardiography 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. 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.

Another portion of this research study contains a health economics review that will be done to assess the costs of the investigational device for the treatment of critical aortic stenosis. As part of the research study, you will be asked to sign a Medical Billing Release Form. This form will be used by the Economic and Qualify of Life Assessment Group of the Harvard Clinical Research Institute (HCRI) to collect hospital bills from the patient accounting department at any hospital to which you are admitted, from the time of your enrollment in the research study through the entire study period. If you are eligible for Medicare or Medicare Plus Choice insurance coverage, you will also be asked to provide your Medicare Beneficiary number to the study personnel. This information will be kept strictly confidential and be used solely to assess the medical expenses which occur as a direct result of participating in research study and to ensure that hospitals receive the appropriate reimbursement when providing this service.

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 to be changed, you will be informed and you will be asked again for your consent.

While participating in this research study, you will not be allowed to participate in any other research study without approval from the study 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.

Experimental Subject'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.

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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 subject, I may contact _____(name) at _____(telephone).

I also acknowledge that I have been given a copy of this Consent Form.
BY SIGNING THIS FORM, I WILLINGLY AGREE TO PARTICIPATE IN THE RESEARCH STUDY DESCRIBED.

_____	_____	_____
Name of Subject (Printed)	Date	Time

_____
Signature of Subject

_____	_____	_____
Name of Legal Representative (Printed, if applicable)	Date	Time

_____
Signature of Legal Representative (Printed, if applicable)

SIGNATURE OF INVESTIGATOR

I have explained the research study to the subject 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 (Printed)	Date	Time

_____	_____
Signature of Investigator	Hospital

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.

_____	_____	_____
Name of Witness (Printed)	Date	Time

_____
Signature of Witness

Appendix D: Echocardiographic and ECG Core Lab Procedure Manual

Edwards Partner-US THV

Transthoracic Echocardiographic Patient Data Acquisition

Duke Core Laboratory Echo and ECG Procedure Manual

Document Number:

Version 1.10 November 2007

PARTNER-US IDE TRIAL PROTOCOL

Document Approval

Document Owner	_____	_____
Clinical Director	_____	_____
Documentation	_____	_____

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Table Of Contents

PARTNER ECHOCARDIOGRAPHY IMAGING PROTOCOL

I. Introduction

The Duke Echo Core Lab has been selected to work collaboratively with Edwards Lifesciences in providing protocol design, management, interpretation, and analysis of echocardiograms obtained for the Edwards Partner-US trial. The Duke Echo Core Lab has extensive experience in providing comprehensive core laboratory support for national and international clinical trials of all sizes utilizing echocardiography. This manual was created by the Duke Echo Core Lab to serve as a guide to sites for the echocardiographic portion of the Edwards Partner-US trial. The Duke Echo Core Lab will be analyzing all the echocardiograms completed in this study and will be providing feedback regarding quality to sites on an ongoing basis as each echo is received.

All sites will be required to complete a certification process related to image acquisition and transfer. Please refer to the Certification Echo Section, section V page 5 in your manual for details regarding this procedure. The Duke Echo Core Lab will send each participating site a survey to complete related to important information about available resources and equipment.

Examples of forms used in this study have been provided in Appendix C of this manual for your reference. A quick reference guide has also been made available as a handy tool for study sonographers, during image acquisition. Once data has been obtained, the sonographer will be required to export the study in DICOM format for the site coordinator to upload to WebPAX® VS (information on WebPAX® VS, Heart IT, is located in section IV page 5 of this manual).

Lastly, the Duke Echo Core Lab provides 7 days a week, 24 hour coverage for questions relating to any part of the echocardiographic portion of the Edwards Partner-US trial. Appendix B of the manual lists the contact information for key personnel. All calls and questions during the business day should be directed to ***Karen Loeffler, Clinical Trials Coordinator at 919-668-8432, (8:00 am – 5:00 pm ET)*** who will triage the call. After hour calls, should be placed to the 24-hour pager. We look forward to working with you on this exciting project!

The goal of the echocardiographic imaging portions of this protocol is to assist sites in obtaining high quality, reproducible, quantitative information about structure, function and hemodynamics of the Transcatheter Heart Valve (THV) in the aortic position. Echocardiographic measures of aortic valve area and function are used as markers of success in this trial.

The echocardiogram will be performed at specified time points. The majority of the echocardiograms will be transthoracic echocardiograms and this document focuses on this technique. The details of the image planes and the measurement conventions are described below. If images are inadequate then transesophageal echo can be performed according to the standards at the site and standard measurement conventions can be applied to the appropriate transesophageal echo views.

II. Echocardiographic Instrumentation

Since the make and model of the echocardiographic instrumentation may vary from one site to another, a description of the Doppler echocardiographic equipment for each site must be recorded for the sponsor and this should include the model and serial number of the echocardiography machine and transducers used in the examination of each subject. In addition, the institution must provide documentation ensuring the equipment has been validated and calibrated (calibration of B mode can be performed with a standard imaging phantom and a flow phantom can be used for Doppler calibration). The minimum requirement mandated by FDA is a validation and calibration check within 3 months prior to the start of the clinical study and at yearly intervals until the conclusion to the study. Each enrolling site should try to use the same echo instrument on all echoes performed on an individual subject throughout the study. If more than one echo machine will be used in this trial then the information above should be provided to the sponsor for all of the machines that will be utilized. Each machine must have the capability to record proper date, time and subject identification (initials and/or number).

Typically the transthoracic images are obtained with the subject in the left lateral decubitis position during quiet respiration or end expiration. The two-dimensional echocardiograms should be recorded on an ultrasound machine that *ALLOWS DIGITAL CAPTURE* and has harmonic imaging capabilities using transducers in the range of 2.5 to 5.0 MHz. A qualified physician or sonographer must perform all ultrasound exams. If possible, participating sites should attempt to utilize the same person for image acquisition throughout the trial. At least three sinus beats of each view should be *DIGITALLY CAPTURED* during quiet respiration or at end expiration. At least 5 beats should be recorded, if the subject is in atrial fibrillation. Multiple individual cardiac cycles can be captured or one long acquisition can be captured depending on the capabilities of the machine. The beats for assessment should not include PVC beats or post-PVC beats. CD-ROMs should be labeled with protocol number, subject number, subject initials, study site, time and date of exam. The file should be stored in a standard DICOM format.

For each view, the gain and compression should be optimized so that the best echocardiographic image of the endocardial borders is obtained. The selection of harmonics or fundamental frequency should depend upon which yields the best definition of structures. The depth should be selected which allows visualization of all of the structures of interest in that view. All images should have a good quality ECG tracing on the screen and clear calibration markings on the imaging sector. For Doppler spectral tracings, the sweep speed should be at least 100 mm/sec and the scale and baseline should be adjusted to make sure that the entire Doppler envelope is visualized. Time and velocity calibration markers must be present on the Doppler tracing. For spectral and color Doppler the appropriate gain level should be selected that detects flow without extraneous noise or extension of signal into adjoining tissue.

If visualization of the left ventricular (LV) endocardial border is inadequate then an approved contrast agent can be administered and harmonic imaging with low to intermediate mechanical index should be performed of the apical views. *However the contrast enhanced imaging should only be performed after all other images and parameters are obtained*. If Doppler signals are obtained during the contrast phase of the study, the gain must be reduced to optimize the velocity signal.

III. Study Visits

For each echocardiographic visit, please follow Section X, pages 7-9.
Each patient enrolled in the trial will have a completed echo at all of the following timepoints:

Visit	Year Range	Range
Baseline		
Discharge or 7 days		Whichever comes first
30 Days		± 7 days
6 Month		± 14 days
12 Month	1st Year	± 30 days
24 month	2nd Year	± 45 days
36 Month	3rd Year	± 45 days
48 Month	4th Year	± 45 days
60 Month	5th Year	± 45 days

IV. Data Transfer

Echo images should be recorded digitally onto a CD. Label CD with Patient Study ID, Patient Initials, Visit, and Exam Date. The sonographer performing the echo should complete the Echo Tracking Form and give the copied CD and tracking form to the study coordinator to upload into WebPAX® VS, a web service that allows for instant access to the images.

To create a WebPAX® VS account, you will need to fill out the application form on page 18. Once your account has been created and you are creating your settings, ***select YES for the option for email notification.*** Once your account is setup, you will ONLY be able to see the patients that you have uploaded for your site.

1. Upload images to WebPAX® VS, for details on uploading the CD to WebPAX® VS see page 17.
2. Complete the Echo Tracking Form in Medidata
3. Verify patient information on the images in WebPAX® VS with the Echo Tracking Form in Medidata. Also confirm that the same number of images on the CD is uploaded successfully in WebPAX® VS.

NOTE: If the study you upload into WebPAX® VS is the wrong patient, notify the Duke Core Lab immediately. The incorrect study will be deleted and you will need to be RELOAD the correct study.

V. Site Certification Process

a. **Purpose**. The purpose of the certification process is to ensure that all participating sites are able to provide standardized views from the Edwards Partner-US protocol (see section V page 5) and that all sites have the capability to download the images to WebPAX® VS .

b. **Site Survey Form**. The first step in the site certification process is ensuring that sites have the equipment needed to obtain the required echocardiogram studies. The Site Survey Form (see example in forms section), will be sent to each site by the Duke Echo Core Lab. It is requested that the site coordinator collaborate with their echo lab and gather all the information needed on the form. The form must be completed and returned to the Duke Echo Core Lab within 3 days (see contact page for fax number).

c. **Certification Echo**. The second step in the certification process is the acquisition of the certification echocardiogram. Once the certification echo has been received, the site coordinator will need to upload the echo into WebPAX® VS.

d. **Feedback Form for Certification**. A feedback form (see example in forms section) will be completed by the Duke Echo Core Lab for each Certification Echo. The feedback form will be returned to the site within 48-72 hours of the receipt of the Certification Echo in WebPAX® VS. Comments / Suggestions may be made to ensure that the media and images are adequate for the protocol. See Section VIII Site Feedback Form for definitions on adequate vs. inadequate echo images.

If the echo is Adequate, the site will receive a statement declaring that the site is officially certified for participation in this clinical study. This certification should be kept for your records. The study sponsor will be notified that the site has been certified.

VI. Echocardiographic Analysis

The core laboratory will review each image, make the required measurements and complete the electronic Case Report Form (eCRF) in Medidata.

VII. Echocardiographic Recordings

Each echocardiographic examination should be recorded DIGITALLY. The images should indicate the investigator, institution name, subject number, and the date of echocardiography exam. Please note that *NO PATIENT INFORMATION SHOULD BE ON THE IMAGES* (this includes the patient name, history number, social security number, etc). The investigator should keep a copy of the exam on site either on a server or CD-ROM.

LABEL THE IMAGES AND CD AS FOLLOWS		
Patient Study ID	**U2606**	__ __ - __ __ __
Subject's Initials		__ __
Visit		example: Baseline TTE
Exam Date		

VIII. Site Feedback Form

A process has been put in place to ensure a high level of echocardiogram quality. Each time an echo study is received by the Duke Echo Core Lab, a feedback form will be completed by one of the dedicated sonographers and faxed to the site. This form will be sent to sites 48 to 72 hours after the echocardiogram is received by the lab. Comments will be made, when applicable, and technical tips given to help site sonographers acquire the best images possible. Please share all feedback forms with the responsible party of the echo to ensure all future studies are adequate.

Feedback Form Definitions

1. Adequate
   An echo will be considered adequate if the images listed on the feedback form are completed correctly specifically zoom of the LVOT, both LVOT pulse wave Doppler samples and Aortic Valve continuous wave Doppler are adequate. *Not all inadequate images will require a resend of the study.*

2. Inadequate = RESEND of the echo with the missing images.
   An echo will be considered Inadequate and need to be RESENT if ANY of the following happens:
   a. Zoom of the LVOT is inadequate
   b. Either of the LVOT pulse wave Doppler samples are inadequate
   c. Aortic Valve continuous wave Doppler is inadequate
   d. Images are unloadable or unreadable

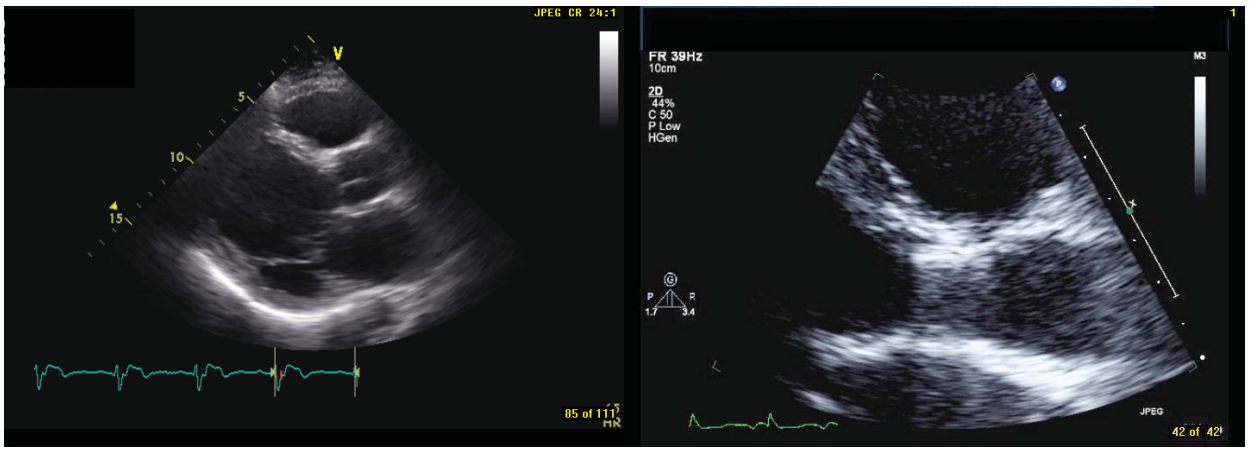
IX. Echo Tracking Form

A hard copy version of the Echo Tracking Form will be completed for each patient and kept as source documentation along with the CD-ROM of the echo image. The Echo Tracking Form will also be completed electronically (eCRF Form 8) in Medidata after the echo images are uploaded to WebPAX® VS. The Echo Tracking Form contains all of the necessary information needed to match the appropriate patient identification number to the echo image in WebPAX® VS***.***

X. Obtain the following echocardiographic views for Core Lab analysis. **Also note that the machine settings on the Echo Tracking Form will need to be filled out at this time. The machine settings you will need to acquire are the Nyquist Limit, Depth, Color Gain, Frame Rate and whether you use Persistance or Smoothing. See the Echo Tracking Form on page 15. Before beginning each exam, make sure that the machine you are using has the correct DATE and TIME stamped on the images.**

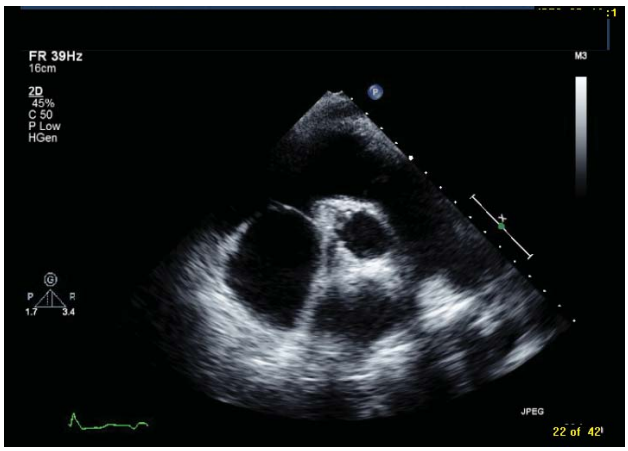
Parasternal Long Axis of LV, LVOT and aortic valve

- 2D
- Color Doppler of MR
- Color Doppler of LVOT and aortic valve for aortic insufficiency
- Magnified views of LVOT and aortic valve – to identify the true LVOT dimension, AV annulus and stent diameter.
- High Parasternal View to see ascending aorta
- Off-axis views to search for aortic paravalvular leak



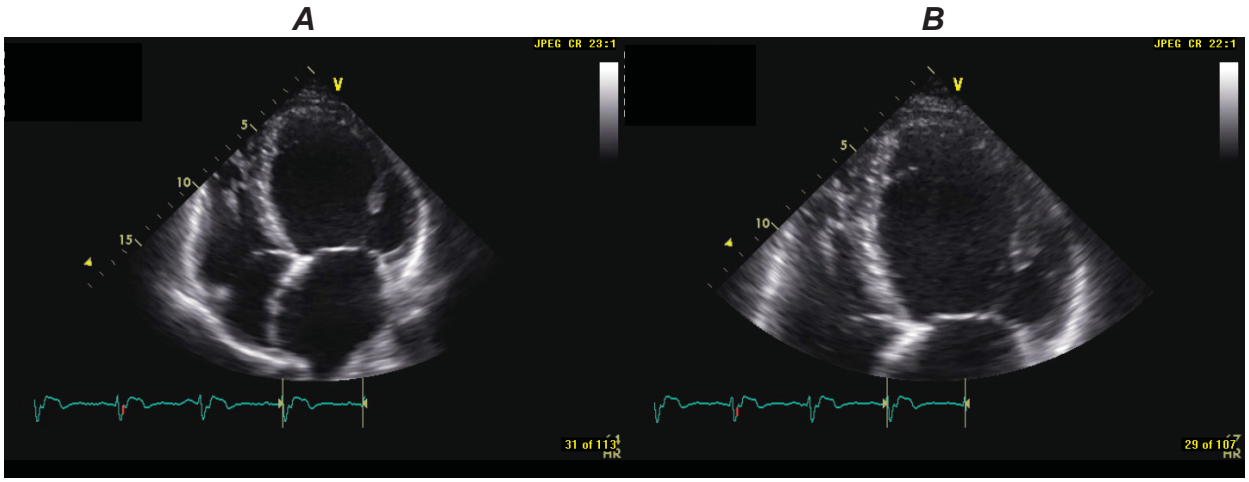
Parasternal Short axis at aortic valve level

- 2D
- color Doppler of aortic valve including sewing ring of prosthesis to search for paravalvular leak



Apical 4 chamber

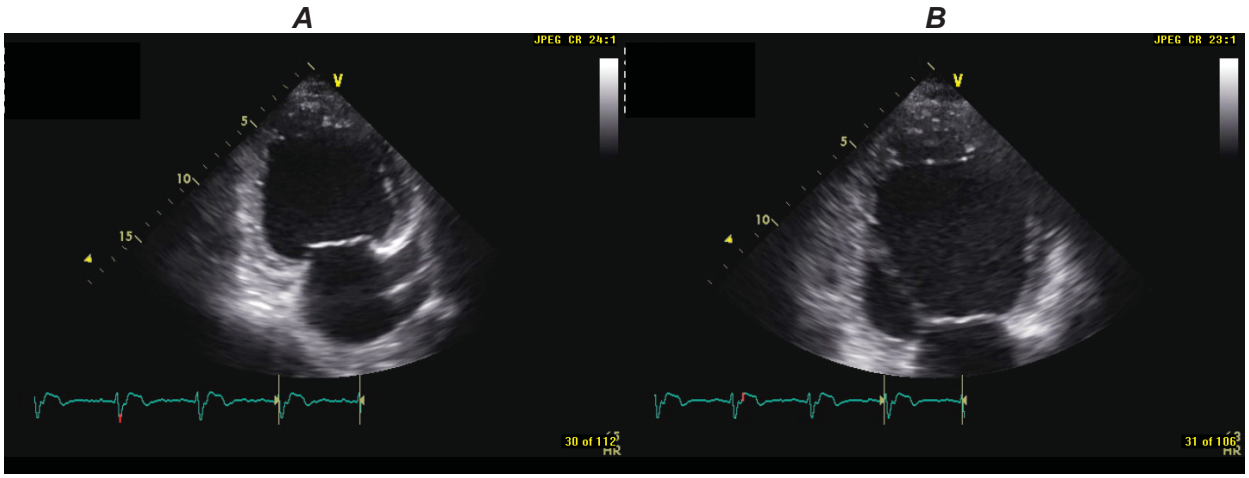
- 2D optimizing LV endocardial borders : *Need to see all aspects of the Lateral Wall, Septum, and Apex*
- Show a loop with decreased depth such that LV occupies most of the imaging sector ensuring all walls are visualized
- Color Doppler of MR



* Image A shows the traditional 4 chamber while image B shows the 4 chamber with *decreased depth*.

Apical 2 chamber

- 2D optimizing LV endocardial borders : *Need to see all aspects of the Anterior Wall, Inferior Wall, and Apex*
- Show a loop with decreased depth such that LV occupies most of the imaging sector ensuring all walls are visualized
- Color Doppler of MR



* Image A shows the traditional 2 chamber while image B shows the 2 chamber with *decreased.*

Apical 5 chamber view – Native Valve (BASELINE ONLY)

- Pulse wave Doppler of LVOT (to avoid the region of flow acceleration - sample volume positioned at valve level and then moved apically until valve noise or “clicks” are no longer detected and then recorded)
- Continuous wave Doppler through the aortic valve
- Color Doppler of LVOT and aortic valve

Apical 5 chamber view – Prosthetic Valve

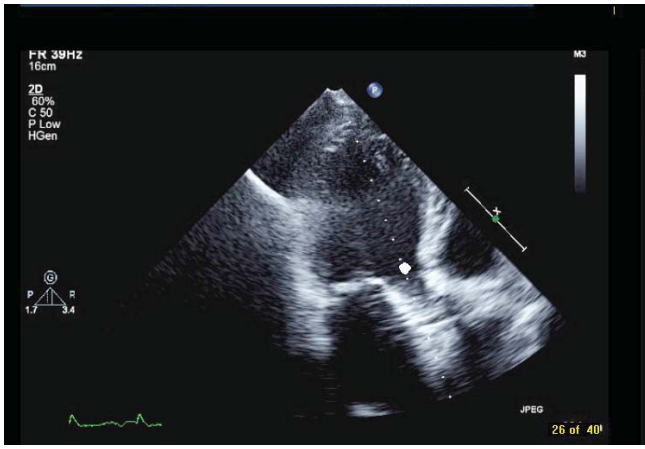
- Continuous wave Doppler through the aortic valve
- Color Doppler of LVOT and aortic valve
- Pulse Wave Doppler of the following *TWO* places: (see Doppler images below for a reference)
    - Sample volume just apical to THV stent
        - 2D of pulse wave sample position
        - Pulse Wave Doppler
    - Sample volume within THV stent on LV side of Aortic Valve leaflets
        - 2D of pulse wave sample position
        - Pulse Wave Doppler

Apical long axis view (also known as 3 chamber view)

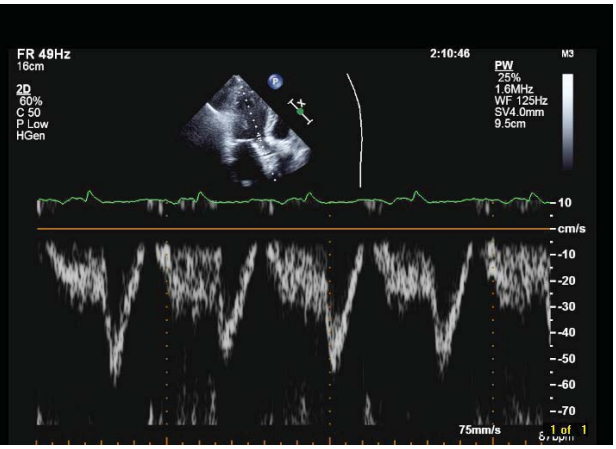
- 2 D optimizing LV endocardial borders
- Color Doppler of MR
- Color Doppler of LVOT and aortic valve for AI
- Pulse Wave Doppler of the following *TWO* places:
  - Sample volume just apical to THV stent
    - 2D of pulse wave sample position (sample A below)
    - Pulse Wave Doppler (sample B below)
  - Sample volume within THV stent on LV side of Aortic Valve leaflets
    - 2D of pulse wave sample position (sample C below)
    - Pulse Wave Doppler (sample D below)

Continuous Wave Doppler through the aortic valve

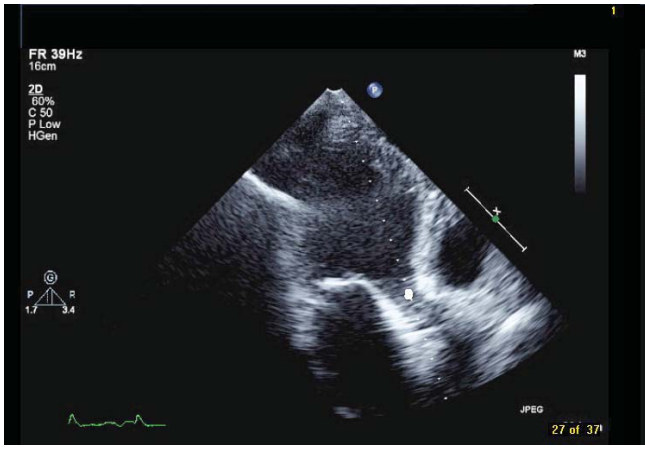
A



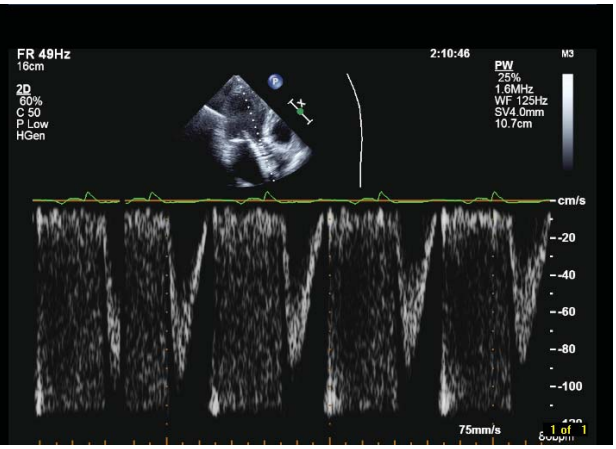
B



C



D



Right Parasternal view

Continuous Wave Doppler of AV if apical Continuous Wave Doppler of AV is inadequate

If significant (moderate or greater) aortic insufficiency is present, spectral Doppler of the descending thoracic aorta from the suprasternal notch should be obtained to assess for reversal of flow.

XI. Specific Comments on Imaging Planes

1) The **parasternal long axis** view is recorded with the transducer in the third or fourth intercostal space immediately to the left of the sternum. The transducer should be angled so that aortic valve, mitral valve and left ventricle are in their long axis.
Structures of interest in this view include:

- Left ventricle - dimensions
- Mitral valve – structure and function
- Aortic valve – structure and function

Color Doppler of the MV and AV should be obtained in planes that can resolve the origins, maximum vena contracta width and maximum paths of the regurgitant jets. Show a loop of a high parasternal LAX with transducer in second or third intercostal space to see ascending aorta.

2) The **parasternal short axis** view is obtained by angling the probe 90° with respect to the parasternal long axis of the LV. The goal of this view is to obtain information about the aortic valve.

3) The **apical four-chamber** view provides considerable information including the relative sizes of the right and the left ventricle and the regional function of the LV. The four-chamber view is defined as a view which maximizes the LV long axis and the tricuspid and mitral annular dimensions. In this view, the full excursion of the mitral and tricuspid valves should be seen. The complete endocardial border of the LV will be traced for chamber volume assessment (method of discs) so all aspects including the apex should be visualized. In the apical four chamber view, color Doppler of mitral regurgitation should be recorded. The four chamber view should visualize the Lateral, Septal and Apical walls.

4) The **apical 2 chamber** view should be obtained for the goal of assessment of LV size and function. The complete endocardial border of the LV will be traced for chamber volume assessment (method of discs) so all aspects including the apex should be visualized. The degree of MR by color Doppler will also be assessed. The two chamber should visualize the Anterior, Inferior and apical walls.

5) The **apical 5 chamber** and **3 chamber** views are obtained to provide detailed information about the aortic valve color, spectral and continuous wave Doppler.

6) If moderate or severe AI is detected on the above views then a pulse wave Doppler assessment of the proximal descending aorta should be performed to look for the presence of reversal of flow in diastole. To do this the **Suprasternal** notch view of the thoracic aorta is used and the Doppler sample volume is placed in the descending thoracic aorta below the take off of the subclavian artery.

XII. Helpful Tips

1) Harmonic imaging should be used if endocardial border definition is not optimized with fundamental frequency. If inadequate border delineation persists, then an intravenous echocardiographic contrast agent should be used for complete LV cavity opacification. If a contrast agent is used, please annotate on the screen what view is what (ex. 4 chamber, 2 chamber, 3 chamber. Body markers are acceptable forms of annotation)

2) Record at least 3 beats of each view (sinus rhythm); 5 beats if arrhythmia

3) Spectral Doppler (pulse wave and continuous wave) should be performed with the line of interrogation as parallel to flow as possible. Record Doppler at 100 mm/sec sweep speed or greater.

4) Ensure good quality ECG signals are recorded on all images.

5) Distance, time and velocity calibrations must be present on each image. Time, date, patient identification should be accurately marked in each image.

XII. Abbreviations

2D	Two-dimensional
AI	Aortic Insufficiency
AR	Aortic Regurgitation
AV	Aortic Valve
AVA	Aortic valve area
BSA	Body Surface Area
CO	Cardiac Output
CSA	Cross sectional area
ED	End diastole
EF	Ejection fraction
ES	End systole
HR	Heart rate
LA	Left atrium
LV	Left Ventricle
LVEDv	Left ventricular end diastolic volume
LVEF	Left ventricular ejection fraction
LVESv	Left ventricular end systolic volume
LVOT	Left ventricular outflow tract
MR	Mitral Regurgitation
MV	Mitral Valve
PI	Performance Index
PW	Pulse wave
SV	Stroke Volume
TR	Tricuspid Regurgitation
TVI	Time Velocity Integral

Edwards

Duke Clinical Research Institute
ECG Core Laboratory

Dear Study Coordinator:
As part of the Edwards PARTNER Study you will be acquiring two standard 12-lead paper ECGs, sending one original ECG per patient, per visit and keeping the other original on site as part of your source documentation. Please also send original ECGs if a recurrent or suspected recurrent ischemic event occur during the follow-up period. If you are unable to provide us with an original ECG, a high quality copy is acceptable.

In Appendix C of this procedural manual are the ECG Tracking Form and ECG labels. Shipping materials will be sent separately to your site. Please use the check list below to ensure that ECGs are collected and shipped to the DCRI ECG Core Lab correctly.

- ☐ Acquire the Baseline ECG prior to the procedure. Print two originals, one to keep and one to send to the DCRI ECG Core Lab.
- ☐ Acquire the Post Procedure ECG following the procedure.
- ☐ Acquire the Discharge or 7 days post procedure ECG, which ever comes first.
- ☐ Acquire the 30 days post procedure ECG within ± 7 days.
- ☐ Acquire the 3 months post procedure ECG within ± 14 days.
- ☐ Acquire the 6 months post procedure ECG within ±14 days.
- ☐ Acquire the 1 year post procedure ECG within ± 30 days.
- ☐ Acquire the 2 years post procedure ECG within ± 45 days.
- ☐ Acquire the 3 years post procedure ECG within ± 45 days.
- ☐ Acquire the 4 years post procedure ECG within ± 45 days.
- ☐ Acquire the 5 years post procedure ECG within ± 45 days.
- ☐ Acquire any ECGs if the patient has a recurrent or suspected recurrent ischemic event, during the follow up period.
- ☐ Remove all patient identifiers from the ECGs and affix the appropriate ECG label and complete patient study id, patient initials, visit, and ECG date and time. When affixing the ECG label, be careful not to obstruct any of the lead intervals.
- ☐ Complete the ECG Tracking Form for each patient in Medidata prior to shipping the original ECGs to the DCRI ECG Core Lab. Complete and retain a hard copy of the ECG Tracking Form, included in this packet, for your source documentation.
- ☐ Submit the original ECGs using the pre-printed FedEx air bills included in this packet. You may send original ECGs for multiple patients in one FedEx packet.
- ☐ If additional Ischemic events occur and ECGs are collected, please indicate the ischemic event on the ECG Tracking Form in Medidata prior to shipping the original ECG to the DCRI ECG Core Lab.

Please send original ECGs to the following address:

Karen Loeffler
ECG Core Laboratory
Hock Plaza
2424 Erwin Rd, Suite 401
Durham, NC 27705

We look forward to working with you on this project.
Best regards,
ECG Core Laboratory

Appendix A

Edwards

Duke Clinical Research Institute
DUKE UNIVERSITY MEDICAL CENTER

Site Sonographer Echocardiogram Checklist	Views Completed
Machine Settings (acquired during Discharge/7 Day visit on the Chest Wall when looking for AI)	
Nyquist Limit ……	_____
Depth	
……	_____
Color Gain ……	_____
Frame Rate (keep around 20Hz)	
……	_____
Persistance (want off)	
……	☐ On ☐ Off
Smoothing (want off) ……	☐ On ☐ Off
Height ……	_____
Weight ……	_____
Long Axis (LAX)	
The Echo Machine has the correct Date and Time Stamp	☐ Yes ☐ No
2D loop of LAX	1 ☐
Color of MR	2 ☐
Color of LVOT and Aortic Valve for AI	3 ☐
Zoom LVOT for dimension	4 ☐
Zoom Aortic Valve for diameter	5 ☐
Zoom of Ascending Aorta for dimension	6 ☐
Off axis views to look for paravalvular leak	7 ☐
Short Axis (SAX)	
2D loop of MV SAX at Papillary Muscle, Apex, and MV Levels	8 ☐
2D loop of Aortic SAX view	9 ☐
Color of Aortic Valve	10 ☐
Zoom of Aortic Valve with good valve definition	11 ☐
Off axis views to look for paravalvular leak	12 ☐
4 Chamber	
2D loop optimizing endocardium	13 ☐
2D loop with decreased depth to visualize LV	14 ☐
* *Good visualization of Lateral, Septal, and Apical walls needed*	15 ☐
Color MR	16 ☐
2 Chamber	
2D loop optimizing endocardium	17 ☐
2D loop with decreased depth to visualize LV	18 ☐
* *Good visualization of Anterior, Inferior and Apical walls needed*	19 ☐
Color MR	20 ☐
5 Chamber : Native Valve *(Baseline ONLY)*	

PW LVOT	21	
CW Aortic Valve	22	
Color LVOT and Aortic Valve for AI	23	

5 Chamber : THV *(follow-ups ONLY)*

Color of LVOT and Aortic Valve for AI	24	
2D loop of PW position just apical (subvalvular) to the THV stent	25	
PW LVOT just apical (subvalvular) to the THV stent	26	
2D loop of PW position within THV stent on LV side of leaflets	27	
PW stent on LV side of leaflets	28	
CW of Aortic Valve	29	

3 Chamber : Native Valve *(Baseline ONLY)*

PW LVOT	30	
CW Aortic Valve	31	
Color LVOT and Aortic Valve for AI	32	

3 Chamber

Color LVOT and Aortic Valve for AI	33	
2D loop of PW position just apical (subvalvular) to the THV stent	34	
PW LVOT just apical (subvalvular) to the THV stent	35	
2D loop of PW position within THV stent on LV side of leaflets	36	
PW stent on LV side of leaflets	37	
CW of the Aortic Valve	38	

*** Right Parasternal**

CW of Aortic Valve ONLY if apical CW is inadequate	39	

*** Suprasternal Notch**

If there is Moderate to Severe AI, do spectral Doppler of Descending AO to assess reversal of flow.	40	

Label Images / Machine

Time, Date, and Patient identification should be accurately marked on each image

Site Number
Patient Number
Patient Initials

Notes

Doppler Sweep Speed set at 100 mm/sec
Record at least 3 beats of each view (sinus rhythm); 5 beats if arrhythmia
Good ECG signal
Distance, Time, and Velocity calibrations must be present on each image
Keep Color Frame Rate at or around 20Hz when looking at AI
Persistance and Smoothing off

Edwards

Contact List

Duke Echo and ECG Core Lab

24 hour pager: HELP LINE 1-800-425-1516

Fed-Ex Address:
Hock Plaza
2424 Erwin Road
Suite 401
Durham, NC 27705
Fax: 919-668-7111

Study Personnel:

Pamela S. Douglas, MD
Ursula Geller Professor of Research in Cardiovascular Diseases
Director, Cardiovascular Imaging Center
Phone: 919-661-2690
Fax: 919-668-7059
Pager: 919-970-9287
Email:Pamela.Douglas@duke.edu

Shelly Duckworth, RDCS
Phone: 919-668-3601
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Edwards

SITE FEEDBACK FORM
Duke Echo Core Lab

Study date: ___ ___ /___ ___ ___ / ___ ___ Date received by lab: ___ ___ / ___ ___ ___ / ___ ___ **CD #** _____
Internal use

Patient ID. U2606 ___ ____ ____ ____ ____ **Patient Initials** _____ _____ _____ **F M L**	Study Visit : ❑ **Baseline** ❑ **Discharge / 7 Day** ❑ **30 Day** ❑ **6 Month** ❑ **1-year** ❑ **2-year** ❑ **3-year** ❑ **4-year** ❑ 5-year ❑ **Other** _____

Criteria to meet	Completed Correctly	Comment / Tech Tip
2D and Color Long Axis	Yes /No /NA	
Zoom LVOT in Long Axis	Yes /No /NA	
2D and Color Short Axis	Yes /No /NA	
2D Four Chamber with good endocardial definition	Yes /No /NA	
Color AV and MV in 4 chamber	Yes /No /NA	
2D Two Chamber with good endocardial definition	Yes /No /NA	
Color MV in 2 chamber	Yes /No /NA	
LVOT and Stent PW Samples	Yes /No /NA	
Aortic Valve CW	Yes /No /NA	
2D and Color Three Chamber	Yes /No /NA	
Right Parasternal	Yes /No /NA	
Suprasternal Notch	Yes /No /NA	
Comments:		

❑ **Adequate ECHO** ❑ **Inadequate – RESEND NEEDED**

Image Quality Rating :
❑ 1 – Excellent Image Quality ❑ 2 – Good data, all images measurable ❑ 3 – Missing Views, most measurements possible ❑ 4 – Missing Views, few measurements possible ❑ 5 – No acceptable data

Signature of Sonographer _____ **Date:** _____
Date of site notification: __ __/ __ __ __ /__ __
by ❑ phone / ❑ fax. Site contact_____Please contact **Karen Loeffler 919-668-8432** (8:00 am – 5:00 pm EST) for any questions you may have. After hours or weekends please call the 24 hour pager at 1-800-425-1516.

Edwards

Echo Tracking Form

Duke Echo Core Lab

PARTNER: **P**lacement of **A**o**RT**ic Tra**N**scathet**ER** Valves Trial

Patient Study ID **U2606** ___ ___ ___ ___ ___ Patients Initials (First, Middle, Last) ____ _____ ____

Note: To maintain confidentiality the patient's name must not appear on any document

1. Valve Size: □ 23mm □ 26mm □ Other, specify_____ □ N/A

2. Assessment Interval: □ Baseline □ Discharge / 7-Day □ 30-Day □ 3-Month □ 6-Month □ 1-Year □ 2-Year □ 3-Year □ 4-Year □ 5-Year □ Other, Specify: _____

3. Echo Date: ___ ___ / __ __ ___ / ___ ___ ___ ___ **(Day Month Year)**

4. Echo Time: __ __: __ __ **(24 hr format)**

5. Source Echo Saved on:
□ **CD**
□ **Mod**
□ **DVD**
□ **Server**
□ **Other, Please specify** _____

6. Echo Type
□ TTE
□ TEE

7. Model of Echo Machine: _____

8. Reason for Echo
□ Per Protocol
□ Symptomatic
□ Other *(Specify):* _____

9. Echo Images Uploaded to WebPAX® VS
□ Yes, date uploaded: ____ / _ _ _ / _ _ _ _
□ No, Explain: _____

10. Physical Assessment: □ N/A
10.1 Weight: __ __ __.__ □ Kg □ N/A
10.2 Height: __ __ __ □ cm □ N/A
10.3 BSA: __.___ __ □ N/A
10.4 Blood Pressure: ____ / ___ mmHg □ N/A
10.5 Heart Rate: _____ bpm □ N/A

11. Sonographer Name: _____

12. MACHINE SETTINGS:
12.1 Nyquist Limit _____ **cm/s** □ **N/A**
12.2 Depth _____ **cm** □ **N/A**
12.3 Color Gain _____ **db** □ **N/A**
12.4 Frame Rate: _____**Hz** □ **N/A**
12.5 Persistance □ **On** □ **Off** □ **N/A**
12.6 Smoothing □ **On** □**Off** □ **N/A**

13. Comments:

Provide Patient ID Number from WebPAX® VS Confirmation Email:_____

I have reviewed and approved all information on this form.

_____ __ __/ __ __ __/ __ __ __ __
(Investigator's or designee Signature) Date: DD MMM YYYY

Edwards

Echo Lab Site Survey

Duke Echo Core Lab

Site No: ___ ____
Site Name: _____
Echocardiography Lab: _____
Address: _____
Phone: (__ __ __) ___ ___ ___ - ___ ___ ___ ___ **ext.** _____
Fax: (__ __ __) ___ ___ ___ - ___ ___ ___ ___
Email: _____
Sonographer contact (name) _____
Phone: (__ __ __) ___ ___ ___ - ___ ___ ___ ___ **ext.** _____

Echo Machine – Please provide Make and Model: _____

_____

1) Does your lab store echo studies in digital format? ☐ **YES** ☐ **NO**
If yes, what system do you use? (Example: EnConcert, Xcelera, ProSolv)

_____

2) If your lab is NOT digital, can your echo machine export in DICOM?

_____

3) You will be required to make a copy of the echo study to retain at your site. If you are unable to do this, please state reason why below.

_____

Please fax this completed form *within three days* of receipt to:

Questions? Please contact: Karen Loeffler at 919-668-8432

Edwards

Instructions for DICOM Upload

(Windows version)

1. **System Requirements.**

   a) **Windows 2000, XP**
   b) **Internet Browser (Internet Explorer, Firefox, Safari)**
   c) **WebPAX® VS Account with staff access or higher.**

2. **Log in to WebPAX® VS**

   a. **Start internet browser.**
   b. **Enter** https://webpax.heartit.com **into the address bar.**
   c. **Enter username (email address) and password on login page.**
   d. **Click on "Upload" menu link.**
   e. **Click on "Run upload application".**
      i. **Internet Explorer users select "Run" instead of "Save".**
      ii. **Firefox and other browsers save the application and execute it after the application has completed downloading.**

3. **Using the upload application.**

   a. **Choose folder containing the DICOM files – Click "Open"**
   b. **From drop down boxes – choose a patient id and scan description – Click "OK"**

Edwards

Application for WebPAX® VS Account – FAX TO +1 866-457-3694

Applicant Information

Site Name: _____ Site Number: _____ _____
(2 digit Medidata Number)

Principle User (this person will be the account administrator and can create other users):

Full Name: _____
(please print)

Email Address: _____ (account correspondence will be sent here)
(please print)

	Account Contact
Full Name	
Street Address	
Telephone	
FAX	
email	

Edwards	***Duke Clinical Research Institute*** ***eECG Core Laboratory*** ***ECG Tracking Form***
Patient Study ID: **U2606** ___ ___ ___ ___ ___	Patient Initials: ___ ___ ___ F M L

	Date (dd/mmm/yyyy)	**Time (24 hr clock 00:00 to 23:59)**
Procedure		

ECG Type	**Date (dd/mmm/yyyy)**	**Time (24 hr clock 00:00:00 to 23:59:59)**	**Completed By:**	**Date Shipped (dd/mmm/yyyy)**	**Courier**	**Courier Tracking Number**
Enrollment □ ND						
Post Procedure □ ND						
Discharge / 7 Day □ ND						
30 Days Post □ ND						
3 Months Post □ ND						
6 Months Post □ ND						
1 Year Post ` □ ND						
2 Years Post □ ND						
3 Years Post □ ND						
4 Years Post □ ND						
5 Years Post □ ND						
Other ECG (specify) _____						

Edwards-PARTNER ECG Labels
Patient Study ID U2606 ____ ____ ____ ____ ____
Date: ____/____/____ Time: _____:____
□ Enrolment □ Post Procedure □ Discharge/ 7 Day
□ 30 Days Post □ 3 Month Post □ 6 Month Post
□ 1 Year Post □ 2 Years Post □ 3 Years Post
□ 4 Years Post □ 5 Years Post □ Other

Edwards-PARTNER ECG Labels
Patient Study ID U2606 ____ ____ ____ ____ ____
Date: ____/____/____ Time: _____:____
□ Enrolment □ Post Procedure □ Discharge/ 7 Day
□ 30 Days Post □ 3 Month Post □ 6 Month Post
□ 1 Year Post □ 2 Years Post □ 3 Years Post
□ 4 Years Post □ 5 Years Post □ Other

Edwards-PARTNER ECG Labels
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□ 4 Years Post □ 5 Years Post □ Other

Edwards-PARTNER ECG Labels
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□ 1 Year Post □ 2 Years Post □ 3 Years Post
□ 4 Years Post □ 5 Years Post □ Other

Edwards-PARTNER ECG Labels
Patient Study ID U2606 ____ ____ ____ ____ ____
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□ 1 Year Post □ 2 Years Post □ 3 Years Post
□ 4 Years Post □ 5 Years Post □ Other

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Date: ____/____/____ Time: _____:____
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□ 30 Days Post □ 3 Month Post □ 6 Month Post
□ 1 Year Post □ 2 Years Post □ 3 Years Post
□ 4 Years Post □ 5 Years Post □ Other

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□ 30 Days Post □ 3 Month Post □ 6 Month Post
□ 1 Year Post □ 2 Years Post □ 3 Years Post
□ 4 Years Post □ 5 Years Post □ Other

Edwards-PARTNER ECG Labels
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□ 1 Year Post □ 2 Years Post □ 3 Years Post
□ 4 Years Post □ 5 Years Post □ Other

Edwards-PARTNER ECG Labels
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□ 30 Days Post □ 3 Month Post □ 6 Month Post
□ 1 Year Post □ 2 Years Post □ 3 Years Post
□ 4 Years Post □ 5 Years Post □ Other

Edwards-PARTNER ECG Labels
Patient Study ID U2606 ____ ____ ____ ____ ____
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□ 30 Days Post □ 3 Month Post □ 6 Month Post
□ 1 Year Post □ 2 Years Post □ 3 Years Post
□ 4 Years Post □ 5 Years Post □ Other

Edwards-PARTNER ECG Labels
Patient Study ID U2606 ____ ____ ____ ____ ____
Date: ____/____/____ Time: _____:____
□ Enrolment □ Post Procedure □ Discharge/ 7 Day
□ 30 Days Post □ 3 Month Post □ 6 Month Post
□ 1 Year Post □ 2 Years Post □ 3 Years Post
□ 4 Years Post □ 5 Years Post □ Other

Edwards-PARTNER ECG Labels
Patient Study ID U2606 ____ ____ ____ ____ ____
Date: ____/____/____ Time: _____:____
□ Enrolment □ Post Procedure □ Discharge/ 7 Day
□ 30 Days Post □ 3 Month Post □ 6 Month Post
□ 1 Year Post □ 2 Years Post □ 3 Years Post
□ 4 Years Post □ 5 Years Post □ Other

Edwards-PARTNER ECG Labels
Patient Study ID U2606 ____ ____ ____ ____ ____
Date: ____/____/____ Time: _____:____
□ Enrolment □ Post Procedure □ Discharge/ 7 Day
□ 30 Days Post □ 3 Month Post □ 6 Month Post
□ 1 Year Post □ 2 Years Post □ 3 Years Post
□ 4 Years Post □ 5 Years Post □ Other

Edwards-PARTNER ECG Labels
Patient Study ID U2606 ____ ____ ____ ____ ____
Date: ____/____/____ Time: _____:____
□ Enrolment □ Post Procedure □ Discharge/ 7 Day
□ 30 Days Post □ 3 Month Post □ 6 Month Post
□ 1 Year Post □ 2 Years Post □ 3 Years Post
□ 4 Years Post □ 5 Years Post □ Other

Edwards-PARTNER ECG Labels
Patient Study ID U2606 ____ ____ ____ ____ ____
Date: ____/____/____ Time: _____:____
□ Enrolment □ Post Procedure □ Discharge/ 7 Day
□ 30 Days Post □ 3 Month Post □ 6 Month Post
□ 1 Year Post □ 2 Years Post □ 3 Years Post
□ 4 Years Post □ 5 Years Post □ Other

Edwards-PARTNER ECG Labels
Patient Study ID U2606 ____ ____ ____ ____ ____
Date: ____/____/____ Time: _____:____
□ Enrolment □ Post Procedure □ Discharge/ 7 Day
□ 30 Days Post □ 3 Month Post □ 6 Month Post
□ 1 Year Post □ 2 Years Post □ 3 Years Post
□ 4 Years Post □ 5 Years Post □ Other

Appendix E: Economics and Quality of Life Core Lab Protocol

Economics and Quality of Life Core Lab Protocol - Quality of Life and Cost-effectiveness Study

The goal of the quality of life study is to analyze health-related quality of life in subjects undergoing transcatheter aortic valve replacement over the 12 month follow-up period and to determine the time course of improvement.

The economic study will assess procedural and follow-up resource utilization for transcatheter aortic valve replacement. The economic study will track cardiovascular resource utilization for the study enrollment, 6 and for the 12 month period following study enrollment.

Quality of Life Instruments

An instrument incorporating both disease-specific and generic health status measures will be used to assess health-related quality of life and functional recovery specifically in elderly subjects with severe, symptomatic aortic stenosis. In addition to having undergone extensive validation studies, the instruments are all available in multiple languages including English, French, German, Flemish, Italian, Spanish and Portuguese. The instruments will include the following:

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

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. (2)

3) **SF 12.** The SF 12 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)

In addition to these specific quality of life measures, a variety of clinical and demographic data will be collected at baseline including each subject's age, sex, race and level of education. A Charlson Comorbidity Index Score will be determined for each subject as well. These data will ultimately be incorporated as covariates into planned multivariable analyses of the quality of life endpoints.

Quality of Life Data Collection: The instruments will be administered by written questionnaire that is given to the subject at the baseline interview as well as at the time of scheduled clinical follow-up at 1 month, 6 months, and 12 months post procedure. For subjects who are hospitalized at the time of scheduled follow-up, the research coordinator will attempt to have the subject complete the quality of life survey while in the hospital or, alternatively, have a proxy complete the survey on the subject's behalf. It will be critical to obtain quality of life follow-up from every eligible subject in order to ensure the validity of the cross-temporal comparisons.

Collection of the quality of life data at baseline, 30 days, 6 months and 12 months post procedure will be the primary responsibility of the study coordinators at each clinical site. Follow-up quality of life surveys will be given to each subject at the time of scheduled clinical follow-up and completed in the same setting so as to minimize respondent

burden and maximize compliance. After completion of the survey, the original will be photocopied and the photocopy transmitted to the data coordinating center for entry into the study database. The original source document will be retained at the study center.

Send Completed Forms to:

EQOL Assessment Group
Harvard Clinical Research Institute
930 Commonwealth Avenue
Boston, MA 02215

References

(1) Spertus JA. Development and evaluation of the Kansas City Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol 2000 Apr;35(5):1245-55.

(2) Dolan P. Modeling valuations for EuroQOL health states. *Medical Care*. 1997;35:1095-1108.

Appendix F: Histopathology Core Lab Protocol

HISTOPATHOLOGY CORE LAB PROTOCOL

Explant Procedure and Histopathology Analysis

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 during the THV procedure should be returned to the Sponsor for evaluation. Please obtain a RGA number and return the product to:

Edwards Lifesciences LLC
1212 Alton Pkwy
Irvine, CA 92606
Attention: Returned Goods
RGA#:_____

Procedure for Clinical Sites (Hospital)

Valve Explantation 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.

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 subject 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.

Fixation

Explanted study valve samples shall be submitted in 10% formalin.

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 subject 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)

Tissue Shipment

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:

Send to: **CV Path**
Attn: Dr. Renu Virmani
19 Firstfield Rd
Gaithersburg, MD 20878

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;
- Leaflet wear or degeneration;
- Leaflet thickness;
- Leaflet fenestrations;
- Fibrosis sheathing;
- Calcification (leaflet and conduit);
- Evidence of infection;
- Aneurysm formation;
- Valve thrombosis;
- Tissue rejection;
- Inflammation.

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.

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.

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.

Appendix G: Instructions For Use (Transfemoral And Transapical Delivery)

Edwards Lifesciences

Edwards SAPIEN Transcatheter Heart Valve

Model 9000TFX

Instructions For Use
Retrograde Approach

CAUTION: Investigational device. Limited by Federal (USA) Law to investigational use.

Exclusively for Clinical Investigations

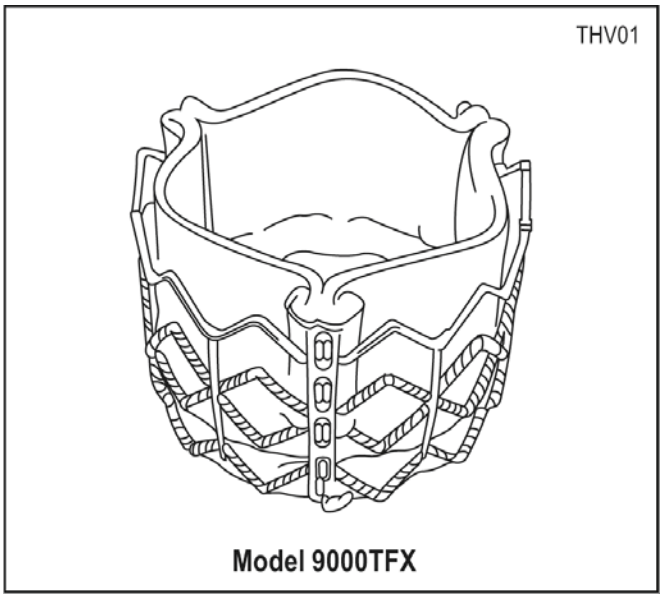
Investigational Device -To be used by Qualified Investigators Only.
Instrument de recherche – Réservé uniquement à l'usage de chercheurs compétents.

For Single Use Only

1. Device Description

1.1 Edwards SAPIEN Transcatheter Heart Valve Model 9000TFX (Figure 1)

The Edwards SAPIEN transcatheter heart valve model 9000TFX combines balloon expandable stent and bioprosthetic valve technology. The bioprosthesis, available in two sizes (23 mm and 26 mm), is designed for transfemoral implantation in patients with severe aortic stenosis (AS). Prior to implantation, the bioprosthesis is carefully mounted and crimped onto a balloon delivery catheter using a specially designed crimping device. The bioprosthesis/balloon assembly is inserted into the femoral artery (retrograde approach) and delivered to the site of the native stenotic aortic valve. The bioprosthesis is positioned and deployed across the stenotic native valve. The balloon delivery system is then removed. This minimally invasive approach is intended to be performed under local and/or general anesthesia using sterile technique, with echocardiographic and fluoroscopic guidance for visualization. The bioprosthesis is comprised of a radiopaque, stainless steel 316LVM 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 cross link the tissue, while preserving its flexibility and strength. The bioprosthesis is treated according to the Edwards ThermaFix process, which involves heat treatment of the tissue in glutaraldehyde and uses ethanol and polysorbate-80 (a surfactant). The bioprosthesis is packaged and terminally sterilized in glutaraldehyde. Glutaraldehyde is shown to both reduce the antigenicity of tissue xenograft valves and increase tissue stability; however, glutaraldehyde alone has not been shown to affect or reduce the calcification rate of the valve.



1.2 Delivery System

The delivery system consists of the following RetroFlex components:

- RetroFlex catheter (Figure 2)
- 22F or 24F RetroFlex introducer sheath set (Figures 3, 4, 5)
- RetroFlex dilator kit (Figure 6)
- RetroFlex balloon catheter (Figure 7)

The RetroFlex catheter is used to advance the bioprosthesis through the RetroFlex sheath over a guidewire and track the bioprosthesis over the aortic arch. It is also used to aid in crossing, and positioning the bioprosthesis within the native valve. The catheter has a shaft made of a stainless steel braid covered in a medical grade plastic with a softer durometer distal section. The handle of the catheter provides a rotational grip for flexing the distal end as well as a hemostasis seal.

The RetroFlex introducer sheath set contains an introducer with a hydrophilic coating and a long soft tip to facilitate introduction into the vessel and improved trackability, and a polymer sheath with a three seal valve that provides hemostasis.

The RetroFlex dilator kit consists of dilators that are used during the catheterization procedure to gradually dilate the femoral artery to accommodate the RetroFlex sheath for bioprosthesis implantation.

The RetroFlex balloon catheter (models 9100BC23 and 9100BC26) is used to deliver and deploy the bioprosthesis. It is advanced through the introducer sheath by the RetroFlex catheter and through the arterial system to the native aortic valve. The balloon expands the bioprosthesis with a controlled volume of saline/contrast. Two outer radiopaque markers indicate the dilating section of the balloon and aid in balloon placement. Two inner radiopaque markers are used to indicate the location of the bioprosthesis on the balloon catheter and aid in positioning of the bioprosthesis in the native valve.

The RetroFlex balloon catheter (models 9100BC20 and 9100BC23) may also be used to predilate the native annulus to ease crossing with the bioprosthesis.

The RetroFlex balloon catheter shaft has a braided multi-durometer outer-shaft. Rapid inflation and deflation time of the balloon is achieved through the 130 cm coaxial shaft design.

1.3 Crimper (Figure 8)

The crimper is a single-use non-patient contacting, compression device that reduces the overall diameter of the bioprosthesis from its expanded size to its collapsed (mounted) size, effectively mounting the bioprosthesis to its delivery balloon catheter. The crimper is comprised of a housing and a compression mechanism (creating the aperture). The aperture is closed by means of a handle located on the housing. The crimper is equipped with two measuring gauges:

- A crimp gauge to verify that the bioprosthesis/balloon assembly has been suitably collapsed.
- A balloon gauge to verify the bioprosthesis/balloon assembly catheter diameter when inflated.

2. Indications

The bioprosthesis is intended for use in symptomatic patients with severe calcific aortic stenosis requiring aortic valve replacement, who are at high risk for open-chest surgery due to co-morbid conditions. The bioprosthesis is intended for transfemoral aortic valve replacement. The procedure is performed without cardiopulmonary bypass.

The RetroFlex delivery system consisting of the RetroFlex catheter, model 9100FC, RetroFlex introducer sheath set, model 9100SL23 and 9100SL26, RetroFlex dilator kit, model 9100DKS or 9100DKS7, and RetroFlex balloon catheter, model 9100BC23 or 9100BC26, are indicated for delivery and deployment of the bioprosthesis. The RetroFlex balloon catheter, model 9100BC20 or 9100BC23, are indicated for predilatation prior to implantation of the bioprosthesis.

The crimper, models 9100CR23 and 9100CR26, is used to crimp the bioprosthesis.

3. Contraindications

Implantation of the bioprosthesis with an antegrade approach is contraindicated.

The bioprosthesis is contraindicated in patients with:

- Non-valvular aortic stenosis
- Congenital aortic stenosis or unicuspid aortic valve
- Non-calcific acquired aortic stenosis
- Evidence of intracardiac mass, thrombus or vegetation
- Untreated clinically significant coronary artery disease requiring revascularization
- Severe deformation of the chest
- Severe coagulation problems
- Active bacterial endocarditis or other active infections
- Previous systemic embolization from the left side of the heart
- Myocardial infarction (MI) within 1 month
- Unstable angina during index hospitalization
- Recent pulmonary emboli
- Recent (within 6 months) cerebrovascular accident (CVA)
- Patients unable to tolerate anticoagulation therapy
- Significant atheroma of the femoral and iliac vessels
- Severe tortuosities of the femoro-iliac vessels
- Femoro-iliac vessels < 7 mm
- Patients with bilateral iliofemoral bypass
- Hypertrophic cardiomyopathy with or without obstruction (HOCM)
- Severe ventricular dysfunction with ejection fraction < 20%

Implantation of the bioprosthesis may be performed if the implanting physician determines that retrograde delivery of the bioprosthesis can be accomplished safely and for the benefit of the patient. Use of the retrograde approach may require a femoral artery cut-down.

4. Warnings

- For Single Use Only
- Correct sizing of the bioprosthesis is essential to prevent paravalvular leak or migration. The bioprosthesis is intended for use in candidates with a native aortic annulus size ranging from 16 mm to 24 mm.
- Do not resterilize the bioprosthesis, RetroFlex delivery system, or crimper by any method. Exposure of the bioprosthesis and container to irradiation, steam, ethylene oxide, or other sterilants will render the bioprosthesis unfit for use.
- Accelerated deterioration due to calcific degeneration of the bioprosthesis (as with any glutaraldehyde cross-linked bioprosthesis) may occur in patients with an altered calcium metabolism.
- Overall durability, especially long-term, has not been established for the bioprosthesis. Careful and continuous medical follow-up is advised so that bioprosthesis-related complications can be diagnosed and properly managed.
- It is recommended that all prosthetic heart valve recipients be prophylactically treated for endocarditis to minimize the possibility of prosthetic valve infection.
- Bioprosthetic valve recipients should be maintained on anticoagulant therapy, except where contraindicated, as determined by their physician.

5. Precautions

5.1 Precautions Prior to Use

- Do not use the bioprosthesis:
  - If the tamper evident seal is broken
  - If the glutaraldehyde storage solution does not completely cover the bioprosthesis
  - If the temperature indicator has been activated
  - If the bioprosthesis is damaged
- Implantation of the bioprosthesis should be preceded by dilatation of the stenotic native aortic valve by means of aortic balloon valvuloplasty.
- Do not use the RetroFlex delivery system:
  - If the packaging seal is broken, or the package has been damaged
  - If the device is damaged
- Do not use the crimper:
  - If not sterile
  - If the aperture jaws or gauges (any parts that come into contact with the bioprosthesis and/or balloon delivery catheter) are

damaged or shown to have any debris and/or non-smooth contact surfaces

5.2 Precautions During Use

- Do not expose the bioprosthesis to solutions other than the storage solution in which it was shipped and the sterile physiologic rinsing and irrigation solutions specified in section 7.3.1.
- Do not allow the leaflet tissue of the bioprosthesis to become dry. Continuous submersion or irrigation of the bioprosthesis is required (refer to section 7.3, Bioprosthesis Handling and Preparation).
- Do not use any devices other than the crimper and RetroFlex delivery system to crimp, deliver, and deploy the bioprosthesis.
- The outside of the bioprosthesis jar is not sterile and must not be placed in the sterile field.
- 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 Material Safety Data Sheet available from Edwards Lifesciences.
- Do not over inflate the balloon catheter. Care should be taken to fully compress the inflation device to fully expand the balloon and bioprosthesis.
- The procedure should be conducted under fluoroscopy.
- Care should be used when handling the catheter. Damage may result from kinking or stretching the catheter.
- Do not add or apply antibiotics to the storage solution, rinse solutions, or to the bioprosthesis.
- Do not mishandle the valve tissue during rinsing, mounting, or crimping. If the bioprosthesis is damaged, it must be replaced.

6. Potential Adverse Events

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

- Allergic reaction to anesthesia or to contrast media
- Arrhythmia
- Cardiovascular injury
- Conduction system injury
- Embolization
- Femoral AV fistula or pseudoaneurysm
- Fever
- Hematoma
- Hemorrhage requiring transfusion
- Hypertension/hypotension
- Infection including septicemia and endocarditis
- Inflammation
- Pericardial effusion/cardiac tamponade
- Peripheral ischemia
- Renal failure/insufficiency
- Restenosis
- Retroperitoneal bleed
- Systemic peripheral ischemia/nerve injury
- Thromboembolic events
- Unintended perforation (vessels and pericardium)
- Valvular tearing or trauma
- Vascular injury at the site of venous or arterial access requiring surgical repair

Complications associated with the use of bioprosthetic heart valves compiled from the literature include:

- Death (procedure related, device related, or unknown)
- Endocarditis
- Hemorrhage (anticoagulant/antiplatelet-related)
- Leak (transvalvular or paravalvular)
- Nonstructural valve dysfunction (i.e. pannus, suture or other), including malfunctions of the valve due to distortion at implant
- Primary bioprosthetic valve thrombosis
- Primary hemolysis
- Structural valve deterioration (calcification, leaflet tear, stenosis, or other)
- Thromboembolism (permanent or transient neurological events)
- Valvular regurgitation

Additional adverse events potentially associated with the use of the bioprosthesis device include:

- Cardiac dysrhythmias
- Device migration (due to improper sizing, deployment, or other)
- Improper implantation location (potentially causing coronary flow obstruction or mitral valve impairment/damage)
- Nonstructural dysfunction (pannus, suture, inappropriate sizing, or other)

Tissue deterioration associated with bioprosthetic heart valves can be caused by:

- Aortic wall detachment from the stent posts
- Calcification
- Degeneration
- Infection
- Instrument trauma
- Leaflet tearing from the stent posts
- Perforation
- Thickening

Complications associated with aortic valve replacement may present clinically as:

- Abnormal heart murmur

- Cardiac failure
- Congestive heart failure
- Dyspnea (i.e., Orthopnea)
- Exercise intolerance
- Fever
- Hemolytic anemia
- Hemorrhage
- Low cardiac output
- Myocardial infarction
- Paralysis
- Pulmonary edema
- Stroke
- Transient ischemic attack

It is possible that catheterization or device-related complications could lead to:

- Reoperation
- Explantation
- Permanent disability
- Death (procedure related, device related, or unknown)

7. Directions for Use

7.1 Physician Training

The implanting physician should be experienced in balloon aortic valvuloplasty (BAV), percutaneous catheterization, the bioprosthesis implantation procedure, and trained on the use of the bioprosthesis, RetroFlex delivery system, and crimper.

7.2 Required Equipment

7.2.1 Equipment and materials for percutaneous catheterization and native aortic valve balloon predilatation:

- Fluoroscopy
- Pressure transducing capabilities
- Transesophageal or transthoracic echocardiography capabilities
- 6F introducer sheath/dilator
- 8F introducer sheath/dilator
- 14F introducer sheath/dilator
- 5F or 6F pigtail catheter
- 8F pulmonary artery (PA) catheter (three-port, flow-directed; e.g., Swan-Ganz catheter) for hemodynamic monitoring
- Standard length, 0.035 inch (0.89 mm) straight guidewire
- 180 cm or 260 cm x 0.035 inch (0.89 mm) extra-stiff guidewire
- 20 mm commercially available balloon valvuloplasty catheter (BVC) or 20 mm RetroFlex balloon catheter (model 9100BC20) for the 23 mm bioprosthesis **OR**
- 23 mm commercially available balloon valvuloplasty catheter (BVC) or 23 mm RetroFlex balloon catheter (model 9100BC23) for the 26 mm bioprosthesis
- 5F to 7F pacemaker (PM) pacing lead
- Sterile physiologic saline solution
- Radiopaque contrast medium
- Atrion Model QL2530 Inflation device
- Optional: percutaneous arterial closure device
- Touhy-Borst adaptors for introducer sheaths/dilators
- Others (syringes, 3-way stopcocks, etc.)

7.2.2 Equipment and materials for model 9000TFX preparation and implantation:

- Model 9000TFX bioprosthesis
- Crimper model 9100CR23 or model 9100CR26
- RetroFlex introducer sheath set with 35 cm sheath, introducer(s) and loader assembly (loader and cap). (model 9100SL23 for the 23 mm bioprosthesis and 9100SL26 for the 26 mm bioprosthesis)
- RetroFlex catheter (model 9100FC)
- 23 mm x 3 cm x 130 cm RetroFlex balloon catheter (model 9100BC23) for the 23 mm bioprosthesis **OR**
- 26 mm x 3 cm x 130 cm RetroFlex balloon catheter (model 9100BC26) for the 26 mm bioprosthesis
- Atrion Model QL2530 Inflation device
- RetroFlex dilator kit (model 9100DKS or 9100DKS7)
- Large clamp (hemostat)
- Sterile rinsing basins
- Sterile physiologic saline solution
- Sterile heparinized saline solution
- Sterile table for bioprosthesis and components preparation
- Diluted radiopaque contrast medium (15:85 medium to saline dilution)
- Others (syringes, 3-way stopcocks, etc.)

7.3 Bioprosthesis Handling and Preparation

Follow sterile technique during device preparation and implantation.

7.3.1 Bioprosthesis Rinsing Procedure

The bioprosthesis 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: Bioprosthetic valves from containers found to be damaged, leaking, without adequate glutaraldehyde sterilant, or missing intact seals must not be used for human implantation.

CAUTION: It is strongly recommended that the bioprosthesis container not be opened unless implantation is certain. This is necessary to reduce the risk of contamination. It has been established that glutaraldehyde alone is not 100 percent effective against all possible contaminants. No attempts should be made to resterilize the bioprosthesis.

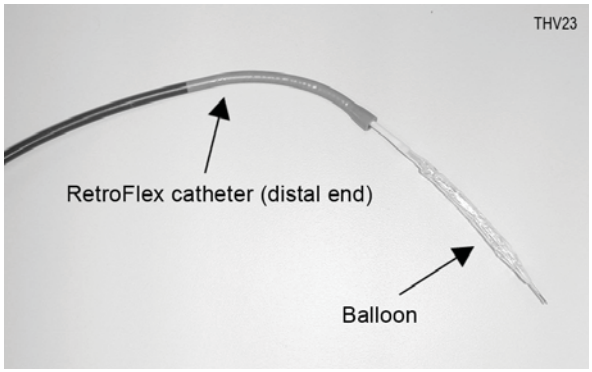
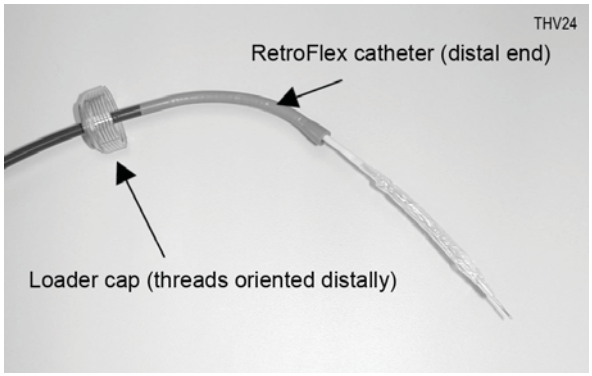
CAUTION: Handle jar contents in an aseptic manner to prevent contamination.

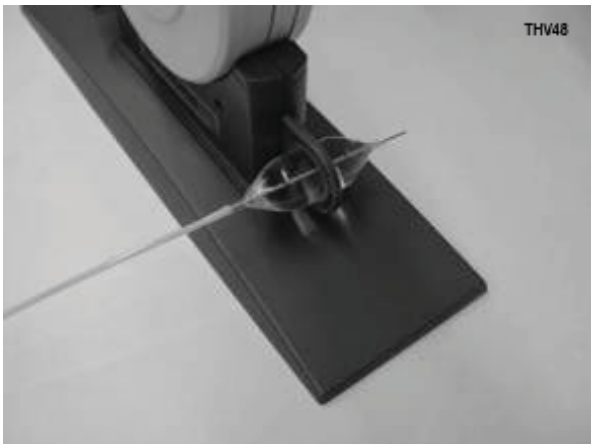
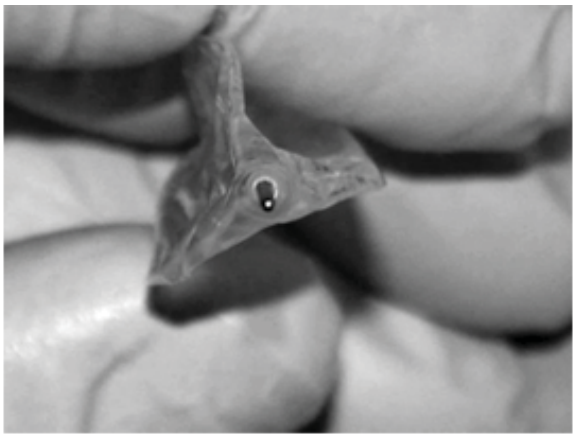
CAUTION: Do not allow the bioprosthesis to come in contact with the bottom or sides of the rinse bowl during agitation or swirling of the bioprosthesis. Care must be taken to ensure that the identification tag does not come in contact with the tissue and damage it. No other objects should be placed in the rinse bowls.

Step	Procedure
1	Set up two (2) sterile bowls with at least 500 ml of sterile physiologic saline to thoroughly rinse the glutaraldehyde sterilant from the bioprosthesis.
2	The bioprosthesis is contained in the jar within a holder. Carefully remove the bioprosthesis/holder assembly from the jar without touching the tissue. The holder is tagged with the bioprosthesis' serial identification number, which must be recorded in the patient information documents. Inspect the bioprosthesis for any signs of damage to the frame or tissue. Do not implant the bioprosthesis if any damage is found (tears or cracks in the tissue, loose sutures, fractured or broken frame struts, etc.).
3	Transfer the bioprosthesis/holder assembly to the first sterile bowl of rinsing solution. Keep the bioprosthesis hydrated at all times.
4	Rinse the bioprosthesis as follows: Place the bioprosthesis and holder in a minimum of 500 ml of sterile, physiological saline solution. Be sure the saline solution completely covers the bioprosthesis and holder. With the bioprosthesis and holder submerged, slowly agitate the basin (to **gently** swirl the bioprosthesis and holder back and forth for a minimum of 1 minute). Discard the rinse solution. Repeat this process once using new saline solution for a minimum of 1 minute. The bioprosthesis should be left in the final rinse solution until needed to prevent the tissue from drying. **CAUTION: The bioprosthesis should be kept hydrated throughout the rest of the preparation procedure to prevent the tissue from drying.**

7.3.2 Prepare the Delivery System

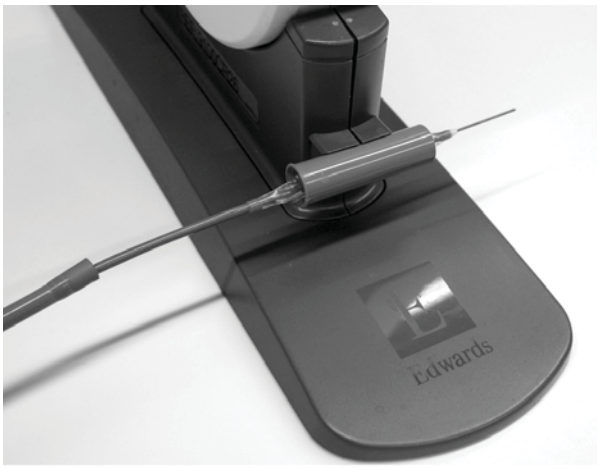
The RetroFlex introducer sheath set (introducer[s], sheath, and loader/loader cap), the appropriate size RetroFlex balloon catheter and the RetroFlex catheter are used for delivery of the bioprosthesis.

Step	Procedure
1	Visually inspect all components for damage.
2	Prime and flush the guidewire lumen of the balloon catheter.
3	Insert a 180 cm or 260 cm x 0.035 inch (0.89 mm) extra stiff guidewire in the distal end of the lumen, leaving a 2 to 3 cm segment of the guidewire protruding from the distal tip.
4	Flush the RetroFlex catheter with heparinized saline. Advance the balloon through the RetroFlex catheter until the proximal end of the balloon has exited through the distal tip of the RetroFlex catheter. 
5	Place the loader onto the RetroFlex catheter with the threads oriented distally. Remove loader from cap and slide loader off catheter for later use. 
6	For the 23 mm bioprosthesis, inflate the balloon catheter with approximately 20 cc of diluted contrast medium (15% dilution of contrast media to sterile heparinized saline). For 26 mm bioprosthesis, inflate the balloon catheter with approximately 25 cc of diluted contrast media.
7	Fully deflate the balloon catheter by pulling back on the inflation device plunger.

Step	Procedure
8	Insert the balloon into the balloon gauge. Inflate the balloon and make sure its diameter fits the gauge with minimal friction. While gently pulling and pushing the balloon, verify that the balloon moves with some resistance within the measuring ring. If the balloon does not reach the correct diameter when fully inflated, add or discard some of the inflating solution in the inflation device. – Make sure there are no air bubbles in the balloon. If a small air bubble is detected, eliminate it while deflating the balloon. – The inflation device must remain connected to the delivery balloon throughout the rest of the procedure. **Note: Correct balloon sizing is critical to successful valve deployment and valve function.**  THV48
9	Deflate the balloon, using your fingers to create a three-wing fold configuration.  THV03

7.3.3 Mount and Crimp the Bioprosthesis on the Balloon Delivery Catheter

Step	Procedure
1	Remove the bioprosthesis from the holder and place the bioprosthesis gently into the crimper aperture.
2	Gradually crimp the bioprosthesis to a diameter of approximately 12 mm.
3	Remove the bioprosthesis from the crimper and place it on the balloon catheter with its inflow aspect (fabric cuff end) towards the distal end of the balloon catheter and with the uncovered stent proximal to the balloon. The longitudinal placement of the bioprosthesis is at the mid-point of the balloon shaft, between its two radiopaque markers.  THV25 **CAUTION: Special attention should be taken when placing the bioprosthesis on the balloon catheter.** **CAUTION: It is recommended that a second operator verify correct mounting/orientation of the bioprosthesis prior to its implantation.**
4	Place the bioprosthesis/balloon assembly back in the crimper aperture and gradually continue to crimp until the bioprosthesis/balloon assembly profile fits inside the crimp gauge. Periodically, open the crimper aperture and inspect the bioprosthesis to make sure that it is still placed properly between the radiopaque markers of the balloon shaft and has not been damaged.

Step	Procedure
5	After completing the mounting and crimping process, inspect the crimped device: – Flush the crimp gauge of the crimper with sterile heparinized saline solution and insert the crimped bioprosthesis/balloon assembly without passing it completely through the gauge as shown in picture THV91. The bioprosthesis/balloon assembly should slide smoothly inside the gauge. – Maintain hydration of the bioprosthesis by placing it in the sterile heparinized saline solution until ready for implantation.  THV91

7.4 Native Valve Predilatation and Prosthetic Valve Delivery

Native valve predilatation and prosthetic valve delivery should be performed under local and/or general anesthesia with hemodynamic monitoring in a catheterization lab with fluoroscopic and electrocardiographic imaging capabilities.

Administer a bolus of heparin at the start of the procedure. During the procedure, heparin should be administered so that the ACT is maintained at ≥ 250 sec.

CAUTION: Excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored.

7.4.1 Baseline Parameters

Step	Procedure
1	Prepare and place a 6F sheath into each femoral artery, per standard technique.
2	Prepare and place an 8F sheath into the femoral vein that is contra-lateral to the artery selected for bioprosthesis implantation.
3	In the same leg used in Step 2, introduce a 5F or a 6F pigtail catheter into the femoral artery and advance the catheter into the aortic root for continuous blood pressure monitoring.
4	Advance an 8F PA catheter into the femoral vein sheath to the pulmonary artery. Collect required measurements.
5	If no diagnostic procedure has been performed within one month, perform the following: – Through the femoral artery sheath, sequentially advance right and left coronary artery diagnostic catheters, and perform a selective coronary angiogram. – Through the femoral artery sheath, perform a supra-aortic angiogram with the projection of the native aortic valve perpendicular to the screen. – Evaluate the height between the inferior aspect of the annulus and the inferior aspects of the lowest coronary ostium for subsequent prosthetic aortic valve implantation.
6	Introduce a 5F to 7F pacemaker (PM) lead through the 8F sheath in the femoral vein and advance the PM lead until its distal end is positioned in the right ventricle.
7	Set the stimulation parameters, test pacing at 200 to 220 b/min (See Edwards Rapid Pacing Protocol) and then start pacing on demand, at 80 b/min or as clinically indicated. **CAUTION: Pacing lead perforation has been found to be a potential complication; observation of the lead throughout the case is essential.**

7.4.2 Native Valve Predilatation

Predilate the native aortic valve using a standard balloon aortic valvuloplasty (BAV) technique with an appropriately sized commercially available BVC or RetroFlex balloon catheter (20 mm or 23 mm) with rapid cardiac pacing. The right (or left) femoral artery can be catheterized percutaneously or by surgical cutdown for valve implantation.

CAUTION: Use of the retrograde approach may require a femoral artery cut-down with surgical closure of the puncture site due to the large size of the arteriotomy. A consultation with vascular surgery is required for arteriotomy creation and closure of the arterial access site.

Step	Procedure
1	Manually pre-shape the tip of the guidewire. Through the 6F sheath in the femoral artery selected for bioprosthesis implantation: – Advance a pigtail catheter over a standard 0.035 inch guidewire and cross the aortic valve per preferred technique. It is recommended to cross the valve in the 50° LAO position, using a straight guidewire. After the valve is crossed, advance the selected catheter over the guidewire into the left ventricle. – Remove the guidewire and record required hemodynamic information. Measure the cardiac output and assess the valve area.
2	Advance a 260 cm extra-stiff guidewire through the catheter (pigtail) into the left ventricle.
3	Remove the catheter, leaving the guidewire in place in the left ventricle.
4	Over this guidewire, advance a 14F sheath into the femoral artery.

Step	Procedure
5	Wipe and flush the balloon catheter with saline. Attach inflation device and stopcock to balloon inflation port and pull vacuum repeatedly to remove air. Close stopcock. Prepare inflation device with approximately 20 ml 15% contrast solution. Use data below for nominal balloon diameter: • 20 mm RetroFlex balloon catheter ○ Nominal Pressure: 6 ATM (608 kPa) ○ Nominal Volume: 13 ml • 23 mm RetroFlex balloon catheter ○ Nominal Pressure: 4 ATM (405 kPa) ○ Nominal Volume: 16 ml
6	Advance the prepared BVC through the sheath over the guidewire, cross the aortic valve, and position the balloon.
7	Using diluted contrast medium (e.g., 15% contrast medium to heparinized saline), fully and rapidly inflate the balloon with the inflation device until the desired size is reached. In case of balloon instability, repeat balloon inflation while ensuring rapid pacing (200-220 b/min) of the right ventricle. Once the blood pressure has decreased to 50 mmHg or below, balloon inflation can commence.
8	Remove the balloon valvuloplasty catheter, leaving the guidewire in place in the left ventricle.

CAUTION: Prosthetic valve implantation should not be carried out if the balloon cannot be fully inflated during predilatation.

7.4.3 Prosthetic Valve Delivery

Step	Procedure
1	Predilate the femoro-iliac vessel by advancing increasing sized dilators over the guidewire. Advance the maximum possible length of the introducer over the guidewire while following its progression on fluoroscopy. Or: Create an arteriotomy in the femoral artery selected for bioprosthesis implantation to allow introduction of the RetroFlex sheath. Use a dilator, if necessary, to expand the puncture site. **NOTE:** If blood loss occurs through the proximal luer of the dilator, a Touhy-Borst type hemostatic adaptor can be attached to the dilator luer to eliminate any leakage from the dilator lumen.
2	Pull the bioprosthesis/balloon assembly into the RetroFlex catheter until the proximal edge of the bioprosthesis butts up against the distal end of the RetroFlex catheter; be careful to fold the proximal balloon to allow easy advancement of the balloon out of the RetroFlex catheter. Deflect the RetroFlex catheter and advance the balloon catheter out to verify ease of advancement.
3	Before advancing the bioprosthesis/balloon assembly through the RetroFlex sheath, test its diameter with the crimp gauge on the crimper. If necessary, re-compress the bioprosthesis/balloon assembly with the crimper so that it will fit through the gauge.
4	Advance the bioprosthesis/balloon assembly into the loader and position the tip of the balloon catheter at the tip of the loader.
5	Screw the loader cap (which is on the RetroFlex catheter shaft) on the loader, and insert the loader into the sheath hemostasis valve.
6	Push the bioprosthesis/balloon/RetroFlex catheter through the RetroFlex sheath until the bioprosthesis exits from the sheath tip. Retract loader to proximal end of RetroFlex catheter. **CAUTION: The bioprosthesis should not be advanced through the sheath if the sheath tip is not past the aortic bifurcation.**
7	Push the RetroFlex catheter up the descending aorta; flex the tip as needed (by rotating its handle "clockwise" or "counter-clockwise") to track over the guidewire and around the aortic arch.
8	Cross the native aortic valve and position the bioprosthesis/balloon assembly so that the bioprosthesis is beside the calcified zone of the diseased valve as visualized on fluoroscopy.
9	Pull the RetroFlex catheter back while maintaining the position of the bioprosthesis/balloon assembly by pulling the handle of the RetroFlex catheter while maintaining position of the balloon catheter shaft. **CAUTION: The balloon must be completely out of the RetroFlex catheter before it is inflated and the bioprosthesis is deployed.**
10	Position the mid-point of the bioprosthesis at the plane of the hinge points of the native valve leaflets.
11	Just prior to bioprosthesis/balloon inflation, start rapid pacing by setting the 5F to 7F PM catheter in the RV to pace at 200-220 b/min. The marked decrease in cardiac output induced by the ventricular tachycardia allows for additional stable balloon inflation.
12	Verify the correct location of the bioprosthesis with respect to the calcified valve using fluoroscopy guidance.
13	Begin bioprosthesis deployment: – Begin rapid pacing at 200-220 bpm; once arterial blood pressure has decreased to 50 mmHg or below, balloon inflation can commence. – Once the desired implantation position is verified, rapidly inflate the balloon catheter with the entire contents of the inflation device to completely deploy the bioprosthesis in the target location. – Once the bioprosthesis has been deployed, rapidly deflate the balloon catheter. – When the balloon catheter has been completely deflated the pacemaker may be turned off, or returned to 80 b/min if clinically indicated. – Uncinch the RetroFlex catheter before retracting the catheter system through the aorta.
14	**CAUTION: Patient injury could occur if the RetroFlex catheter is not uncinched prior to removal of the catheter system.** – Remove the RetroFlex catheter and the balloon catheter. – Remove the guidewire.

7.5 Verification of Prosthetic Valve Position and Measurements

Measure and record both the invasive and non-invasive hemodynamic parameters required by the protocol.

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 catheters and sheaths when the ACT level is appropriate (e.g., reaches < 150 sec).
4	Apply local hemostatic compression on the catheterization puncture sites, or close surgically if clinically indicated.
5	The patient should remain on clopidogrel (75 mg/day) for 6 months post procedure and aspirin (75-100 mg/day) for life. Ticlopidine may be used instead of clopidogrel at the Investigator's discretion.

8. How Supplied

8.1 Available Sizes

The bioprosthesis is available in sizes 23 mm and 26 mm (outer diameter, fully expanded). The stent heights are 14.3 mm and 16.1 mm, respectively.

8.2 Packaging

The bioprosthesis is supplied sterile and nonpyrogenic packaged in buffered glutaraldehyde, in a plastic jar to which a seal has been applied. Sterility is not compromised if the package is unopened or undamaged. The outside of the container is NOT sterile and should not be placed in the sterile field. Each jar is shipped in a styrofoam enclosure containing a temperature indicator to determine if the bioprosthesis has been exposed to extreme temperatures during transit. Upon receipt, immediately remove the styrofoam and inspect the indicator.

WARNING: The bioprosthesis must be carefully inspected before implantation for evidence of extreme temperature exposure or other damage.

If the indicator shows that the bioprosthesis has been exposed to extreme temperatures during transit, do not use the bioprosthesis. Contact the local supplier or representative of Edwards Lifesciences to make arrangements for return, authorization, and replacement. Any bioprosthesis returned to the company should be shipped in the same styrofoam enclosure in which it was received.

Due to the biological nature of the bioprosthesis, and its sensitivity to physical handling and environmental conditions, it cannot be returned, except as noted above.

The crimper (models 9100CR23 and 9100CR26) with built-in balloon and crimp gauges is supplied sterile for single use only. The crimper is single pouched, and sterilized by ethylene oxide.

The RetroFlex delivery system components are supplied sterile for single use only.

- The RetroFlex catheter (model 9100FC) is mounted on a card, double pouched, and sterilized by ethylene oxide.
- The RetroFlex dilator kit (model 9100DKS and 9100DKS7) consists of dilators that are packaged together in a thermoformed tray, single pouched, and sterilized by ethylene oxide.
- The sheath kit (model 9100SL23 or 9100SL26) includes a sheath, introducer(s), and loader assembly. The components are mounted in a tray, single pouched, and sterilized by ethylene oxide.
- The RetroFlex balloon catheter (model 9100BC20, 9100BC23 or 9100BC26) is placed into a catheter hoop, double pouched, and sterilized by ethylene oxide.

8.3 Storage

The model 9000TFX bioprosthesis must be stored between 10 °C and 25 °C (50 °F and 77 °F). Stock inspections and rotation at regular intervals are recommended to ensure that the bioprostheses are used before the expiration date stamped on the package label.

Warning: Do not freeze. Always store bioprostheses in a dry, contamination-free area. Any bioprosthesis that has been frozen, or is suspected of having been frozen, should not be used for human implantation.

The RetroFlex delivery system components (crimper, RetroFlex dilators, RetroFlex introducer sheath set, RetroFlex catheter, and RetroFlex balloon catheters) should be stored in a cool, dry place.

9. MR Safety

Non-clinical testing has demonstrated that the Edwards SAPIEN transcatheter heart valve is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 3 Tesla or less.
- Spatial gradient field of 720 Gauss/cm or less.
- Maximum whole-body-averaged specific absorption rate (SAR) of 3.0 W/kg for 15 minutes of scanning.

In non-clinical testing, the device produced a maximum temperature increase of 0.5 °C at a maximum whole body averaged specific absorption rate (SAR) of 3.0 W/kg for 15 minutes of MRI.

MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the device.

10. Patient Information

A patient registration form is provided with each device. After implantation, please complete all requested information. The serial number may be found on the package and on the identification tag attached to the bioprosthesis. 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. This information becomes an important part of the records maintained on each bioprosthesis. Your cooperation in providing accurate and legible information is appreciated. The accurate completion and return of this form is essential for the purpose of bioprosthesis tracking and patient notification. An Implanted Device Card is provided to the patient. The card contains the name and telephone number of the patient's physician, as well as information that medical personnel would require in the event of an emergency.

11. Recovered Clinical Bioprostheses

Edwards Lifesciences is interested in obtaining recovered clinical specimens of the Edwards SAPIEN transcatheter heart valve for analysis. A written report summarizing our findings will be provided upon completion of our evaluation. The explanted model 9000TFX bioprostheses 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.

Disposal of Used Delivery Systems and Crimper

The used delivery and crimper system 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 device.

12. Clinical Experience

The Edwards SAPIEN transcatheter heart valve model 9000TFX, the RetroFlex delivery system and the crimper are available exclusively for investigational use. References reporting clinical experience with percutaneous delivery of the bioprosthesis are provided in section 13.

This product is manufactured and sold under one or more of the following US patent(s): US Patent No. 5,411,552; 5,840,081; 5,931,969; 6,168,614; 6,214,054; 6,547,827; 6,561,970; 6,582,462; 6,893,460; and 6,908,481. Likewise, additional US and foreign patents are pending.

13. References

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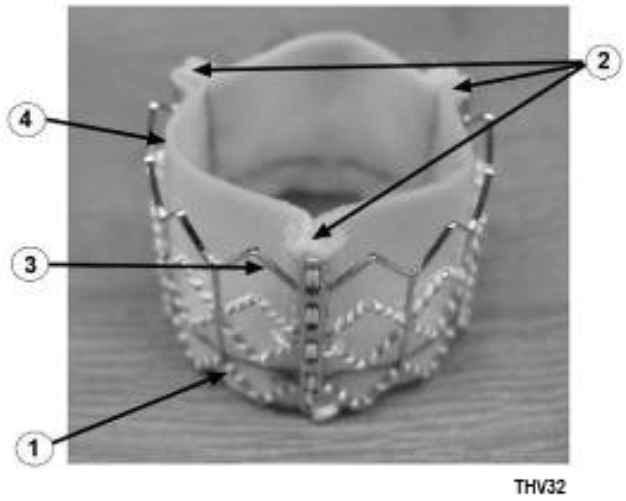
8. Webb JG, Chandavimol M, Thompson CR, et al. Percutaneous aortic valve implantation retrograde from the femoral artery. *Circulation* 2006;113:842-50.
9. Cribier A, Eltchaninoff H, Tron C, et al. Treatment of calcific aortic stenosis with the percutaneous heart valve: mid-term follow-up from the initial feasibility studies: the French experience. *J Am Coll Cardiol* 2006;47(6):1214-23.

14. Figures



1. PET Cuff
2. Commissures (in the valve) and Supporting bars (in the frame)
3. Frame
4. A unidirectional valve

Figure 1. Model 9000TFX Bioprosthesis

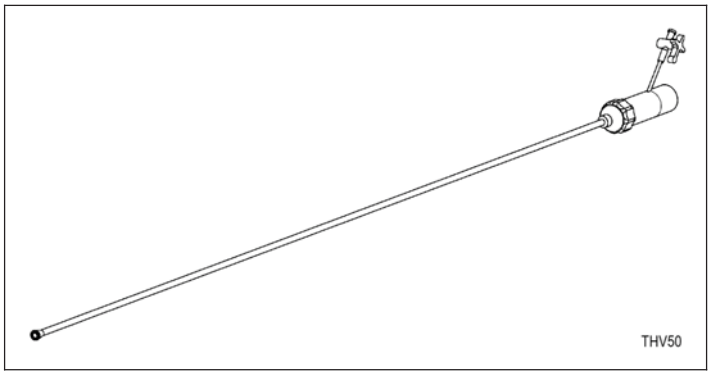


Figure 2. RetroFlex Catheter

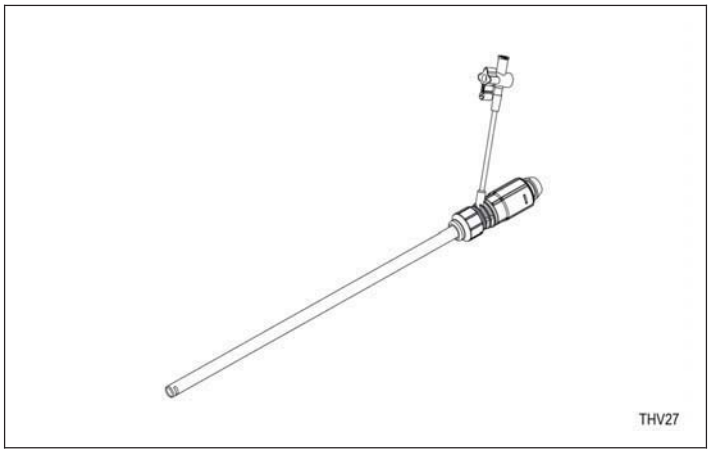


Figure 3. Sheath

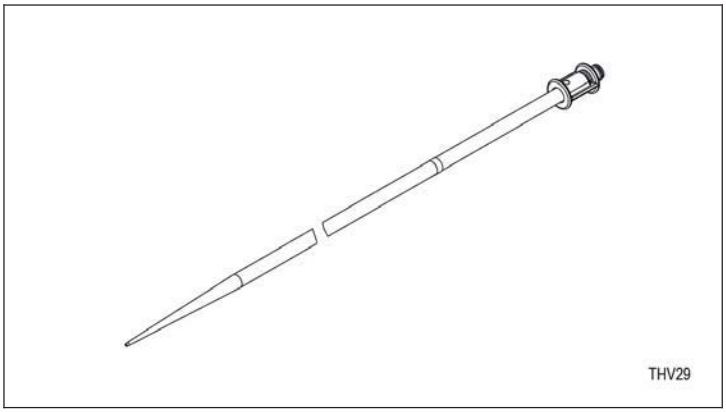


Figure 4. Introducer

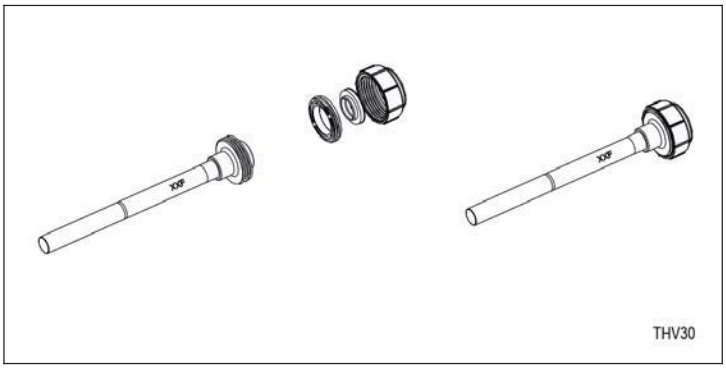


Figure 5. Loader

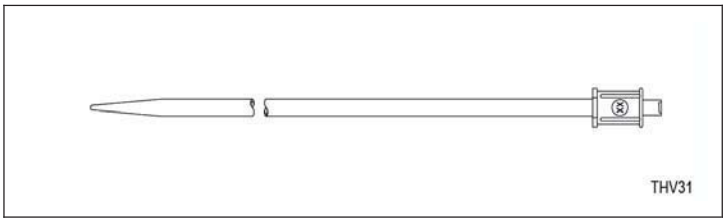


Figure 6. RetroFlex Dilator

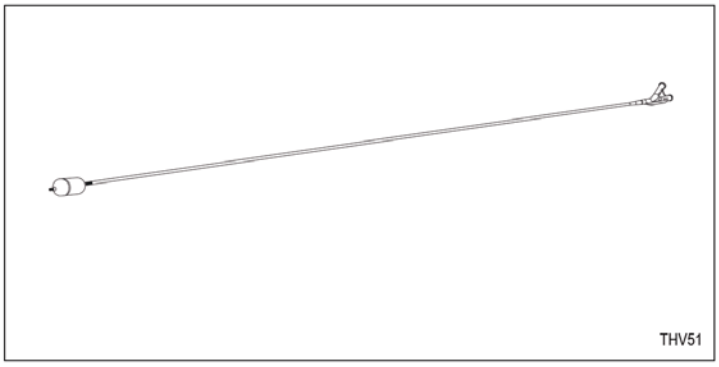


Figure 7. RetroFlex Balloon Catheter

14. Figures (cont)

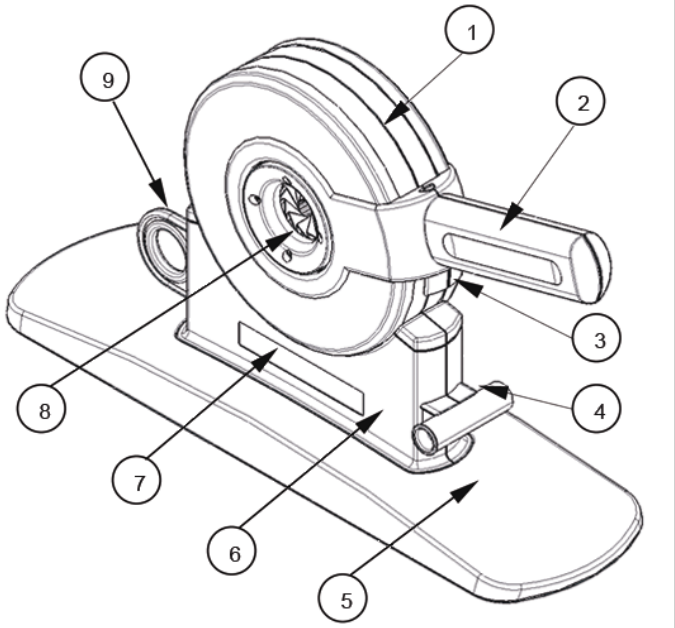


Figure 8. Crimper

1 - Housing
2 - Handle
3 - Stopper
4 - Crimp Gauge
5 - Base
6 - Stand
7 – ID Label
8 - Aperture
9 - Balloon Gauge

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Edwards Lifesciences

Edwards SAPIEN Transcatheter Heart Valve

Model 9000TFX

Instructions For Use
Retrograde Approach

CAUTION: Investigational device. Limited by Federal (USA) Law to investigational use.

Exclusively for Clinical Investigations

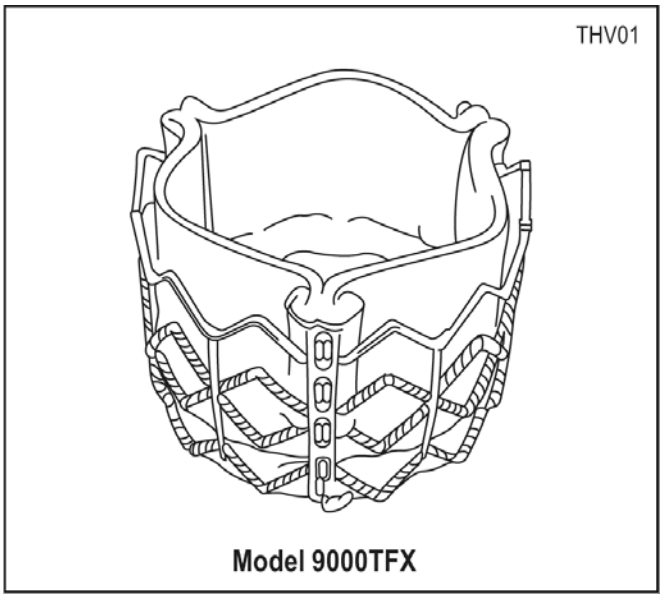
Investigational Device -To be used by Qualified Investigators Only.
Instrument de recherche – Réservé uniquement à l'usage de chercheurs compétents.

For Single Use Only

1. Device Description

1.1 Edwards SAPIEN Transcatheter Heart Valve Model 9000TFX (Figure 1)

The Edwards SAPIEN transcatheter heart valve model 9000TFX combines balloon expandable stent and bioprosthetic valve technology. The bioprosthesis, available in two sizes (23 mm and 26 mm), is designed for transfemoral implantation in patients with severe aortic stenosis (AS). Prior to implantation, the bioprosthesis is carefully mounted and crimped onto a balloon delivery catheter using a specially designed crimping device. The bioprosthesis/balloon assembly is inserted into the femoral artery (retrograde approach) and delivered to the site of the native stenotic aortic valve. The bioprosthesis is positioned and deployed across the stenotic native valve. The balloon delivery system is then removed. This minimally invasive approach is intended to be performed under local and/or general anesthesia using sterile technique, with echocardiographic and fluoroscopic guidance for visualization. The bioprosthesis is comprised of a radiopaque, stainless steel 316LVM 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 cross link the tissue, while preserving its flexibility and strength. The bioprosthesis is treated according to the Edwards ThermaFix process, which involves heat treatment of the tissue in glutaraldehyde and uses ethanol and polysorbate-80 (a surfactant). The bioprosthesis is packaged and terminally sterilized in glutaraldehyde. Glutaraldehyde is shown to both reduce the antigenicity of tissue xenograft valves and increase tissue stability; however, glutaraldehyde alone has not been shown to affect or reduce the calcification rate of the valve.



1.2 Delivery System

The delivery system consists of the following RetroFlex components:

- RetroFlex II catheter (Figure 2)
- 22F or 24F RetroFlex introducer sheath set (Figures 3, 4, 5)
- RetroFlex dilator kit (Figure 6)
- RetroFlex balloon catheter (Figure 7)

The RetroFlex II catheter is used to deliver and deploy the appropriate size bioprosthesis. The RetroFlex II catheter is used to advance the bioprosthesis through the RetroFlex sheath over a guidewire and track the bioprosthesis over the aortic arch. It is also used to aid in crossing, and positioning the bioprosthesis within the native valve. The catheter has a shaft made of a stainless steel braid covered in a medical grade plastic with a softer durometer distal section. The handle of the catheter provides a rotational grip for flexing the distal end as well as a hemostasis seal. There is a tapered nose cone tip at the distal end of the RetroFlex II catheter which allows the system to cross the native valve easily. The nose is advanced or pulled back over the distal portion of the balloon by a knob on the proximal end of the handle. The RetroFlex II catheter also incorporates a balloon catheter which expands the bioprosthesis with a controlled volume of saline/contrast.

The RetroFlex introducer sheath set contains an introducer with a hydrophilic coating and a long soft tip to facilitate introduction into the vessel and improved trackability, and a polymer sheath with a three seal valve that provides hemostasis.

The RetroFlex dilator kit consists of dilators that are used during the catheterization procedure to gradually dilate the femoral artery to accommodate the RetroFlex sheath for bioprosthesis implantation.

The RetroFlex balloon catheter (models 9100BC20 and 9100BC23) may also be used to predilate the native annulus to ease crossing with the bioprosthesis. The radiopaque markers indicate the dilating section of the balloon and aid in balloon placement. The shaft has a braided multi-durometer outer-shaft. Rapid inflation and deflation time of the balloon is achieved through the 130 cm coaxial shaft design.

1.3 Crimper (Figure 8)

The crimper is a single-use non-patient contacting, compression device that reduces the overall diameter of the bioprosthesis from its expanded size to its collapsed (mounted) size, effectively mounting the bioprosthesis to its delivery balloon catheter. The crimper is comprised of a housing and a compression mechanism (creating the aperture). The aperture is closed

by means of a handle located on the housing. The crimper is equipped with two measuring gauges:

- A crimp gauge to verify that the bioprosthesis/balloon assembly has been suitably collapsed.
- A balloon gauge to verify the bioprosthesis/balloon assembly catheter diameter when inflated.

2. Indications

The bioprosthesis is intended for use in symptomatic patients with severe calcific aortic stenosis requiring aortic valve replacement, who are at high risk for open-chest surgery due to co-morbid conditions. The bioprosthesis is intended for transfemoral aortic valve replacement. The procedure is performed without cardiopulmonary bypass.

The RetroFlex delivery system consisting of the RetroFlex II catheter, models 9100HDSLT23 and 9100HDSLT26, RetroFlex introducer sheath set, models 9100SL23 and 9100SL26, and RetroFlex dilator kit, model 9100DKS or 9100DKS7, are indicated for delivery and deployment of the bioprosthesis. The RetroFlex balloon catheter, models 9100BC20 and 9100BC23, are indicated for predilatation prior to implantation of the bioprosthesis.

The crimper, models 9100CR23 and 9100CR26, is used to crimp the bioprosthesis.

3. Contraindications

Implantation of the bioprosthesis with an antegrade approach is contraindicated.

The bioprosthesis is contraindicated in patients with:

- Non-valvular aortic stenosis
- Congenital aortic stenosis or unicuspid aortic valve
- Non-calcific acquired aortic stenosis
- Evidence of intracardiac mass, thrombus or vegetation
- Untreated clinically significant coronary artery disease requiring revascularization
- Severe deformation of the chest
- Severe coagulation problems
- Active bacterial endocarditis or other active infections
- Previous systemic embolization from the left side of the heart
- Myocardial infarction (MI) within 1 month
- Unstable angina during index hospitalization
- Recent pulmonary emboli
- Recent (within 6 months) cerebrovascular accident (CVA)
- Patients unable to tolerate anticoagulation therapy
- Significant atheroma of the femoral and iliac vessels
- Severe tortuosities of the femoro-iliac vessels
- Femoro-iliac vessels < 7 mm
- Patients with bilateral iliofemoral bypass
- Hypertrophic cardiomyopathy with or without obstruction (HOCM)
- Severe ventricular dysfunction with ejection fraction < 20%

Implantation of the bioprosthesis may be performed if the implanting physician determines that retrograde delivery of the bioprosthesis can be accomplished safely and for the benefit of the patient. Use of the retrograde approach may require a femoral artery cut-down.

4. Warnings

- For Single Use Only
- Correct sizing of the bioprosthesis is essential to prevent paravalvular leak or migration. The bioprosthesis is intended for use in candidates with a native aortic annulus size ranging from 16 mm to 24 mm.
- Do not resterilize the bioprosthesis, RetroFlex delivery system, or crimper by any method. Exposure of the bioprosthesis and container to irradiation, steam, ethylene oxide, or other sterilants will render the bioprosthesis unfit for use.
- Accelerated deterioration due to calcific degeneration of the bioprosthesis (as with any glutaraldehyde cross-linked bioprosthesis) may occur in patients with an altered calcium metabolism.
- Overall durability, especially long-term, has not been established for the bioprosthesis. Careful and continuous medical follow-up is advised so that bioprosthesis-related complications can be diagnosed and properly managed.
- It is recommended that all prosthetic heart valve recipients be prophylactically treated for endocarditis to minimize the possibility of prosthetic valve infection.
- Bioprosthetic valve recipients should be maintained on anticoagulant therapy, except where contraindicated, as determined by their physician.

5. Precautions

5.1 Precautions Prior to Use

- Do not use the bioprosthesis:
  - If the tamper evident seal is broken
  - If the glutaraldehyde storage solution does not completely cover the bioprosthesis
  - If the temperature indicator has been activated
  - If the bioprosthesis is damaged
- Implantation of the bioprosthesis should be preceded by dilatation of the stenotic native aortic valve by means of aortic balloon valvuloplasty.
- Do not use the RetroFlex delivery system:
  - If the packaging seal is broken, or the package has been damaged
  - If the device is damaged
- Do not use the crimper:
  - If not sterile
  - If the aperture jaws or gauges (any parts that come into contact with the bioprosthesis and/or balloon delivery catheter) are damaged or shown to have any debris and/or non-smooth contact surfaces

5.2 Precautions During Use

- Do not expose the bioprosthesis to solutions other than the storage solution in which it was shipped and the sterile physiologic rinsing and irrigation solutions specified in section 7.3.1.
- Do not allow the leaflet tissue of the bioprosthesis to become dry. Continuous submersion or irrigation of the bioprosthesis is required (refer to section 7.3, Bioprosthesis Handling and Preparation).

- Do not use any devices other than the crimper and RetroFlex delivery system to crimp, deliver, and deploy the bioprosthesis.
- The outside of the bioprosthesis jar is not sterile and must not be placed in the sterile field.
- 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 Material Safety Data Sheet available from Edwards Lifesciences.
- Do not over inflate the balloon catheter. Care should be taken to fully compress the inflation device to fully expand the balloon and bioprosthesis.
- The procedure should be conducted under fluoroscopy.
- Care should be used when handling the catheter. Damage may result from kinking or stretching the catheter.
- Do not add or apply antibiotics to the storage solution, rinse solutions, or to the bioprosthesis.
- Do not mishandle the valve tissue during rinsing, mounting, or crimping. If the bioprosthesis is damaged, it must be replaced.

6. Potential Adverse Events

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

- Allergic reaction to anesthesia or to contrast media
- Arrhythmia
- Cardiovascular injury
- Conduction system injury
- Embolization
- Femoral AV fistula or pseudoaneurysm
- Fever
- Hematoma
- Hemorrhage requiring transfusion
- Hypertension/hypotension
- Infection including septicemia and endocarditis
- Inflammation
- Pericardial effusion/cardiac tamponade
- Peripheral ischemia
- Renal failure/insufficiency
- Restenosis
- Retroperitoneal bleed
- Systemic peripheral ischemia/nerve injury
- Thromboembolic events
- Unintended perforation (vessels and pericardium)
- Valvular tearing or trauma
- Vascular injury at the site of venous or arterial access requiring surgical repair

Complications associated with the use of bioprosthetic heart valves compiled from the literature include:

- Death (procedure related, device related, or unknown)
- Endocarditis
- Hemorrhage (anticoagulant/antiplatelet-related)
- Leak (transvalvular or paravalvular)
- Nonstructural valve dysfunction (i.e. pannus, suture or other), including malfunctions of the valve due to distortion at implant
- Primary bioprosthetic valve thrombosis
- Primary hemolysis
- Structural valve deterioration (calcification, leaflet tear, stenosis, or other)
- Thromboembolism (permanent or transient neurological events)
- Valvular regurgitation

Additional adverse events potentially associated with the use of the bioprosthesis device include:

- Cardiac dysrhythmias
- Device migration (due to improper sizing, deployment, or other)
- Improper implantation location (potentially causing coronary flow obstruction or mitral valve impairment/damage)
- Nonstructural dysfunction (pannus, suture, inappropriate sizing, or other)

Tissue deterioration associated with bioprosthetic heart valves can be caused by:

- Aortic wall detachment from the stent posts
- Calcification
- Degeneration
- Infection
- Instrument trauma
- Leaflet tearing from the stent posts
- Perforation
- Thickening

Complications associated with aortic valve replacement may present clinically as:

- Abnormal heart murmur
- Cardiac failure
- Congestive heart failure
- Dyspnea (i.e., Orthopnea)
- Exercise intolerance
- Fever
- Hemolytic anemia
- Hemorrhage
- Low cardiac output
- Myocardial infarction

- Paralysis
- Pulmonary edema
- Stroke
- Transient ischemic attack

It is possible that catheterization or device-related complications could lead to:

- Reoperation
- Explantation
- Permanent disability
- Death (procedure related, device related, or unknown)

7. Directions for Use

7.1 Physician Training

The implanting physician should be experienced in balloon aortic valvuloplasty (BAV), percutaneous catheterization, the bioprosthesis implantation procedure, and trained on the use of the bioprosthesis and the RetroFlex delivery system and crimper.

7.2 Required Equipment

7.2.1 Equipment and materials for percutaneous catheterization and native aortic valve balloon predilatation:

- Fluoroscopy
- Pressure transducing capabilities
- Transesophageal or transthoracic echocardiography capabilities
- 6F introducer sheath/dilator
- 8F introducer sheath/dilator
- 14F introducer sheath/dilator
- 5F or 6F pigtail catheter
- 8F pulmonary artery (PA) catheter (three-port, flow-directed; e.g., Swan-Ganz catheter) for hemodynamic monitoring
- Standard length, 0.035 inch (0.89 mm) straight guidewire
- 180 cm or 260 cm x 0.035 inch (0.89 mm) extra-stiff guidewire
- 20 mm commercially available balloon valvuloplasty catheter (BVC) or 20 mm RetroFlex balloon catheter (model 9100BC20) for the 23 mm bioprosthesis
- 23 mm commercially available balloon valvuloplasty catheter (BVC) or 23 mm RetroFlex balloon catheter (model 9100BC23) for the 26 mm bioprosthesis
- 5F to 7F pacemaker (PM) pacing lead
- Sterile physiologic saline solution
- Radiopaque contrast medium
- Atrion Model QL2530 Inflation device
- Optional: percutaneous arterial closure device
- Touhy-Borst adaptors for introducer sheaths/dilators
- Others (syringes, 3-way stopcocks, etc.)

7.2.2 Equipment and materials for model 9000TFX preparation and implantation:

- Model 9000TFX bioprosthesis
- Crimper model 9100CR23 or model 9100CR26
- RetroFlex introducer sheath set with 35 cm sheath, introducer(s) and loader assembly (loader and cap). (model 9100SL23 for the 23 mm bioprosthesis and 9100SL26 for the 26 mm bioprosthesis)
- RetroFlex II catheter (model 9100HDSLT23 and 9100HDSLT26)
- Atrion Model QL2530 Inflation device
- RetroFlex dilator kit (model 9100DKS or 9100DKS7)
- Large clamp (hemostat)
- Sterile rinsing basins
- Sterile physiologic saline solution
- Sterile heparinized saline solution
- Sterile table for bioprosthesis and components preparation
- Diluted radiopaque contrast medium (15:85 medium to saline dilution)
- Others (syringes, 3-way stopcocks, etc.)

7.3 Bioprosthesis Handling and Preparation

Follow sterile technique during device preparation and implantation.

7.3.1 Bioprosthesis Rinsing Procedure

The bioprosthesis 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: Bioprosthetic valves from containers found to be damaged, leaking, without adequate glutaraldehyde sterilant, or missing intact seals must not be used for human implantation.

CAUTION: It is strongly recommended that the bioprosthesis container not be opened unless implantation is certain. This is necessary to reduce the risk of contamination. It has been established that glutaraldehyde alone is not 100 percent effective against all possible contaminants. No attempts should be made to resterilize the bioprosthesis.

CAUTION: Handle jar contents in an aseptic manner to prevent contamination.

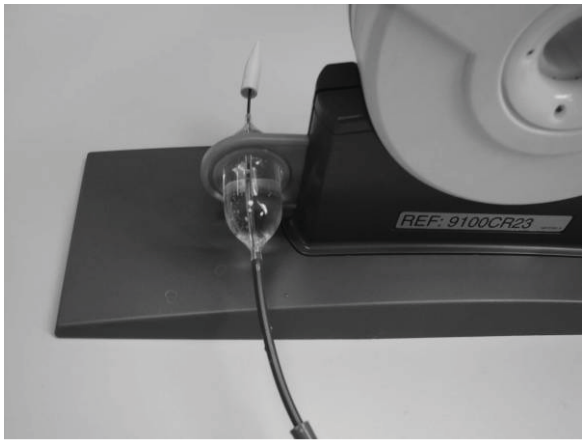
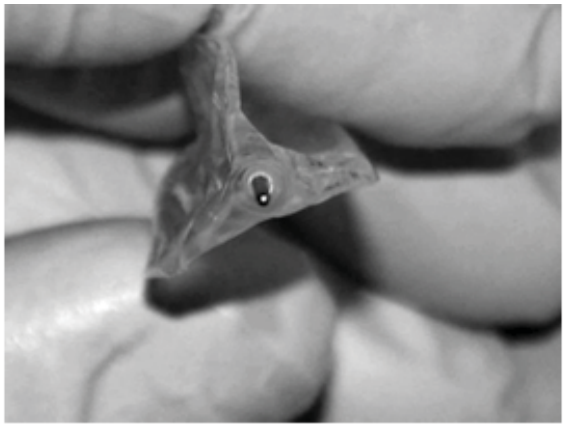
CAUTION: Do not allow the bioprosthesis to come in contact with the bottom or sides of the rinse bowl during agitation or swirling of the bioprosthesis. Care must be taken to ensure that the identification tag does not come in contact with the tissue and damage it. No other objects should be placed in the rinse bowls.

Step	Procedure
1	Set up two (2) sterile bowls with at least 500 ml of sterile physiologic saline to thoroughly rinse the glutaraldehyde sterilant from the bioprosthesis.
2	The bioprosthesis is contained in the jar within a holder. Carefully remove the bioprosthesis/holder assembly from the jar without touching the tissue. The holder is tagged with the bioprosthesis' serial identification number, which must be recorded in the patient information documents. Inspect the bioprosthesis for any signs of damage to the frame or tissue. Do not implant the bioprosthesis if any damage is found (tears or cracks in the tissue, loose sutures, fractured or broken frame struts, etc.).

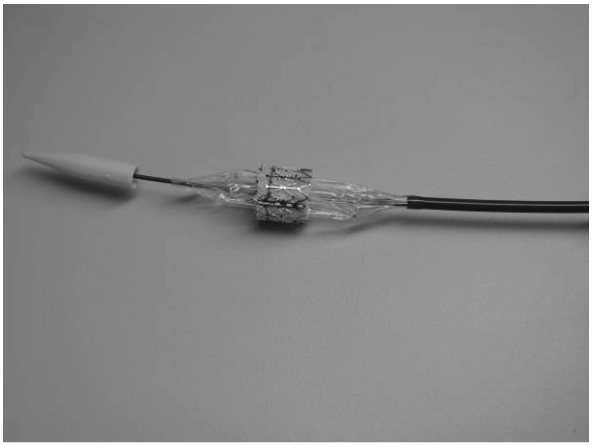
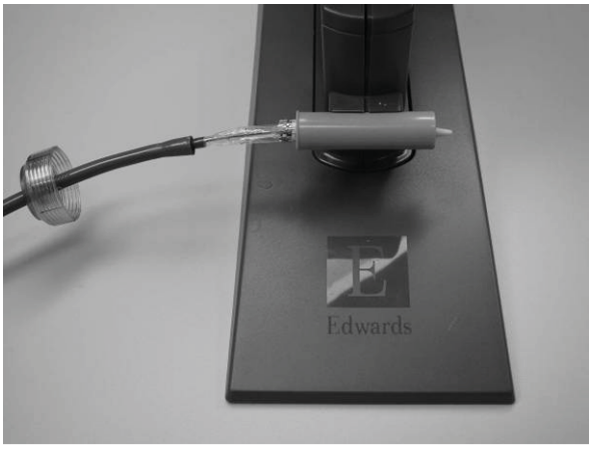
Step	Procedure
3	Transfer the bioprosthesis/holder assembly to the first sterile bowl of rinsing solution. Keep the bioprosthesis hydrated at all times.
4	Rinse the bioprosthesis as follows: Place the bioprosthesis and holder in a minimum of 500 ml of sterile, physiological saline solution. Be sure the saline solution completely covers the bioprosthesis and holder. With the bioprosthesis and holder submerged, slowly agitate the basin (to **gently** swirl the bioprosthesis and holder back and forth for a minimum of 1 minute). Discard the rinse solution. Repeat this process once using new saline solution for a minimum of 1 minute. The bioprosthesis should be left in the final rinse solution until needed to prevent the tissue from drying. **CAUTION: The bioprosthesis should be kept hydrated throughout the rest of the preparation procedure to prevent the tissue from drying.**

7.3.2 Prepare the Delivery System

The RetroFlex introducer sheath set (introducer[s], sheath, and loader/loader cap), and the appropriate size RetroFlex II catheter are used for delivery of the bioprosthesis.

Step	Procedure
1	Visually inspect all components for damage.
2	Prime and flush the guidewire lumen of the nose catheter on the RetroFlex II catheter.
3	Insert a 180 cm or 260 cm x 0.035 inch (0.89 mm) extra stiff guidewire in the distal end of the lumen, leaving a 2 to 3 cm segment of the guidewire protruding from the distal tip.
4	Flush the RetroFlex II catheter with heparinized saline through both flushing ports (one for the nose to balloon catheter and the other for the balloon to flex catheter lumen).
5	Place the loader cap onto the RetroFlex II catheter with the threads oriented distally.  THV53
6	RetroFlex II catheter for the 23 mm bioprosthesis: Inflate the balloon with 20 cc of diluted contrast medium (15% dilution of contrast media to sterile heparinized saline). RetroFlex II catheter for the 26 mm bioprosthesis: Inflate the balloon with 25 cc of diluted contrast media.
7	Fully deflate the balloon catheter by pulling back on the inflation device plunger.
8	Insert the balloon into the balloon gauge. Inflate the balloon and make sure its diameter fits the gauge with minimal friction. While gently pulling and pushing the balloon, verify that the balloon moves with some resistance within the measuring ring. If the balloon does not reach the correct diameter when fully inflated, add or discard some of the inflating solution in the inflation device. – Make sure there are no air bubbles in the balloon. If a small air bubble is detected, eliminate it while deflating the balloon. – The inflation device must remain connected to the delivery balloon throughout the rest of the procedure. **Note: Correct balloon sizing is critical to successful valve deployment and valve function.**  THV54
9	Deflate the balloon, using your fingers to create a three-wing fold configuration. (Nose catheter not shown for clarity.)  THV03

7.3.3 Mount and Crimp the Bioprosthesis on the RetroFlex II Catheter (Models 9100HDSLT23 and 9100HDSLT26)

Step	Procedure
1	Remove the bioprosthesis from the holder and place the bioprosthesis gently into the crimper aperture.
2	Gradually crimp the bioprosthesis to a diameter of approximately 12 mm.
3	Remove the bioprosthesis from the crimper and place it on the RetroFlex II catheter with its inflow aspect (fabric cuff end) towards the distal end of the balloon catheter and with the uncovered stent proximal to the balloon. The longitudinal placement of the bioprosthesis is at the mid-point of the balloon shaft, between its two radiopaque markers.  THV55 **CAUTION: Special attention should be taken when placing the bioprosthesis on the balloon catheter.** **CAUTION: It is recommended that a second operator verify correct mounting/orientation of the bioprosthesis prior to its implantation.**
4	Place the bioprosthesis/balloon assembly back in the crimper aperture and gradually continue to crimp until the bioprosthesis/balloon assembly profile fits inside the crimp gauge. Periodically, open the crimper aperture and inspect the bioprosthesis to make sure that it is still placed properly between the radiopaque markers of the balloon shaft and has not been damaged.  THV56
5	After completing the mounting and crimping process, inspect the crimped device: – Flush the crimp gauge of the crimper with sterile heparinized saline solution and insert the crimped bioprosthesis/balloon assembly without passing it completely through the gauge. The bioprosthesis/balloon assembly should slide smoothly inside the gauge. – Maintain hydration of the bioprosthesis by placing it in the sterile heparinized saline solution until ready for implantation.

7.4 Native Valve Predilatation and Prosthetic Valve Delivery

Native valve predilatation and prosthetic valve delivery should be performed under local and/or general anesthesia with hemodynamic monitoring in a catheterization lab with fluoroscopic and electrocardiographic imaging capabilities.

Administer a bolus of heparin at the start of the procedure. During the procedure, heparin should be administered so that the ACT is maintained at ≥ 250 sec.

CAUTION: Excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored.

7.4.1 Baseline Parameters

Step	Procedure
1	Prepare and place a 6F sheath into each femoral artery, per standard technique.
2	Prepare and place an 8F sheath into the femoral vein that is contra-lateral to the artery selected for bioprosthesis implantation.
3	In the same leg used in Step 2, introduce a 5F or a 6F pigtail catheter into the femoral artery and advance the catheter into the aortic root for continuous blood pressure monitoring.
4	Advance an 8F PA catheter into the femoral vein sheath to the pulmonary artery. Collect required measurements.
5	If no diagnostic procedure has been performed within one month, perform the following: – Through the femoral artery sheath, sequentially advance right and left coronary artery diagnostic catheters, and perform a selective coronary angiogram. – Through the femoral artery sheath, perform a supra-aortic angiogram with the projection of the native aortic valve perpendicular to the screen. – Evaluate the height between the inferior aspect of the annulus and the inferior aspects of the lowest coronary ostium for subsequent prosthetic aortic valve implantation.
6	Introduce a 5F to 7F pacemaker (PM) lead through the 8F sheath in the femoral vein and advance the PM lead until its distal end is positioned in the right ventricle.
7	Set the stimulation parameters, test pacing at 200 to 220 b/min (See Edwards Rapid Pacing Protocol) and then start pacing on demand, at 80 b/min or as clinically indicated. **CAUTION: Pacing lead perforation has been found to be a potential complication; observation of the lead throughout the case is essential.**

7.4.2 Native Valve Predilatation

Predilate the native aortic valve using a standard balloon aortic valvuloplasty (BAV) technique with a commercially available BVC or a RetroFlex balloon catheter (20 mm or 23 mm) with rapid cardiac pacing. The right (or left) femoral artery can be catheterized percutaneously or by surgical cutdown for valve implantation. A bolus of heparin should be administered after sheath insertion.

CAUTION: Use of the retrograde approach may require a femoral artery cut-down with surgical closure of the puncture site due to the large size of the arteriotomy. A consultation with vascular surgery is required for arteriotomy creation and closure of the arterial access site.

Step	Procedure
1	Manually pre-shape the tip of the guidewire. Through the 6F sheath in the femoral artery selected for bioprosthesis implantation: – Advance a pigtail catheter over a standard 0.035 inch guidewire and cross the aortic valve per preferred technique. It is recommended to cross the valve in the 50° LAO position, using a straight guidewire. After the valve is crossed, advance the selected catheter over the guidewire into the left ventricle. – Remove the guidewire and record required hemodynamic information. Measure the cardiac output and assess the valve area.
2	Advance a 260 cm extra-stiff guidewire through the catheter (pigtail) into the left ventricle.
3	Remove the catheter, leaving the guidewire in place in the left ventricle.
4	Over this guidewire, advance a 14F sheath into the femoral artery.
5	Wipe and flush the balloon catheter with saline. Attach inflation device and stopcock to balloon inflation port and pull vacuum repeatedly to remove air. Close stopcock. Prepare inflation device with approximately 20 ml 15% contrast solution. Use data below for nominal balloon diameter: • 20 mm RetroFlex balloon catheter o Nominal Pressure: 6 ATM (608 kPa) o Nominal Volume: 13 ml • 23 mm RetroFlex balloon catheter o Nominal Pressure: 4 ATM (404 kPa) o Nominal Volume: 16 ml
6	Advance the prepared BVC through the sheath over the guidewire, cross the aortic valve, and position the balloon.
7	Using diluted contrast medium (e.g., 15% contrast medium to heparinized saline), fully and rapidly inflate the balloon with the inflation device until the desired size is reached. In case of balloon instability, repeat balloon inflation while ensuring rapid pacing (200-220 b/min) of the right ventricle. Once the blood pressure has decreased to 50 mmHg or below, balloon inflation can commence.
8	Remove the balloon valvuloplasty catheter, leaving the guidewire in place in the left ventricle.

CAUTION: Prosthetic valve implantation should not be carried out if the balloon cannot be fully inflated during predilatation.

7.4.3 Prosthetic Valve Delivery

Step	Procedure
1	Predilate the femoro-iliac vessel by advancing increasing sized dilators over the guidewire. Advance the maximum possible length of the introducer over the guidewire while following its progression on fluoroscopy. Or: Create an arteriotomy in the femoral artery selected for bioprosthesis implantation to allow introduction of the RetroFlex sheath. Use a dilator, if necessary, to expand the puncture site. **NOTE:** If blood loss occurs through the proximal luer of the dilator, a Touhy-Borst type hemostatic adaptor can be attached to the dilator luer to eliminate any leakage from the dilator lumen.
2	Pull the bioprosthesis/balloon assembly into the RetroFlex II catheter until the proximal edge of the bioprosthesis butts up against the distal end of the catheter; be careful to fold the proximal balloon to allow easy advancement of the balloon out of the catheter. Deflect the RetroFlex II catheter and advance the balloon catheter out to verify ease of advancement.  THV57
3	Before advancing the bioprosthesis/RetroFlex II catheter assembly through the RetroFlex sheath, test its diameter with the crimp gauge on the crimper. If necessary, re-compress the bioprosthesis/balloon assembly with the crimper so that it will fit through the gauge.
4	Advance the bioprosthesis/balloon assembly into the loader and position the distal end of the nose tip at the distal end of the loader.
5	Screw the loader cap (which is on the RetroFlex II catheter shaft) on the loader, and insert the loader into the sheath hemostasis valve.
6	Push the bioprosthesis/ RetroFlex II catheter through the RetroFlex sheath. Verify guidewire position in the LV. Continue to push the assembly through the sheath until the bioprosthesis exits from the sheath tip. Retract loader to proximal end of RetroFlex II catheter. **CAUTION: The bioprosthesis should not be advanced through the sheath if the sheath tip is not past the aortic bifurcation.**
7	Push the RetroFlex II catheter up the descending aorta; deflect the tip as needed (by rotating its handle "clockwise" to articulate or "counter-clockwise" to straighten out the shaft) to track over the guidewire and around the arch.
8	Cross the native aortic valve and position the bioprosthesis/balloon assembly so that the bioprosthesis is beside the calcified zone of the diseased valve as visualized on fluoroscopy.

Step	Procedure
9	Hold the bioprosthesis/balloon assembly and retract the RetroFlex II catheter by pushing the button located on the catheter handle and pulling the RetroFlex II catheter back, leaving the bioprosthesis in position across the native valve. Advance the tapered tip forward beyond the distal end of the balloon. **CAUTION: Verify under fluoroscopy that the balloon is completely out of the RetroFlex II catheter and tapered tip before it is inflated and the bioprosthesis is deployed.**
10	Position the mid-point of the bioprosthesis at the plane of the hinge points of the native valve leaflets.
11	Just prior to bioprosthesis/balloon inflation, start rapid pacing by setting the pacemaker catheter to pace at 200-220 b/min. The marked decrease in cardiac output induced by the ventricular tachycardia allows for additional stable balloon inflation.
12	Verify the correct location of the bioprosthesis with respect to the calcified valve using fluoroscopy guidance.
13	Begin bioprosthesis deployment: – Begin rapid pacing at 200-220 bpm; once arterial blood pressure has decreased to 50 mmHg or below, balloon inflation can commence. – Once the desired implantation position is verified, rapidly inflate the balloon catheter with the entire contents of the inflation device to completely deploy the bioprosthesis in the target location. – Once the bioprosthesis has been deployed, rapidly deflate the balloon catheter. – When the balloon catheter has been completely deflated the pacemaker may be turned off, or returned to 80 b/min if clinically indicated. – Pull the tapered tip onto the balloon and retract the RetroFlex II catheter system out of the bioprosthesis and into the descending aorta. Uncinch the RetroFlex II catheter before retracting the catheter system through the aorta. **CAUTION: Make sure the tapered nose tip does not interfere with the bioprosthesis while retracting the system.**
14	**CAUTION: Patient injury could occur if the RetroFlex II catheter is not un-flexed prior to removal of the catheter system.** – Advance the tapered tip to its most distal position. – Retract the balloon into the RetroFlex II catheter causing it to re-fold completely inside the RetroFlex II catheter shaft. The balloon catheter should be pulled back by pushing on the button to start the movement of the balloon catheter. Once the catheter has moved out of its locked position the button should be released and continue to pull the balloon catheter inside the RetroFlex II catheter until the next positive lock. – Re-advance the balloon out of the RetroFlex II catheter to the first locking position. – Pull the tapered tip back onto the balloon securely and lock into position with the locking mechanism on the handle. – Remove the RetroFlex II catheter out of the sheath. – Remove the guidewire.

7.5 Verification of Prosthetic Valve Position and Measurements

Measure and record both the invasive and non-invasive hemodynamic parameters required by the protocol.

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 catheters and sheaths when the ACT level is appropriate (e.g., reaches < 150 sec).
4	Apply local hemostatic compression on the catheterization puncture sites, or close surgically if clinically indicated.
5	The patient should remain on clopidogrel (75 mg/day) for 6 months post procedure and aspirin (75-100 mg/day) for life. Ticlopidine may be used instead of clopidogrel at the Investigator's discretion.

8. How Supplied

8.1 Available Sizes

The bioprosthesis is available in sizes 23 mm and 26 mm (outer diameter, fully expanded). The stent heights are 14.3 mm and 16.1 mm, respectively.

8.2 Packaging

The bioprosthesis is supplied sterile and nonpyrogenic packaged in buffered glutaraldehyde, in a plastic jar to which a seal has been applied. Sterility is not compromised if the package is unopened or undamaged. The outside of the container is NOT sterile and should not be placed in the sterile field. Each jar is shipped in a styrofoam enclosure containing a temperature indicator to determine if the bioprosthesis has been exposed to extreme temperatures during transit. Upon receipt, immediately remove the styrofoam and inspect the indicator.

WARNING: The bioprosthesis must be carefully inspected before implantation for evidence of extreme temperature exposure or other damage.

If the indicator shows that the bioprosthesis has been exposed to extreme temperatures during transit, do not use the bioprosthesis. Contact the local supplier or representative of Edwards Lifesciences to make arrangements for return, authorization, and replacement. Any bioprosthesis returned to the company should be shipped in the same styrofoam enclosure in which it was received.

Due to the biological nature of the bioprosthesis, and its sensitivity to physical handling and environmental conditions, it cannot be returned, except as noted above.

The crimper (models 9100CR23 and 9100CR26) with built-in balloon and crimp gauges is supplied sterile for single use only. The crimper is single pouched, and sterilized by ethylene oxide.

The RetroFlex delivery system components are supplied sterile for single use only.

- The RetroFlex II catheter (model 9100HDSLT23 and 9100HDSLT26) is mounted on a card, single pouched, and sterilized by ethylene oxide.
- The RetroFlex dilator kit (model 9100DKS and 9100DKS7) consists of dilators that are packaged together in a thermoformed tray, single pouched, and sterilized by ethylene oxide.
- The RetroFlex introducer sheath kit (model 9100SL23 or 9100SL26) includes a sheath, introducer(s), and loader assembly. The components are mounted in a tray, single pouched, and sterilized by ethylene oxide.

- The RetroFlex balloon catheter (model 9100BC20 or 9100BC23) is placed into a catheter hoop, double pouched, and sterilized by ethylene oxide.

8.3 Storage

The model 9000TFX bioprosthesis must be stored between 10 °C and 25 °C (50 °F and 77 °F). Stock inspections and rotation at regular intervals are recommended to ensure that the bioprostheses are used before the expiration date stamped on the package label.

Warning: Do not freeze. Always store bioprostheses in a dry, contamination-free area. Any bioprosthesis that has been frozen, or is suspected of having been frozen, should not be used for human implantation.

The RetroFlex delivery system components (crimper, RetroFlex dilators, RetroFlex introducer sheath set, RetroFlex II catheter, and RetroFlex balloon catheters) should be stored in a cool, dry place.

9. MR Safety

Non-clinical testing has demonstrated that the Edwards SAPIEN transcatheter heart valve is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 3 Tesla or less.
- Spatial gradient field of 720 Gauss/cm or less.
- Maximum whole-body-averaged specific absorption rate (SAR) of 3.0 W/kg for 15 minutes of scanning.

In non-clinical testing, the device produced a maximum temperature increase of 0.5 °C at a maximum whole body averaged specific absorption rate (SAR) of 3.0 W/kg for 15 minutes of MRI.

MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the device.

10. Patient Information

A patient registration form is provided with each device. After implantation, please complete all requested information. The serial number may be found on the package and on the identification tag attached to the bioprosthesis. 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. This information becomes an important part of the records maintained on each bioprosthesis. Your cooperation in providing accurate and legible information is appreciated. The accurate completion and return of this form is essential for the purpose of bioprosthesis tracking and patient notification. An Implanted Device Card is provided to the patient. The card contains the name and telephone number of the patient's physician, as well as information that medical personnel would require in the event of an emergency.

11. Recovered Clinical Bioprostheses

Edwards Lifesciences is interested in obtaining recovered clinical specimens of the Edwards SAPIEN transcatheter heart valve for analysis. A written report summarizing our findings will be provided upon completion of our evaluation. The explanted model 9000TFX bioprostheses 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.

Disposal of Used Delivery Systems and Crimper

The used delivery and crimper system 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 device.

12. Clinical Experience

The Edwards SAPIEN transcatheter heart valve model 9000TFX, the RetroFlex delivery system and the crimper are available exclusively for investigational use. References reporting clinical experience with percutaneous delivery of the bioprosthesis are provided in section 13.

This product is manufactured and sold under one or more of the following US patent(s): US Patent No. 5,411,552; 5,840,081; 5,931,969; 6,168,614; 6,214,054; 6,547,827; 6,561,970; 6,582,462; 6,730,118; 6,893,460; and 6,908,481. Likewise, additional US and foreign patents are pending.

13. References

1. Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis. *Circulation* 2002;106;3006-8.
2. Eltchaninoff H, Tron C, Cribier A. Percutaneous implantation of aortic valve prosthesis in patients with calcific aortic stenosis: technical aspects. *J Interv Cardiol* 2003;16(6):515-21.
3. Cribier A, Eltchaninoff H, Tron C, et al. Early experience with percutaneous transcatheter implantation of heart valve prosthesis for the treatment of end-stage inoperable patients with calcific aortic stenosis. *J Am Coll Cardiol* 2004;43:698-703.
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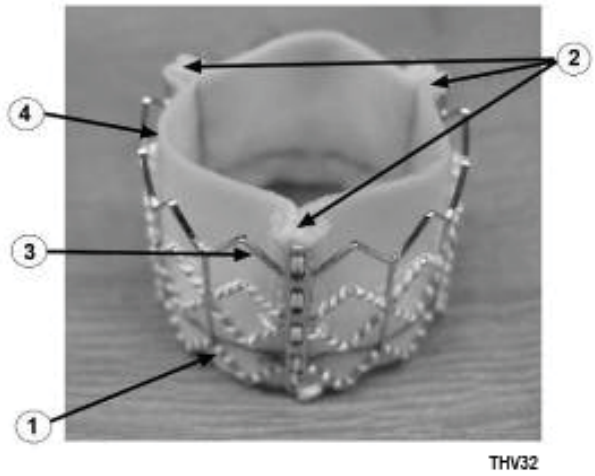
7. Hanzel GS, Harrity PH, Schreiber TL, O'Neill WW. Retrograde percutaneous aortic valve implantation for critical aortic stenosis. *Catheter Cardiovasc Interv* 2005;64(3):322-6.
8. Webb JG, Chandavimol M, Thompson CR, et al. Percutaneous aortic valve implantation retrograde from the femoral artery. *Circulation* 2006;113:842-50.
9. Cribier A, Eltchaninoff H, Tron C, et al. Treatment of calcific aortic stenosis with the percutaneous heart valve: mid-term follow-up from the initial feasibility studies: the French experience. *J Am Coll Cardiol* 2006;47(6):1214-23.

14. Figures



1. PET Cuff
2. Commissures (in the valve) and Supporting bars (in the frame)
3. Frame
4. A unidirectional valve

Figure 1. Model 9000TFX Bioprosthesis

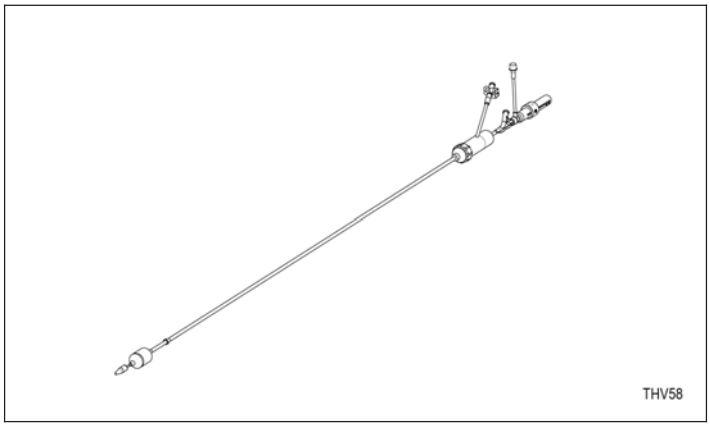


Figure 2. RetroFlex II Catheter

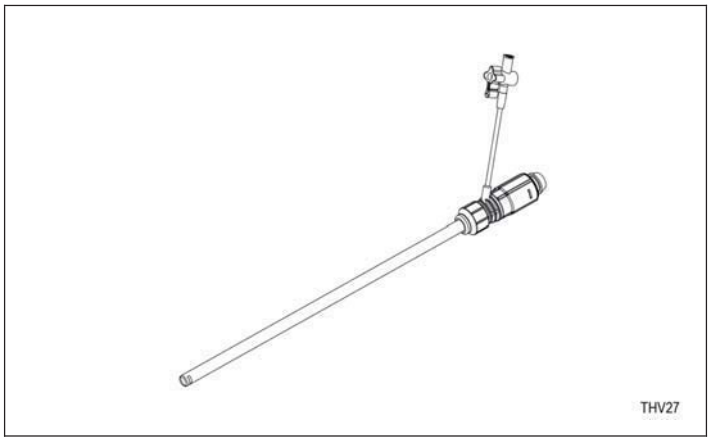


Figure 3. Sheath

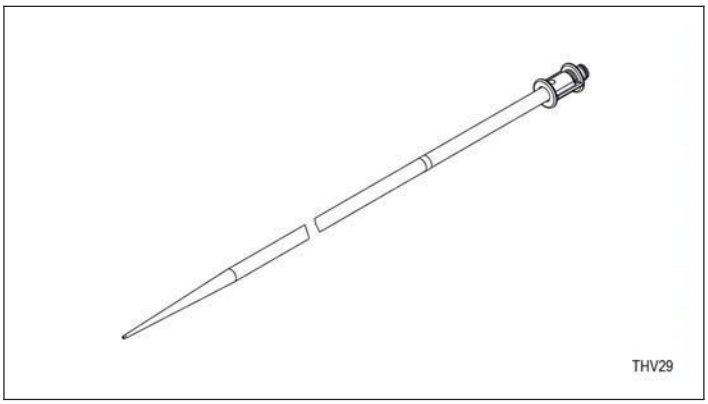


Figure 4. Introducer

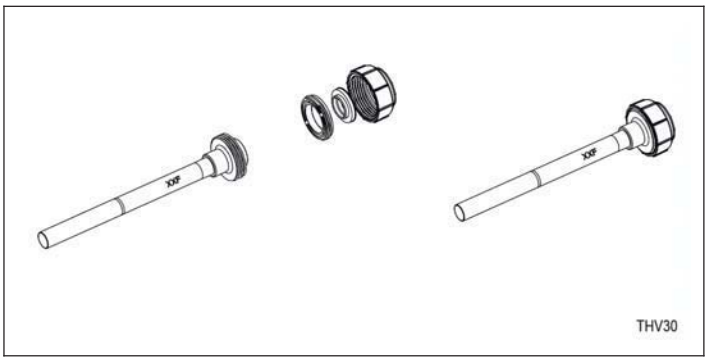


Figure 5. Loader

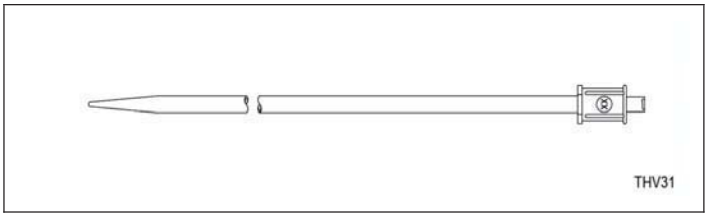


Figure 6. RetroFlex Dilator

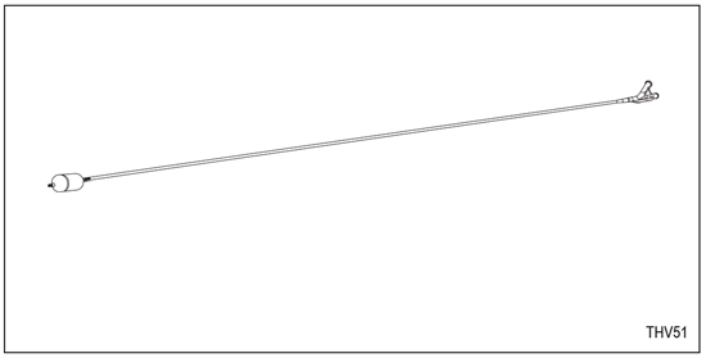


Figure 7. RetroFlex Balloon Catheter

14. Figures (cont)

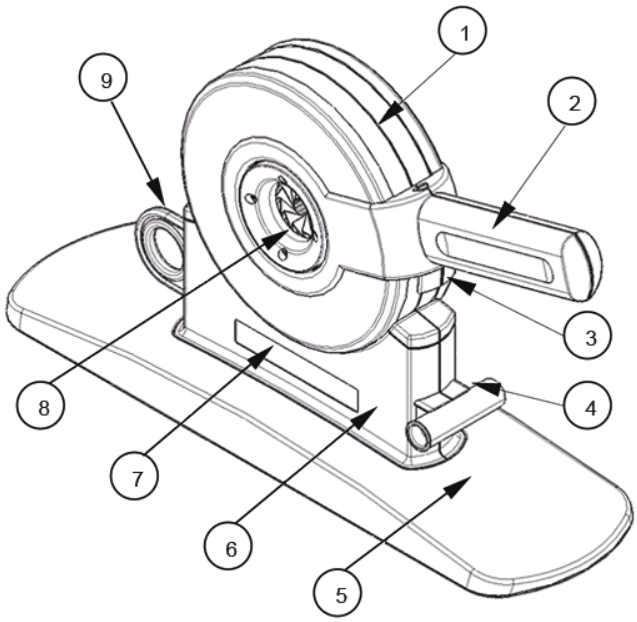


Figure 8. Crimper

1 - Housing
2 - Handle
3 - Stopper
4 - Crimp Gauge
5 - Base
6 - Stand
7 – ID Label
8 - Aperture
9 - Balloon Gauge

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Edwards SAPIEN Transcatheter Heart Valve (THV)

Model 9000TFX

Ascendra Delivery System:

- Edwards MIS Introducer Sheath Set
  Model 9100MISIS or
- Ascendra Introducer Sheath Set
  Model 9100IS
- Ascendra Balloon Aortic Valvuloplasty Catheter
  Model 9100BAVC
- Ascendra Balloon Catheter
  Model 9100BCL23, 9100BCL26

Crimper

Model 9100CR23, 9100CR26

Instructions for Use - Transapical Approach

CAUTION: Investigational Device. Limited by Federal (USA) Law to investigational use.

Exclusively for Clinical Investigations

Caution: To be used by qualified investigators only

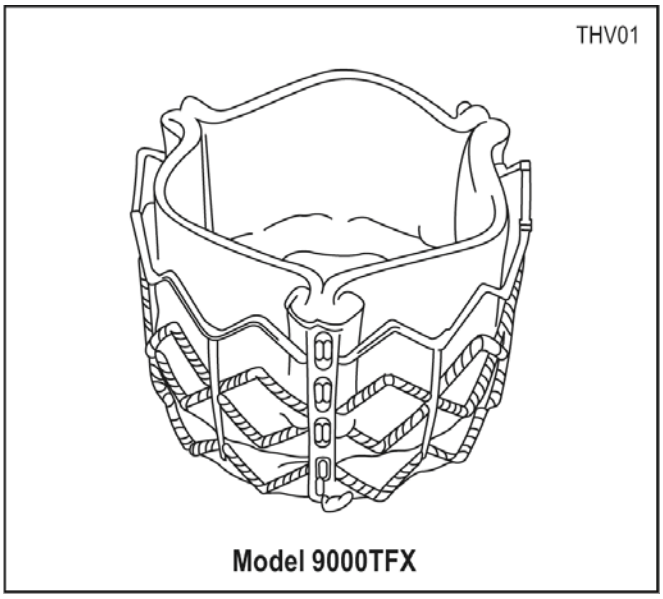
Instrument de recherche – Réservé uniquement à l'usage de chercheurs compétents.

For single use only

1. Device Description

1.1 Edwards SAPIEN Transcatheter Heart Valve

The Edwards SAPIEN transcatheter heart valve model 9000TFX (Figure 1) combines balloon expandable stent and bioprosthetic valve technology. The Edwards SAPIEN transcatheter heart valve is available in two sizes (23 mm and 26 mm), and is designed for transcatheter implantation in patients with severe aortic stenosis (AS).



Prior to implantation, the bioprosthesis is carefully mounted and crimped onto a balloon delivery catheter using a specially designed crimping device. The bioprosthesis is inserted through the apex of the left ventricle and delivered to the site of the native stenotic aortic valve using the Ascendra delivery system described in section 1.2. The bioprosthesis is positioned and deployed across the stenotic native valve. The balloon delivery system is then removed.

This minimally invasive surgical approach is intended to be performed under general anesthesia using sterile technique, with echocardiographic and fluoroscopic guidance for visualization. The bioprosthesis is comprised of a radiopaque, stainless steel 316LVM expandable support structure (stent), an integrated unidirectional trileaflet tissue valve, and 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 cross link the tissue, while preserving its flexibility and strength. The bioprosthesis is treated according to the Edwards ThermaFix process, which involves heat treatment of the tissue in glutaraldehyde and uses ethanol and polysorbate-80 (a surfactant). The bioprosthesis is packaged and terminally sterilized in glutaraldehyde. Glutaraldehyde is shown to both reduce the antigenicity of tissue xenograft valves and increase tissue stability; however, glutaraldehyde alone has not been shown to affect or reduce the calcification rate of the valve.

1.2 Ascendra Delivery System

The Ascendra delivery system consists of the following:

- 33F (11.0 mm) Edwards MIS introducer sheath set, model 9100MISIS (Figure 2)

OR

- 26F (8.6 mm) Ascendra introducer sheath set, model 9100IS (Figure 2)
- Ascendra balloon catheter, model 9100BCL23, which includes both the 23 mm x 3 cm x 64 cm Edwards balloon catheter and the 26F (8.6 mm) Edwards loader for the 23 mm bioprosthesis (Figure 3a, 3b and 3c)

OR

- Ascendra balloon catheter, model 9100BCL26, which includes both the 26 mm x 3 cm x 64 cm Edwards balloon catheter and the 26F (8.6 mm) Edwards loader for the 26 mm bioprosthesis (Figure 3a, 3b and 3c)

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 side port and three hemostasis valves. A dilator is supplied with the introducer sheath. The dilator has a radiopaque marker at the distal end where the taper begins.

The Ascendra balloon catheter system consists of a balloon catheter and a loader. Two radiopaque markers on the balloon serve as indicators for bioprosthesis placement during crimping, as well as visualization of the balloon. The catheter has a deflecting mechanism to steer the balloon. The loader allows for the delivery of the crimped bioprosthesis through the hemostasis valves.

1.3 Crimper (Model 9100CR23 and 9100CR26)

The crimper is a single use non-patient contacting, compression device (Figure 4) that reduces the overall diameter of the bioprosthesis from its expanded size to its collapsed (mounted) size, effectively mounting the bioprosthesis to its delivery balloon catheter. The crimper is comprised of a housing and a plastic compression mechanism (creating the aperture). The aperture is closed by means of a handle located on the housing. The crimper is equipped with two measuring gauges:

- A crimp gauge to verify that the bioprosthesis/balloon catheter assembly has been suitably collapsed.
- A balloon gauge to verify the balloon catheter diameter when inflated.

2. Indications

The Edwards SAPIEN transcatheter heart valve is intended for use in symptomatic patients with severe calcific aortic stenosis requiring aortic valve replacement, who are at high risk for open-chest surgery due to co-morbid conditions. The bioprosthesis is intended for transcatheter aortic valve replacement. The procedure may be performed without cardiopulmonary bypass.

The Ascendra delivery system consisting of the Edwards MIS introducer sheath set, model 9100MISIS, or Ascendra introducer sheath set, model 9100IS, Ascendra balloon aortic valvuloplasty catheter, model 9100BAVC and Ascendra balloon catheter, model 9100BCL23 or 9100BCL26 is indicated for delivery and deployment of the bioprosthesis.

The crimper, model 9100CR23 or 9100CR26, is used to crimp the bioprosthesis.

3. Contraindications

Implantation of the bioprosthesis is contraindicated for patients with:

- Non-valvular aortic stenosis
- Congenital aortic stenosis or unicuspid or bicuspid aortic valve
- Presence of mitral bioprosthesis
- Non-calcific acquired aortic stenosis
- Evidence of intracardiac mass, thrombus or vegetation
- Untreated clinically significant coronary disease requiring revascularization
- Myocardial infarction (MI) within 1 month
- Severe deformation of the chest
- Severe coagulation problems
- Active bacterial endocarditis or other active infections
- Severe ventricular dysfunction with ejection fraction < 20%
- Patients unable to tolerate anticoagulation therapy
- Recent (within 6 months) cerebrovascular accident (CVA)
- Hypertrophic cardiomyopathy with or without obstruction (HOCM)

The bioprosthesis is not to be used if the implanting physician believes its implantation would be contrary to the best interest of the patient.

The bioprosthesis is not to be used in positions other than the aortic valve.

There are no known contraindications for the Ascendra delivery system other than standard risks associated with insertion of a cardiovascular catheter.

4. Warnings

- For Single Use Only
- Correct sizing of the bioprosthesis is essential to prevent paravalvular leak or migration. The bioprosthesis is intended for use in candidates with a native aortic annulus size ranging from 16 mm to 24 mm.
- Do not resterilize the bioprosthesis, Ascendra delivery system or crimper. Exposure of the bioprosthesis and container to irradiation, steam, ethylene oxide, or other steriliants will render the bioprosthesis unfit for use.
- Accelerated deterioration due to calcific degeneration of the bioprosthesis (as with any glutaraldehyde cross linked bioprosthesis) may occur in patients with altered calcium metabolism.
- Overall durability, especially long-term, has not been established for the bioprosthesis. Careful and continuous medical follow-up is advised so that bioprosthesis-related complications can be diagnosed and properly managed.
- It is recommended that all prosthetic heart valve recipients be prophylactically treated for endocarditis to minimize the possibility of prosthetic valve infection.
- Bioprosthetic valve recipients should be maintained on anticoagulant therapy, except where contraindicated, as determined by their physician.

- Do not add or apply antibiotics to the storage solution, rinse solutions, or to the bioprosthesis.

5. Precautions

5.1 Precautions Prior to Use

- Do not use the bioprosthesis:
  - if the tamper evident seal is broken
  - if the glutaraldehyde storage solution does not completely cover the bioprosthesis
  - if the temperature indicator provided in the packaging has been activated
  - if the bioprosthesis is damaged
- Do not mishandle the valve tissue during rinsing, mounting, or crimping. If the bioprosthesis is damaged, it must be replaced.
- Do not use the Ascendra delivery system:
  - if the packaging seal is broken, or the package has been damaged
  - if the device is damaged
- Do not use the crimper:
  - if not sterile
  - if the aperture jaws or gauges (any parts that come into contact with the bioprosthesis and/or balloon delivery catheter) are damaged or shown to have any debris and/or non-smooth contact surfaces
- Careful attention must be paid to the maintenance of tight catheter connections and aspiration before proceeding to avoid air introduction into the system.

5.2 Precautions During Use

- Do not expose the bioprosthesis to solutions other than the storage solution in which it was shipped and the sterile biologic rinsing and irrigation solutions specified in section 7.3.1.
- Do not allow the leaflet tissue of the bioprosthesis to become dry. Continuous submersion or irrigation is required (refer to section 7.3 Bioprosthesis Handling and Preparation).
- Do not use any devices other than the crimper and Ascendra delivery system to crimp, deliver, and deploy the bioprosthesis.
- The outside of the bioprosthesis jar is not sterile and must not be placed in the sterile field.
- Glutaraldehyde may cause irritation of the skin, eyes, nose and throat. Avoid prolonged or repeated exposure 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.
- Do not over inflate the Ascendra balloon catheter. Care should be taken to fully compress the inflation device to fully expand the balloon and bioprosthesis.
- The procedure should be conducted under fluoroscopic guidance.
- Care should be used when handling the catheter. Damage may result from kinking or stretching the catheter.

6. Potential Adverse Events

6.1 Potential Adverse Events, Bioprosthesis

Complications associated with the use of bioprosthetic heart valves compiled from the literature include:

- Death (procedure related, device related, or unknown)
- Thromboembolism (permanent or transient neurological events)
- Primary bioprosthetic valve thrombosis
- Structural valve deterioration (calcification, leaflet tear, stenosis, or other)
- Nonstructural valve dysfunction (i.e. pannus, suture or other), including malfunctions of the valve due to distortion at implant
- Valvular regurgitation
- Hemorrhage (anticoagulant/antiplatelet)
- Leak (transvalvular or paravalvular)
- Endocarditis
- Primary hemolysis

Tissue deterioration associated with bioprosthetic heart valves can be caused by:

- Infection
- Calcification
- Thickening
- Perforation
- Degeneration
- Instrument trauma
- Leaflet tearing/detachment from stent posts

Complications associated with bioprosthetic valve replacement may present clinically as:

- Abnormal heart murmur
- Exercise intolerance

- Fever
- Dyspnea (i.e. Orthopnea)
- Hemolytic anemia
- Hemorrhage
- Transient ischemic attack
- Stroke
- Paralysis
- Low cardiac output
- Pulmonary edema
- Congestive heart failure
- Cardiac failure
- Myocardial infarction

Complications associated with a transapical cardiac incision and balloon aortic valvuloplasty:

- Unintended perforation (vessels and pericardium)
- Conduction system injury
- Thromboembolic events
- Hematoma
- Cardiovascular injury
- Arrhythmia
- Valvular tearing or trauma
- Restenosis
- Inflammation
- Infection
- Allergic reaction to anesthesia or to contrast media
- Embolization
- Fever
- Hemorrhage requiring transfusion
- Hypertension/hypotension
- Pericardial effusion/cardiac tamponade
- Renal failure/insufficiency
- Retroperitoneal bleed

Additional adverse events potentially associated with the use of the bioprosthesis (in alphabetical order) include:

- Cardiac dysrhythmias
- Device migration (due to improper sizing or deployment or other)
- Improper implantation location (potentially causing coronary flow obstruction or mitral valve impairment/damage)
- Nonstructural dysfunction (pannus, suture, inappropriate sizing, or other)

6.2 Potential Adverse Events, Ascendra Delivery System

Potential complications and related adverse effects associated with the use of the delivery system include but are not limited to:

- Perforation
- Thromboembolic events
- Hematoma
- Myocardial injury
- Conduction system injury
- Arrhythmia development
- Valvular tearing or trauma
- Inflammation
- Infection

It is possible that procedural or device-related complications could lead to:

- Reoperation
- Explantation
- Permanent disability
- Death (procedure related, device related, or unknown)

7. Directions for Use

7.1 Physician Training

The implanting physician should be experienced in balloon aortic valvuloplasty, port access catheterization techniques, the bioprosthesis implantation procedure, and trained on the use of the bioprosthesis, Ascendra delivery system and crimper.

7.2 Required Equipment

7.2.1 Equipment and materials for surgical access and native aortic valve balloon predilatation:

- Fluoroscopy
- Pressure transducing capabilities
- Transesophageal echocardiography capabilities
- Two 8F (2.7 mm) introducer sheaths/dilators
- 5F (1.67 mm) or 6F (2.0 mm) pigtail catheter
- 8F (2.7 mm) pulmonary artery (PA) catheter (three-port, flow-directed; e.g., Swan-Ganz) for hemodynamic monitoring
- Standard length, 0.035" (0.89 mm) straight guidewire
- 18 gauge (1.2 mm) percutaneous needle
- 180 cm or 260 cm x 0.035" (0.89 mm) extra-stiff guidewire
- 20 mm commercially available balloon valvuloplasty catheter (BVC) or Ascendra balloon aortic valvuloplasty catheter (model 9100BAVC) for the 23 mm and 26 mm bioprosthesis
- Pacemaker and pacing leads
- Diluted radiopaque contrast medium (15:85 medium to saline dilution)
- Sterile physiologic saline solution
- Atrion Model QL2530 Inflation Device
- Others (syringes, 3-way stopcocks, etc.)

7.2.2 Equipment and materials required for model 9000TFX preparation and implantation:

- Model 9000TFX bioprosthesis
- Edwards MIS introducer sheath set (model 9100MISIS), 33F (11.0 mm) or Ascendra introducer sheath set (model 9100IS), 26F (8.6 mm)
- Atrion Model QL2530 Inflation Device
- Large clamp (hemostat)
- Two sterile rinsing containers (stainless steel bowls recommended)
- Sterile physiologic saline solution
- Sterile heparinized saline solution
- Diluted radiopaque contrast medium (15:85 medium to saline dilution)
- Additional sterile table for model 9000TFX and accessories preparation
- Others (syringes, 3-way stopcocks, etc.)

For use with model 9000TFX 23 mm:

- Ascendra balloon catheter (model 9100BCL23) with 23 mm x 30 mm balloon and loader
- Crimper model 9100CR23

For use with model 9000TFX 26 mm:

- Ascendra balloon catheter (model 9100BCL26) with 26 mm x 30 mm balloon and loader
- Crimper model 9100CR26

7.3 Bioprosthesis Handling and Preparation

Follow sterile technique during device preparation and implantation.

7.3.1 Bioprosthesis Rinsing Procedure

The bioprosthesis 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: Bioprosthetic valves from containers found to be damaged, leaking, without adequate glutaraldehyde sterilant, or missing intact seals must not be used for human implantation.

CAUTION: It is strongly recommended that the bioprosthesis container not be opened unless implantation is certain. This is necessary to reduce the risk of contamination. It has been established that glutaraldehyde alone is not 100 percent effective against all possible contaminants. No attempts should be made to resterilize the bioprosthesis.

CAUTION: Handle jar contents in an aseptic manner to prevent contamination.

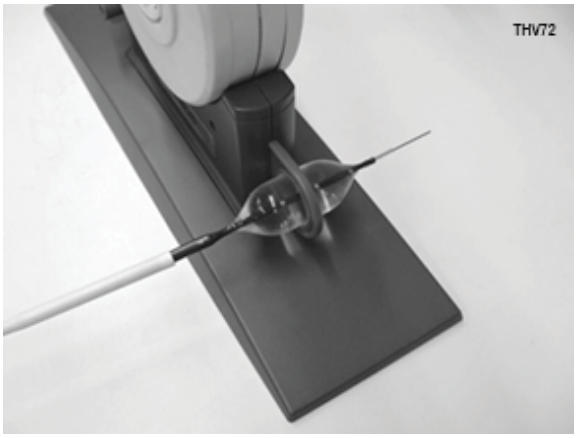
CAUTION: Do not allow the bioprosthesis to come in contact with the bottom or sides of the rinse bowl during agitation or swirling of the bioprosthesis. Care must be taken to ensure that the identification tag does not come in contact with the tissue and damage it. No other objects should be placed in the rinse bowls.

Step	Procedure
1	Set up two (2) sterile bowls with at least 500 ml of sterile physiologic saline to thoroughly rinse the glutaraldehyde sterilant from the bioprosthesis.
2	The bioprosthesis is contained in the jar within a holder. At least 30 minutes before implantation, carefully remove the bioprosthesis/holder assembly from the jar without touching the tissue. The holder is tagged with the bioprosthesis' serial identification number, which must be recorded in the patient information documents. Inspect the bioprosthesis for any signs of damage to the frame or tissue. Do not implant the bioprosthesis if any damage is found (tears or cracks in the tissue, loose sutures, fractured or broken frame struts, etc.).

Step	Procedure
3	Transfer the bioprosthesis/holder assembly to the first sterile bowl of rinsing solution. Keep the bioprosthesis hydrated at all times.
4	Rinse the bioprosthesis as follows: Place the bioprosthesis and holder in a minimum of 500 ml of sterile, physiological saline solution. Be sure the saline solution completely covers the bioprosthesis and holder. With the bioprosthesis and holder submerged, slowly agitate the basin (to **gently** swirl the bioprosthesis and holder back and forth for a minimum of 1 minute). Discard the rinse solution. Repeat this process once using new saline solution for a minimum of 1 minute. The bioprosthesis should be left in the final rinse solution until needed to prevent the tissue from drying. **CAUTION: The bioprosthesis should be kept hydrated throughout the rest of the preparation procedure to prevent the tissue from drying.**

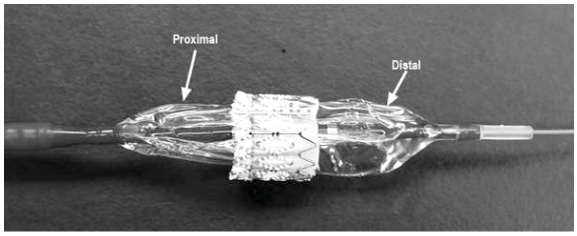
7.3.2 Prepare the Delivery System

Step	Procedure
1	Visually inspect all components for damage.
2	Prime and flush the introducer sheath.
3	Advance the dilator through the hemostasis valves and into the introducer sheath until the tapered portion is extended approximately 1 cm past the end of the sheath.
4	Prime and flush the guidewire lumen of the dilator. Prime and flush the space between the introducer sheath and dilator through the sideport.
5	Remove and discard the cover on the balloon catheter. Prime and flush the balloon catheter with heparinized saline.
6	Slide the loader cap, nylon washers and silicone seal proximally on the balloon catheter shaft so that they are out of the way during the crimping procedure.
7	Loosen the proximal pusher nut and slide the pusher as far proximal as possible on the balloon catheter shaft. Tighten the pusher nut to secure its location.
8	Prime and flush the guidewire lumen of the balloon catheter with heparinized saline.
9	Insert the 0.035" (0.89 mm) guidewire or stylet in the distal end of the lumen, leaving a 2-3 cm segment of the guidewire protruding from the distal tip.
10	Attach balloon extension tubing to balloon inflation “y” if preferred. Inflate the balloon with approximately 20 cc of diluted contrast medium (15% dilution of contrast media to sterile heparinized saline).
11	Make sure there are no air bubbles in the balloon catheter. If a small air bubble is detected, eliminate it while deflating the balloon.

Step	Procedure
12	Insert the balloon into the balloon gauge. Inflate the balloon and make sure its diameter fits the balloon gauge with minimal friction. While gently pulling and pushing the balloon, verify that the balloon moves with little resistance to the measuring ring. If the balloon does not reach the correct diameter when fully inflated, add or discard some of the inflating solution in the inflation device**.** **Note: Correct balloon sizing is critical to successful valve deployment and valve function.** 
13	The inflation device should stay connected to the delivery balloon throughout the rest of the procedure.
14	Deflate the balloon, using fingers to create a three-wing fold configuration. 

7.3.3 Mount and Crimp the Bioprosthesis onto the Ascendra Balloon Catheter

Step	Procedure
1	Remove the bioprosthesis from the holder and place the bioprosthesis gently into the crimper aperture.
2	Gradually crimp the bioprosthesis to a diameter of approximately 12 mm.

Step	Procedure
3	Remove the bioprosthesis from the crimper and place it on the balloon catheter with its inflow aspect (fabric cuff end) towards the proximal end of the balloon catheter. The longitudinal placement of the bioprosthesis is at the mid-point of the balloon shaft, between its two radiopaque markers.  THV62 **CAUTION: Special attention should be taken when placing the bioprosthesis on the Ascendra balloon catheter.** **CAUTION: It is recommended that a second operator verify correct mounting/orientation of the bioprosthesis prior to its implantation.**
4	Place the bioprosthesis/balloon assembly back in the crimper aperture and gradually continue to crimp until the bioprosthesis/balloon assembly profile fits easily inside the crimp gauge. Periodically open the crimper aperture and inspect the bioprosthesis to make sure that it is still placed properly between the radiopaque markers of the balloon shaft and has not been damaged.

Step	Procedure
5	After completing the mounting and crimping process, inspect the crimped device: – Flush the crimp gauge of the crimper with sterile heparinized saline solution and insert the crimped bioprosthesis/balloon assembly without passing it completely through the gauge as shown in picture THV90. As a final check ensure that the bioprosthesis/balloon assembly also slides smoothly through the loader. If necessary, re-crimp the bioprosthesis/balloon assembly with the crimper so that it will fit through the loader. – Maintain hydration of the bioprosthesis by placing it in the sterile heparinized saline solution until ready for implantation.  THV90
6	Loosen the pusher nut and advance the pusher as far distal as possible on the balloon catheter shaft. The end of the pusher will meet the proximal most edge of the crimped bioprosthesis, covering the proximal portion of the balloon. Take care not to damage the balloon during advancement over the balloon. Tighten the pusher nut.
7	At the distal tip of the delivery balloon catheter, slide the threaded end of the loader over the crimped bioprosthesis/balloon. Ensure loader covers valve.
8	Slide the two washers and silicone seal on the balloon catheter shaft distally and insert them into the proximal cavity of the loader. Ensure that the washers and seal are seated flat against each other within the loader, otherwise leakage may occur.
9	Slide the black loader cap on the balloon catheter shaft distally. The cap should only be pushed distally to the point where the seal just contacts the white pusher. Tighten the cap onto the loader until resistance between the catheter and loader seal is encountered. Do not overtighten. NOTE: The loader must fully cover the valve.
10	Maintain hydration of the bioprosthesis prior to implantation by placing it in the sterile heparinized saline or injecting sterile heparinized saline into the side port on the white y-connector of the balloon catheter.

Step	Procedure
11	Remove the guidewire or stylet from the bioprosthesis/balloon assembly.

7.4 Native Valve Predilatation and Prosthetic Valve Delivery

Native valve predilatation and prosthetic valve delivery should be performed under general anesthesia with hemodynamic monitoring in an operating room with fluoroscopic and electrocardiographic imaging capabilities.

The use of cardiopulmonary bypass is not required; however, bypass has been used in some cases, as a conservative measure during the learning curve or to address apical bleeding post-procedure.

Administer a bolus of heparin at the start of the procedure. During the procedure, heparin should be administered so that the ACT is maintained at ≥ 250 sec.

CAUTION: Excessive contrast media may lead to renal failure. Measure the patient's creatinine level prior to the procedure. Contrast media usage should be monitored.

7.4.1 Baseline Parameters

Step	Procedure
1	Place radial arterial line for continuous arterial blood pressure monitoring.
2	Place an internal jugular vein line for monitoring central venous pressures and volumes via standard techniques.
3	Prepare and place a 6F (2.0 mm) sheath into a femoral artery, per standard techniques. Through the femoral artery sheath, 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 screen.
4	Evaluate the height between the inferior aspect of the annulus and the inferior aspects of the lowest coronary ostium for subsequent prosthetic aortic valve implantation.
5	Set the stimulation parameters, test pacing at 200 to 220 b/min (See Edwards Rapid Pacing Protocol) and then start pacing on demand at 80 b/min or as clinically indicated.

7.4.2 Apical Access and Native Valve Predilatation

Step	Procedure
1	Access the apex of the pericardium through a mini anterior 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 and plug proximal end of leads into pacemaker.
3	Place a reinforced double purse string on the LV apex to access the left ventricle. Ensure the patient is anticoagulated with heparin to obtain an ACT of ≥ 250 seconds.
4	Under image guidance, place an 18 gauge (1.2 mm) percutaneous needle through the purse string into the LV cavity and advance a short 0.035" (0.89 mm) stiff guidewire through the needle into the LV. Remove the needle and place an 8F (2.7 mm) introducer over the guidewire; then remove the guidewire. Advance the 260 cm x 0.035" (0.89 mm) extra-stiff guidewire through the 8F (2.7 mm) introducer and the native valve into the descending aorta.
5	Remove the 8F (2.7 mm) sheath and replace with 14F (4.7 mm) sheath or use the Ascendra introducer sheath set, model 9100IS, 26F (8.6 mm), or the Edwards MIS introducer sheath set, model 9100MISIS 33F (11.0 mm).
6	Prepare a 20 mm commercially available balloon valvuloplasty catheter (BVC), or the Ascendra balloon aortic valvuloplasty catheter, model 9100BAVC per its instructions for use.
7	Advance the prepared BVC through the sheath over the guidewire, cross the aortic valve, and position the balloon.
8	Begin predilation: – Begin rapid pacing at 200-220 bpm; once arterial blood pressure has decreased to 50 mmHg or below, balloon inflation can commence. – Once the desired implantation position is verified, rapidly inflate the BVC. – Rapidly deflate the BVC. – When the BVC has been completely deflated the pacemaker may be turned off, or returned to 80 b/min, if clinically indicated.
9	Remove the balloon valvuloplasty catheter, leaving the guidewire in place in the descending aorta.
10	If applicable, remove 14F (4.7 mm) sheath and advance the Edwards model 9100MISIS 33F (11.0 mm) or model 9100IS, 26F (8.6 mm) introducer sheath system over the guidewire. Insert the tip of the introducer sheath through the apex of the LV and locate the sheath tip in the LV outflow immediately below the aortic valve; withdraw the dilator slowly, keeping the introducer sheath in place. Continue to hold the guidewire centered relative to the introducer sheath.

7.4.3 Prosthetic Valve Delivery

Step	Procedure
1	Advance the bioprosthesis/balloon catheter delivery assembly with the loader over the guidewire.
2	Insert the tip of the loader into the introducer sheath housing while maintaining a firm grip. The loader will lock into place when it is fully advanced into the housing.
3	Tap lightly on the introducer sheath housing to release air bubbles to the proximal end of the loader. Loosen the loader cap to release the air bubbles from the loader, then tighten the cap until the loader is sealed but the catheter can be moved with minimal resistance.
4	Cross the native aortic valve and position the bioprosthesis/balloon assembly so that the mid-point of the bioprosthesis is beside the calcified zone of the diseased valve as visualized on fluoroscopy.

Step	Procedure
5	Loosen the pusher nut and pull the pusher sleeve as far proximal as possible. Tighten the pusher nut. **CAUTION: The pusher sleeve MUST be pulled back for proper balloon inflation and bioprosthesis deployment.**
6	The bioprosthesis/balloon assembly position may be adjusted within the annulus by pulling back on the knob on the handle to deflect the catheter tip. The deflection occurs in the same plane as the knob. If deflection is used, the knob must be held until deployment of the bioprosthesis is complete.
7	Just prior to bioprosthesis/balloon inflation, start rapid pacing by setting the PM to pace at 200-220 b/min. The marked decrease in cardiac output induced by the ventricular tachycardia allows for a more stable balloon inflation.
8	Verify the correct location of the bioprosthesis with respect to the calcified valve using image guidance.
9	Begin bioprosthesis deployment: – Begin rapid pacing at 200-220 bpm; once arterial blood pressure has decreased to 50 mmHg or below, balloon inflation can commence. – Rapidly inflate the balloon catheter with the entire contents of the inflation device to completely deploy the bioprosthesis in the target location. – Once the bioprosthesis has been deployed, rapidly deflate the balloon catheter. – When the balloon catheter has been completely deflated the pacemaker may be turned off, or returned to 80 b/min, if clinically indicated.
10	– If deflection was used, straighten the catheter tip. – Retract the balloon catheter and guidewire into the introducer sheath.

7.5 Verification of Prosthetic Valve Position and Measurements

Measure and record both the invasive and non-invasive hemodynamic parameters required by the protocol.

Step	Procedure
1	Perform a supra aortic angiogram to evaluate device performance and coronary patency.
2	Upon satisfactory deployment, remove the sheath, balloon catheter and guidewire.
3	Tie the apical purse string in place and confirm hemostasis.
4	Measure and record the transvalvular pressure gradients.
5	Remove all catheters and sheaths when the ACT level is appropriate (e.g., reaches < 150 sec).
6	Apply local hemostatic compression on the catheterization puncture sites, or close surgically if clinically indicated.
7	The patient should remain on clopidogrel (75 mg/day) for 6 months post procedure and aspirin (75-100 mg/day) for life. Ticlopidine may be used instead of clopidogrel at the physician's discretion.

8. How Supplied

8.1 Available Sizes

The model 9000TFX is available in a fully expanded size of 26 mm (outer diameter) and a stent height of 16.1 mm or 23 mm (outer diameter) and a stent height of 14.3 mm.

Model 9100BCL23 and 9100BCL26 Information

DESIGNATION OF MODEL 9100BCL23 and 9100BCL26 NOMINAL SIZE	
Diameter of inflated balloon	23 mm or 26 mm
Effective length of the balloon	30 mm
Effective length of the catheter (from distal end of pusher to distal tip of catheter, with pusher in the distal position)	64 cm
Diameter of the largest guidewire that can be used	0.035" (0.89 mm)
Position of the radio-detectable markers	Two radiopaque bands on the catheter shaft define the position on the balloon where the 9000TFX bioprosthesis should be crimped. The inside edges define the proximal and distal positions of the crimped bioprosthesis.
Balloon inflation pressure required to achieve the nominal balloon diameter(s)	**For 23 mm 9100BCL23:** 4.82 ATM (488 kPa) **For 26 mm 9100BCL26:** 3.27 ATM (331 kPa)

8.2 Packaging

The bioprosthesis is supplied sterile and nonpyrogenic packaged in buffered glutaraldehyde, in a plastic jar to which a seal has been applied. Sterility is not compromised if the package is unopened or undamaged. The outside of the container is NOT sterile and should not be placed in the sterile field. Each jar is shipped in a styrofoam enclosure containing a temperature indicator to determine if the bioprosthesis has been exposed to extreme temperatures during transit. Upon receipt, immediately remove the styrofoam and inspect the indicator.

Warning: The bioprosthesis must be carefully inspected before implantation for evidence of extreme temperature exposure or other damage.

If the indicator shows that the bioprosthesis has been exposed to extreme temperatures during transit, do not use the bioprosthesis. Contact the local supplier or representative of Edwards Lifesciences to make arrangements for return, authorization, and replacement. Any bioprosthesis returned to the company should be shipped in the same styrofoam enclosure in which it was received.

Due to the biological nature of this bioprosthesis, and its sensitivity to physical handling and environmental conditions, it cannot be returned, except as noted above.

The Ascendra delivery system is supplied sterile and nonpyrogenic within sealed plastic pouches. Sterility is not compromised if the package is unopened or undamaged. The outside of the pouch is NOT sterile and should not be placed in the sterile field.

The crimper (models 9100CR23 and 9100CR26) with built-in balloon and crimp gauges is supplied sterile for single use only. The crimper is single pouched, and sterilized by ethylene oxide.

8.3 Storage

The model 9000TFX bioprosthesis must be stored between 10 °C and 25 °C (50 °F and 77 °F). Stock inspections and rotation at regular intervals are recommended to ensure that the devices are used before the expiration date stamped on the package label.

Warning: Do not freeze. Always store bioprostheses in a dry, contamination-free area. Any bioprosthesis that has been frozen, or is suspected of having been frozen, should not be used for human implantation.

The delivery system components (9100MISIS, 9100IS, 9100BCL23, 9100BCL26, 9100CR23 and 9100CR26) should be stored in a cool, dry place.

9. MR Safety Information

MR Conditional

Non-clinical testing has demonstrated that the Edwards SAPIEN transcatheter heart valve is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 3 Tesla or less.
- Spatial gradient field of 720 Gauss/cm or less.
- Maximum whole-body-averaged specific absorption rate (SAR) of 3.0 W/kg for 15 minutes of scanning.

In non-clinical testing, the device produced a maximum temperature increase of 0.5 °C at a maximum whole body averaged specific absorption rate (SAR) of 3.0 W/kg for 15 minutes of MRI.

MR image quality may be compromised if the area of interest is in the exact same area or relatively close to the position of the device.

10. Patient Information

A patient registration form is included in each device package. After implantation, please complete all requested information. The serial number may be found on the package and on the identification tag attached to the bioprosthesis. 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. This information becomes an important part of the records maintained on each model 9000TFX. Your cooperation in providing accurate and legible information is appreciated. The accurate completion and return of this form is essential for the purpose of valve tracking and patient notification. An Implanted Device Card is provided to the patient. The card contains the name and telephone number of the patient's physician, as well as information that medical personnel would require in the event of an emergency.

11. Recovered Clinical Bioprostheses

Edwards Lifesciences is interested in obtaining recovered clinical specimens of the Edwards SAPIEN transcatheter heart valve for analysis. A written report summarizing our findings will be provided upon completion of our evaluation. The explanted model 9000TFX bioprostheses 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.

Disposal of Used Clinical Delivery Systems and Crimper

The used delivery system and crimper 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 device.

12. Clinical Experience

References reporting clinical experience with percutaneous delivery of current and prior versions of the bioprosthesis are provided in section 14.

This product is manufactured and sold under one or more of the following US patents: 5,411,552; 5,840,081; 5,931,969; 6,168,614; 6,214,054; 6,547,827; 6,561,970; 6,582,462; 6,893,460; and 6,908,481 and corresponding foreign patents. Additional patents are pending.

13. Devices and Accessories

13.1 Model 9000TFX Bioprosthesis

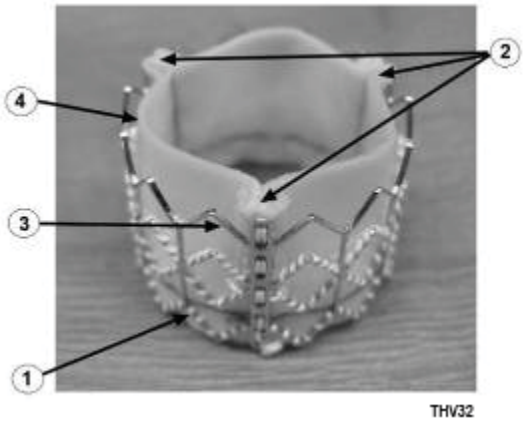


Figure 1

1. Polyethylene terephthalate (PET) fabric cuff
2. Commissures (in the valve) and Supporting bars (in the frame)
3. Frame
4. A unidirectional valve

13.2 Model 9100MISIS and 9100IS Introducer Sheath and Dilator

1. Housing
2. Side Port with Stopcock
3. 33F (11.0 mm) or 26F (8.6 mm) Sheath
4. Radiopaque Marker
5. Non-Radiopaque Depth Markers
6. 33F (11.0 mm) or 26F (8.6 mm) Dilator

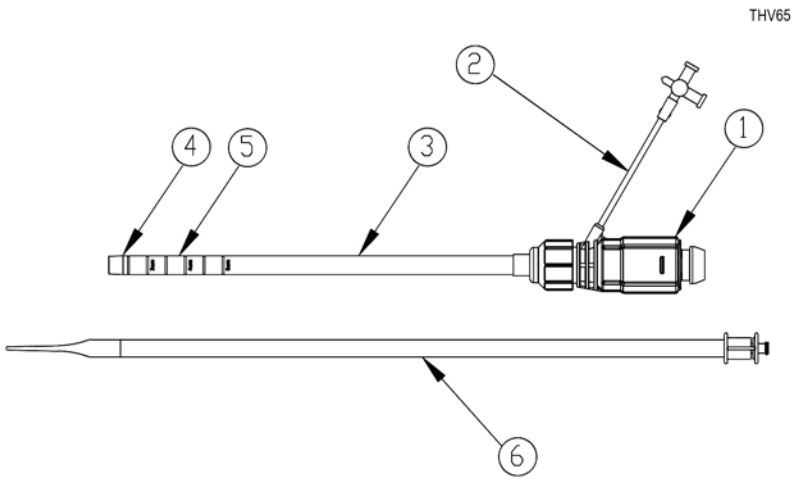


Figure 2

13.3 Model 9100BCL23 and 9100BCL26 Ascendra Balloon Catheter

1. Balloon with Radiopaque Markers
2. Pusher Tip
3. Washers, Seal, and Loader Cap
4. Pusher Y-Fitting
5. Proximal Pusher Nut
6. Deflecting Mechanism
7. Balloon Inflation “Y”
8. Balloon Extension Tubing with Stopcock
9. 26F (8.6 mm) Loader

THV68

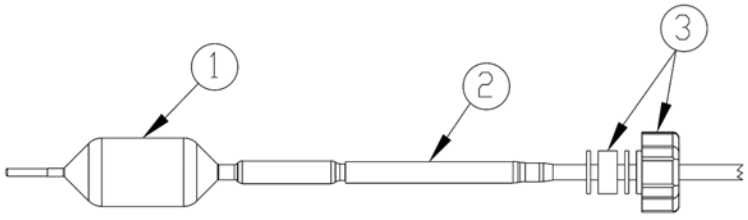


Figure 3a

THV67

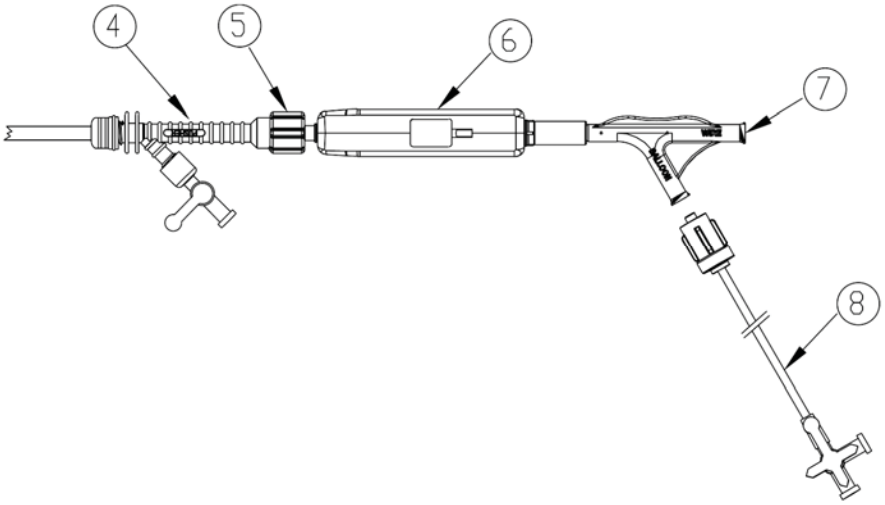


Figure 3b

THV66

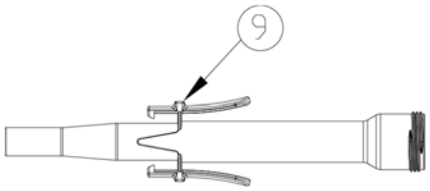


Figure 3c

13.4 Model 9100CR23 and 9100CR26 Crimper

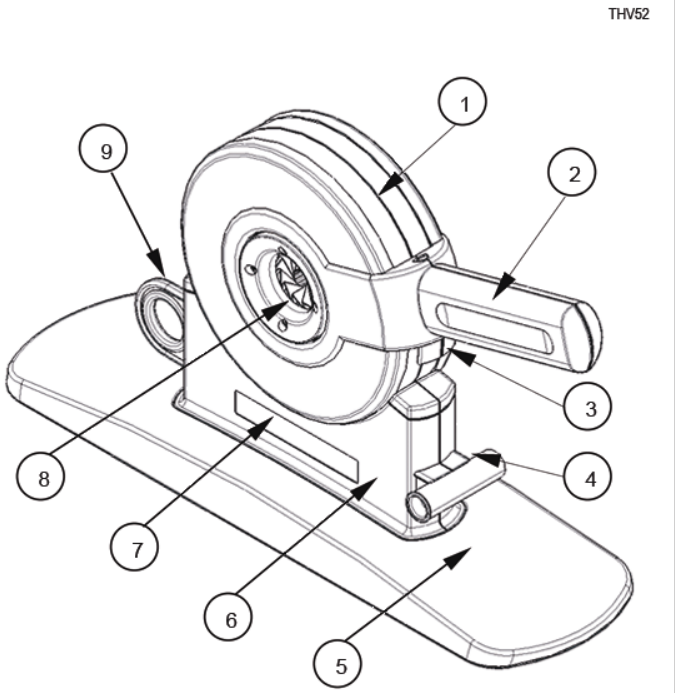


Figure 4. Crimper

1 - Housing
2 - Handle
3 - Stopper
4 - Crimp Gauge
5 - Base
6 - Stand
7 - ID Label
8 - Aperture
9 - Balloon Gauge

14. References

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Made in USA

Edwards Lifesciences

Ascendra Balloon Aortic Valvuloplasty Catheter

Model 9100BAVC

Instructions for Use - Transapical Approach

CAUTION: Investigational Device. Limited by Federal (USA) Law to investigational use.

Exclusively for Clinical Investigations

Caution: To be used by qualified investigators only

Instrument de recherche – Réservé uniquement à l'usage de chercheurs compétents.

For single use only

The maximum guidewire diameter which may be used with the 9100BAVC is 0.035" (0.89 mm).

Minimum sheath compatibility is 14F (4.62 mm).

Minimum guidewire length is 100 cm.

STERILE EO

1. Device Description

The Ascendra balloon aortic valvuloplasty catheter (Figure 1) is a coaxial designed catheter with a distal inflatable balloon. Two radiopaque marker bands indicate the dilating section of the balloon and aid in balloon placement. At the proximal end of the catheter, there is a standard "Y" connector for balloon inflation and a guidewire lumen. An additional balloon extension tubing is optional for user preference. The balloon is inflated by injecting a diluted contrast medium solution through the luer port (marked "BALLOON") on the "Y" connector.

Contents of unopened, undamaged package are:

- Sterile
- Nonpyrogenic

Table 1 Compliance Table
Pressure and/or Volume vs. Diameter

Volume (ml)	Volume w/ Balloon Extension (ml)	Applied Pressure (ATM)	Diameter (mm)
10.4	11.4	1.0	17.4
10.8	11.8	1.5	17.6
11.1	12.1	2.0	17.8
11.3	12.3	2.5	18.2
11.7	12.7	3.0	18.5
12.1	13.1	3.5	18.8
12.5	13.5	4.0	19.0
12.7	13.7	4.5	19.2
13.1	14.1	5.0	19.4
13.4	14.4	5.5	19.5
13.8	14.8	6.0	19.7
14.1	15.1	6.5	19.9
14.5	**15.5**	**7.0**	**20.0**
14.9	15.9	7.5	20.2
15.1	**16.1**	**8.0**	**20.4**

Note: Nominal sizing must be based on volume only.

The upper figures in bold face represent the balloon diameter at Nominal Inflation Volume, Pressure and Diameter.

The lower figures in bold face represent the balloon diameter at Rated Burst Volume, Pressure and Diameter.

2. Indications

The 9100BAVC is indicated for valvuloplasty of a stenotic aortic valve prior to implantation of an Edwards SAPIEN transcatheter heart valve.

3. Contraindications

The device is contraindicated for patients with:

- Non-valvular aortic stenosis
- Congenital aortic stenosis, unicuspid or bicuspid aortic valve
- Non-calcific acquired aortic stenosis
- Presence of mitral bioprosthesis
- Evidence of intracardiac mass, thrombus, or vegetation
- Untreated clinically significant coronary disease requiring revascularization
- Myocardial infarction (MI) within 1 month
- Severe deformation of the chest
- Severe coagulation problems
- Active bacterial endocarditis or other active infections
- Severe ventricular dysfunction with ejection fraction < 20%

- Patients unable to tolerate anticoagulation therapy
- Recent (within 6 months) cerebrovascular accident (CVA)
- Hypertrophic cardiomyopathy with or without obstruction (HOCM)

The device is not to be used if the implanting physician believes its use would be contrary to the best interest of the patient.

There are no known contraindications for the device other than standard risks associated with balloon aortic valvuloplasty.

4. Warnings

- This device is intended for single use only. DO NOT re-sterilize and/or reuse it.
- Use only appropriate balloon inflation medium. Do not use air or gaseous medium to inflate the balloon.
- Use the catheter prior to the “Use By” date specified on the package.
- Catheter balloon inflation diameter must be carefully considered in selecting a particular size for any patient. The inflated balloon diameter should not be significantly greater than the annulus diameter being pre-dilated.
- Catheter is not intended for redilation of deployed transcatheter heart valves.
- While the catheter is exposed within the body, advancement and retrieval should not be done without the aid of fluoroscopic equipment. Do not advance or retract the catheter unless the balloon is fully deflated under vacuum.
- Do not use if package is opened or damaged.

5. Precautions

- Prior to use, the catheter should be examined to verify functionality and ensure that its size and shape are suitable for the specific procedure for which it is to be used.
- Dilation procedure should be conducted under fluoroscopic guidance with appropriate fluoroscopic equipment.
- Careful attention must be paid to the maintenance of tight catheter connections and aspiration before proceeding to avoid air introduction into the system.
- Under no circumstances should any portion of the catheter system be advanced against resistance. The cause of the resistance should be identified with fluoroscopy and action taken to remedy the problem.
- If resistance is felt upon removal, then the balloon, guidewire and the sheath should be removed together as a unit, particularly if balloon rupture or leakage is known or suspected. This may be accomplished by firmly grasping the balloon catheter and sheath as a unit and withdrawing both together, using a gentle twisting motion combined with traction.
- Minimum acceptable sheath French size is printed on the package label. Do not attempt to pass the Ascendra balloon aortic valvuloplasty catheter through a smaller sheath introducer than indicated on the label.
- Before withdrawing the catheter from the sheath, the balloon must be fully deflated.

6. Potential Adverse Events

- Perforation
- Conduction System Injury
- Thromboembolic Events
- Hematoma
- Cardiovascular Injury and Infundibulum
- Arrhythmia Development
- Valvular Tearing or Trauma
- Inflammation
- Infection
- Chordae Damage or Trauma

7. Directions for Use

7.1 Ascendra Balloon Aortic Valvuloplasty Catheter Preparation

Step	Procedure
1	Remove catheter from package.
2	Remove balloon cover and inspect the catheter for damage.
3	Flush the delivery system guidewire lumen (located at the “Y” connector) with saline.
4	Wipe outside of catheter and balloon extension using saline solution.
5	Prepare an inflation device with a mixture of contrast medium and saline (approximately 20% contrast medium).
6	If using the balloon extension tubing, flush tubing with saline.
7	Attach balloon extension tubing to “Y” connector.
8	Attach the inflation device to the inflation port of the catheter.
9	Induce a negative pressure to remove any air from the balloon and inflation lumen. Repeat until all air is expelled. Close stopcock.
10	Remove inflation device from catheter. Fill inflation device with the appropriate volume for desired balloon diameter (Table 1).
11	Attach filled inflation device to stopcock and open stopcock. Allow the inflation lumen to fill with the diluted contrast medium and maintain at neutral pressure.

7.2 Catheter Use

Step	Procedure
1	Wipe the exposed guidewire with normal saline to remove residual tissue or contrast medium.
2	Advance the Ascendra balloon aortic valvuloplasty catheter over the guidewire to the intended site. An introducer should be utilized to facilitate catheter insertion.
3	Under fluoroscopic guidance, continue to advance the balloon aortic valvuloplasty catheter to the intended site. Position balloon markers at the intended site.
4	Once desired position is achieved, begin rapid pacing.
5	Perform dilation using inflation device. Patient monitoring is required during dilatation. Balloon can be either partially or fully inflated to achieve dilatation. **DO NOT EXCEED THE RATED BURST VOLUME (TABLE 1).**
6	Fully inflate and rapidly deflate balloon by drawing a vacuum with an inflation device.
7	When the balloon is fully deflated, the pacemaker may be turned off.
8	Gently withdraw the deflated catheter into the sheath, then remove the sheath and balloon catheter. **Note: The greater the vacuum applied and held during withdrawal, the lower the deflated balloon profile.** **Note: If resistance is felt upon removal, then the balloon, guidewire and the sheath should be removed together as a unit under fluoroscopic guidance, particularly if balloon rupture or leakage is known or suspected. This may be accomplished by firmly grasping the balloon catheter and sheath as a unit and withdrawing both together, using a gentle twisting motion combined with traction.**
9	Discard the Ascendra balloon aortic valvuloplasty catheter after use.

8. Storage

The model 9100BAVC must be stored in a cool and dry place.

9. Device Disposal

The device 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 device.

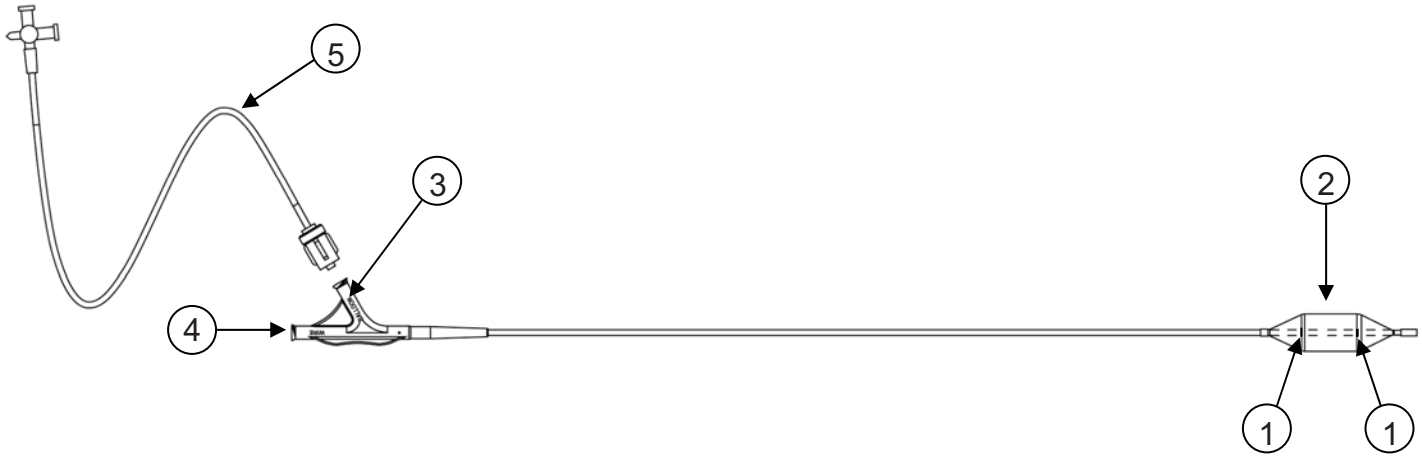

Figure 1

1. **Radiopaque Marker Bands**
2. **Balloon**
3. **“Y” connector**
4. **Guidewire Lumen**
5. **Balloon Extension Tubing**

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Made in USA

Appendix H: NIH Stroke Scale Assessment

NIH STROKE SCALE

Subject ID#

_____ _____ _____

Date of Exam: _____/_____/_____ Time: _____ : _____

Interval: [ ] Baseline [ ] During procedure [ ] Discharge / 7 days [ ] 30-days
[ ] 6 months [ ] 12 months [ ] Other _____ (specify)

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

NOTE:

If there is an increase from the baseline stroke scale score, or evidence of a suspected stroke or TIA, capture the increase as an adverse neurological event and document the reason for the score increase. Administer the NIH Stroke Scale 30 days and 60 days after any neurological adverse event.

Instructions	Scale Definitions	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 score is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = Alert; keenly responsive. 1 = Not alert; but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and flexic.	____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct – there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.	____
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.	____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = Normal. 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.	____

NIH STROKE SCALE

Subject ID#

_____ _____ _____

Date of Exam: _____/_____/_____ Time: _____ : _____

Interval: [ ] Baseline [ ] During procedure [ ] Discharge / 7 days [ ] 30-days
[ ] 6 months [ ] 12 months [ ] Other _____ (specify)

Instructions	Scale Definitions	Score
3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = No visual loss. 1 = Partial hemianopia. 2 = Complete hemianopia. 3 = Bilateral hemianopia (blind including cortical blindness).	____
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = Normal symmetrical movements. 1 = Minor paralysis (flattened nasolabial fold, asymmetry on smiling). 2 = Partial paralysis (total or near-total paralysis of lower face). 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face).	____
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = No drift; limb holds 90 (or 45) degrees for full 10 seconds. 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity; limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity; limb falls. 4 = No movement. UN = Amputation or joint fusion, explain: _____ **5a. Left Arm** **5b. Right Arm**	 ____ ____
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the store as untestable (UN), and clearly write the explanation for this choice.	0 = No drift; leg holds 30-degree position for full 5 seconds. 1 = Drift; leg falls by the end of the 5-second period but does not hit bed. 2 = Some effort against gravity; leg falls to bed by 5 seconds, but has some effort against gravity. 3 = No effort against gravity; leg falls to bed immediately. 4 = No movement. UN = Amputation or joint fusion, explain: **6a. Left Leg** **6b. Right Leg**	 _____ _____

NIH STROKE SCALE

Subject ID#

_____ _____ _____

Date of Exam: _____/_____/_____ Time: _____ : _____

Interval: [ ] Baseline [ ] During procedure [ ] Discharge / 7 days [ ] 30-days
[ ] 6 months [ ] 12 months [ ] Other _____ (specify)

Instructions	Scale Definitions	Score
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = Absent. 1 = Present in one limb. 2 = Present in two limbs. UN = Amputation or joint fusion, explain:	_____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a come (item 1a=3) are automatically given a 2 on this item.	0 = Normal; no sensory loss. 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.	_____
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = No aphasia; normal. 1 = Mild-to-moderate aphasia; some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = Severe aphasia; all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = Mute, global aphasia; no usable speech or auditory comprehension.	_____
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = Normal. 1 = Mild-to-moderate dysarthria; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe dysarthria; patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = Intubated or other physical barrier, explain: _____	_____

NIH STROKE SCALE

Subject ID#

_____ _____ _____

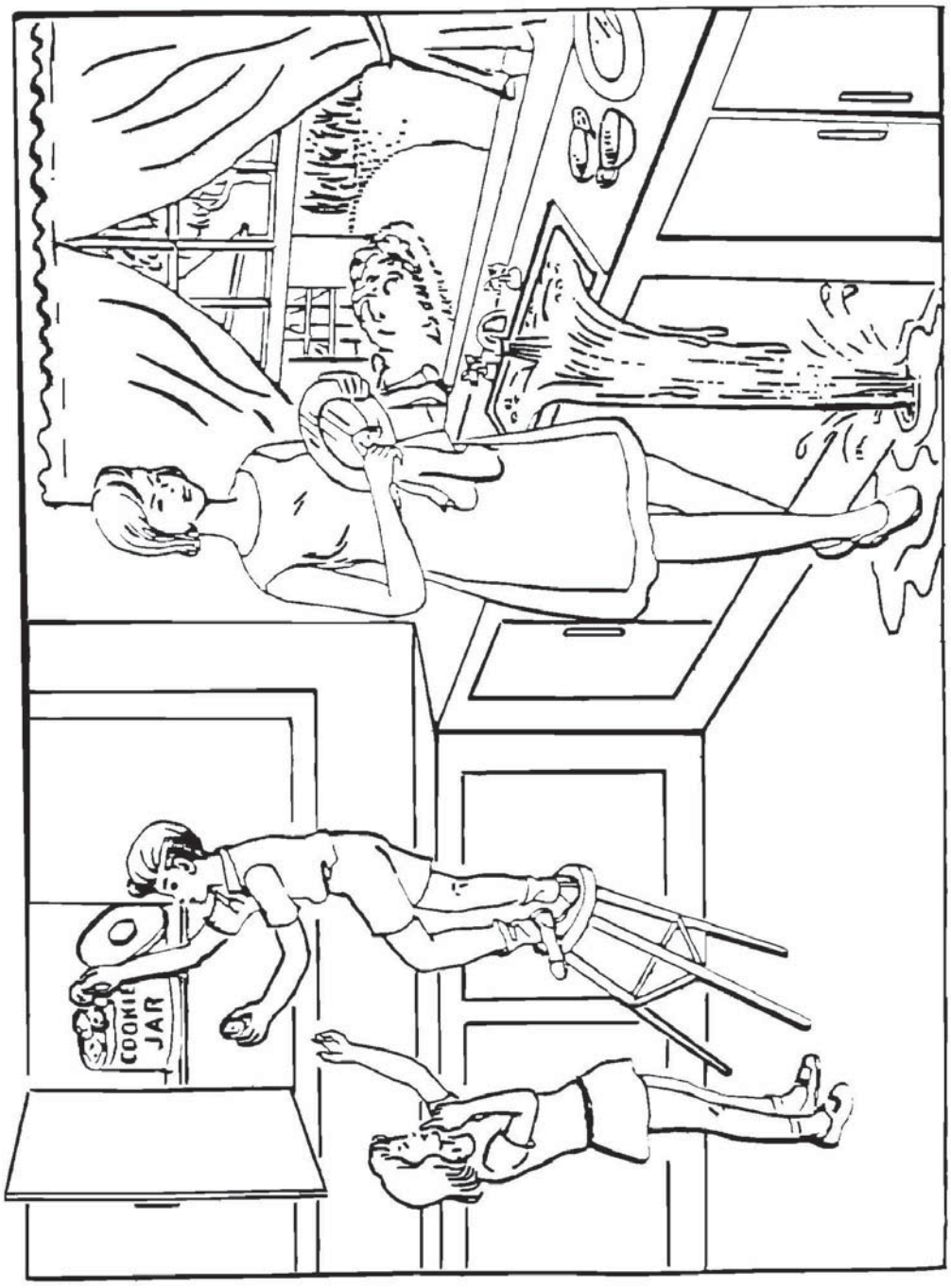
Date of Exam: _____/_____/_____ Time: _____ : _____

Interval: [ ] Baseline [ ] During procedure [ ] Discharge / 7 days [ ] 30-days
[ ] 6 months [ ] 12 months [ ] Other _____ (specify)

Instructions	Scale Definitions	Score
11. Extinction and inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space.	____

_____

Print Name of Person Administering Scale


COOKIE
JAR

You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.

MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

Appendix I: Mini Mental State Exam

MMSE™

Date of Examination ___/___/___ Examiner _____

Name _____ Age _____ Years of School Completed _____

Instructions: Words in boldface type should be read aloud clearly and slowly to the examinee. Item substitutions appear in parentheses. Administration should be conducted privately and in the examinee's primary language. Circle 0 if the response is incorrect, or 1 if the response is correct. Begin by asking the following two questions:

Do you have any trouble with your memory? **May I ask you some questions about your memory?**

ORIENTATION TO TIME		RESPONSE	SCORE (circle one)	
What is the...	**year?**		0	1
	season?		0	1
	month of the year?		0	1
	day of the week?		0	1
	date?		0	1

ORIENTATION TO PLACE*			
Where are we now? What is the...			
state (province)**?**		0	1
county (or city/town)**?**		0	1
city/town (or part of city/neighborhood)**?**		0	1
building (name or type)**?**		0	1
floor of the building (room number or address)**?**		0	1

*Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted.

REGISTRATION*

Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are... APPLE [*pause*], **PENNY** [*pause*], **TABLE** [*pause*]. **Now repeat those words back to me.**
[*Repeat up to 5 times, but score only the first trial.*]

APPLE		0	1
PENNY		0	1
TABLE		0	1

Now keep those words in mind. I am going to ask you to say them again in a few minutes.

*Alternative word sets (e.g., PONY, QUARTER, ORANGE) may be substituted and noted when retesting an examinee.

ATTENTION AND CALCULATION [Serial 7s]*

Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.

What is 100 take away 7?	[93]		0	1
If needed, say: **Keep going.**	[86]		0	1
If needed, say: **Keep going.**	[79]		0	1
If needed, say: **Keep going.**	[72]		0	1
If needed, say: **Keep going.**	[65]		0	1

*Alternative item (WORLD backward) should only be administered if the examinee refuses to perform the Serial 7s task. →

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Substitute and score this item only if the examinee refuses to perform the Serial 7s task.

Spell WORLD forward, then backward.
Correct forward spelling if misspelled,
but score only the backward spelling.

(D = 1)	(L = 1)	(R = 1)	(O = 1)	(W = 1)	(0 to 5)
_____	_____	_____	_____	_____	_____

RECALL	RESPONSE	SCORE (circle one)	
What were those three words I asked you to remember? [*Do not offer any hints.*]			
APPLE	_____	0	1
PENNY	_____	0	1
TABLE	_____	0	1

NAMING*

What is this? [*Point to a pencil or pen.*]	_____	0	1
What is this? [*Point to a watch.*]	_____	0	1

*Alternative common objects (e.g., eyeglasses, chair, keys) may be substituted and noted.

REPETITION

Now I am going to ask you to repeat what I say. Ready? "NO IFS, ANDS, OR BUTS." Now you say that.
[*Repeat up to 5 times, but score only the first trial.*]

NO IFS, ANDS, OR BUTS.	_____	0	1

Detach the next page along the lengthwise perforation, and then tear it in half along the horizontal perforation. Use the upper half of the page (blank) for the Comprehension, Writing, and Drawing items that follow. Use the lower half of the page as a stimulus form for the Reading ("CLOSE YOUR EYES") and Drawing (intersecting pentagons) items.

COMPREHENSION

Listen carefully because I am going to ask you to do something.
Take this paper in your right hand [*pause*]**, fold it in half** [*pause*]**, and put it on the floor (*or* table).**

TAKE IN RIGHT HAND	_____	0	1
FOLD IN HALF	_____	0	1
PUT ON FLOOR (*or* TABLE)	_____	0	1

READING

Please read this and do what it says. [*Show examinee the words on the stimulus form.*]

CLOSE YOUR EYES	_____	0	1

WRITING

Please write a sentence. [*If examinee does not respond, say:* **Write about the weather.**] 0 1

Place the blank piece of paper (unfolded) in front of the examinee and provide a pen or pencil. Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling.

DRAWING

Please copy this design. [*Display the intersecting pentagons on the stimulus form.*] 0 1

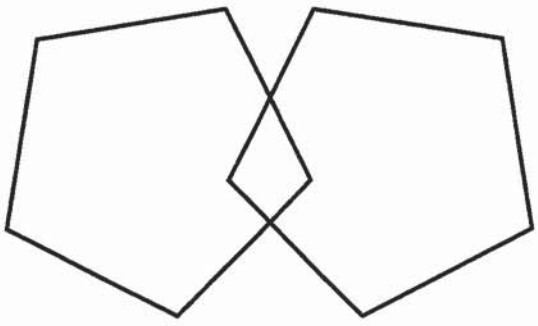
Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure.

Total Score = _____	
(*Sum all item scores.*)	(30 points max.)

Assessment of level of consciousness.

Alert/ Responsive | **Drowsy** | **Stuporous** | **Comatose/ Unresponsive**

CLOSE YOUR EYES



Appendix J: Six Minute Walk Test Guidelines

American Thoracic Society

ATS Statement: Guidelines for the Six-Minute Walk Test

THIS OFFICIAL STATEMENT OF THE AMERICAN THORACIC SOCIETY WAS APPROVED BY THE ATS BOARD OF DIRECTORS
MARCH 2002

CONTENTS

PURPOSE AND SCOPE

This statement provides practical guidelines for the 6-minute walk test (6MWT). Specifically, it reviews indications, details factors that influence results, presents a brief step-by-step protocol, outlines safety measures, describes proper patient preparation and procedures, and offers guidelines for clinical interpretation of results. These recommendations are not intended to limit the use of alternative protocols for research studies. We do not discuss the general topic of clinical exercise testing.

As with other American Thoracic Society statements on pulmonary function testing, these guidelines come out of a consensus conference. Drafts were prepared by two members (P.L.E. and R.J.Z.) and were based on a comprehensive Medline literature search from 1970 through 2001, augmented by suggestions from other committee members. Each draft responded to comments from the working committee. The guidelines follow previously published methods as closely as possible and provide a rationale for each specific recommendation. The final recommendations represent a consensus of the committee. The committee recommends that these guidelines be reviewed in five years and in the meantime encourages further research in areas of controversy.

BACKGROUND

There are several modalities available for the objective evaluation of functional exercise capacity. Some provide a very complete assessment of all systems involved in exercise performance (high tech), whereas others provide basic information but are low tech and are simpler to perform. The modality used should be chosen based on the clinical question to be addressed and on available resources. The most popular clinical exercise tests in order of increasing complexity are stair climbing, a 6MWT, a shuttle-walk test, detection of exercise-induced asthma, a cardiac stress test (e.g., Bruce protocol), and a cardiopulmonary exercise test (1, 2). Other professional organizations have published standards for cardiac stress testing (3, 4).

Assessment of functional capacity has traditionally been done by merely asking patients the following: "How many flights of stairs can you climb or how many blocks can you walk?" However, patients vary in their recollection and may report overestimations or underestimations of their true functional capacity. Objective measurements are usually better than self-reports. In the early 1960s, Balke developed a simple test to evaluate the functional capacity by measuring the distance walked during a defined period of time (5). A 12-minute field performance test was then developed to evaluate the level of physical fitness of healthy individuals (6). The walking test was also adapted to assess disability in patients with chronic bronchitis (7). In an attempt to accommodate patients with respiratory disease for whom walking 12 minutes was too exhausting, a 6-minute walk was found to perform as well as the 12-minute walk (8). A recent review of functional walking tests concluded that "the 6MWT is easy to administer, better tolerated, and more reflective of activities of daily living than the other walk tests" (9).

The 6MWT is a practical simple test that requires a 100-ft hallway but no exercise equipment or advanced training for technicians. Walking is an activity performed daily by all but the most severely impaired patients. This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes (the 6MWD). It evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism. It does not provide specific information on the function of each of the different organs and systems involved in exercise or the mechanism of exercise limitation, as is possible with maximal cardiopulmonary exercise testing. The self-paced 6MWT assesses the submaximal level of functional capacity. Most patients do not achieve maximal exercise capacity during the 6MWT; instead, they choose their own intensity of exercise and are allowed to stop and rest during the test. However, because most activities of daily living are performed at submaximal levels of exertion, the 6MWD may better reflect the functional exercise level for daily physical activities.

INDICATIONS AND LIMITATIONS

The strongest indication for the 6MWT is for measuring the response to medical interventions in patients with moderate to severe heart or lung disease. The 6MWT has also been used as a one-time measure of functional status of patients, as well as a predictor of morbidity and mortality (*see* Table 1 for a list of these indications). The fact that investigators have used the 6MWT in these settings does not prove that the test is clinically useful (or the best test) for determining functional capacity or changes in functional capacity due to an intervention in patients with these diseases. Further studies are necessary to determine the utility of the 6MWT in various clinical situations.

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Formal cardiopulmonary exercise testing provides a global assessment of the exercise response, an objective determination of functional capacity and impairment, determination of the appropriate intensity needed to perform prolonged exercise, quantification of factors limiting exercise, and a definition of the underlying pathophysiologic mechanisms such as the contribution of different organ systems involved in exercise. The 6MWT does not determine peak oxygen uptake, diagnose the cause of dyspnea on exertion, or evaluate the causes or mechanisms of exercise limitation (1, 2). The information provided by a 6MWT should be considered complementary to cardiopulmonary exercise testing, not a replacement for it. Despite the difference between these two functional tests, some good correlations between them have been reported. For example, a significant correlation ($r = 0.73$) between 6MWD and peak oxygen uptake has been reported for patients with end-stage lung diseases (36, 37).

In some clinical situations, the 6MWT provides information that may be a better index of the patient's ability to perform daily activities than is peak oxygen uptake; for example, 6MWD correlates better with formal measures of quality of life (38). Changes in 6MWD after therapeutic interventions correlate with subjective improvement in dyspnea (39, 40). The reproducibility of the 6MWD (with a coefficient of variation of approximately 8%) appears to be better than the reproducibility of 1-second forced expiratory volume in patients with chronic obstructive pulmonary disease (COPD) (8, 41–43). Questionnaire indices of functional status have a larger short-term variability (22–33%) than does the 6MWD (37).

The shuttle-walking test is similar to the 6MWT, but it uses an audio signal from a tape cassette to direct the walking pace of the patient back and forth on a 10-m course (44–47). The walking speed is increased every minute, and the test ends when the patient cannot reach the turnaround point within the required time. The exercise performed is similar to a symptom-limited, maximal, incremental treadmill test. An advantage of the shuttle walking test is that it has a better correlation with peak oxygen uptake than the 6MWD. Disadvantages include less validation, less widespread use, and more potential for cardiovascular problems.

CONTRAINDICATIONS

Absolute contraindications for the 6MWT include the following: unstable angina during the previous month and myocardial infarction during the previous month. Relative contraindications include a resting heart rate of more than 120, a systolic blood pressure of more than 180 mm Hg, and a diastolic blood pressure of more than 100 mm Hg.

Patients with any of these findings should be referred to the physician ordering or supervising the test for individual clinical assessment and a decision about the conduct of the test. The results from a resting electrocardiogram done during the previous 6 months should also be reviewed before testing. Stable exertional angina is not an absolute contraindication for a 6MWT, but patients with these symptoms should perform the test after using their antiangina medication, and rescue nitrate medication should be readily available.

Rationale

Patients with the previously mentioned risk factors may be at increased risk for arrhythmias or cardiovascular collapse during testing. However, each patient determines the intensity of their exercise, and the test (without electrocardiogram monitoring) has been performed in thousands of older persons (31, 48–50) and thousands of patients with heart failure or cardiomyopathy (32, 51, 52) without serious adverse events. The contraindications listed previously here were used by study investigators based on their impressions of the general safety of the 6MWT and their desire to be prudent, but it is unknown whether adverse events would occur if such patients performed a 6MWT; they are, therefore, listed as relative contraindications.

TABLE 1. INDICATIONS FOR THE SIX-MINUTE WALK TEST

Pretreatment and posttreatment comparisons
Lung transplantation (9, 10)
Lung resection (11)
Lung volume reduction surgery (12, 13)
Pulmonary rehabilitation (14, 15)
COPD (16–18)
Pulmonary hypertension
Heart failure (19, 20)
Functional status (single measurement)
COPD (21, 22)
Cystic fibrosis (23, 24)
Heart failure (25–27)
Peripheral vascular disease (28, 29)
Fibromyalgia (30)
Older patients (31)
Predictor of morbidity and mortality
Heart failure (32, 33)
COPD (34, 35)
Primary pulmonary hypertension (10, 36)

Definition of abbreviation: COPD = chronic obstructive pulmonary disease.

SAFETY ISSUES

1. Testing should be performed in a location where a rapid, appropriate response to an emergency is possible. The appropriate location of a crash cart should be determined by the physician supervising the facility.
2. Supplies that must be available include oxygen, sublingual nitroglycerine, aspirin, and albuterol (metered dose inhaler or nebulizer). A telephone or other means should be in place to enable a call for help.
3. The technician should be certified in cardiopulmonary resuscitation with a minimum of Basic Life Support by an American Health Association–approved cardiopulmonary resuscitation course. Advanced cardiac life support certification is desirable. Training, experience, and certification in related health care fields (registered nurse, registered respiratory therapist, certified pulmonary function technician, etc.) are also desirable. A certified individual should be readily available to respond if needed.
4. Physicians are not required to be present during all tests. The physician ordering the test or a supervising laboratory physician may decide whether physician attendance at a specific test is required.
5. If a patient is on chronic oxygen therapy, oxygen should be given at their standard rate or as directed by a physician or a protocol.

Reasons for immediately stopping a 6MWT include the following: (*1*) chest pain, (*2*) intolerable dyspnea, (*3*) leg cramps, (*4*) staggering, (*5*) diaphoresis, and (*6*) pale or ashen appearance.

Technicians must be trained to recognize these problems and the appropriate responses. If a test is stopped for any of these reasons, the patient should sit or lie supine as appropriate depending on the severity or the event and the technician's assessment of the severity of the event and the risk of syncope. The following should be obtained based on the judgment of the technician: blood pressure, pulse rate, oxygen saturation, and a physician evaluation. Oxygen should be administered as appropriate.

TECHNICAL ASPECTS OF THE 6MWT

Location

The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. If the weather is comfortable, the test may be performed outdoors. The walking course must be 30 m in length. A 100-ft hallway is, therefore, required. The length of the corridor should be marked every 3 m. The turnaround points should be marked with a cone (such as an orange traffic cone). A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor using brightly colored tape.

Rationale. A shorter corridor requires patients to take more time to reverse directions more often, reducing the 6MWD. Most studies have used a 30-m corridor, but some have used 20- or 50-m corridors (52–55). A recent multicenter study found no significant effect of the length of straight courses ranging from 50 to 164 ft, but patients walked farther on continuous (oval) tracks (mean 92 ft farther) (54).

The use of a treadmill to determine the 6MWD might save space and allow constant monitoring during the exercise, but the use of a treadmill for 6-minute walk testing is not recommended. Patients are unable to pace themselves on a treadmill. In one study of patients with severe lung disease, the mean distance walked on the treadmill during 6 minutes (with the speed adjusted by the patients) was shorter by a mean of 14% when compared with the standard 6MWD using a 100-ft hallway (57). The range of differences was wide, with patients walking between 400–1,300 ft on the treadmill who walked 1,200 ft in the hallway. Treadmill test results, therefore, are not interchangeable with corridor tests.

REQUIRED EQUIPMENT

1. Countdown timer (or stopwatch)
2. Mechanical lap counter
3. Two small cones to mark the turnaround points
4. A chair that can be easily moved along the walking course
5. Worksheets on a clipboard
6. A source of oxygen
7. Sphygmomanometer
8. Telephone
9. Automated electronic defibrillator

PATIENT PREPARATION

1. Comfortable clothing should be worn.
2. Appropriate shoes for walking should be worn.
3. Patients should use their usual walking aids during the test (cane, walker, etc.).
4. The patient's usual medical regimen should be continued.
5. A light meal is acceptable before early morning or early afternoon tests.
6. Patients should not have exercised vigorously within 2 hours of beginning the test.

MEASUREMENTS

1. Repeat testing should be performed about the same time of day to minimize intraday variability.
2. A "warm-up" period before the test should not be performed.
3. The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Compete the first portion of the worksheet (*see* the APPENDIX).
4. Pulse oximetry is optional. If it is performed, measure and record baseline heart rate and oxygen saturation (SpO_2) and follow manufacturer's instructions to maximize the signal and to minimize motion artifact (56, 57). Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable.

   > The rationale for measuring oxygen saturation is that although the distance is the primary outcome measure, improvement during serial evaluations may be manifest either by an increased distance or by reduced symptoms with the same distance walked (39). The SpO_2 should not be used for constant monitoring during the exercise. The technician must not walk with the patient to observe the SpO_2. If worn during the walk, the pulse oximeter must be lightweight (less than 2 pounds), battery powered, and held in place (perhaps by a "fanny pack") so that the patient does not have to hold or stabilize it and so that stride is not affected. Many pulse oximeters have considerable motion artifact that prevents accurate readings during the walk. (57)

5. Have the patient stand and rate their baseline dyspnea and overall fatigue using the Borg scale (*see* Table 2 for the Borg scale and instructions [58]).
6. Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment (lap counter, timer, clipboard, Borg Scale, worksheet) and move to the starting point.
7. Instruct the patient as follows:

   > "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.
   >
   > You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."
   >
   > Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.
   >
   > "Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.
   >
   > Start now, or whenever you are ready."

TABLE 2. THE 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)

This Borg scale should be printed on heavy paper (11 inches high and perhaps laminated) in 20-point type size. At the beginning of the 6-minute exercise, show the scale to the patient and ask the patient this: "Please grade your level of shortness of breath using this scale." Then ask this: "Please grade your level of fatigue using this scale."

At the end of the exercise, remind the patient of the breathing number that they chose before the exercise and ask the patient to grade their breathing level again. Then ask the patient to grade their level of fatigue, after reminding them of their grade before the exercise.

8. Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.
9. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

   After the first minute, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go."

   When the timer shows 4 minutes remaining, tell the patient the following: "Keep up the good work. You have 4 minutes to go."

   When the timer shows 3 minutes remaining, tell the patient the following: "You are doing well. You are halfway done."

   When the timer shows 2 minutes remaining, tell the patient the following: "Keep up the good work. You have only 2 minutes left."

   When the timer shows only 1 minute remaining, tell the patient: "You are doing well. You have only 1 minute to go."

   Do not use other words of encouragement (or body language to speed up).

   If the patient stops walking during the test and needs a rest, say this: "You can lean against the wall if you would like; then continue walking whenever you feel able." Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

   When the timer is 15 seconds from completion, say this: "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."

   When the timer rings (or buzzes), say this: "Stop!" Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.
10. Post-test: Record the postwalk Borg dyspnea and fatigue levels and ask this: "What, if anything, kept you from walking farther?"
11. If using a pulse oximeter, measure SpO_2 and pulse rate from the oximeter and then remove the sensor.
12. Record the number of laps from the counter (or tick marks on the worksheet).
13. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.
14. Congratulate the patient on good effort and offer a drink of water.

QUALITY ASSURANCE

Sources of Variability

There are many sources of 6MWD variability (*see* Table 3). The sources of variability caused by the test procedure itself should be controlled as much as possible. This is done by following the standards found in this document and by using a quality-assurance program.

Practice Tests

A practice test is not needed in most clinical settings but should be considered. If a practice test is done, wait for at least 1 hour before the second test and report the highest 6MWD as the patient's 6MWD baseline.

Rationale. The 6MWD is only slightly higher for a second 6MWT performed a day later. The mean reported increase ranges from 0 to 17% (23, 27, 40, 41, 54, 59). A multicenter study of 470 highly motivated patients with severe COPD performed two 6MWTs 1 day apart, and on average, the 6MWD was only 66 ft (5.8%) higher on the second day (54).

Performance (without an intervention) usually reaches a plateau after two tests done within a week (8, 60). The training effect may be due to improved coordination, finding optimal stride length, and overcoming anxiety. The possibility of a practice or training effect from tests repeated after more than a month has not been studied or reported; however, it is likely that the effect of training wears off (does not persist) after a few weeks.

Technician Training and Experience

Technicians who perform 6MWTs should be trained using the standard protocol and then supervised for several tests before performing them alone. They should also have completed cardiopulmonary resuscitation training.

Rationale. One multicenter study of older people found that after correction for many other factors, two of the technicians had mean 6MWDs that were approximately 7% lower than the other two sites (31).

Encouragement

Only the standardized phrases for encouragement (as specified previously here) must be used during the test.

Rationale. Encouragement significantly increases the distance walked (42). Reproducibility for tests with and without encouragement is similar. Some studies have used encouragement every 30 seconds, every minute, or every 2 minutes. We have chosen every minute and standard phrases. Some studies (53) have instructed patients to walk as fast as possible. Although larger mean 6MWDs may be obtained thereby, we recommend that such phrases not be used, as they emphasize initial speed at the expense of earlier fatigue and possible excessive cardiac stress in some patients with heart disease.

TABLE 3. 6MWD SOURCES OF VARIABILITY

Factors reducing the 6MWD
Shorter height
Older age
Higher body weight
Female sex
Impaired cognition
A shorter corridor (more turns)
Pulmonary disease (COPD, asthma, cystic fibrosis, interstitial lung disease)
Cardiovascular disease (angina, MI, CHF, stroke, TIA, PVD, AAI)
Musculoskeletal disorders (arthritis, ankle, knee, or hip injuries, muscle wasting, etc.)
Factors increasing the 6MWD
Taller height (longer legs)
Male sex
High motivation
A patient who has previously performed the test
Medication for a disabling disease taken just before the test
Oxygen supplementation in patients with exercise-induced hypoxemia

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; 6MWD = 6-minute walking distance.

Supplemental Oxygen

If oxygen supplementation is needed during the walks and serial tests are planned (after an intervention other than oxygen therapy), then during all walks by that patient oxygen should be delivered in the same way with the same flow. If the flow must be increased during subsequent visits due to worsening gas exchange, this should be noted on the worksheet and considered during interpretation of the change noted in 6MWD. The type of oxygen delivery device should also be noted on the report: for instance, the patient carried liquid oxygen or pushed or pulled an oxygen tank, the delivery was pulsed or continuous, or a technician walked behind the patient with the oxygen source (not recommended). Measurements of pulse and SpO_2 should be made after waiting at least 10 minutes after any change in oxygen delivery.

Rationale. For patients with COPD or interstitial lung disease, oxygen supplementation increases the 6MWD (17, 59, 61, 63). Carrying a portable gas container (but not using it for supplemental oxygen) reduced the mean 6MWD by 14% in one study of patients with severe respiratory disability, but using the container to deliver supplemental oxygen during the exercise increased the mean 6MWD by 20–35% (59).

Medications

The type of medication, dose, and number of hours taken before the test should be noted.

Rationale. Significant improvement in the distance walked, or the dyspnea scale, after administration of bronchodilators has been demonstrated in patients with COPD (62, 63), as well as cardiovascular medications in patients with heart failure (19).

INTERPRETATION

Most 6MWTs will be done before and after intervention, and the primary question to be answered after both tests have been completed is whether the patient has experienced a clinically significant improvement. With a good quality-assurance program, with patients tested by the same technician, and after one or two practice tests, short-term reproducibility of the 6MWD is excellent (37). It is not known whether it is best for clinical purposes to express change in 6MWD as (*1*) an absolute value, (*2*) a percentage change, or (*3*) a change in the percentage of predicted value. Until further research is available, we recommend that change in 6MWD be expressed as an absolute value (e.g., the patient walked 50 m farther).

A statistically significant mean increase in 6MWD in a group of study participants is often much less than a clinically significant increase in an individual patient. In one study of 112 patients (half of them women) with stable, severe COPD, the smallest difference in 6MWD that was associated with a noticeable clinical difference in the patients' perception of exercise performance was a mean of 54 m (95% confidence interval, 37–71 m) (64). This study suggests that for individual patients with COPD, an improvement of more than 70 m in the 6MWD after an intervention is necessary to be 95% confident that the improvement was significant. In an observational study of 45 older patients with heart failure, the smallest difference in 6MWD that was associated with a noticeable difference in their global rating of worsening was a mean of 43 m (20). The 6MWD was more responsive to deterioration than to improvement in heart failure symptoms.

Reported Mean Changes in 6MWD After Interventions

Supplemental oxygen (4 L/min) during exercise in patients with COPD or interstitial lung disease increased mean 6MWD by approximately 95 m (36%) in one study (59). Patients taking an inhaled corticosteroid experienced a mean 33 m (8%) increase in 6MWD in an international COPD study (16). Patients with COPD in a study of the effects of exercise and diaphragmatic strength training experienced a mean increase in 6MWD of 50 m (20%) (65). Lung volume reduction surgery in patients with very severe COPD has been reported to increase 6MWD by a mean of 55 m (20%) (13).

Cardiac rehabilitation in patients referred with various heart diseases increased 6MWD by a mean of 170 m (15%) in a recent study (66). In 25 older patients with heart failure, an angiotensin-converting enzyme inhibitor medication (50 mg captopril per day) improved 6MWD a mean of 64 m (39%) compared with a mean increase of only 8% in those receiving a placebo (19).

Interpreting Single Measurements of Functional Status

Optimal reference equations from healthy population-based samples using standardized 6MWT methods are not yet available. In one study, the median 6MWD was approximately 580 m for 117 healthy men and 500 m for 173 healthy women (50). A mean 6MWD of 630 m was reported by another study of 51 healthy older adults (55). Differences in the population sampled, type and frequency of encouragement, corridor length, and number of practice tests may account for reported differences in mean 6MWD in healthy persons. Age, height, weight, and sex independently affect the 6MWD in healthy adults; therefore, these factors should be taken into consideration when interpreting the results of single measurements made to determine functional status. We encourage investigators to publish reference equations for healthy persons using the previously mentioned standardized procedures.

A low 6MWD is nonspecific and nondiagnostic. When the 6MWD is reduced, a thorough search for the cause of the impairment is warranted. The following tests may then be helpful: pulmonary function, cardiac function, ankle–arm index, muscle strength, nutritional status, orthopedic function, and cognitive function.

Conclusions

The 6MWT is a useful measure of functional capacity targeted at people with at least moderately severe impairment. The test has been widely used for preoperative and postoperative evaluation and for measuring the response to therapeutic interventions for pulmonary and cardiac disease. These guidelines provide a standardized approach to performing the 6MWT. The committee hopes that these guidelines will encourage further research into the 6MWT and allow direct comparisons among different studies.

This statement was developed by the ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories.

Members of the committee are:

Robert O. Crapo, M.D., *Chair**
Richard Casaburi, Ph.D, M.D.
Allan L. Coates, M.D.
Paul L. Enright, M.D.*
Neil R. MacIntyre, M.D.
Roy T. McKay, Ph.D.
Douglas Johnson, M.D.
Jack S. Wanger, M.S.
R. Jorge Zeballos, M.D.*

Ad Hoc Committee members are:

Vera Bittner, M.D.
Carl Mottram, R.R.T.

*Writing Committee Members

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APPENDIX

The following elements should be present on the 6MWT worksheet and report:

Lap counter: __

Patient name: _____ Patient ID# _____

Walk # _____ Tech ID: _____ Date: _____

Gender: M F Age: ____ Race: ____ Height: ___ft ____in, ____ meters

Weight: _____ lbs, _____kg Blood pressure: _____ / _____

Medications taken before the test (dose and time): _____

Supplemental oxygen during the test: No Yes, flow _____ L/min, type _____

	Baseline	End of Test
Time	___:___	___:___
Heart Rate	_____	_____
Dyspnea	____	____ (Borg scale)
Fatigue	____	____ (Borg scale)
SpO_2	____ %	____%

Stopped or paused before 6 minutes? No Yes, reason: _____

Other symptoms at end of exercise: angina dizziness hip, leg, or calf pain

Number of laps: ____ (×60 meters) + final partial lap: _____ meters =

Total distance walked in 6 minutes: _____ meters

Predicted distance: _____ meters Percent predicted: _____%

Tech comments:

Interpretation (including comparison with a preintervention 6MWD):

Appendix K: Data Safety Monitoring Board (DSMB) Charter

THE PARTNER TRIAL: Placement of AoRTic TraNscathetER Valves Trial
Edwards Lifesciences SAPIEN™ Transcatheter Heart Valve

The PARTNER TRIAL

DATA AND SAFETY MONITORING BOARD CHARTER

Final
February 13, 2008

TABLE OF CONTENTS

1.0 INTRODUCTION

The Data and Safety Monitoring Board (DSMB) is the primary data and safety advisory group for the PARTNER Trial entitled "THE PARTNER TRIAL: Placement of AoRTic TraNscathetER Valves Trial". The DSMB reviews study data, evaluates the treatment for excess adverse events, judges whether the overall conduct and integrity of the study remain acceptable, and makes recommendations to the Chairman of the Executive Operations Committee. The chair of the Executive Operations Committee will notify Edwards Lifesciences regarding recommendations of potential protocol/study modifications.

2.0 COMPOSITION OF THE DSMB

The DSMB consists of five members (see Appendix A). All members have experience and expertise in their field of practice and in the conduct of device clinical trials. Members will be selected by the Executive Operations Committee.

Each member of the committee is expected to serve for the duration of the trial. In the unlikely event that a member is unable to continue participation on the DSMB, the DSMB Chairperson in conjunction with the Executive Operations Committee will select a replacement.

3.0 FUNCTIONS AND RESPONSIBILITIES OF THE DSMB

Specific responsibilities include the following:

1. Edwards Lifesciences will inform the DSMB of any potential safety concern(s) that were previously unreported.

2. Edwards Lifesciences is responsible for notifying regulatory authorities and investigators if necessary. Edwards Lifesciences will be responsible for expedited regulatory reporting of unanticipated adverse device effects according to regulations.

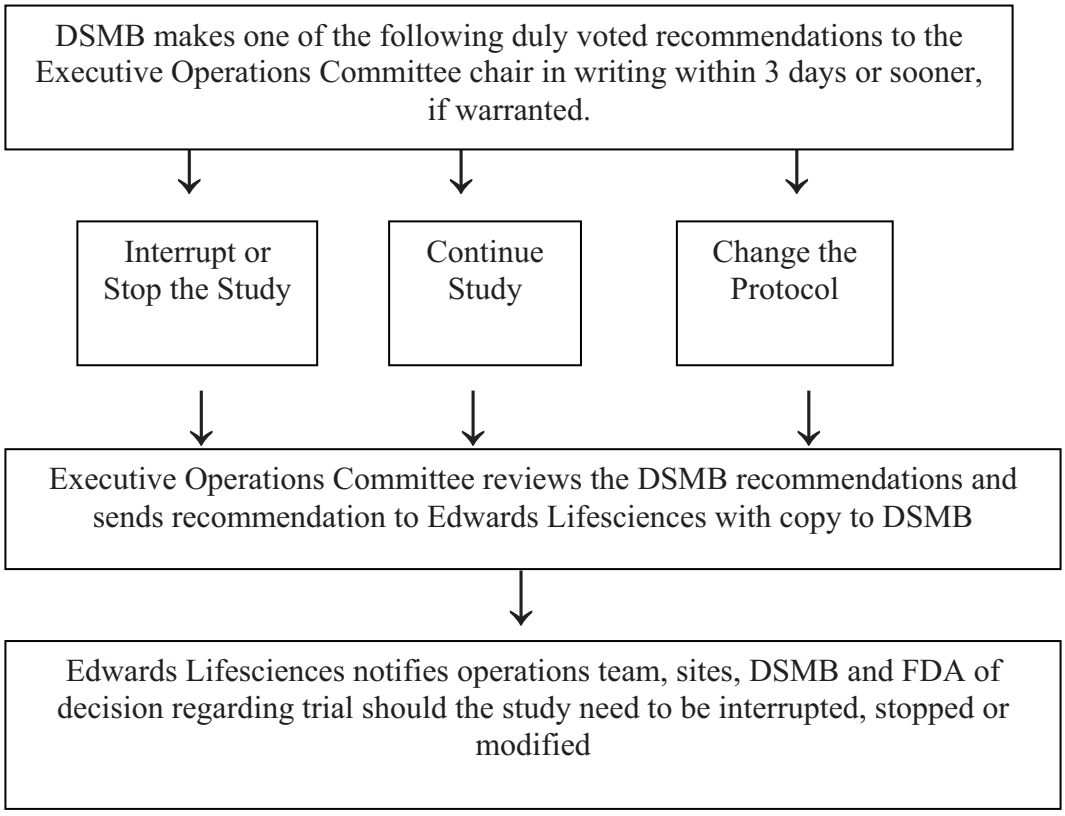
3. The Trial Statistician, appointed by Edwards LifeSciences, will prepare summary reports of relevant data for the DSMB.

4. During the closed sessions of the DSMB conference call, the trial statistician will be available for the presentation of results and entire discussion portion of all calls to answer questions. However, it remains the prerogative of the DSMB to determine if any or all portions of DSMB conference calls are limited to members of the DSMB.

5. Following every DSMB conference call or meeting, the Chairman will prepare a summary letter detailing the findings of the Board and any recommendations to the Chairman of the Executive Operations Committee.

6. The Executive Operations Committee will review the DSMB recommendations as outlined in figure 1 specified below.

Actions upon receipt of a DSMB recommendation:



4.0 CONDUCT AND FUNCTIONS OF THE DSMB

4.1 Open Session of the DSMB

The first face to face meeting of the DSMB will be an organizational meeting. This meeting is intended to formally establish the DSMB and to thoroughly acquaint the DSMB with the study protocol and the interim analysis plan. It also affords the DSMB an opportunity to recommend final revisions to the interim analysis plan, the DSMB charter, mock tables, and the plan for communication between the DSMB and the Executive Operations Committee. This meeting will take place after the first patient is enrolled.

4.2 Closed Sessions of the DSMB

Only the DSMB members and the trial statistician will attend the DSMB closed sessions. The DSMB members will review a report addressing the safety and efficacy issues of the trial. These meetings are planned to take place via a scheduled conference call organized by the Duke Clinical Research Institute (DCRI).

A quorum (minimum of 3 members) of the DSMB is required for all conference calls. A majority of total membership (3 or more members) is required for any proposal, motion, or recommendation to be made to the Executive Operations Committee. In case of a tie, the DSMB chair's vote will be used to reach a decision.

The DSMB members vote on all recommendations which will be submitted to Edwards Lifesciences via the Executive Operations Committee chair.

4.3 Responsibilities of the DSMB

1. The DSMB will review the draft DSMB charter and data tables and make recommendations for change(s).

2. The DSMB will monitor the safety of the trial and the amount of missing data via the report by the Statistics group.

3. The DSMB assessment will include, at a minimum, a review of study enrollment, site compliance with reporting requirements, all study related adverse events (both serious and non-serious) and primary endpoints identified in the clinical investigational protocol.

4. The DSMB will make recommendations to the Executive Operations Committee chair regarding modification of the protocol, continuation/discontinuation of enrollment and/or temporary suspension of enrollment in the trial. However, all final decisions regarding trial modifications rest with the Executive Operations Committee and Edwards Lifesciences as specified above.

5. The DSMB Chair will review the adverse events and protocol deviations on approximately a monthly basis to check for any emerging substantial safety trends, in which case an emergency meeting of the global DSMB may be called by the Chair. These monthly looks at the data are for the purpose of safety review. Edwards Lifesciences and DCRI will provide a timeline to the DSMB for study monitoring and adjudication of events by the Clinical Events Committee.

5.0 PROPOSED SCHEDULE OF THE DSMB

1. The initial scheduled review of data by the full DSMB is expected to take place after post-enrollment day 30 CRF data are available for the first 35 patients enrolled in the study. The second scheduled DSMB meeting will be held after the first 250 total patients have been enrolled and completion of 30 day follow-up for at least 50 patients. A third DSMB meeting will take place after the enrollment is completed for the first 500 patients and/or completion of Cohort B, whichever occurs first, using the best available data for all patients enrolled. . The fourth DSMB will take place after 30 day data are completed for the study cohort (1040 patients). The fifth and final meeting will occur after the study cohort (1040 patients) has completed the 12 month aortogram follow-up. The DSMB chair will

receive weekly reports of all procedural and in-hospital deaths, whether device or study related, and monthly updates (approx every 4-6 weeks) including an adverse events listing, protocol deviations listing, enrollment summary and tables for overall primary and secondary endpoints available. If study enrollment lags in one arm or the study design is modified, the DSMB schedule may also be modified to accommodate such changes in order to best monitor patient safety. Any such modifications of the DSMB charter during the course of the study will be detailed in written communications between the DSMB, the Executive Operations Committee and the sponsor, Edwards Lifesciences.

Table 1.0 Proposed Frequency of Data Review by the DSMB

Timeline	***Data Review by***	***Type of Data***
Weekly reporting	DSMB Chairperson	E-mail message reports of all procedural and in-hospital deaths and stroke, whether device- or study-related
Weekly reporting	DSMB Chairperson	E-mail site narratives of all procedural and in-hospital deaths and stroke, whether device- or study-related.
Monthly (approximately every 4-6 weeks)	DSMB Chairperson	Adverse Events listing, Protocol deviations listing, Enrollment Summary and tables for overall primary and secondary endpoints available.
Enrollment completed for first 50 total patients and completion of 30 day follow-up for at least 35 patients	Entire DSMB	Data summaries pre-approved by the entire DSMB
Enrollment completed for first 250 total patients and completion of 30 day follow-up for at least 50 patients	Entire DSMB	Data summaries pre-approved by the entire DSMB
Enrollment completed for first 500 patients and/or completion of Cohort B, whichever occurs first, using best available data for all patients enrolled.	Entire DSMB	Data summaries pre-approved by the entire DSMB
Enrollment completed of either	Entire DSMB	Data summaries pre-approved by the entire DSMB

Cohort A or B, OR completion of total enrollment of 1040 if Cohort B had previously completed enrollment. Includes completion of 30-day follow-up and other best available data for all 1040 patients enrolled.		
Enrollment completed for all 1040 patients enrolled in both trial programs and completion of 12 month clinical and echocardiogram follow-up.	Entire DSMB	Data summaries pre-approved by the entire DSMB

2. Additional reviews of the data may be determined by the DSMB chairperson or the full DSMB based on unforeseen concerns. If necessary, the DSMB can request frequent reports.

3. The DSMB reports will be developed by the Independent Statistics Consultant, and sent by DCRI to the DSMB Chairperson and all DSMB members before scheduled calls. In the event a DSMB member will be away from his/her usual location, notification of phone numbers and an address where the report can be sent is to be shared with DCRI as soon as this information becomes available. This will help to facilitate participation on the call and ensure receipt of the DSMB report in a timely manner.

4. The DSMB will review the reports containing predetermined data summaries and discuss them during the scheduled conference call.

5. Following each meeting, the chairperson will prepare a letter to the Executive Operations Committee regarding the safety and continuation of the trial based on the DSMB recommendation.

6. In the unlikely event, should the DSMB believe that evidence of a concern for patient safety, beyond a reasonable doubt, exists such that a specific recommendation related to the alteration of the study would be made, the Chairperson will notify the Executive Operations Committee chair by phone followed by the written letter.

7. The minutes of each DSMB meeting will be recorded by a non-voting member of the committee, and reviewed and approved by the Chairperson of the DSMB. As with other confidential documents, the minutes will not circulate outside the committee until the final results are public.

6.0 ELEMENTS OF THE DSMB REPORT

Dichotomous and categorical data will be reported as total numbers and percentages. Continuous data will be reported as medians and quartiles.
The DSMB tables include:

1. Number of patients enrolled
2. Number of patients enrolled with completely missing data in report
3. Selected demographic/baseline factors to include gender, race and age
4. Primary endpoint events (adjudicated and unadjudicated)
5. Secondary endpoint events (adjudicated and unadjudicated)
6. All adverse events and unanticipated adverse device effects, including narrative descriptions.
7. Protocol deviations
8. Compliance with time-based follow-up milestones

A detailed set of table shells has been developed to provide supplementary details to the charter.

The information provided in the summaries prepared by the trial statistician will be the best available data available at the time of analysis. The DSMB report will include the total number of patients whose data were derived from cleaned CRFs, how many endpoints have been adjudicated, and how many are based on site investigator determination only. In addition, the DSMB will review the 6 month compliance reports which will include the compliance reports in which the amount of missing data will be described.

7.0 GUIDELINES FOR STOPPING OR MODIFICATION OF THE TRIAL

Upon review of the data for the trial, the DSMB will make decisions regarding the continuation of the trial. The following DSMB stopping rules will be applied for the PARTNER trial:

The DSMB will review the rate of the combined endpoint of death or stroke at 30 days. If the treatment arm is statistically worse than the comparison group for this combined endpoint, the DSMB may recommend stopping either, or both, cohorts of the study. For both cohorts the latest available data, including actions taken by the Clinical Events Committee, will be included. Statistical comparison will be by means of the log-rank test, considering only data through 30 days.

1. For cohort A (transfemoral Test, high risk surgery Control) the comparison group will be the cohort A control arm in the PARTNER trial,

2. For cohort B (transfemoral Test, medical management Control) the comparison group will be the latest available data from the transfemoral patients in the Revival II study.

   The reason for not using the cohort B control patients in this comparison is that the cohort B test patients have been exposed to an invasive implant procedure, including anesthesia, while the cohort B control patients have not been exposed to this procedure. Accordingly the cohort B test patients will almost surely have higher 30 day event rates than the cohort B control patients. The Revival II event rates were made known to the FDA as part of the process of obtaining approval for the PARTNER trial; updated information will be furnished to the DSMB.

3. Because of the potentially large number of data looks by the DSMB, and the possibility that early data will be misleading, the DSMB will use alpha = 0.01 in judging statistical significance. Regardless of the choice of alpha, the DSMB may express a concern if the observed event rates in either test arm are worse than those in the appropriate comparison arm.

4. The DSMB may recommend stopping either (or both) of the trial cohorts for futility if the conditional power falls below 20% at any of the DSMB analysis time points. The DSMB may choose the statistical method for determining this conditional power. In analyzing futility the DSMB will not assume a constant death hazard over time for arms of cohort A and in the test arm of cohort B; rather the DSMB will consider at least two stages for the hazard – one for the first 30 days and one for later time points.

5. There are no stopping rules for efficacy. In the absence of futility findings or safety concerns, the trial will not be stopped for efficacy.

6. In addition to the stopping rules defined above, the DSMB may recommend stopping the study at any time, in the event of other unforeseen or excessive adverse effects or other safety concerns.

If the DSMB recommends discontinuation or modification of the study, the Chair of the DSMB will meet with the Executive Operations Committee at the earliest opportunity to review the basis for the recommendation.

8.0 CONFLICT OF INTEREST GUIDELINES

Members of the DSMB, and their immediate families, will not buy, sell, or hold stock in the Sponsor for the following periods: from the first meeting of the DSMB until the last meeting and the study results are made public; or from the DSMB first meeting until the member's active personal involvement in the DSMB ends.

No members of the DSMB are allowed to take part in the clean-up of the trial databases or database release. No members of the DSMB can have the responsibility

of device patients enrolled into the PARTNER trial. No member of the DSMB can take part in the evaluation of patient data in the CEC. Members will keep reports, meeting discussions, minutes, and recommendations of the DSMB confidential for the entire study.

Indemnification section for members of the DSMB.

Indemnification has been arranged through Edwards Lifesciences with the individual members.

9.0 APPROVALS

I have reviewed and agree to the procedure of the Data and Safety Monitoring Committee as outlined above

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Martin B Leon, MD (Co - Principal Investigator)

Craig Smith, MD (Co - Principal Investigator)

Joseph P. Carrozza, MD (Chairman, DSMB)

Jodi J. Akin, MSN (Edwards Lifesciences)

10.0 APPENDIX A
List of DSMB Voting Members

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11.0 APPENDIX B

General Considerations for the DSMB

This appendix lists some of the considerations to be taken into account by the DSMB. These issues include both the magnitude of the observed differences and their consistency as well as the importance of the differences to the health and safety of the patients in the study. It is important for these issues to be stated in advance to assure both the patients and the investigators, that the DSMB will carefully consider the issues of safety and recommend protocol changes if questions of safety arise.

If important adverse experiences occur between planned meetings, and a substantial trend emerges, an emergency meeting of the DSMB will be called by the Chair. It is important to recognize that the DSMB will review all relevant data available and may request additional data prior to making any suggestions which will alter the study.

Interpretation for the safety data is very complex and requires both clinical and statistical experts reviewing the data. A number of considerations for interpretation of these data can be stated and these include:

a. Whether the results could be explained by possible differences in the baseline variables between the groups;
b. Whether outcomes could be biased because of differences in treatment programs;
c. Whether the results are consistent for other variables which should be associated with the primary outcome variables in question;
d. Whether the results are consistent among various sub-groups of patients and across various centers involved in the study;
e. Whether the risk which is under consideration is outweighed by assessment of the overall benefits of therapy;
f. Whether results could be due to confounding factors and not due to the device;
g. Whether it is likely that the current trends could be reversed if the trial were to be continued unmodified.

All of these considerations require expert evaluation and are the major role of the DSMB. The DSMB will consider these issues on a regular basis to assure the safety of the patients and to assure the investigators, the FDA and the medical community that the risks of this study are being evaluated and the patient's safety is being kept foremost in mind. At the point where the DSMB believes that the evidence of a meaningful difference beyond a reasonable doubt exists between observed and expected values such that a specific recommendation related to alteration of the study would be made, the Executive Operations Committee will be notified of the DSMB recommendations for trial modification.

Appendix L: Clinical Events Committee (CEC) Charter

Clinical Endpoint Committee Charter

THE PARTNER TRIAL: Placement of AoRTic TraNscathetER Valves Trial

Edwards SAPIEN™ Transcatheter Heart Valve

CEC Charter Effective Date:

November 20, 2007

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Section Page

1. Introduction

The purpose of the PARTNER clinical trial program is to evaluate the safety and efficacy of the Edwards SAPIEN™ Transcatheter Heart Valve. The overall clinical trial program consists of two randomized clinical trials (RCT), Cohort A and Cohort B. In Cohort A, high risk patients being considered for Aortic Valve Replacement (AVR) will be randomized to either trans-femoral delivery of the SAPIEN™ device, or to standard AVR. In Cohort B, patients not thought to be suitable candidates for standard Aortic Valve Replacement will be randomized to medical therapy alone or transfemoral delivery of the SAPIEN™ device. Additionally, at selected sites, patients deemed ineligible for the transfemoral approach due to inappropriate vascular anatomy but otherwise eligible for enrollment will be followed in a registry of the transapical approach to device delivery.

The PARTNER Study will be conducted in the United States, Canada, and Europe and will enroll approximately 600 subjects. Cohort A is anticipated to enroll approximately 350 subjects and Cohort B is expected to enroll 250 subjects.

All subjects will have clinical follow-up at hospital discharge or 7 days, 30 days, 6 months, and 1 year. Additional follow up will occur annually for a minimum of 5 years post procedure.

The primary endpoint for Cohort A is freedom from death at 1 year, and the study is designed to demonstrate non-inferiority of the SAPIEN device compared with standard AVR. The primary endpoint for Cohort B is freedom from death over the duration of the trial, and the study is designed to demonstrate superiority of the SAPIEN device compared with best medical therapy.

Secondary endpoints include improvement in NYHA class, freedom from MACCE (death, myocardial infarction (MI) stroke or aortic valve intervention), prosthetic valve dysfunction (hemolysis, infection, thrombosis, perivalvular leak, or migration), length of hospital stay and total hospital days, Quality of Life (Kansas City Cardiomyopathy Questionnaire, EuroQOL), and improvement in Aortic valve area.

2. Role of the DCRI CEC

The Clinical Events Classification (CEC) group systematically identifies, adjudicates, and classifies suspected safety and efficacy endpoint events while blinded to treatment assignment. The CEC group develops trial specific processes for the identification of suspected endpoint events, the collection of required clinical data, and the adjudication of the suspected endpoint events using pre-specified criteria.

The following suspected clinical events occurring post enrollment will be adjudicated by the CEC for each patient using pre-specified criteria in a two step adjudication process: blinded and then unblinded to determine causation (*see Section 4).*

1) Death
   a) Cardiac and sub-classifications
   b) Non-Cardiac and sub-classifications
   c) Unknown
2) Myocardial Infarctions
   a) Clinical Periprocedure and sub-classifications
   b) Clinical Non-procedural and sub-classifications
3) CNS Events
   a) TIA
   b) Stroke and sub-classifications
4) Aortic Valve Re-Intervention
5) Vascular Complications and sub-classifications
6) Hemorrhagic Events and sub-classifications
7) Embolic Events
8) Bradyarrhythmic Events
9) Renal Failure Events
10) Arterial Vascular Procedures
11) Sternal Wound Infections
12) New or Worsening Heart Failure

3. CEC Committee Organization

3.1. Selection of CEC Members

The CEC will consist of physicians selected mostly from Duke University and the Duke Clinical Research Institute (DCRI). Physicians from outside of Duke and North America may also be selected. No sponsor representatives will serve on the CEC. The CEC physicians provide clinical expertise in the development of the CEC processes including the development of event criteria, eCRF, CEC adjudication and reporting forms, as well as in the adjudication of suspected events.

The DCRI CEC Clinical Faculty Leader, Dr. John Petersen, is responsible for the initial selection of the CEC members. The sponsor will approve the final membership of the CEC and any changes to the membership during the duration of the PARTNER study.

A CEC member cannot be directly involved in the care of PARTNER clinical study participants. Membership is for the duration of the PARTNER study unless the member is deemed by the CEC, Edwards, or their designee as being unable to fulfill his/her responsibilities. These responsibilities include, but are not limited to, adherence to the event adjudication timeline, and accurate and consistent application of the event criteria.

3.2. Qualifications of the CEC Members

Both cardiologist and neurologist CEC members will have clinical and research experience and expertise. Documentation of the required qualifications is maintained at the DCRI in the form of current curriculum vitae for the selected CEC members.

3.3. CEC Members

The CEC process involves the following personnel: Clinical Faculty Leader, Clinical Coordinators, Physicians, Clinical Data Assistants and Clerical Support

Clinical Faculty Leader, John L. Petersen, MD

The CEC Clinical Faculty oversees the CEC process for a specific trial and provides physician level support to the Clinical Coordinator during the trial. Along with the clinical coordinator, the CEC Clinical Faculty is the primary contact for the trial coordinating team, the regional coordinating centers, and other functional groups within the DCRI working on a specific trial.

CEC Clinical Trials Coordinator, Lauren Price, RCIS

The clinical coordinator is responsible for the overall conduct of the CEC process for a given trial. Responsibilities include assisting with the development of trial-specific CEC documents and forms, distribution of cases with suspected events, and reconciliation of cases adjudicated by physicians. The clinical coordinator is the key contact person for the trial coordinating team, regional coordinating centers, and other functional groups within DCRI.

Physicians

The composition of physician reviewers for PARTNER will be composed of cardiology, cardiac surgery, vascular interventional, and neurology faculty members. Physicians are also available for clinical support for the CEC clinical coordinator during the trial. Physician reviewers receive training regarding the CEC process and the trial-specific endpoints and definitions.

Clinical Data Assistants

The clinical data assistants are responsible for the coordination of the chart review process. The assistants assemble cases for review and track the status of the review process.

Clerical Support Team

The clerical support team performs the daily processing of documents. Responsibilities include copying and distributing files to the clinical trial assistants when needed.

The CEC members are responsible for the following:

3.3.1 Adjudicate and classify the following events in a blinded manner in the PARTNER study:

- Death
- Myocardial infarction
- CNS Events
- Aortic Valve Re-Intervention
- Hemorrhagic Events
- Vascular Complications
- Embolic Events
- Bradyarrhythmic Events
- Renal Failure Events
- Arterial Vascular Procedures
- Sternal Wound Infections
- New or Worsening Heart Failure

3.3.2 To participate in discussions related to event criteria and the application of the criteria, CEC conference calls and meetings

3.3.3 CEC members will communicate schedule conflicts, including extended time away from office, to the CEC Coordinator and chairperson

3.4. DCRI CEC Faculty Leader

The specific responsibilities of the CEC Faculty Leader include:

- To preside over CEC adjudication conference calls and meetings or delegate to an appropriate designee from the CEC
- To finalize and communicate endpoint criteria and any revisions that may be necessary during the course of the study
- To ensure, via on going QC reviews of adjudicated events and feedback received from the CEC Coordinator, that the adjudication process is being conducted according to the CEC Charter, and that event criteria are being accurately applied to independent and full committee event adjudications
- To participate in the adjudication process
- To participate in the resolution of any adjudication disagreement

3.5. DCRI CEC Coordinator

The DCRI CEC Coordinator is responsible for the overall conduct of the CEC for PARTNER. Specific responsibilities include but are not limited to:

- Collaborate in the development of CEC processes, including the event criteria, and associated documents with the CEC Chairman, committee members and sponsor
- In collaboration with the sponsor, design eCRF to include and facilitate the collection of ancillary data required for event adjudication
- In collaboration with the sponsor, provide the sites with the necessary tools and training to provide the CEC with complete data required for event adjudication
- Facilitate the finalization and sign-off of the CEC Charter and associated documents
- Train and oversee the day-to-day work of the PARTNER CEC team members
- Organize, facilitate and participate in the CEC meetings
- Manage the workflow and insure timelines are met
- Facilitate the collection of additional source documents and any additional data requested from the committee by posting the query directly in the electronic data capture system

- Review of all endpoint specific source documents and eCRF data to ensure that data required by the CEC physicians is complete

3.6. Sponsor

The roles and responsibilities in support of the CEC include:

- Collaborate with the DCRI in designing eCRF to include and facilitate the collection of ancillary data required for event adjudication
- Collaborate with the DCRI to develop the data specifications for programming the patient data listings, CEC adjudication forms, and CEC reports that will be available and printable via electronic data capture platform
- Program and maintain patient data listings, CEC adjudication forms, and CEC reports that are required for the CEC to manage the CEC effort
- Collaborate with DCRI to identify and develop specifications for event triggers
- Program event "triggers" (see Section 4.2 for a detailed definition of "event trigger")
- In collaboration with the CEC, provide the sites with the necessary tools and training to provide the CEC with complete data required for event adjudication
- Prepare and submit completed event packages to the CEC Coordinator
- Provide the CEC coordinator with a point of contact that will assist in the resolution of outstanding CEC eCRF and/or source document queries

4. Operations

4.1. CEC Meetings

The DCRI CEC will determine the need and timing of meetings of the CEC. The CEC will have an initial face-to-face training meeting. In addition, the members of the CEC will have face-to-face meetings and/or conference calls to adjudicate events where there was a disagreement, to QC events, and adjudicate difficult events. During these meetings, the CEC will assess and refine processes and definitions as necessary and provide clarifications of issues/answers that arise during the adjudication process.

4.2. Identification of Suspected Events

All suspected endpoint events will be identified by the sponsor and forwarded to the CEC at DCRI for adjudication. In order to maintain an accurate and efficient adjudication process, query resolution should be complete on all patient data before a suspected event is sent for adjudication. Suspected clinical events will be reported on the PARTNER eCRF by the site investigator.

The sponsor will be responsible for assuring that prior to completion of the trial all patients have been screened for possible events through the entire duration of study follow-up.

4.3. Collection of Data

CEC Dossier Preparation

All patients having a suspected event will be triggered for review by the CEC. Supporting source documents will be provided to the DCRI CEC Coordinator for filing in the patients CEC dossiers. Documents will be reviewed for text that may lead to unblinding of the treatment assignment and these sections will be removed if unnecessary or blacked out with a China Black Ink marker. Once all appropriate documents are assembled for an event, the dossier will be sent to the CEC Committee for review and formal adjudication. The CEC Coordinator may withhold an event from adjudication if documents from an associated event are not available so that all events from a single incident can be adjudicated together. The CEC dossier for adjudication will include a paper copy of the relevant pages on the eCRF, all appropriate source documents, all appropriate core laboratory reports, and CEC adjudication forms.

The sponsor will provide the following necessary records to the CEC for event adjudication.

1. eCRF data (Medidata™ system)
2. Supporting source documentation from the patient's medical record (*see Section 7*)
3. Echocardiography Reports from the Echo Core Lab
4. ECG final read from ECG Core Lab.

The source documents required to adjudicate suspected events vary with the endpoints to be adjudicated *(see Section 7)*. Case Report Form data will be query resolved before

being sent to the CEC. All narrative reports (i.e. discharge summaries, operative reports, etc.) will be blinded for patient identifiers and translated into English prior to being posted on the Medidata™ system. If it is determined by the CEC that additional source documents are necessary for event adjudication, they will be requested through the sponsor.

Electronic Case Report Form (eCRF) data and all supporting source documents used for review will be blinded to treatment assignment. Edwards will ensure that all data is blinded before being posted on the Medidata™ system and the review process begins.

4.4. CEC Adjudication

CEC Structure

All events will be reviewed independently by a Core CEC consisting of 3 physicians. During the blinded review, the Core CEC will review the CEC Dossier and apply the definitions as specified in the study protocol to determine if an event occurred. This will occur with blinded source documents and without the echocardiographic imaging so that the reviewers will be blinded to treatment assignment.

Events that require specialty expertise, specifically strokes, vascular complications, and renal failure events, will be reviewed initially by the specialty reviewer. This adjudication will be subsequently reviewed by the blinded Core CEC. If there is agreement between the Core CEC and the specialty reviewer, the event will be considered resolved. If there is disagreement, the event will be tabled until the specialty reviewer can attend a CEC meeting and the event can be resolved.

During the next phase of the Core CEC review, all events that have adjudicated positively by the blinded review will be adjudicated for relationship to the investigational device in an unblinded manner. During this review, all imaging and source documents will be made available to the committee. Specifically, echocardiographic images will be reviewed for all patients in whom causation is to be assessed.

A flowchart of the overall CEC process is shown in *Section 8*.

5. Event Definitions

5.1. Death

The CEC will assess all deaths for device and procedural relationship. Further, the CEC will consider all clinically relevant information to classify all deaths as:

1) ***Cardiovascular:*** Deaths resulting from a cardiac cause. This category includes valve-related deaths, (including sudden unexplained deaths) and non-valve related cardiac deaths (e.g., congestive heart failure, acute myocardial infarction, documented fatal arrhythmias) in which a cardiac cause cannot be excluded. All cardiovascular deaths will be sub-classified into the following categories:
   a) **Sudden, unexpected and unexplained death**: The cause of these deaths is unknown and the relationship to an operated valve is also unknown. Therefore, these deaths should be reported as a separate category of valve related mortality if the cause cannot be determined by clinical data or autopsy.
   b) **CHF**: documented myocardial failure or overt symptoms of CHF at time of death in absence of MI or other precipitating cause of CHF syndrome.
   c) **MI**: meets study definition of MI (see MI definition below)
   d) **Arrhythmia**: documented arrhythmia occurring in absence of MI or CHF as primary cause of death
   e) **Endocarditis of Prosthetic Study Valve**: meeting Duke Endocarditis Criteria as Definite or Possible
      i) **Definite Endocarditis**
         (1) **Pathologic criteria**
            (a) **Microorganisms:** demonstrated by culture or histology in a vegetation, *or* in a vegetation that has embolized, *or* in an intracardiac abscess, *or*
            (b) **Pathologic lesions:** vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis
         (2) **Clinical criteria:** 2 major criteria, *or* 1 major and 3 minor criteria, *or*5 minor criteria
            (a) **Major Criteria**
               (i) Positive blood culture for infective endocarditis
                  1. Typical microorganism for infective endocarditis from two separate blood cultures
                     a. Viridans streptococci, *Streptococcus bovis*, HACEK group, *or* Community-acquired *Staphyloccus aureus* or enterococci, in the absence of a primary focus, *or*
                  2. Persistently positive blood culture, defined as recovery of a microorganism consistent with infective endocarditis from:
                     a. Blood cultures drawn more than 12 hours apart, *or*
                     b. All of three or a majority of four of more separate blood cultures, with first and last drawn at least 1 hour apart
               (ii) Evidence of endocardial involvement
                  1. Positive echocardiogram for infective endocarditis

a. Oscillating intracardiac mass, on valve or supporting structures, *or* in the path of regurgitant jets, *or* on implanted material, in the absence of an alternative anatomic explantation, *or*
b. Abscess, *or*
c. New partial dehiscence of prosthetic valve, *or*

2. New valvular regurgitation (increase or change in pre-existing murmur not sufficient)

(b) **Minor Criteria**

(i) Predisposition: predisposing heart condition *or* intravenous drug use
(ii) Fever ≥ 38.0°C (100.4°F)
(iii) Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions
(iv) Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor
(v) Microbiologic evidence: positive blood culture but not meeting major criterion as noted previously *or* serologic evidence of active infection with organism consistent with infective endocarditis
(vi) Echocardiogram: consistent with infective endocarditis but not meeting major criterion as noted previously

ii) **Possible Infective Endocarditis:** Findings consistent with infective endocarditis that fall short of "Definite," but not "rejected."

iii) **Rejected**

(1) Firm alternate diagnosis for manifestations of endocarditis, *or*
(2) Resolution of manifestations of endocarditis, with antibiotic therapy for 4 days or less, *or*
(3) No pathologic evidence of infective endocarditis at surgery or autopsy, after antibiotic therapy for 4 days or less

f) **CNS Event**: meets study definition of CNS Event (see CNS Event definition below). Further classified as:
i) stroke
ii) TIA

g) **Non-Cerebral Hemorrhage**: meets study definition of major hemorrhage. Further classified as:
i) surgical site
ii) non-surgical site
iii) catheter access site

h) **Peripheral Arterial Embolism**: meets study definition of peripheral arterial embolism (not cerebral or pulmonary embolism)

i) **Vascular Complication**, further classified as:
i) aortic dissection
ii) aortic perforation
iii) non-aortic artery dissection
iv) non-aortic perforation

v) cardiac perforation

j) **Peripheral Arterial Disease**: death due to acute peripheral ischemia or sequellae of therapy for peripheral arterial disease

k) **Other** (examples include: perforated/damaged aortic valve, pericardial tamponade not related to perforation, non-prosthetic endocarditis, pulmonary embolus)

2) ***Non-cardiovascular death:*** Defined as a death not due to cardiac causes (as defined above). All non-cardiac deaths will be sub-classified into the following categories

a) **Malignancy**

b) **Accidental** (e.g. trauma, suicide, overdose)

c) **Infection/ Sepsis**

d) **Renal Disease**

e) **Other** (e.g. hepatic failure, diabetes, COPD)

3) ***Unknown***

Unblinded Review of Deaths: All events, including deaths will be reviewed once as a blinded review and then as an unblinded review. During the unblinded review, deaths will be evaluated to determine if the event was related to the valve and/or procedure. Following are the definitions for these two categories:

a) **Valve related death**: 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.

b) **Procedure related death**: Deaths directly related to the procedure or complications thereof or any death occurring ≤ 30 days of the producer will be classified as procedure related.

5.2. Myocardial Infarction

The CEC will assess all myocardial infarctions adjudicated positively for device and procedural relationship. Any of the following criteria will meet the definition of MI:

1) Any Acute MI demonstrated by autopsy

2) Any emergent PCI performed for acute ST-elevation myocardial infarction

3) Any administration of thrombolytics for acute myocardial infarction

4) Clinical Periprocedural MI: Occurs through 7 days post index procedure.

a) Periprocedural Q-wave MI: Development of new pathologic Q waves in 2 or more contiguous leads with elevation of CK-MB or CK in absence of CK-MB data. New Q waves in the absence of symptoms or elevated markers will NOT be considered an MI.

b) Periprocedural Non-Q-wave MI: Documented signs or symptoms of ischemia and/or new ischemic changes on ECG **AND** CK-MB elevation > 10 X ULN. In the absence of CK-MB data, CK should be used.

c) Points of clarification

i) In the absence of CK-MB data, CK can be used with the same > 10 X ULN criteria. If both markers are available, CK-MB will be used.

ii) Troponin values will not be considered in the adjudication of Periprocedural MIs.

iii) New ischemic ECG changes will include ST segment deviations and T wave inversions thought to be ischemic by the ECG core lab. Changes thought to represent post-operative pericarditis will not qualify as ischemic changes.

iv) Timing of MI will be based on date and time of onset of symptoms. If symptoms cannot be used, order will then be 1) ECG changes, then 2) first enzyme elevation above ULN (assuming there is a set consistent with the > 10 criteria).

5) Clinical Non-procedural MI

a) Q-wave MI: Development of new pathologic Q waves in 2 or more contiguous leads with elevation of CK, CK-MB or Troponin in clinical setting with signs or symptoms of myocardial ischemia.

b) Non-Q-wave MI: Elevation of CK > 2 times ULN with elevation of CK-MB or Troponin in clinical setting with signs or symptoms of myocardial ischemia.

5.3. CNS Events

The CEC will assess all Strokes and TIAs adjudicated positively for device and procedural relationship.

1) Stroke
   a) Focal neurologic deficit lasting ≥ 24 hours OR
   b) Focal neurologic deficit lasting < 24 hours with imaging findings of acute infarction or hemorrhage. Further classified as:
      i) Ischemic
      ii) Hemorrhagic (epidural, subdural, subarachnoid)
      iii) Ischemic with Hemorrhagic Conversion
2) TIA: Focal neurologic event that is fully reversible in < 24 hours in the absence of any new imaging findings of infarction or other primary medical cause (hypoglycemia, hypoxia, etc).

5.4. Aortic Valve Re-Intervention

The CEC will assess all Aortic Valve Re-interventions adjudicated positively for device and procedural relationship.

Aortic Valve Re-intervention is defined as any operation that repairs, alters or replaces a previously operated valve. Events will be classified as:

1) Aortic balloon valvuloplasty
2) Open aortic valve replacement

3) Open revision of existing aortic valve without replacement
4) Implantation of percutaneous aortic valve
5) Other

5.5. Hemorrhagic Events

The CEC will assess all Aortic Valve Re-interventions adjudicated positively for device and procedural relationship.

Hemorrhagic Events will be classified as:

1) Major Bleed: Clear source documentation of a site of bleeding and meets any one of the following criteria:
    a) Bleeding event that causes death.
    b) Bleeding event that causes a hospitalization or prolongs hospitalization ≥ 24 hours due to treatment of bleeding.
    c) Requires pericardiocentesis or open and/or endovascular procedure for repair or hemostasis. Thrombin injection or US compression of pseudoanuerysm and nasal packing for epistaxsis are not included as a major bleed. However, return to OR for bleeding after AVR does qualify as a major bleed.
    d) Causes permanent disability (e.g. blindness, paralysis, hearing loss).
    e) Requires transfusion of > 3 units of blood within 24 hour period. Note: Three and partial transfusion of fourth unit qualifies as a major bleed.
2) Minor Bleed: Must meet all of the following criteria:
    a) Event does not meet criteria for major bleed.
    b) Clear source documentation of a site for bleeding
    c) Loss of Hemoglobin > 3 g/dL or loss of Hematocrit > 9%. Adjustment for transfusions will be included at 1 g/dL or 3% for each unit of blood.
        i) Note: Intraocular hemorrhage or spinal cord hemorrhage that does not lead to permanent disability and does not require a surgical procedure (laser photocoagulation is not considered a surgical procedure) are included.

5.6. Vascular Complications

The CEC will assess all Vascular Complications adjudicated positively for device and procedural relationship. Vascular Complications will be classified as:

1) Access site Hematoma: size >5 cm in dimension
2) Access Site False (Pseudo) Aneurysm: based on documented imaging findings
3) Arterio-Venous Fistula: based on documented imaging findings
4) Retroperitonal bleeding: defined by at least two of the following
    a) Clinical signs or symptoms
    b) Imaging confirming retroperitonal bleeding

c) Laboratory evidence of blood loss

5) Peripheral nerve injury: based on documented findings
6) Vascular Perforation
   a) Defined by at least one of the following
      i) Radiographic or sonographic evidence of vascular extravasation
      ii) Surgical confirmation of peripheral vascular perforation
   b) Classified into the following locations
      i) Ascending Aorta
      ii) Aortic Arch
      iii) Descending Aorta
      iv) Iliac (R, L or both)
      v) Femoral (R, L or both)
      vi) Other
7) Vascular Dissection
   a) Defined by at least one of the following
      i) Radiographic or sonographic evidence of vascular extravasation
      ii) Surgical confirmation of peripheral vascular dissection
   b) Classified into the following locations
      i) Ascending Aorta
      ii) Aortic Arch
      iii) Descending Aorta
      iv) Iliac (R, L or both)
      v) Femoral (R, L or both)
      vi) Other
8) Gastro-Intestinal Ischemia: Clinical findings of intestinal ischemia, including physical signs and symptoms, lactic acidosis or presumed lactic acidosis, radiographic imaging, intra-operative findings.

5.7. Embolic Events

The CEC will assess all Embolic Events adjudicated positively for device and procedural relationship. Embolic Events are defined as radiographic or clinical evidence of an embolic event. Location of the embolic event will be classified as:

1) Cerebral
2) Cardiovascular
3) Upper extremity
4) Lower extremity
5) Renal
6) Mesenteric
7) Splenic
8) Hepatic
9) Ocular/retinal
10) Other

Also, the interventional procedure required will be classified as:

1) Thrombectomy

2) Revascularization
3) Surgical resection or amputation
4) Other

5.8. Bradyarrhythmic Events

The CEC will assess all Bradyarrhthmic Events adjudicated positively for device and procedural relationship. Bradyarrhthmic Events are defined as implantation of a permanent pacing device for bradyarrhythmia. The date of event will be based on the date of device implantation.

5.9. Renal Failure Events

The CEC will assess all Renal Failure Events adjudicated positively for device and procedural relationship. Renal Failure Events are defined as the initiation of dialysis of any sort (hemodialysis, CVVHD, peritoneal) at any point following randomization. The date of event will be based on the date of the first treatment with renal replacement therapy.

5.10. Arterial Vascular Procedures

The CEC will assess all Arterial Vascular Procedures adjudicated positively for device and procedural relationship. Arterial Vascular Procedures will be classified into by type of procedure, reason for procedure and whether or not the procedure was planned prior to randomization.

5.11. Sternal Wound Infection Events

The CEC will assess all Sternal Wound Infections adjudicated positively for device and procedural relationship. Deep sternal infection involves muscle, bone, and/or mediastinum (we will need to clarify that infection that is contiguous with the sternum on imaging will constitute involvement of the sternum).

Must have one of the following conditions:

1. Wound opened with excision of tissue (I&D)

2. Positive Culture

3. Treatment with antibiotics

5.12. New or Worsening Heart Failure

The CEC will assess all New or Worsening Heart Failures adjudicated positively for device and procedural relationship. These events will be defined as: unplanned presentation that requires an overnight stay (or admission) in which the subject receives IV treatment with diuretics, inotropes and/or vasodilator therapy.

OR

Episode of CHF occurring during a hospitalization for another reason but requires IV treatment with diuretics, inotropes and/or vasodilator therapy.

6. Documentation

The following guidelines should be followed for retention of clinical endpoint committee documents:

- Originals of source documents should be archived at the investigative site.
- At the end of the study, CEC adjudication forms and supporting documents will be sent to sponsor for archiving. Relevant documents pertaining to events will be collated by subject number and kept in a confidential archive forwarded to sponsor.
- An exact copy of each dossier submitted to the CEC, as well as any data collected in response to CEC requests for additional documentation, will be maintained on file by the sponsor.
- Original, final CEC adjudication forms and resolved adjudication form queries will be maintained by the sponsor.

7. Required Data for CEC Review

Suspected Event	Source Document to Submit
Death	Death Summary Autopsy Report (if applicable) Narrative summary if death outside of hospital setting
Myocardial Infarction	All ECGs All cardiac enzyme reports (CK, CK-MB, Troponin); Include ULN's Discharge Summary / Narrative Summary of Hospitalization Angiography Report from Angiographic Core Lab
Central Nervous System Event	Angiography Report Discharge summary with operative report (if applicable) All pertinent interventional/cath lab reports Functional ischemia study reports
Aortic Valve Re-Intervention	Discharge Summary / Narrative Summary of Hospitalization Echo Report from Echo Core Lab (if applicable) Operative Report (if applicable) Cath Lab Report (if applicable)
Hemorrhagic Events	All pertinent labs (H&H) Discharge Summary / Narrative Summary of Hospitalization Transfusion History Diagnostic Test Results
Vascular Complications and Procedures	Discharge summary with operative report (if applicable) Diagnostic Test Results Operative Report (if applicable)
Embolic Events	Discharge summary with operative report (if applicable) Diagnostic Test Results Operative Report (if applicable)
Bradyarrhythmic Events	All ECGs Discharge Summary / Narrative Summary of Hospitalization
Renal Failure Events	All pertinent labs Diagnostic Test Results Procedure Report (if applicable) Discharge Summary / Narrative Summary of Hospitalization
Sternal Wound Infections	All pertinent labs Diagnostic Test Results Procedure/Operative Report (if applicable) Discharge Summary / Narrative Summary of Hospitalization
New or Worsening Heart Failure	Discharge Summary / Narrative Summary of Hospitalization Diagnostic Test Results All pertinent labs

8. CEC Process Flow