



Edwards

Clinical Trial of the Edwards Aortic Bioprosthesis,
Model 11000

NCT01651052

May 8, 2012

Edwards Lifesciences LLC

One Edwards Way • Irvine, CA USA • 92614

Phone: 949.250.2500 • Fax: 949.250.2525 • www.edwards.com

Clinical Trial of the Edwards Pericardial Aortic Bioprosthesis, Model 11000

CLINICAL PROTOCOL (Clinical Investigational Plan)

Clinical Trial Number: 2010-03

Revision: C

Effective Date: May 8, 2012

Trial Sponsor:

Edwards Lifesciences LLC

One Edwards Way

Irvine, CA 92614 USA

PROPRIETARY DATA: This document and the information contained herein may not be reproduced, used or disclosed without written permission from Edwards Lifesciences LLC

Edwards Lifesciences, Edwards, the stylized E logo, Carpentier-Edwards, Magna Ease, PERIMOUNT, PERIMOUNT Magna, and TheraFix are trademarks of Edwards Lifesciences Corporation.

1 PROTOCOL SIGNATURE PAGE

Trial Title: **Clinical Trial of the Edwards Pericardial Aortic Bioprosthesis,
Model 11000**

Protocol Number: **2010-03**

Version Number: **Rev. C**

Date: **8 MAY 2012**

I have read this protocol and agree to participate in the clinical investigation of the Model 11000 sponsored by Edwards Lifesciences, LLC. I agree to conduct this investigation according to the requirements of the trial protocol and in accordance with Good Clinical Practice, applicable State and U.S. Federal regulations and conditions imposed by the reviewing Institutional Review Board/Ethics Committee/Research Ethics Board. I agree to supervise all sub-investigators at my site as well as the use of all of the investigational devices at my institution and to ensure appropriate informed consent is obtained from all subjects prior to inclusion in this trial.

INVESTIGATOR NAME

INVESTIGATOR TITLE

INVESTIGATOR SIGNATURE

DATE

SPONSOR NAME

SPONSOR TITLE

SPONSOR SIGNATURE

DATE



2 TRIAL CONTACT PERSONNEL

2.1 SPONSOR CONTACT

TRIAL DIRECTOR
[REDACTED] Director, HVT Clinical Affairs One Edwards Lifesciences Way [REDACTED] Irvine, CA 92614 Tel: [REDACTED] Fax: [REDACTED] Email: [REDACTED]

PROJECT MANAGER
[REDACTED] Clinical Manager, HVT Clinical Affairs One Edwards Lifesciences Way [REDACTED] Irvine, CA 92614 Tel: [REDACTED] Fax: [REDACTED] Email: [REDACTED]

2.2 TRIAL CONTACT

CLINICAL MONITORING
D-Target Premier Research Contact: [REDACTED] [REDACTED] Tel: [REDACTED] Mobile: [REDACTED] Email: [REDACTED]
Kraków
Prof. Dr. [REDACTED] [REDACTED] [REDACTED] Tel: [REDACTED] Fax: [REDACTED]

ECHOCARDIOGRAPHY CORE LAB
RadCore Labs Contact: [REDACTED] [REDACTED] Tel: [REDACTED] Fax: [REDACTED] Email: [REDACTED] www.radcorelabs.com
WARSAW
Prof. Dr. [REDACTED] [REDACTED] [REDACTED] Tel: [REDACTED] Fax: [REDACTED]

Table of Contents

1	PROTOCOL SIGNATURE PAGE	2
2	TRIAL CONTACT PERSONNEL.....	3
2.1	SPONSOR CONTACT	3
2.2	TRIAL CONTACT	3
3	PROTOCOL SYNOPSIS	7
4	ABBREVIATIONS	10
5	INTRODUCTION	11
5.1	INTRODUCTION AND BACKGROUND	11
5.2	DEVICE DESCRIPTION	11
5.2.1	<i>Indication for use</i>	12
5.2.2	<i>Prior Testing</i>	12
5.2.3	<i>Prior clinical studies</i>	12
6	BENEFITS AND RISKS.....	13
6.1	BENEFITS.....	13
6.2	RISKS.....	13
7	CLINICAL TRIAL DESIGN.....	14
7.1	JUSTIFICATION	14
7.2	PURPOSE	14
7.3	ENDPOINTS	15
7.3.1	<i>Safety endpoints</i>	15
7.3.2	<i>Performance endpoints</i>	15
7.3.3	<i>Other Data</i>	15
8	SUBJECT POPULATION	15
8.1	DEMOGRAPHIC AND CLINICAL CHARACTERISTICS	15
8.2	INCLUSION CRITERIA.....	16
8.3	EXCLUSION CRITERIA	16
8.4	WITHDRAWAL CRITERIA AND PROCEDURES	17
9	STATISTICAL METHODS.....	18
9.1	SAMPLE SIZE.....	18
9.2	ANALYSIS POPULATION	18
9.3	SAFETY ANALYSIS.....	18
9.4	PERFORMANCE ANALYSIS	18
9.5	OTHER DATA	19
9.6	MISSING DATA.....	19
10	TRIAL PROCEDURES.....	19
10.1	BASILINE EVALUATION	20
10.1.1	<i>Subject screening</i>	20
10.1.2	<i>Informed consent</i>	20
10.1.3	<i>Baseline assessment</i>	20
10.2	SURGICAL PROCEDURE	21
10.2.1	<i>Procedure preparation</i>	21
10.2.2	<i>Model 11000 Implanting Procedure</i>	21

10.2.3	<i>Implant Assessment</i>	21
10.3	SUBJECT ENROLLMENT	21
10.4	POST-PROCEDURE	22
10.4.1	<i>Post-procedure care</i>	22
10.4.2	<i>Discharge</i>	22
10.4.3	<i>Follow-up assessments</i>	22
10.5	ECHOCARDIOGRAM	23
10.6	DEVICE REMOVAL / EXPLANT	23
10.7	MISSED SUBJECT VISITS	23
10.8	TRIAL SUBJECT EXIT	24
10.9	CLINICAL TRIAL TERMINATION	24
11	ADVERSE EVENTS	24
11.1	REPORTING PROCEDURE	24
11.2	ADVERSE EVENT DEFINITIONS	25
11.2.1	<i>Adverse event</i>	25
11.2.2	<i>Adverse device effect</i>	25
11.2.3	<i>Serious adverse event</i>	25
11.2.4	<i>Serious adverse device effect</i>	25
11.2.5	<i>Unanticipated serious adverse device effect</i>	25
11.3	DEATHS AND EXPLANTS	25
11.3.1	<i>Subject deaths</i>	25
11.4	CLINICAL EVENTS COMMITTEE	26
12	TRIAL AND DATA MANAGEMENT	26
12.1	TRIAL CORE LABS	26
12.1.1	<i>ECHOCARDIOGRAPHY CORE LAB</i>	26
12.2	DEVICE SHIPMENTS	26
12.3	INVENTORY AND ACCOUNTABILITY RECORDS	26
12.4	DEVICE STORAGE	26
12.5	DEVICE RETURN	27
12.6	PROTOCOL DEVIATIONS	27
12.6.1	<i>Exceptions</i>	27
12.7	TRAINING	27
12.7.1	<i>Training of trial site personnel</i>	27
12.7.2	<i>Devices</i>	28
12.8	MONITORING	28
12.8.1	<i>SITE INITIATION</i>	28
12.8.2	<i>monitoring methods</i>	28
12.9	DOCUMENTATION REQUIREMENTS	28
12.9.1	<i>Source documentation requirements</i>	29
12.9.2	<i>Data collection methods</i>	29
12.9.3	<i>Quality control and quality assurance procedures</i>	30
12.9.4	<i>communication procedures</i>	30
12.10	PROTOCOL AMENDMENTS	30
12.11	AUDITS AND INSPECTIONS	30
13	ETHICAL AND REGULATORY CONSIDERATIONS	30
13.1	APPLICABLE REGULATIONS AND GUIDELINES	30
13.2	DATA PROTECTION AND SUBJECT CONFIDENTIALITY	31
13.3	INFORMED CONSENT AND REVIEW COMMITTEES	31

13.4	INVESTIGATOR RESPONSIBILITIES.....	31
13.4.1	<i>General duties</i>	31
13.4.2	<i>Investigator records</i>	32
13.4.3	<i>Investigator reports</i>	32
13.5	TRIAL SPONSOR RESPONSIBILITIES.....	32
13.5.1	<i>General duties</i>	32
13.5.2	<i>Selection of investigators</i>	33
13.5.3	<i>Monitoring the clinical trial</i>	33
13.5.4	<i>Sponsor records</i>	33
13.5.5	<i>Sponsor reports</i>	33
13.6	PUBLICATION POLICY.....	33
14	REFERENCES.....	34
15	APPENDICES.....	34
15.1	ADVERSE EVENT (CODES AND DEFINITIONS).....	35
15.2	SAMPLE INFORMED CONSENT FORM.....	36
15.3	CASE REPORT FORMS.....	37
15.4	PROTOCOL DEVIATION CODES.....	38
15.5	DEVICE DEFICIENCY CODES.....	39
15.6	ECHO MANUAL.....	40
15.7	EQ-5D QUESTIONNAIRE.....	41
15.8	SF-12 V2 QUESTIONNAIRE.....	42

3 PROTOCOL SYNOPSIS

Trial Number:	2010-03
Title:	Clinical trial of the Edwards Pericardial Aortic Bioprosthesis, Model 11000
Trial Sponsor:	Edwards Lifesciences LLC One Edwards Way, Irvine, CA 92614 USA
Krakow Principal Investigator:	[REDACTED]
Warsaw Principal Investigator:	[REDACTED]
Trial Purpose:	The purpose of this observational trial is to gather further clinical data to confirm the safety and performance of the Edwards Pericardial Aortic Bioprosthesis, Model 11000 in this trial population.
Trial Device:	Edwards Pericardial Aortic Bioprosthesis, Model 11000. An identical valve model, Model 11000A, has labeling that bears the CE marking of conformity under EC Design-Examination Certificate No. 2103732DE04 and CE Marking of Conformity Certificate No. 2103732CE04.
Intended Use:	The Model 11000 valve is intended for subjects who require replacement of their native or prosthetic aortic valve.
Trial Design:	This is a prospective, non-randomized, non-controlled, observational clinical trial. Up to 200 subjects will be enrolled at up to 6 participating trial sites. Each subject is consented for a period of 5 years. All subjects will be assessed clinically at the following intervals: Baseline, Implant, discharge, 3 months, and annually to 5 years.
Population:	Adult subjects diagnosed with aortic valve disease requiring replacement of the native or prosthetic aortic valve.
Enrollment Criteria:	<p>Inclusion Criteria</p> <ul style="list-style-type: none"> • Is 18 years or older • Provides written informed consent prior to trial procedures • Diagnosed with aortic valve disease requiring a planned replacement as indicated in the preoperative evaluation • Scheduled to undergo planned aortic valve replacement with or without concomitant bypass surgery • Geographically stable and agrees to attend all follow-up assessments at the hospital of surgical services for up to 5 years

	<p>Exclusion Criteria</p> <ul style="list-style-type: none"> • Requires emergency surgery¹ • Has prior mitral, tricuspid or pulmonic valve surgery, which included implant of a bioprosthetic valve, mechanical valve, or annuloplasty ring that will remain <i>in situ</i> • Requires multiple valve replacement/repair • Requires a surgical procedure outside of the cardiac area (e.g. vascular bypass) • Has aneurysm of the aortic root and/or ascending aorta requiring surgical intervention • Has active endocarditis/myocarditis or endocarditis/myocarditis within 3 months to the scheduled aortic valve replacement (AVR) surgery • Has renal insufficiency as determined by creatinine (S-Cr) level ≥ 2.5 mg/dL or end-stage renal disease requiring chronic dialysis at screening visit • Has MRI or CT scan confirmed stroke, cerebrovascular accident (CVA) or transient ischemic attack (TIA) within 6 months (180 days) prior to AVR surgery • Has acute myocardial infarction (MI) within 30 days prior to AVR surgery • Has presence of non-cardiac disease limiting life expectancy to less than 12 months • Diagnosed with hypertrophic obstructive cardiomyopathy (HOCM) • Diagnosed with hyperparathyroidism • Exhibits left ventricular ejection fraction $\leq 30\%$ as validated by diagnostic procedure within 30 days prior to AVR surgery • Echocardiographic evidence of an intra-cardiac mass, thrombus, or vegetation • Hemodynamic or respiratory instability requiring inotropic support, mechanical circulatory support, or mechanical ventilation within 60 days prior to AVR surgery • Documented leukopenia ($WBC < 3.5 \times 10^3/\mu L$), acute anemia ($Hgb < 10.0$ gm/dL or 6 mmol/L), thrombocytopenia (platelet count $< 50 \times 10^3/\mu L$) or history of bleeding diathesis or coagulopathy • Diagnosed with myxomatous disease/connective tissue disorders (e.g. Marfan's Syndrome) • Has prior organ transplant • Current or recent participation (within 6 weeks prior to surgery) in an investigational drug or device trial • Was previously implanted with trial device²
--	--

¹ Emergent surgery – surgery is carried out on the referral day before the beginning of the next working day.

² Note: Previously implanted means that the index aortic valve replacement procedure was completed. The procedure is complete when the surgeon takes the subject off cardiopulmonary bypass and restarts the heart.

	<ul style="list-style-type: none"> • Pregnant (female subject of childbearing potential only), lactating or planning to become pregnant during the duration of participation in trial • Currently incarcerated or unable to give voluntary informed consent • Documented history of substance (drug or alcohol) abuse within the last 5 years prior to implant
Trial Endpoints:	<p>Safety Endpoints:</p> <p>Descriptive information of early rates and late linearized rates of the following:</p> <ul style="list-style-type: none"> • Structural valve deterioration • Thromboembolism • All bleeding/hemorrhage • Major bleeding/hemorrhage • All paravalvular leak • Major paravalvular leak • Non-structural valve dysfunction • Endocarditis • Hemolysis • All cause mortality • Trial valve-related mortality • Explant <p>Performance Endpoints:</p> <ul style="list-style-type: none"> • Clinically acceptable hemodynamic performance confirmed by core lab evaluation of echocardiography • New York Heart Association (NYHA) functional class compared to baseline • Change in Quality of Life questionnaires EQ-5D (EuroQol) and Short Form 12 version 2 (SF-12v2) from baseline/screening to 1-year
Other data:	Blood Data

4 ABBREVIATIONS

ACC	American College of Cardiology	IFU	Instructions for Use
AE	Adverse Event	INR	International Normalized Ratio
AHA	American Heart Association	IRB	Institutional Review Board
AS	Aortic Stenosis	ISO	International Standardization Organization
ASD	Atrial Septal Defect	LVOT	Left Ventricular Outflow Tract
AVR	Aortic Valve Replacement	MI	Myocardial Infarction
CABG	Coronary Artery Bypass Graft	MOF	Multi-system Organ Failure
CBC	Complete Blood Count	MR	Magnetic Resonance
CEC	Clinical Events Committee	NSVD	Nonstructural Valve Dysfunction
CFR	Code of Federal Regulations	NYHA	New York Heart Association
CO/CI	Cardiac Output/Cardiac Index	OPC	Objective Performance Criteria
CRF	Case Report Form	PFO	Patent Foramen Ovale
CV	Critical Value	PMA	Premarket Approval
CVA	Cerebrovascular Accident	POD	Postoperative Day
DIC	Disseminated Intravascular Coagulation	PT	Prothrombin Time
EC	Ethics Committee	PTFE	Polytetrafluoroethylene
eCRF	Electronic Case Report Form	PTT	Partial Thromboplastin Time
ECG	Electrocardiogram	PVL	Paravalvular Leak
EDC	Electronic Data Capture	QOL	Quality of Life
EOA	Effective Orifice Area	RBC	Red Blood Cell
EQ-5D	EuroQol health questionnaire	REB	Research Ethics Board
FDA	Food and Drug Administration	RGA	Returned Good Authorization
FMEA	Failure Modes and Effects Analysis	SAE	Serious Adverse Effect
GCP	Good Clinical Practice	SAR	Specific Absorption Rate
GLP	Good Laboratory Practices	SAVR	Surgical Aortic Valve Replacement
HGB	Hemoglobin	SF-12	Short Form 12 health questionnaire
HIPAA	Health Insurance Portability & Accountability Act	SVD	Structural Valve Deterioration
HCT	Hematocrit	TAD	Tissue Annulus Diameter
HIT	Heparin Induced Thrombocytopenia	TEE	Transesophageal Echocardiography
HOCM	Hypertrophic Obstructive Cardiomyopathy	TIA	Transient Ischemic Attack
ICF	Informed Consent Form	UADE	Unanticipated Adverse Device Effect
ICU	Intensive Care Unit	WBC	White Blood Cell
ID	Identification		
IDE	Investigational Device Exemption		

5 INTRODUCTION

5.1 INTRODUCTION AND BACKGROUND

Valvular heart disease is a life-threatening disease that afflicts millions of people worldwide and leads to approximately 250,000 valve repairs and/or replacements each year. The number of subjects requiring aortic valve replacement (AVR) is increasing due to prolonged life expectancy. Many subjects are asymptomatic until the disease is well advanced and, once diagnosed, have poor prognosis depending on the severity of valve calcification and history of cardiac events.¹ Diseased heart valves can be treated by medication, surgical repair or surgical replacement.

5.1.1.1 AORTIC HEART DISEASE

Aortic valvular heart disease includes conditions involving any of the following – obstructions of the aortic heart valve or stenosis; leakage of the aortic valve, known as regurgitation, incompetence, or insufficiency, and combinations of the two, sometimes referred to as mixed disease or combined lesions. Valvular heart disease may be caused by any number of factors, including congenital abnormalities, infection by various micro-organisms, degenerative calcification and rheumatic heart disease. When subjects become symptomatic, angina, syncope, and congestive heart failure (CHF) are the primary clinical signs observed. Studies report that among symptomatic subjects with medically treated moderate-to-severe AS, mortality rates after the onset of symptoms are approximately 25% at one year and 50% at two years. Other studies show that subjects with symptomatic AS have a life expectancy between 2 – 4 years.² Neither aortic stenosis nor aortic insufficiency can be effectively treated medically; however, the symptoms of aortic valve disease can be managed medically.

5.1.1.2 TREATMENT OF AORTIC VALVULAR HEART DISEASE

Aortic stenosis and insufficiency can be treated by surgical intervention, including balloon valvuloplasty, valve repair, and valve replacement. Balloon valvuloplasty, a treatment option for aortic stenosis, utilizes a balloon-tipped catheter to stretch open the narrowed valve. Valvuloplasty is predominately used to treat children or adults who are poor surgical candidates. Valve repair techniques include annuloplasty for dilated valve disease, patching leaflet perforations, resected vegetations, or tears, and leaflet extension.^{3,4} Aortic valve repair for stenosis does not show good clinical results.⁵ Replacement of the aortic valve is indicated for symptomatic subjects and asymptomatic subjects with left ventricular dysfunction.

5.1.1.3 BIOPROSTHETIC HEART VALVES

Bioprosthetic heart valves are indicated for use in subjects suffering from valvular heart disease. These tissue valves are used particularly in those subjects for whom long-term anticoagulation therapy is contraindicated or who may be difficult to maintain on anticoagulation therapy.

5.2 DEVICE DESCRIPTION

Refer to the *Instructions for Use* in the Clinical Investigator's Brochure (CIB) for a complete description of the device.

The Edwards pericardial aortic bioprosthesis, Model 11000, is a trileaflet bioprosthesis comprised of bovine pericardium that has been preserved in a buffered glutaraldehyde solution and mounted on a flexible frame. It is available in sizes 19, 21, 23, 25, 27, and 29 mm. The bioprosthesis is stored in non-liquid packaging.

The frame is designed to be compliant at the orifice as well as at the commissures. The compliance of the commissure supports is intended to reduce the loading shock at the valve commissures and free margin of the leaflets. The compliance of the orifice is intended to reduce the stress on the leaflets. The compliant orifice concept is based on the physiology and mechanics of natural heart valves and reported experience with implantation of unstented homografts.

The lightweight wireform is made of a corrosion-resistant cobalt-chromium alloy, chosen because of its superior efficiency and fatigue-resistant characteristics, and is covered with a woven polyester fabric.

A thin cobalt-chromium alloy/polyester film laminate band surrounds the base of the wireform frame providing structural support for the orifice. A silicone-rubber sewing ring covered with a porous, seamless polytetrafluoroethylene (PTFE) cloth attached to the wireform frame, which facilitates tissue ingrowth and encapsulation. The aortic sewing ring has been scalloped to conform to the natural aortic root. The compliant nature of the sewing ring facilitates coaptation between the bioprosthesis and an often irregular or calcific tissue bed.

To facilitate implantation in patients with small aortic roots, the Model 11000A has a low profile height. The sewing ring has three, equally spaced black silk suture markers at the cusp centers to aid in bioprosthesis orientation and suture placement.

The Model 11000 bioprosthesis does not require rinsing prior to implantation.

A holder is attached to the bioprosthesis by means of sutures to facilitate handling and suturing the bioprosthesis during implantation. The holder is easily detached by the surgeon.

Edwards Pericardial Aortic Bioprosthesis, Model 11000. An identical valve model, Model 11000A, has labeling that bears the CE marking of conformity under EC Design-Examination Certificate No. 2103732DE04 and CE Marking of Conformity Certificate No. 2103732CE04.

5.2.1 INDICATION FOR USE

The Model 11000 is intended for patients who require replacement of their native or prosthetic aortic valve.

Refer to the *Instructions for Use* in the Clinical Investigator's Brochure (CIB) for contraindications, procedure steps, and cautions.

5.2.2 PRIOR TESTING

A Clinical Investigator's Brochure (CIB) is prepared for the Model 11000; please refer to this document for pre-clinical testing.

5.2.3 PRIOR CLINICAL STUDIES

Twenty (20) subjects are implanted with the Model 11000 Pericardial Bioprosthesis under Version A of this ongoing clinical trial.

A summary of prior clinical studies on similar pericardial valves are included in the Clinical Investigator's Brochure.

6 BENEFITS AND RISKS

6.1 BENEFITS

The benefits of the Model 11000 are assumed the same as other bioprosthetic valves including improved valvular function, acute alleviation of symptoms related to aortic stenosis or insufficiency, and/or improved morbidity and mortality. The additional benefits of this valve are not yet proven.

The anticipated additional benefits of aortic valve, Model 11000 are to eliminate the need for rinsing the index valve prior to implant, less exposure to the risks of glutaraldehyde, and elimination of hazardous waste requiring special disposal.

6.2 RISKS

As with all prosthetic heart valves, serious complications, sometimes leading to death may be associated with the use of tissue valves. Complications due to individual subject reaction to an implanted device, or to physical or chemical changes in the components, particularly those of biological origin, may occur at varying intervals (hours or days) necessitating reoperation and replacement of the prosthetic device. Some or all of the risks listed below could require a reoperation or explant, and/or they may lead to permanent disability or death.

Known/potential risks associated with stented bioprosthetic heart valves include but not limited to:

- Angina
- Bleeding diatheses (coagulopathy) related to anticoagulant therapy
- Cardiac arrhythmias
- Cardiac failure
- Coronary ostial blockage
- Endocarditis
- Hemolysis/Hemolytic anemia
- Hemorrhage
- Immunological response
- Leaflet entrapment (impingement)
- Myocardial infarction
- Nonstructural valve dysfunction
- Paravalvular/Perivalvular leak
- Malfunctions of valve due to distortion at implant, fracture of wireform, physical and or chemical deterioration of valve components
- Patient prosthetic mismatch (PPM)
- Regurgitation/insufficiency
- Stenosis
- Thromboembolism/stroke
- Tissue deterioration including infection, calcification, thickening, perforation, degeneration, suture abrasion, instrument trauma, and or leaflet detachment
- Transient ischemic attack (TIA)
- Valve pannus
- Valve thrombosis

Potential risks associated with aortic valve replacement surgery include but not limited to:

- Allergic reaction
- Annular dissection
- Aortic dissection
- Arterial dissection
- Bleeding, anticoagulant related
- Bleeding, procedural
- Bleeding, post-procedural
- Cardiac arrest
- Cardiogenic shock
- Disseminated intravascular coagulation (DIC)
- Esophageal rupture
- Heart failure
- Hematoma
- Heparin induced thrombocytopenia (HITs)
- Hypotension
- Hypertension
- Hypoxemia
- Infection, local or wound
- Infection, systemic (septicemia)
- Myocardial infarction
- Multi-system organ failure (MOF)
- Pericardial effusion
- Pericardial tamponade
- Pleural effusion
- Pulmonary edema
- Pneumonia
- Renal dysfunction
- Respiratory failure
- Thromboembolism
 - Venous, peripheral or central
 - Arterial, peripheral or central
 - Pulmonary, thrombus or other

Risks associated with Model 11000 are anticipated to be the same as those listed above for other aortic bioprosthetic valves and valve replacement surgery. Based on pre-clinical testing, there are no new risks anticipated with the Model 11000 tissue process or sterilization method.

There may be other unknown risks. All safety events will be collected and reviewed throughout the entire trial and follow-up period. Investigators will be notified of any additional risks identified that could affect the health, safety or welfare of the trial subjects.

7 CLINICAL TRIAL DESIGN

This is a prospective, non-randomized, non-controlled, observational clinical trial. Up to 200 subjects will be enrolled at up to 6 participating trial sites. Each subject is consented for a period of 5 years. All subjects will be assessed clinically at the following intervals: Baseline, Implant, discharge, 3 months and annually to 5 years.

7.1 JUSTIFICATION

This trial is designed to confirm that the performance observed in pre-clinical testing also is observed in the human population.

7.2 PURPOSE

The purpose of this observational trial is to gather further clinical data to confirm the safety and performance of the Edwards Pericardial Aortic Bioprosthesis, Model 11000 in this trial population.

7.3 ENDPOINTS

7.3.1 SAFETY ENDPOINTS

Descriptive information of early rates and late linearized rates of the following:

- Structural valve deterioration
- Thromboembolism
- All bleeding/hemorrhage
- Major bleeding/hemorrhage
- All paravalvular leak
- Major paravalvular leak
- Non-structural valve dysfunction
- Endocarditis
- Hemolysis
- All cause mortality
- Trial valve-related mortality
- Explant

7.3.2 PERFORMANCE ENDPOINTS

The following performance endpoints will be assessed at each scheduled follow-up visit:

- Clinically acceptable hemodynamic performance confirmed by core lab evaluation of echocardiography
- New York Heart Association (NYHA) functional class compared to baseline
- Change in Quality of Life questionnaires EQ-5D (EuroQol) and Short Form 12 version 2 (SF-12v2) from baseline/screening to 1-year

7.3.3 OTHER DATA

The following blood data also will be collected at baseline, 3 months, and at each annual visit:

Complete blood count (CBC): including White Blood Cell Count (WBC), Red Blood Cell Count (RBC), Hemoglobin (Hgb), Hematocrit (HCT), and platelet count (PLT), and plasma free hemoglobin.

Serum creatinine will be collected at baseline only.

Coagulation profile will be collected at baseline, discharge, 3 months, and at the 1, 3, and 5 year follow-up visits.

8 SUBJECT POPULATION

8.1 DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Adult subjects diagnosed with aortic valve disease and scheduled to undergo aortic valve replacement are eligible for participation in the clinical trial.

8.2 INCLUSION CRITERIA

The principal investigator at the trial site has the responsibility of screening potential subjects to determine if the patients meet all the inclusion criteria. The following are requirements for entry into the clinical trial:

- Is 18 years or older
- Provides written informed consent prior to trial procedures
- Diagnosed with aortic valve disease requiring a planned replacement as indicated in the preoperative evaluation
- Scheduled to undergo planned aortic valve replacement with or without concomitant bypass surgery
- Geographically stable and agrees to attend all follow-up assessments at the hospital of surgical services for up to 5 years

8.3 EXCLUSION CRITERIA

The principal investigator at the trial site must exclude subjects if any of the exclusion criteria are present. The following are the criteria for exclusion from participating in the clinical trial:

- Requires emergency surgery³
- Has prior mitral, tricuspid or pulmonic valve surgery, which included implant of a bioprosthetic valve, mechanical valve, or annuloplasty ring that will remain *in situ*
- Requires multiple valve replacement/repair
- Requires a surgical procedure outside of the cardiac area (e.g. vascular bypass)
- Has aneurysm of the aortic root and/or ascending aorta requiring surgical intervention
- Has active endocarditis/myocarditis or endocarditis/myocarditis within 3 months to the scheduled aortic valve replacement (AVR) surgery
- Has renal insufficiency as determined by creatinine (S-Cr) level ≥ 2.5 mg/dL or end-stage renal disease requiring chronic dialysis at screening visit
- Has MRI or CT scan confirmed stroke, cerebrovascular accident (CVA) or transient ischemic attack (TIA) within 6 months (180 days) prior to AVR surgery
- Has acute myocardial infarction (MI) within 30 days prior to AVR surgery
- Has presence of non-cardiac disease limiting life expectancy to less than 12 months
- Diagnosed with hypertrophic obstructive cardiomyopathy (HOCM)
- Diagnosed with hyperparathyroidism
- Exhibits left ventricular ejection fraction $\leq 30\%$ as validated by diagnostic procedure within 30 days prior to AVR surgery
- Echocardiographic evidence of an intra-cardiac mass, thrombus, or vegetation
- Hemodynamic or respiratory instability requiring inotropic support, mechanical circulatory support, or mechanical ventilation within 60 days prior to AVR surgery

³ Emergent surgery – surgery is carried out on the referral day before the beginning of the next working day.

- Documented leukopenia ($WBC < 3.5 \times 10^3/\mu L$), acute anemia ($Hgb < 10.0 \text{ gm/dL}$ or 6 mmol/L), thrombocytopenia (platelet count $< 50 \times 10^3/\mu L$) or history of bleeding diathesis or coagulopathy
- Diagnosed with myxomatous disease/connective tissue disorders (e.g. Marfan's Syndrome)
- Has prior organ transplant
- Current or recent participation (within 6 weeks prior to surgery) in an investigational drug or device trial
- Was previously implanted with trial device⁴
- Pregnant (female subject of childbearing potential only), lactating or planning to become pregnant during the duration of participation in trial
- Currently incarcerated or unable to give voluntary informed consent
- Documented history of substance (drug or alcohol) abuse within the last 5 years prior to implant

8.4 WITHDRAWAL CRITERIA AND PROCEDURES

Subjects may voluntarily withdraw consent at any time during the clinical trial with no loss of benefit or penalty. Subjects will be exempt from follow-up after withdrawing from the clinical trial. For subjects consented but have withdrawn, the trial site must retain the subject's informed consent and all documents pertaining to the subject prior to the subject's withdrawal.

The Investigator may withdraw any subject due to any of the following conditions:

1. Participation in the clinical trial may be contrary to the subject's current medical treatment, based on new information or changes in the subject's medical condition.
2. Any anatomical findings that would determine subject not suitable for implant with the Edwards aortic valve, Model 11000, which are discovered, intra-operatively. These may include findings such as:
 - a. The position of the coronary ostia relative to the Edwards aortic valve, Model 11000 would result in obstruction of blood flow,
 - b. the subject is hemodynamically unstable during the procedure requiring the procedure to be aborted prior to implanting the trial device,
 - c. A device is not available in the correct size for the subject;

The Investigator will document the withdrawal of trial subjects and notify the Trial Sponsor within five (5) working days. Additional subjects will be screened to replace those subjects who are withdrawn by the Investigator during the surgical procedure prior to implant.

Edwards will inform the Investigator of any new information about the trial that may affect the health, safety or welfare of the subjects or that may influence subject's decision to continue participating in the trial.

⁴ Note: Previously implanted means that the index aortic valve replacement procedure was completed. The procedure is complete when the surgeon takes the subject off cardiopulmonary bypass and restarts the heart.

9 STATISTICAL METHODS

9.1 SAMPLE SIZE

Up to 200 subjects will be enrolled in the trial at up to 6 participating sites.

9.2 ANALYSIS POPULATION

The analyses of safety data will include all enrolled subjects. Subjects are considered enrolled in the clinical trial after meeting the enrollment criteria, signing the informed consent and the surgeon determines that the index valve can be implanted.

The analyses of performance data will include the index valve population, defined as all subjects that are enrolled into the trial and that are implanted with the index valve.

9.3 SAFETY ANALYSIS

Early adverse events within 30 days of procedure will be reported as the number of events divided by the number of enrolled subjects. Linearized rates will be used to summarize adverse events for the late (>30 days) post-operative period. The linearized rates will be calculated as the number of late events divided by the total number of late-subject years.

Percentages for the early events and linearized rates for the late events also will be calculated for all other complications observed in the trial.

Actuarial rates based on the method of Kaplan-Meier will be calculated for each of the safety endpoints at each of the follow-up time points.

9.4 PERFORMANCE ANALYSIS

Hemodynamic Variables

Valvular regurgitation will be summarized by the number and percentage of subjects in each level of regurgitation. Other hemodynamic parameters will be summarized by N, mean, and standard deviation. These summaries will be summarized at baseline and each applicable follow-up visit for all subjects in the investigational valve population, and will be stratified by valve size.

NYHA Class

A comparison of preoperative and postoperative NYHA functional class (presented as the percentage of subjects in each class at baseline, at each follow-up time-point, and as the percentage of subjects at each follow-up time-point who improved, worsened, or did not change in class) will be presented. This comparison will be based on the investigational valve population. Additionally, a cross-tabulation of baseline vs. 1-year NYHA Class will be presented for all subjects in the investigational valve population with both baseline and 1-year NYHA data.

Quality of Life

The number, mean and standard deviation for the Quality of Life (EQ-5D) summary measurement will be presented at the pre-procedure and at the 1-year post procedure follow-up visit. In addition, the number and mean for the change from pre-procedure to the 1-year post procedure follow-up visit will be calculated and presented.

The number, mean, and standard deviation for the SF-12 physical and mental health summary measures (PCS-12 and MCS-12, respectively) will be calculated at the pre-procedure and at the 1-year post procedure follow-up visit. In addition, the number and mean for the change from pre-procedure to the 1-year follow-up in PCS-12 and MCS-12 will be presented.

9.5 OTHER DATA

The mean and standard deviation of blood data will be calculated and presented.

9.6 MISSING DATA

All analyses will apply to any available valid data. No data imputation will be performed for missing data.

10 TRIAL PROCEDURES

Table 3 summarizes all procedures to be conducted during the trial.

Table 3: Summary of Trial Assessments

Trial Procedure	Baseline	Implant	Discharge	3 months	1, 3, 5 year	2 & 4 years
Written Informed Consent	X					
Pregnancy Test	X					
Medical History	X					
Medical Evaluation	X		X	X	X	X
Height	X					
Weight	X		X	X	X	X
12-lead ECG	X		X	X	X	X
NYHA	X			X	X	X
Medications	X		X	X	X	X
Adverse Events		X	X	X	X	X
Echocardiography ¹ (TTE)	X		X	X	X	X ²
Echocardiography ³ (TEE)		X				
Auscultation						X ²
Quality of Life (EQ-5D and SF-12v2) ⁴	X				X	
Blood tests						
Complete Blood Count ⁵	X		X	X	X	X
Plasma free hemoglobin	X		X	X	X	X
Serum Creatinine	X					
Coagulation Profile	X		X	X	X	

Procedure table notes:

- 1 TTE will be the standard echo assessment for the aortic valve
- 2 If murmur heard then echo required
- 3 TEE intra-operatively and within 1 hour (from cross clamp removal) to confirm placement of the device and confirm initial function
- 4 Quality of Life only required at Baseline and at 1-year post-procedure
- 5 Complete blood count includes red blood cells, white blood cells, hemoglobin, hematocrit, platelet count

10.1 BASELINE EVALUATION

10.1.1 SUBJECT SCREENING

All subjects diagnosed with aortic valve disease requiring aortic valve replacement seen by cardiac surgeons participating in this clinical trial should be pre-screened for eligibility. All subjects who meet initial eligibility requirements will be asked to participate. A Screening Log will be provided to the trial sites to maintain a cumulative log of all screened subjects admitted for aortic valve replacement by the cardiac surgeons participating in this trial. For subjects listed as not eligible for participation in the clinical trial, a reason supporting the disqualification of the subject must be entered on the screening log. The Screening Log shall be completed and faxed to the Trial Sponsor regularly (at least once per month). Any subject deemed ineligible due to active endocarditis, recent myocardial infarction, pregnancy or lactating, or due to participation in another clinical trial may be re-screened later. Re-screened subjects must be re-entered on the Screening Log.

10.1.2 INFORMED CONSENT

Subjects who are eligible for participation in the clinical trial shall be provided with patient consent information, approved by the site's ethics committee (EC). Each subject shall be given ample time to read the Informed Consent in its entirety and ask questions to make an informed decision. The subject must sign and date the trial approved Informed Consent prior to participation, i.e. prior to any trial procedures. Subjects who provide informed consent will be assigned a trial subject identification number. The Investigator, or designee, and any witnesses shall also sign and date the consent form, as applicable. Failure to provide Informed Consent renders the subject ineligible for participation in the clinical trial including undergoing treatment with the trial device. Subjects who do not provide informed consent are recorded on the Screening Log.

10.1.3 BASELINE ASSESSMENT

After a written informed consent has been obtained from the subject the following baseline data will be obtained (see **Table 4**); demographic and medical history, 12-lead electrocardiogram (ECG), transthoracic echocardiograph (TTE) per protocol, blood studies per protocol, an assessment of NYHA Functional Classification, Quality of Life (EQ-5D and SF-12v2), and coagulation profile (via INR or PTT). Test results conducted within 30 days before aortic valve surgery may be used for this trial if all values per protocol are available and there has been no significant change in the subject's condition that would affect the test results.

Table 4 Baseline Assessment

Clinical/Physical Assessment		Blood Studies	Echocardiography (TTE)
Date of Assessment	Anti-thromboembolic	Blood Draw Date	Date of Exam
Date of Birth	Therapy	White Blood Cell Count	REFER TO ECHO MANUAL
Sex/Gender	(medications)	Red Blood Cell Count	
Height	Cardiovascular Risk Factors	Hemoglobin	
Weight	Cardiovascular Conditions	Hematocrit	
Heart Rate	Previous Procedures /	Platelet Count	
Blood Pressure	Interventions	Plasma Free	
Cardiac Rhythm (12-lead ECG)	Non-Cardiovascular	Hemoglobin	
NYHA Classification	Conditions	Serum Creatinine	
Quality of Life (EQ-5D & SF-12v2)	Pregnancy Test	Coagulation Profile	

10.2 SURGICAL PROCEDURE

10.2.1 PROCEDURE PREPARATION

The surgical approach used will be at the discretion of the investigator per his/her routine surgical practice. At the time of aortic valve replacement, a transesophageal echocardiogram to further assess the anatomy is recommended prior to aortic valve (to ensure no withdrawal criteria are met per section 8.4). After performing the aortotomy, the native valve and surrounding anatomy should be examined for compatibility with the device again to ensure no withdrawal criteria are met.

10.2.2 MODEL 11000 IMPLANTING PROCEDURE

A detailed description of device preparation and use is provided in the Instructions for Use (IFU), (See Clinical Investigator's Brochure). Investigators must be familiar with Precautions and Implant Technique described in the IFU prior to use of the index valve.

10.2.3 IMPLANT ASSESSMENT

A Transesophageal echo (TEE) should be performed within 1 hour after the index valve is implanted (from cross clamp removal) to assess placement and index valve function. The echo requirements are in the Echo Manual.

Procedural information, findings, results and device identification information to be recorded is identified in Error! Reference source not found..

Table 5 :Procedural information

General information	Clinical information	Device performance
Date of Admission	Etiology	Valve size and serial number
Date of Procedure	Diagnosis for replacement	Post-operative TEE (within 1 hour)
Implanting Surgeon	Valve implant	REFER TO ECHO MANUAL
Type of Operation	Condition of the native aortic valve	
	Sizing	
	Concomitant procedures	
	Intraoperative Adverse Events	

10.3 SUBJECT ENROLLMENT

Subjects will be considered enrolled in the clinical trial after meeting the enrollment criteria, signing the informed consent and the surgeon determines that the index valve can be implanted. The point of enrollment in the clinical trial is established in the Operating Room when the investigator confirms that the subject is an appropriate candidate for the index valve or trial device and attempts to implant the valve. Additional subjects will not be enrolled to replace those subjects implanted with the index valve who choose to withdraw from the clinical trial.

10.4 POST-PROCEDURE

10.4.1 POST-PROCEDURE CARE

At the discretion of the investigator, bioprosthetic heart valve recipients should be maintained on anticoagulant therapy (except when contraindicated) during the initial healing stages after implant, approximately 2 to 3 months in accordance with the ACC/AHA 2008 Guidelines for the Management of Patients with Valvular Heart Disease.⁶ Anticoagulants should then be discontinued over a period of 10 days, except in those patients for whom ongoing anticoagulant protection is indicated, i.e. in the absence of sinus rhythm and in patients with a dilated left atrium, calcification of the atrial wall, history of previous atrial thrombus, or any other medical condition requiring anticoagulation therapy. However, the appropriate anticoagulation therapy must be determined by the physician on an individual basis.

10.4.2 DISCHARGE

Table 6 identifies the medical information and clinical evaluation of trial subjects at discharge, which includes an echocardiogram (refer to Section 10.5).

Table 6 Discharge Information

Clinical/Physical Assessment	Blood Studies	Echocardiography (TTE)
Date of Discharge	Blood Draw Date	Date of Exam
Weight	White Blood Cell Count	<i>REFER TO ECHO MANUAL</i>
Heart Rate	Red Blood Cell Count	
Blood Pressure	Hemoglobin	
Cardiac Rhythm (12-lead ECG)	Hematocrit	
Anti-thromboembolic Therapy (medications)	Platelet Count	
Adverse Events	Plasma Free Hemoglobin Coagulation Profile	

Subjects, who are not discharged within 10 days post procedure must have an echocardiogram (refer to Section 10.5) to further assess placement and performance of the index valve. This echocardiogram is required to complete the evaluation of valve short-term function. Those subjects will not require an additional echocardiogram at discharge.

10.4.3 FOLLOW-UP ASSESSMENTS

Post-procedure clinical evaluation will be performed on all enrolled trial subjects at scheduled visits at the trial site. The follow-up windows are listed in **Table 7**.

Table 7: Follow-up Windows

Follow-up Assessment*	Assessment Window
3 months	± 1 month
1 year	± 1 month
2 years	± 3 month
3 years	± 3 month
4 years	± 3 month
5 years	± 3 month

*Follow-up visits are calculated from the implant date.

During each postoperative follow-up visit, the investigator(s) will determine the subject's availability for future follow-up visits. If any subject needs to be seen, at a time other than a regularly scheduled follow-up visit, due to an index device related event, the required data collection would be the same as the 1 year follow-up evaluation.

Table 8 Follow-Up Information at all Post-Discharge Visits (3 months and annually to 5 years)

Clinical/Physical Assessment	Blood Studies	Echocardiography (TTE) ³
Date of Discharge	Blood Draw Date	Years 1, 3, 5:
Physical Assessment	White Blood Cell Count	Date of exam
Cardiac Rhythm (12-lead ECG)	Red Blood Cell Count	SEE ECHO MANUAL
NYHA Classification	Hemoglobin	Years 2, 4:
Quality of Life (EQ-5D & SF12-v2) ¹	Hematocrit	Date of exam
Anti-thromboembolic Therapy (medications)	Platelet Count	Auscultation ⁴
Adverse Events	Plasma Free Hemoglobin	
	Coagulation Profile ²	

¹ Quality of Life (EQ-5D and SF12-v2) will be completed only at the 1-year follow-up visit

² Coagulation profile will be completed only at years 1, 3, and 5

³ Exam to be performed as described in the Echo Manual. Data evaluation performed by a Core Lab.

⁴ TE will be the standard echo assessment for the aortic valve but will only be completed if murmur is heard on auscultation at year 2 and year 4 interval visits.

10.5 ECHOCARDIOGRAM

Echocardiograms will be independently analyzed by the Echocardiography Core Lab. Each sonographer participating in the clinical trial must be trained on the requirements of the Echo Manual.

10.6 DEVICE REMOVAL / EXPLANT

Index valve 'removal' is the excision of the investigational valve, before implant of the investigational valve is complete, i.e., the heart is not restarted with the investigational valve in place. If the surgeon is unable to satisfactorily position or sew in the index valve, it will be removed and returned to the trial Sponsor who will provide a return valve kit. If the heart is restarted, the valve will be considered implanted and if removal is required from this point forward, it will be considered an explant.

In the event a valve is explanted, a copy of the procedure report must be provided to the trial Sponsor. Information on the cause of explant and its relationship to the valve will be provided by the investigator(s). Explanted valves must be returned to the trial Sponsor for analysis. Return kits for devices will be provided by the trial Sponsor.

10.7 MISSED SUBJECT VISITS

The Investigator(s) will make every attempt to follow the subjects and subjects will be encouraged by the Investigator(s) to report any address or telephone number changes to the trial site. They will also be informed of the importance of returning for scheduled follow-up visits even if they are not having any problems.

If a subject cannot be reached for a follow-up visit, the Investigator will document on the CRF, the efforts undertaken to contact the subject or the subject's primary health care provider. These efforts should include 2 attempts of telephone contact at separate dates and times, and a registered letter before the end of the follow-up window. If a subject cannot be reached for a follow-up visit, or misses a scheduled visit, the visit will be recorded as a missed visit on the date of last attempted contact. Subjects who miss a visit will not be considered withdrawn. At the next visit interval, the Investigator and/or designee will attempt to contact the subject again for follow-up. Should this attempt to contact the subject fail, a family member should be contacted in addition to the subject. Subjects who miss 2 sequential follow-up visits will be considered lost to follow-up at the second missed visit and exempt from further trial follow-up. After the subject is terminated from the trial, the Investigator will attempt to determine if the subject is alive, including searching national mortality registries as permitted by local laws.

10.8 TRIAL SUBJECT EXIT

Trial Subjects exit the trial when no additional follow-up visits, procedures, or data collection are required. A subject is exited from the trial in the following instances:

- Subject fails enrollment criteria after written consent
- Subject is considered enrolled as "intent to treat" however surgeon is unable to complete the implant procedure*
- Subject has trial device explanted*
- Subject is lost-to-follow-up
- Subject withdraws from the trial
- Subject death
- Subject completes trial follow-up

* Subjects will be followed for 30 days or until any adverse events experienced by this cohort are resolved and then will be exited from the trial.

10.9 CLINICAL TRIAL TERMINATION

The principal investigator(s) will be notified in writing upon termination of the clinical trial. The Trial Sponsor retains the right to suspend or terminate this clinical trial at any time. Upon trial termination, the Investigator will contact the trial subjects to perform a final follow-up assessment within 2 months of trial termination. If a subject completed a protocol scheduled clinical evaluation within 6 months prior to trial termination, the final follow-up assessment may be completed by telephone. Subjects should continue seeing their physicians as part of routine clinical follow-up after heart valve replacement surgery.

11 ADVERSE EVENTS

11.1 REPORTING PROCEDURE

Adverse event information will be reported throughout the clinical trial as they occur. Adverse events will be followed until they are adequately resolved or explained. The investigator(s) should report any serious adverse event to the Trial Sponsor's Clinical Research department within 48 hours after the investigator's first knowledge of the event, followed by a written report in ten working days. **Notification should be done via email to HVTClinicalResearch@edwards.com or faxed to +1 (949) 250-5010.** In addition, trial sites will

report all adverse events to their local EC in accordance with the review committee's requirements.

11.2 ADVERSE EVENT DEFINITIONS

11.2.1 ADVERSE EVENT

An adverse event (AE) is defined in ISO 14155:2011 (referred to hereafter as ISO 14155) as any untoward medical occurrence in a subject.

11.2.2 ADVERSE DEVICE EFFECT

An adverse device effect (ADE) is defined in ISO 14155 as 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.

11.2.3 SERIOUS ADVERSE EVENT

A serious adverse event (SAE) is defined in ISO 14155 as an adverse event that: led to death, led to a serious deterioration in the health of the subject that resulted in a life-threatening illness or injury, resulted in a permanent impairment of a body structure or a body function, required inpatient hospitalization or prolongation of existing hospitalization, or resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function, or led to fetal distress, fetal death or a congenital abnormality or birth defect.

11.2.4 SERIOUS ADVERSE DEVICE EFFECT

A serious adverse device effect (SADE) is defined in ISO 14155 as an 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.

11.2.5 UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT

An unanticipated serious adverse device effect (USADE) is defined as serious adverse device effect, which by its nature, incidence, severity or outcome is not identified in the Clinical Investigator's Brochure.

11.3 DEATHS AND EXPLANTS

11.3.1 SUBJECT DEATHS

In the event of subject death, every effort should be made to obtain a copy of the autopsy report and/or death summary. Information on the cause of death and its relationship to the device used in this clinical trial will be determined by the principal investigator. Copies of an autopsy report, if available, and/or a death summary are to be sent to the Trial Sponsor.

If a device is explanted during autopsy, the device should be returned to the Trial Sponsor for analysis. Return kits for devices will be provided upon request by the clinical monitor.

11.4 CLINICAL EVENTS COMMITTEE

The Clinical Events Committee (CEC) evaluates adverse events that are endpoint related. The CEC adjudicates events for their relatedness to the investigational device and/or the surgical procedure. The CEC will be composed of physicians familiar with the treatment of valvular heart disease and cardiac surgery who are not participating in the investigational trial.

The trial Sponsor will provide the CEC completed case report forms and any relevant source documentation/subject information as provided by the clinical site investigators. Trial Sponsor will insure that all information is de-identified before presenting to the committee. The CEC documents its findings or rulings on each event. All meeting minutes and supporting documentation are maintained by the CEC administrator with a copy provided to the trial Sponsor.

12 TRIAL AND DATA MANAGEMENT

12.1 TRIAL CORE LABS

12.1.1 ECHOCARDIOGRAPHY CORE LAB

The Echo Core Lab is responsible for independently evaluating echocardiograms submitted preoperatively and postoperatively by trial sites, and for reporting of hemodynamic and other valvular function results. Echocardiograms will be sent directly from the investigational sites to the Echo Core Lab. See **Appendix 15.7** for the Echo Core Lab Manual.

12.2 DEVICE SHIPMENTS

An initial set of Edwards's aortic valve, Model 11000 will be shipped to the trial site once the following conditions are met: the trial site has obtained Ministry of Health and Ethics Committee approval, a signed Clinical Trial Agreement is in place, and the Site Initiation Visit, including Principal Investigator training, has been completed. Additional devices will be sent to the trial site as devices are used or as needed.

12.3 INVENTORY AND ACCOUNTABILITY RECORDS

All device shipments will have inventory and shipment records. Devices may be hand carried to participating trial sites by Trial Sponsor personnel. Shipment will be accompanied by trial device documentation of delivery. The principal investigator(s) or designee will take inventory of the product and complete the delivery documentation with receipt date, condition of the device and signature. Both the trial site and the trial Sponsor will retain copies of these documents.

The investigator will maintain a Device Accountability Log of all trial devices received for use during this clinical trial. The log will be kept with the documents for the clinical trial and will be available for review during Trial Sponsor monitoring visits.

12.4 DEVICE STORAGE

The device inventory will be stored in a locked, controlled, cool, dry and clean area as described in the Instructions for Use (IFU). This storage area shall be accessible only to the principal investigator(s), his/her co-investigator or approved designee. Only cardiac surgeons identified in

the Clinical Trial Agreement and/or on the Delegation of Authority form on file at the Trial Sponsor may implant the trial device.

12.5 DEVICE RETURN

The principal investigator(s) will be notified in writing upon termination of the clinical trial. All unused devices in original package and/or those in opened packages as well as those removed from the original package will be returned upon receipt of this notice as described in the IFU. The Investigator's copy of the Device Accountability log must document any unused devices that have been returned. Contact Edwards Lifesciences, the Trial Sponsor, for additional instructions.

12.6 PROTOCOL DEVIATIONS

A protocol deviation is defined as an event where the Investigator or trial personnel did not conduct the trial according to the clinical protocol or the Clinical Trial Agreement.

Deviations shall be reported to the Trial Sponsor regardless of whether medically justifiable or taken to protect the subject in an emergency. Subject specific deviations and non-subject specific deviations, (e.g. unauthorized use of a trial device outside the trial, unauthorized use of a trial device by a physician who is not listed in the Clinical Trial Agreement, etc.) will be reported in writing. Investigators will also adhere to procedures for reporting trial deviations to their EC in accordance with their specific EC's reporting policies and procedures.

For reporting purposes, deviations are classified as major or minor:

- Major deviations:
 - Any deviation from subject inclusion and exclusion criteria;
 - Any deviation from subject informed consent procedures;
 - Unauthorized use of an trial device outside the trial;
 - Unauthorized use of a trial device by a physician who is not listed in the Clinical Trial Agreement.
- Minor deviations:
 - Deviation from a protocol requirement such as incomplete/inadequate testing procedures;
 - Follow-up performed outside specified time windows.

12.6.1 EXCEPTIONS

Some information collected in this trial is not essential to the trial endpoints and will not be considered deviation if absent.

12.7 TRAINING

12.7.1 TRAINING OF TRIAL SITE PERSONNEL

Principal investigator(s) and support staff will be trained by the Trial Sponsor on the use of the Edwards aortic valve, Model 11000 and accessories, the Protocol, the Clinical Investigator's Brochure, electronic Case Report Forms (eCRF) and Electronic Data Capture (EDC) system, device accountability procedures, GCP (Good Clinical Practices) Guidelines and other trial documents as applicable. A "Delegation of Authority Form" will be completed at each trial site designating which individuals are allowed to perform specific clinical trial related tasks. The

delegated tasks will determine what the training requirements are for each member of the trial support staff.

12.7.2 DEVICES

Each cardiac surgeon participating in the clinical trial must be trained on the use of the device and the clinical protocol before screening potential subjects or using the Edwards aortic valve, Model 11000.

12.8 MONITORING

12.8.1 SITE INITIATION

Prior to subject enrollment, an initiation visit will be completed at each trial site to ensure the following:

- Ethics Committee and applicable regulatory body approvals have been obtained and documented,
- The investigators and clinical trial personnel are appropriately trained and clearly understand the trial,
- The investigators and clinical trial personnel accept the obligations incurred in undertaking this clinical trial.
- The Delegation of Authority form has been completed properly

12.8.2 MONITORING METHODS

The Trial Sponsor will assign a monitor to monitor the progress of the clinical trial at each trial site. The monitor will remain in close contact with each trial site throughout the duration of the trial to provide any needed materials, (i.e. trial forms) or answer any questions. The monitor will be responsible for verifying that the subject signed the consent, reviewing date recorded on the eCRF, and visiting each trial site periodically to observe trial progress and compliance with clinical protocol and regulations applicable to this clinical trial.

Monitoring visits will be scheduled throughout the duration of the clinical trial between the monitor and the principal investigator at a mutually convenient and available time. These visits will assure that the facilities are still acceptable, the protocol and investigational plan are being followed, the EC has been notified of approved protocol changes as required, complete records are being maintained, appropriate timely reports have been made to the Trial Sponsor and the EC, device inventory are accounted for and controlled, and the investigator is carrying out all agreed activities. Any personnel changes must be reported to the monitor immediately and a training program scheduled and documented.

Periodic monitoring visits will be made at all enrolling trial sites in accordance with center enrollment rates. Trial sites should be visited a minimum of once each year by the monitor. Upon termination or conclusion of the clinical trial, the monitor will perform a close-out visit.

12.9 DOCUMENTATION REQUIREMENTS

Training will be documented on a training record provided by the Trial Sponsor, which the trainee must sign and date. The training of trial support staff must be completed and

documented before the staff member may perform the specific clinical trial related tasks delegated to them by the Principal Investigator.

12.9.1 SOURCE DOCUMENTATION REQUIREMENTS

Clinical regulations require that Investigators maintain information in the clinical trial subject's medical records that corroborate data collected on the eCRF. Some examples of critical information to be maintained for review by the regulatory inspectors and Trial Sponsor monitors are:

- Medical history and physical condition of the clinical trial subject before involvement in the clinical trial sufficient to verify protocol entry criteria
- Dated and signed notes in the subject's medical record on the day of entry into the clinical trial.
- Dated and signed notes, laboratory records, and test reports, from each clinical trial subject visit with reference to the eCRF for further information, if appropriate (for specific results of procedures and exams).
- Notations on abnormal lab results, adverse events reported and their resolution.
- Notes regarding concomitant anticoagulant/antithrombotic medications taken during the clinical trial
- Subject's condition upon completion of or withdrawal from the clinical trial.

To protect subject confidentiality, the subject's name must not appear anywhere on the imaging media sent to Edwards e.g. for reporting serious adverse events (SAE), or prepared for evaluation by the core lab. Each page should be identified with the subject's unique trial ID number. All other subject identifiers (i.e. medical record number, personal number) are to be obscured. Original copies of all data must be kept at the site.

12.9.2 DATA COLLECTION METHODS

All required data for this trial are to be collected with standardized Case Report Forms (CRF) for individual subjects; the eCRF outline is included in Appendix 16.5. Electronic CRF (eCRF) will be utilized for this trial. All eCRF must be electronically signed by the Principal Investigator or co-Investigator listed in the Clinical Trial Agreement and Delegation of Authority Log. If for any reason the eCRF are unavailable and/or inaccessible, paper CRF will be provided by the Trial Sponsor to be completed, signed by the Principal Investigator or designee and submitted to the Trial Sponsor.

Primary data collection should be drawn from the subject's hospital chart and operator worksheet (source document) reviews. All eCRF must be kept current to reflect subject status during the course of the trial.

Case Report Form Instructions will be provided to assist the Investigator(s) and appropriate trial staff with the completion of the required eCRF.

Data Management personnel will employ a full-featured relational Oracle database application on a central server. The application provides the capability of data collection remotely through the Internet so the participating site personnel may log on to the system securely and enter the data. Other data management programming and/or data analyses will be done in the database

system through the sponsor's internal network. All subjects' data collected in the system will be extensively verified through data validation programs, database integrity rules, and trial-specific data entry conventions for data accuracy and logical meaningfulness. Periodic analysis of all subjects' collected data will be performed in order to examine the expected distributions of data and to identify outliers for possible data entry errors.

12.9.3 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

All data collected for the purposes of the trial must be documented in the subject's medical notes. Copies of relevant procedural records, examinations and laboratory test results should be kept on file in the Investigator's subject files, e.g. a copy of echo examination sent to the core lab should be kept with the subject records. Medical notes, eCRF and copies of test results must be available at all times for inspection by the trial monitor.

12.9.4 COMMUNICATION PROCEDURES

During the course of the clinical trial, all correspondence (letters, records of telephone calls, emails and faxes) regarding the trial must be maintained in the trial binder provided by the Trial Sponsor. This binder must be made available for monitoring visits or audits.

12.10 PROTOCOL AMENDMENTS

Changes in the protocol may be made only by written amendment agreed upon by the sponsor, the regulatory agency, and if pertinent, the EC. As appropriate, the Trial Sponsor will submit changes in the protocol to the pertinent regulatory agencies and investigators to obtain EC re-approval.

12.11 AUDITS AND INSPECTIONS

In the event that audits are initiated by the sponsor or national/international regulatory authorities, the investigator shall allow access to the original medical records and provide all requested information.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 APPLICABLE REGULATIONS AND GUIDELINES

The regulations listed in Table 9 must be observed to comply with the Trial Sponsor's policy for conduct of clinical studies; they also represent sound research practice. It is the responsibility of the investigator(s) to comply with the requirements set forth in their country specific regulations.

Table 9: Applicable Regulations and Guidelines

Region	Regulation / Guideline
Europe	<ul style="list-style-type: none"> - 93/42/EEC European Medical Device Directive (MDD) - ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects) - ISO 5840: 2009 (Cardiovascular implants-Cardiac valve prostheses) - Declaration of Helsinki (2008)
Canada	<ul style="list-style-type: none"> - Canadian Medical Device Regulations (CMDR) - Canadian Investigational Testing Authorization as defined in the Medical Devices Regulation, May 1998

Furthermore, the investigator should use *Good Clinical Practice (GCP)* and must comply with the laws of the country, whichever will afford greater protection to subjects screened for participation in the clinical trial and subjects who participate in the trial.

13.2 DATA PROTECTION AND SUBJECT CONFIDENTIALITY

The Trial Sponsor is dedicated to maintaining the confidentiality and privacy of subjects who volunteer to participate in the clinical trial. Passwords are issued to appropriate personnel to insure confidentiality and protection of the database by allowing variable levels of access to the computer system. In addition, the principal investigator is responsible for maintaining confidentiality throughout the clinical trial. Hard copies of source documentation are to be maintained in a secure area with limited access. All subject identifiers will be obliterated from all photocopies of source documents that have been removed from the trial site. Subject identifiers include, but are not limited to subject's name, subject's initials, social security number or equivalent, and medical / hospital number. All documents for the clinical trial will identify the subject by a subject identification number assigned by the Trial Sponsor.

13.3 INFORMED CONSENT AND REVIEW COMMITTEES

All subjects must provide written informed consent in accordance with the local trial site's EC rules and regulations. A copy of the consent form from each center must be forwarded to the Trial Sponsor for review and approval prior to submitting it to the EC. Each center must provide the Trial Sponsor with a copy of the trial site's EC approval letter (stating at a minimum, the clinical trial name or identification number, protocol revision being approved and an approval date) and the informed consent prior to the initiation of enrollment at that center. If yearly approvals for the continuation of the trial at each trial site are required, they must also be forwarded to the Trial Sponsor.

13.4 INVESTIGATOR RESPONSIBILITIES

13.4.1 GENERAL DUTIES

The investigator shall ensure that all work and services described herein, or incidental to those described herein, shall be conducted in accordance with the highest standards of medical and clinical research practice and the applicable regulations. The investigator shall be responsible for the day to day conduct of the clinical trial and for the safety and well-being of human subjects enrolled. The investigator will provide copies of the current clinical protocol to all staff responsible for conduct of the clinical trial.

The principal investigator is responsible for obtaining EC approval to start the clinical trial at his/her trial site.

If there is a change or addition of co-investigator, an amended Clinical Trial Agreement must be completed promptly.

13.4.2 INVESTIGATOR RECORDS

The principal investigator will maintain accurate, complete, and current records relating to the site and their subjects participation in this clinical trial. Records including eCRF and supporting data, hardcopies of all blood and diagnostic exams, signed Clinical Trial Agreement, protocols and protocol amendments, signed informed consents, device tracking log and use of devices, EC approval letters, EC submissions, correspondence, including required reports and other documents pertaining to the conduct of the clinical trial must be kept on file by the investigator. If the investigator(s) wishes to assign the responsibility for maintaining files to someone else or remove them to another location, he/she should consult with the Trial Sponsor in writing as to this change. Files for the clinical trial must be maintained in a known location for a period in accordance with Edwards Lifesciences record retention requirements.

13.4.3 INVESTIGATOR REPORTS

The principal investigator will prepare and submit the following accurate and complete reports to the Trial Sponsor and EC in a timely manner:

- Unanticipated serious adverse device effects (USADE) occurring during the clinical trial will be reported immediately (without any delay that could not be justified) after the principal investigator first learns of the event.
- Serious adverse device effects (SADE) occurring during the clinical trial will be reported as described in Section 11.1
- Deviation from the clinical protocol. Deviations to protect the subject's life or physical well-being in an emergency will be reported to the Trial Sponsor within 5 working days and the EC within their reporting policy.
- Use of devices without informed consent will be reported to the Trial Sponsor within 5 working days after the use occurs.
- A final written report is submitted to the Trial Sponsor and the EC within three months of completion or termination of the trial.
- Upon request by a reviewing EC or the pertinent regulatory agencies, the principal investigator will provide current information about any aspect of the trial.

13.5 TRIAL SPONSOR RESPONSIBILITIES

13.5.1 GENERAL DUTIES

As the sponsor of this clinical trial, Edwards Lifesciences has the overall responsibility for the conduct of the clinical trial, including assurance that the trial meets the regulatory requirements of the pertinent regulatory agencies. In this clinical trial, Edwards Lifesciences will have certain direct responsibilities and will delegate other responsibilities to an Echocardiography Core Laboratory.

13.5.2 SELECTION OF INVESTIGATORS

Edwards Lifesciences will select qualified investigators and will ship trial devices to participating trial sites only. Edwards Lifesciences will obtain signed investigator agreements and provide the Investigators with the information and supplies necessary to conduct the clinical trial.

13.5.3 MONITORING THE CLINICAL TRIAL

Edwards will ensure compliance with the signed investigator's agreement, the protocol (investigational plan), the requirements of applicable regulations and guidelines (see section 13.1), and any conditions of clinical trial approval by the EC and regulatory bodies per written monitoring procedures.

Edwards will conduct an immediate investigation of any unanticipated serious adverse device effects (USADE). If an event is found to present an unreasonable risk to subjects, participating in this clinical trial Edwards will inform investigators as required.

13.5.4 SPONSOR RECORDS

Edwards Clinical Research will maintain accurate, complete, and current records relating to this clinical trial. Records include eCRF, signed Investigator Agreement, financial disclosure, protocols and protocol amendments, signed informed consents, device use, EC approval letters, EC submissions, correspondence, including required reports, and other documents. Edwards will maintain documentation during the clinical trial and for a period of 100 years after the clinical trial is terminated or completed, or the records are no longer required to support a regulatory submission. Storage of the records may be designated to a third party.

13.5.5 SPONSOR REPORTS

Edwards Clinical Research will prepare and submit the following accurate and complete reports to the EC and the pertinent regulatory agencies in a timely manner:

- Withdrawal of EC approval will be reported to all EC and the pertinent regulatory agencies within 5 working days of receipt of withdrawal of approval.
- Withdraw of the pertinent regulatory agencies approval will be reported to trial sites and EC within 5 working days after receiving the notice of approval withdrawal.
- Current investigator list will be submitted to the pertinent regulatory agencies at 6-month intervals.
- Progress reports to the EC at least annually and to the pertinent regulatory agencies as required.
- A final written report is to be completed and submitted to the EC and the pertinent regulatory agencies within six months after completion or termination of the trial.
- Use of the devices without informed consent will be reported to regulatory authorities within 5 working days after notification of device use.
- Upon request by a reviewing EC or the pertinent regulatory agencies, Edwards will provide current information about any aspect of the trial.

13.6 PUBLICATION POLICY

The publication of trial results will require prior approval and consent from the trial sponsor. Any analyses generated from the trial database for a manuscript will require review and approval by the trial sponsor prior to publication submission.

14 REFERENCES

1. Rosenhek R, Binder R, Porenta G et al. Predictors of outcome in severe asymptomatic aortic stenosis. *N Engl J Med* 2000; 343(9): 611-7.
2. Horstkotte D, Loogen F. The natural history of aortic valve stenosis. *Eur Heart J Suppl E* 1998; 57-64.
3. Carpentier A. Cardiac valve surgery. The French Correction. *J Thorac Cardiovasc Surg* 1983; 86: 323-37.
4. Carpentier A. *Carpentier's Reconstructive Valve Surgery*. Maryland Heights: Saunders, 2010.
5. Craver JM. Aortic valve debridement by ultrasonic surgical aspirator: A word of caution. *Ann Thorac Surg* 1990; 49: 746-52.
6. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2008; 52(13):e1-142.

15 APPENDICES

Appendices could be updated independently from the Clinical Investigation Plan

15.1 ADVERSE EVENT (CODES AND DEFINITIONS)

Clinical Investigational Plan
 Protocol Number: 2010-03

AE CODE LIST		
CODE	LABEL/NAME	DEFINITION
AE.1	BLOOD AND LYMPHATIC (INCLUDING ALL BLEEDING COMPLICATIONS)	
AE101	ANEMIA – NON-BLEEDING RELATED	A CONDITION IN WHICH RED BLOOD CELL COUNT AND/OR HEMOGLOBIN ARE LESS THAN NORMAL DUE TO LACK OF PRODUCTION OF RED BLOOD CELLS, AND THAT REQUIRES TREATMENT OR TRANSFUSION.
AE102	ANEMIA – BLEEDING RELATED - MAJOR	A CONDITION IN WHICH RED BLOOD CELL COUNT AND/OR HEMOGLOBIN ARE LESS THAN NORMAL DUE TO BLOOD LOSS, AND THAT REQUIRES TREATMENT OR TRANSFUSION.
AE103	ANEMIA – BLEEDING RELATED - MINOR	A CONDITION IN WHICH RED BLOOD CELL COUNT AND/OR HEMOGLOBIN ARE LESS THAN NORMAL DUE TO BLOOD LOSS, AND THAT REQUIRES TREATMENT OR TRANSFUSION.
AE104	BLEEDING - CARDIOVASCULAR - MAJOR	ANY EPISODE OF MAJOR INTERNAL OR EXTERNAL BLEEDING THAT CAUSES DEATH, HOSPITALIZATION, OR PERMANENT INJURY (E.G., VISION LOSS) OR NECESSITATES TRANSFUSION. MAJOR BLEEDING UNEXPECTEDLY ASSOCIATED WITH MINOR TRAUMA SHOULD BE REPORTED AS A BLEEDING EVENT, BUT BLEEDING ASSOCIATED WITH MAJOR TRAUMA OR A MAJOR OPERATION (INCLUDING THE INDEX PROCEDURE) SHOULD NOT. THE LOCATION OF THE BLEEDING (GASTROINTESTINAL, GENITOURINARY, ETC.) MUST BE REPORTED. FOR EACH REPORTED BLEEDING EVENT, INDICATE IF SUBJECT IS TAKING ANTICOAGULANTS OR ANTI-PLATELET AGENTS.
AE105	BLEEDING - CARDIOVASCULAR - MINOR	"
AE106	BLEEDING - GENITOURINARY - MAJOR	"
AE107	BLEEDING - GENITOURINARY - MINOR	"
AE108	BLEEDING - GASTROINTESTINAL UPPER -MAJOR	"
AE109	BLEEDING - GASTROINTESTINAL UPPER -MINOR	"
AE110	BLEEDING - GASTROINTESTINAL LOWER -MAJOR	"
AE111	BLEEDING - GASTROINTESTINAL LOWER -MINOR	"
AE112	BLEEDING - MUSCULOSKELETAL/DERMATOLOGICAL -MAJOR	" (E.G. ECCHYMOSIS)
AE113	BLEEDING - MUSCULOSKELETAL/DERMATOLOGICAL -MINOR	" (E.G. ECCHYMOSIS)
AE114	BLEEDING - NEUROLOGICAL - MAJOR	" (E.G. CEREBRAL VASCULAR ACCIDENT)
AE115	BLEEDING - NEUROLOGICAL - MINOR	" (E.G. CEREBRAL VASCULAR ACCIDENT)
AE116	BLEEDING - PERIPHERAL VASCULAR -MAJOR	" (E.G. NOSEBLEEDS; HEMATOMAS)
AE117	BLEEDING - PERIPHERAL VASCULAR - MINOR	" (E.G. NOSEBLEEDS; HEMATOMAS)
AE118	BLEEDING - PULMONARY/RESPIRATORY - MAJOR	" (E.G. HEMOTHORAX)
AE119	BLEEDING - PULMONARY/RESPIRATORY MINOR	" (E.G. HEMOTHORAX)
AE120	BLOOD SEPSIS	POSITIVE BLOOD CULTURE AND CLINICAL EVIDENCE OF INFECTION (E.G. FEVER, ELEVATED WBC COUNT, HYPOTENSION, END ORGAN DYSFUNCTION) EVENT MUST BE CONFIRMED BY 2 CONSECUTIVE POSITIVE BLOOD CULTURES, EXPLANT OR AUTOPSY.

Clinical Investigational Plan
 Protocol Number: 2010-03

AE CODE LIST	
CODE	DEFINITION
AE.1	BLOOD AND LYMPHATIC (INCLUDING ALL BLEEDING COMPLICATIONS) (CONTINUED)
AE122	PLASMA -FREE HEMOGLOBIN > 40 MG/DL ON TWO CONSECUTIVE MEASUREMENTS WITHIN 48 HOURS; OR CLINICAL DIAGNOSIS OF HEMOLYSIS EVIDENCED BY LABORATORY TESTING SUCH AS SERUM HEMOGLOBIN, HEMATOCRIT, AND/OR PLASMA-FREE HEMOGLOBIN (NOT IMMUNOLOGICALLY BASED)
AE123	DIFFUSE, NONSURGICAL, MICROVASCULAR HEMORRHAGE AND/OR THROMBOSES.
AE124	THROMBOCYTOPENIA (<150,000 PER CUBIC MILLIMETER), OR A RELATIVE DECREASE OF 50 PERCENT OR MORE FROM BASELINE, OR NEW THROMBOSIS IN A SUBJECT RECEIVING HEPARIN OR LMWH; CONFIRMED BY SEROLOGIC TESTING FOR PF4-HEPARIN ANTIBODIES.
AE125	THROMBOCYTOPENIA (<150,000 PER CUBIC MILLIMETER), OR A RELATIVE DECREASE OF 50 PERCENT OR MORE FROM BASELINE, ACCOMPANIED BY A LOW INDEX OF SUSPICION FOR HIT (I.E., NOT ASSOCIATED WITH HEPARIN USE, THE PRESENCE OF OTHER CAUSES OF THROMBOCYTOPENIA, SUCH AS DRUGS OTHER THAN HEPARIN, DIC OR OTHER CONSUMPTIVE PROCESSES, POST-TRANSFUSION PURPURA).
AE126	OTHER BLOOD OR LYMPHATIC EVENT THAT DOES NOT FIT IN ONE OF THE OTHER "BLOOD" CATEGORIES THAT REQUIRES HOSPITALIZATION OR MEDICAL INTERVENTION.
AE.2	CARDIOVASCULAR - ARRHYTHMIA
AE158	AN ABNORMAL HEARTBEAT IN WHICH THE HEART RHYTHM IS FAST AND IRREGULARLY IRREGULAR. EVENT SHOULD BE DOCUMENTED AND CONFIRMED BY ECG TEST RESULTS. AF IS CONSIDERED PERMANENT WHEN IT HAS PERSISTED BEYOND 1 YEAR AND ATTEMPTS AT CONVERSION HAVE FAILED OR COULD NOT BE ATTEMPTED.
AE149	ARRHYTHMIA - PERMANENT ATRIAL FIBRILLATION
AE157	AN ABNORMAL HEARTBEAT IN WHICH THE HEART RHYTHM IS FAST AND IRREGULARLY IRREGULAR. EVENT SHOULD BE DOCUMENTED AND CONFIRMED BY ECG TEST RESULTS. AF IS CONSIDERED PAROXYSMAL WHEN EPISODES OF AF TERMINATE SPONTANEOUSLY WITHIN 7 DAYS (MOST EPISODES LAST LESS THAN 24 HOURS)
AE141	ARRHYTHMIA - PAROXYSMAL ATRIAL FIBRILLATION (PAF)
AE142	ARRHYTHMIA - PERSISTENT ATRIAL FIBRILLATION
AE143	ARRHYTHMIA - ATRIAL FLUTTER
AE144	ARRHYTHMIA - PERSISTENT ATRIAL FIBRILLATION
AE145	ARRHYTHMIA - AV BLOCK - 1ST DEGREE
AE146	ARRHYTHMIA - AV BLOCK - 2ND DEGREE
AE147	ARRHYTHMIA - AV BLOCK - 3RD DEGREE
AE148	AV BLOCK I: A CONDUCTION DISORDER OF NERVOUS IMPULSE AT THE LEVEL OF THE ATRIOVENTRICULAR JUNCTION, I.E. BETWEEN ATRIUM AND VENTRICLE.
AE149	" AV BLOCK II: THERE ARE TWO TYPES: MOBILT I PROGRESSIVE PROLONGATION OF PR INTERVAL WITH DROPPED BEATS (THE PR INTERVAL GETS LONGER AND LONGER; FINALLY ONE BEAT DROPS) MOBILT II PR INTERVAL REMAINS UNCHANGED PRIOR TO THE P-WAVE WHICH SUDDENLY FAILS TO CONDUCT TO THE VENTRICLES;
AE150	" AV BLOCK III: NO P-WAVES CONDUCT TO THE VENTRICLE AND AV DISSOCIATION IS COMPLETE. ANY LEVEL OF AV BLOCK EVENT SHOULD BE DOCUMENTED AND CONFIRMED BY ECG TEST RESULTS.



AE CODE LIST	
CODE	DEFINITION
AE145	ARRHYTHMIA - BUNDLE BRANCH BLOCK - LEFT
AE.2	CARDIOVASCULAR – ARRHYTHMIA (CONTINUED)
AE146	ARRHYTHMIA - BUNDLE BRANCH BLOCK - RIGHT
AE147	ARRHYTHMIA - SUPRAVENTRICULAR TACHYCARDIA (SVT)
AE148	ARRHYTHMIA - PAROXYSMAL ATRIAL TACHYCARDIA (PAT)
AE150	ARRHYTHMIA - VENTRICULAR FIBRILLATION
AE151	ARRHYTHMIA - TACHYCARDIA - VENTRICULAR
AE152	ARRHYTHMIA - TACHYCARDIA - NON-VENTRICULAR
AE153	ARRHYTHMIA - BRADYCARDIA
AE154	ARRHYTHMIA - TACHY-BRADYCARDIA
AE155	ARRHYTHMIA - PACEMAKER/ICD MALFUNCTION
AE156	ARRHYTHMIA - OTHER
AE.3	CARDIOVASCULAR - REGURGITATION
	IF THE VALVE INVOLVED IS THE STUDY VALVE, THEN THIS DEFINITION SHOULD BE USED, BUT THE EVENT SHOULD BE REPORTED AS STRUCTURAL OR NON-STRUCTURAL VALVE DYSFUNCTION (AS APPROPRIATE) REGURGITATION, AORTIC: ALSO KNOWN AS AORTIC INSUFFICIENCY AND INCOMPETENCE OF THE AORTIC VALVE, IN WHICH A PORTION OF THE LEFT VENTRICULAR FORWARD STROKE VOLUME RETURNS TO THE CHAMBER DURING DIASTOLE. THIS CATEGORY DOES NOT INCLUDE PARAVULVAR LEAK, WHICH SHOULD BE CAPTURED UNDER NON-STRUCTURAL VALVE DYSFUNCTION. REGURGITATION, CENTRAL: OCCURS WHEN THE VALVE LEAFLETS DO NOT COMPLETELY CLOSE AND ALLOW SOME BLOOD TO LEAK BACK INTO THE HEART. REGURGITATION, INDETERMINATE: OCCURS WHEN BLOOD LEAKS BACK INTO THE HEART AND CANNOT BE CATEGORIZED BY LOCATION AND OR SEVERITY. REGURGITATION, MITRAL: ALSO KNOWN AS MITRAL INCOMPETENCE AND MITRAL INSUFFICIENCY IN WHICH THE BLOOD FLOWS BACKWARDS THROUGH THE MITRAL VALVE EACH TIME THE LEFT VENTRICLE CONTRACTS. DIAGNOSED BY AUSCULTATION (MURMUR) OR ECHOCARDIOGRAPHY. REGURGITATION, TRICUSPID: INSUFFICIENCY OF THE TRICUSPID VALVE CAUSING BLOOD FLOW FROM THE RIGHT VENTRICLE TO THE RIGHT ATRIUM DURING SYSTOLE.
AE160	REGURGITATION - AORTIC-CENTRAL/TRANSVALVULAR-+1
AE161	REGURGITATION - AORTIC-CENTRAL/TRANSVALVULAR-+2



Clinical Investigational Plan
Protocol Number: 2010-03

AE CODE LIST		
CODE	LABEL/NAME	DEFINITION
AE162	REGURGITATION - AORTIC-CENTRAL/TRANSVALVULAR-+3	MODERATE
AE163	REGURGITATION - AORTIC-CENTRAL/TRANSVALVULAR-+4	SEVERE
AE168	REGURGITATION - AORTIC-INDETERMINATE-+1	TRIVIAL/TRACE
AE.3	CARDIOVASCULAR - REGURGITATION (CONTINUED)	
AE169	REGURGITATION - AORTIC-INDETERMINATE-+2	MILD
AE170	REGURGITATION - AORTIC-INDETERMINATE-+3	MODERATE
AE171	REGURGITATION - AORTIC-INDETERMINATE-+4	SEVERE
AE172	REGURGITATION - MITRAL-CENTRAL/TRANSVALVULAR-+1	TRIVIAL/TRACE
AE173	REGURGITATION - MITRAL-CENTRAL/TRANSVALVULAR-+2	MILD
AE174	REGURGITATION - MITRAL-CENTRAL/TRANSVALVULAR-+3	MODERATE
AE175	REGURGITATION - MITRAL-CENTRAL/TRANSVALVULAR-+4	SEVERE
AE180	REGURGITATION - MITRAL-INDETERMINATE-+1	TRIVIAL/TRACE
AE181	REGURGITATION - MITRAL-INDETERMINATE-+2	MILD
AE182	REGURGITATION - MITRAL-INDETERMINATE-+3	MODERATE
AE183	REGURGITATION - MITRAL-INDETERMINATE-+4	SEVERE
AE190	REGURGITATION - PULMONARY-CENTRAL/TRANSVALVULAR-+1	TRIVIAL/TRACE
AE191	REGURGITATION - PULMONARY-CENTRAL/TRANSVALVULAR-+2	MILD
AE192	REGURGITATION - PULMONARY-CENTRAL/TRANSVALVULAR-+3	MODERATE
AE193	REGURGITATION - PULMONARY-CENTRAL/TRANSVALVULAR-+4	SEVERE
AE198	REGURGITATION - PULMONARY-INDETERMINATE-+1	TRIVIAL/TRACE
AE199	REGURGITATION - PULMONARY-INDETERMINATE-+2	MILD
AE200	REGURGITATION - PULMONARY-INDETERMINATE-+3	MODERATE
AE201	REGURGITATION - PULMONARY-INDETERMINATE-+4	SEVERE
AE202	REGURGITATION - TRICUSPID-CENTRAL/TRANSVALVULAR-+1	TRIVIAL/TRACE
AE203	REGURGITATION - TRICUSPID-CENTRAL/TRANSVALVULAR-+2	MILD
AE204	REGURGITATION - TRICUSPID-CENTRAL/TRANSVALVULAR-+3	MODERATE
AE205	REGURGITATION - TRICUSPID-CENTRAL/TRANSVALVULAR-+4	SEVERE

Clinical Investigational Plan
Protocol Number: 2010-03

AE CODE LIST		
CODE	LABEL/NAME	DEFINITION
AE210	REGURGITATION - TRICUSPID-INDETERMINATE--1	TRIVIAL/TRACE
AE211	REGURGITATION - TRICUSPID-INDETERMINATE--2	MILD
AE212	REGURGITATION - TRICUSPID-INDETERMINATE--3	MODERATE
AE213	REGURGITATION - TRICUSPID-INDETERMINATE--4	SEVERE
AE.5	CARDIOVASCULAR - STENOSIS	*IF THE VALVE INVOLVED IS THE STUDY VALVE, THEN THIS DEFINITION SHOULD BE USED, BUT THE EVENT SHOULD BE REPORTED AS STRUCTURAL OR NON-STRUCTURAL VALVE DYSFUNCTION (AS APPROPRIATE)
		AORTIC: FLOW OBSTRUCTION OF THE AORTIC VALVE DUE TO RESTRICTED LEAFLET OPENING. THE SEVERITY IS CATEGORIZED AS: MILD - JET VELOCITY (M/S) <3.0; MEAN GRADIENT (MMHG) <25; VALVE AREA (CM2) >1.5.MODERATE - JET VELOCITY (M/S) 3.0-4.0; MEAN GRADIENT (MMHG) 25-40; VALVE AREA (CM2) 1.0- 1.5. OR SEVERE - JET VELOCITY (M/S) >4.0; MEAN GRADIENT (MMHG) >40; VALVE AREA (CM2) <1.0; VALVE AREA INDEX<0.6. MITRAL: MITRAL STENOSIS (MS) REFERS TO NARROWING OF THE MITRAL VALVE ORIFICE, RESULTING IN IMPEDANCE OF FILLING OF THE LEFT VENTRICLE IN DIASTOLE. THE SEVERITY OF MS IS CATEGORIZED AS: MILD - MEAN GRADIENT (MM HG) < 5, PULMONARY ARTERY SYSTOLIC PRESSURE (MM HG) < 30, VALVE AREA (CM2) >1.5. MODERATE - MEAN GRADIENT (MM HG) 5-10, PULMONARY ARTERY SYSTOLIC PRESSURE (MM HG) 30-50, VALVE AREA (CM2) 1.0-1.5. SEVERE - MEAN GRADIENT (MM HG) > 10, PULMONARY ARTERY SYSTOLIC PRESSURE (MM HG)> 50, VALVE AREA (CM2) <1.0. TRICUSPID: A NARROWING OF THE TRICUSPID VALVE OPENING THAT INCREASES RESISTANCE TO BLOOD FLOW FROM THE RIGHT ATRIUM TO THE RIGHT VENTRICLE. SEVERE TRICUSPID STENOSIS IS DEFINED AS A VALVE AREA LESS THAN 1.0 CM2.
AE220*	STENOSIS - AORTIC - MILD	"
AE221*	STENOSIS - AORTIC - MODERATE	"
AE222*	STENOSIS - AORTIC - SEVERE	"
AE223	STENOSIS - MITRAL- MILD	"
AE224	STENOSIS - MITRAL - MODERATE	"
AE225	STENOSIS - MITRAL - SEVERE	"
AE226	STENOSIS - PULMONARY- MILD	"
AE227	STENOSIS - PULMONARY - MODERATE	"
AE228	STENOSIS - PULMONARY - SEVERE	"
AE229	STENOSIS - TRICUSPID- MILD	"
AE230	STENOSIS - TRICUSPID- MODERATE	"
AE231	STENOSIS - TRICUSPID - SEVERE	"

AE CODE LIST	
CODE	DEFINITION
AE.6	<p>CARDIOVASCULAR - THROMBOEMBOLIC EVENT/VALVE THROMBOSIS</p> <p>ANY EMBOLIC EVENT THAT OCCURS IN THE ABSENCE OF INFECTION AFTER THE IMMEDIATE PERIOPERATIVE PERIOD AND MAY BE MANIFESTED BY A NEUROLOGIC EVENT OR A NON-CEREBRAL EMBOLIC EVENT. EMBOLI CONSISTING OF NON-THROMBOTIC MATERIAL (E.G., ATHEROSCLEROSIS, MYXOMA) ARE NOT COUNTED.</p>
AE250	<p>THROMBOEMBOLIC EVENT – STROKE</p> <p>INCLUDES ANY CENTRAL, NEW NEUROLOGIC DEFICIT, WHETHER TEMPORARY OR PERMANENT AND WHETHER FOCAL OR GLOBAL, THAT OCCURS AFTER THE SUBJECT EMERGES FROM ANESTHESIA. POSTOPERATIVE NEUROLOGIC SYMPTOMS THAT MIMIC THOSE OF A PREOPERATIVELY DOCUMENTED NEUROLOGIC EVENT AND THAT ARE CONFIRMED RADIOGRAPHICALLY TO BE CONSISTENT WITH THE FORMER EVENT ARE NOT COUNTED. CENTRAL NEUROLOGIC EVENTS THAT ARE CLEARLY RELATED TO AORTIC, INTERNAL CAROTID ARTERY, OR VERTEBRAL ARTERY DISEASE ARE ALSO NOT COUNTED. PSYCHOMOTOR DEFICITS FOUND BY SPECIALIZED TESTING ARE NOT CONSIDERED NEUROLOGIC EVENTS RELATED TO OPERATED VALVES. SUBJECTS WHO DO NOT AWAKEN OR WHO AWAKEN AFTER OPERATION WITH A NEW STROKE ARE NOT CONSIDERED TO HAVE SUSTAINED VALVE-RELATED NEUROLOGIC EVENTS. STROKE: A PROLONGED (>72 HOURS) OR PERMANENT NEUROLOGIC DEFICIT THAT IS USUALLY ASSOCIATED WITH ABNORMAL RESULTS OF MRI OR CT SCANS. SUBJECTS WITH MINIMAL, ATYPICAL, OR PROTEAN SYMPTOMS THAT LEAD TO RADIOGRAPHIC IMAGING DEMONSTRATING AN ACUTE ISCHEMIC EVENT ARE CONSIDERED TO HAVE SUSTAINED A STROKE. TIA: CHARACTERIZED BY FULLY REVERSIBLE SYMPTOMS OF SHORT DURATION. IF RADIOGRAPHIC IMAGING DEMONSTRATES AN ACUTE CENTRAL NEUROLOGIC LESION, HOWEVER, SUCH SUBJECTS ARE RECLASSIFIED AS HAVING SUSTAINED A STROKE.</p>
AE255	<p>THROMBOEMBOLIC EVENT – TRANSIENT ISCHEMIC ATTACK (TIA)</p> <p>INCLUDES ANY CENTRAL, NEW NEUROLOGIC DEFICIT, WHETHER TEMPORARY OR PERMANENT AND WHETHER FOCAL OR GLOBAL, THAT OCCURS AFTER THE SUBJECT EMERGES FROM ANESTHESIA. POSTOPERATIVE NEUROLOGIC SYMPTOMS THAT MIMIC THOSE OF A PREOPERATIVELY DOCUMENTED NEUROLOGIC EVENT AND THAT ARE CONFIRMED RADIOGRAPHICALLY TO BE CONSISTENT WITH THE FORMER EVENT ARE NOT COUNTED. CENTRAL NEUROLOGIC EVENTS THAT ARE CLEARLY RELATED TO AORTIC, INTERNAL CAROTID ARTERY OR VERTEBRAL ARTERY DISEASE ARE ALSO NOT COUNTED. PSYCHOMOTOR DEFICITS FOUND BY SPECIALIZED TESTING ARE NOT CONSIDERED NEUROLOGIC EVENTS RELATED TO OPERATED VALVES. SUBJECTS WHO DO NOT AWAKEN OR WHO AWAKEN AFTER OPERATION WITH A NEW STROKE ARE NOT CONSIDERED TO HAVE SUSTAINED VALVE-RELATED NEUROLOGIC EVENTS. STROKE: A PROLONGED (>72 HOURS) OR PERMANENT NEUROLOGIC DEFICIT THAT IS USUALLY ASSOCIATED WITH ABNORMAL RESULTS OF MRI OR CT SCANS. SUBJECTS WITH MINIMAL, ATYPICAL, OR PROTEAN SYMPTOMS THAT LEAD TO RADIOGRAPHIC IMAGING DEMONSTRATING AN ACUTE ISCHEMIC EVENT ARE CONSIDERED TO HAVE SUSTAINED A STROKE. TIA: CHARACTERIZED BY FULLY REVERSIBLE SYMPTOMS OF SHORT DURATION. IF RADIOGRAPHIC IMAGING DEMONSTRATES AN ACUTE CENTRAL NEUROLOGIC LESION, HOWEVER, SUCH SUBJECTS ARE RECLASSIFIED AS HAVING SUSTAINED A STROKE.</p>
AE256	<p>THROMBOEMBOLIC EVENT - OTHER - PERIPHERAL NO PARESIS</p> <p>A PERIPHERAL EMBOLIC EVENT IS AN OPERATIVE, AUTOPSY, OR CLINICALLY DOCUMENTED EMBOLUS THAT PRODUCES SYMPTOMS FROM COMPLETE OR PARTIAL OBSTRUCTION OF A PERIPHERAL (NON-CEREBRAL) ARTERY. LOCATION SHOULD BE REPORTED. REPORT UNDER PULMONARY EMBOLISM IF EVENT OCCURS IN THE LUNG.</p>
AE257	<p>THROMBOEMBOLIC EVENT - OTHER – PERIPHERAL</p> <p>" HEMIPARESIS</p>
AE258	<p>THROMBOEMBOLIC EVENT - OTHER - PERIPHERAL</p> <p>" FULL PARESIS</p>
AE259	<p>THROMBOEMBOLIC EVENT - OTHER - CENTRAL</p> <p>" NO PARESIS</p>

Clinical Investigational Plan
 Protocol Number: 2010-03

AE CODE LIST	
CODE	DEFINITION
AE260	THROMBOEMBOLIC EVENT - OTHER - CENTRAL " HEMIPARESIS
AE.6	CARDIOVASCULAR - THROMBOEMBOLIC EVENT/VALVE THROMBOSIS (CONTINUED)
AE261	THROMBOEMBOLIC EVENT - OTHER - CENTRAL " FULL PARESIS
AE262	VALVE THROMBOSIS - AORTIC ANY THROMBUS NOT CAUSED BY INFECTION ATTACHED TO OR NEAR AN OPERATED VALVE THAT OCCLUDES PART OF THE BLOOD FLOW PATH, INTERFERES WITH VALVE FUNCTION, OR IS SUFFICIENTLY LARGE TO WARRANT TREATMENT. VALVE THROMBUS FOUND AT AUTOPSY IN A SUBJECT WHOSE CAUSE OF DEATH WAS NOT VALVE RELATED OR FOUND AT OPERATION FOR AN UNRELATED INDICATION SHOULD ALSO BE COUNTED.
AE263	VALVE THROMBOSIS - MITRAL "
AE264	VALVE THROMBOSIS - PULMONARY "
AE265	VALVE THROMBOSIS - TRICUSPID "
AE.7	CARDIOVASCULAR - MISC
AE270	ANGINA, STABLE CHEST PAIN, TIGHT OR HEAVY FEELING IN THE CHEST, OR DISCOMFORT WHICH SPREADS FROM THE CHEST TO THE ARM, BACK, NECK, JAW, OR STOMACH, NUMBNESS OR TINGLING IN THE SHOULDERS, ARMS OR WRISTS, SHORTNESS OF BREATH, AND NAUSEA RELIEVED BY REST OR NITROGLYCERINE AND/OR CONFIRMED BY ECG. STABLE ANGINA IS ANGINA THAT IS CONTROLLED BY ORAL AND/OR TRANSCUTANEOUS MEDICATION.
AE271	ANGINA, UNSTABLE UNSTABLE ANGINA IS ANGINA, WHICH NECESSITATES THE INITIATION, CONTINUATION OR INCREASE OF ANGINA CONTROL THERAPIES THAT MAY INCLUDE: NITROGLYCERIN DRIP, HEPARIN DRIP, OR IABP PLACEMENT. THE TYPE OF ANGINA MAY INCLUDE, BUT IS NOT LIMITED TO: REST ANGINA, NEW ONSET EXERTIONAL ANGINA OF AT LEAST NEW YORK HEART ASSOCIATION (NYHA) CLASS III IN SEVERITY, RECENT ACCELERATION IN PATTERN AND INCREASE OF ONE NYHA CLASS TO AT LEAST NYHA CLASS III, VARIANT ANGINA, NON-Q WAVE MYOCARDIAL INFARCTION, OR POST-INFARCTION ANGINA.
AE272	ANNULAR DISSECTION DISSECTION OF THE VALVULAR ANNULUS EXTENDING INTO THE AORTA. ANNULAR DISSECTION OCCURRING WITHIN 30 DAYS OF THE INDEX PROCEDURE WILL BE CONSIDERED VALVE RELATED. SHOULD BE CONFIRMED BY IMAGING, OR DIRECT VISUAL INSPECTION.
AE273	AORTIC DISSECTION DISRUPTION OF THE MEDIA LAYER OF THE AORTA WITH BLEEDING WITHIN AND ALONG THE WALL OF THE AORTA. AORTIC DISSECTION MAY OCCUR IN THE ASCENDING THORACIC AORTA (TYPE A DISSECTION) OR IN THE DESCENDING THORACIC AORTA (TYPE B DISSECTION). DISSECTION SHOULD BE CONFIRMED BY IMAGING OR DIRECT VISUAL INSPECTION.
AE274	ARTERIAL DISSECTION DISRUPTION OF THE MEDIA LAYER OF AN ARTERY OTHER THAN THE AORTA WITH BLEEDING WITHIN AND ALONG THE WALL OF THE VESSEL. SHOULD BE CONFIRMED BY IMAGING OR DIRECT VISUAL INSPECTION.
AE275	CARDIAC ARREST CARDIAC ARREST DOCUMENTED BY ONE OF THE FOLLOWING: VENTRICULAR FIBRILLATION, RAPID VENTRICULAR TACHYCARDIA WITH HEMODYNAMIC INSTABILITY, ASYSTOLE.
AE276	CARDIAC DECOMPENSATION AN INABILITY OF THE HEART TO MAINTAIN ADEQUATE CIRCULATION; IT IS MARKED BY DYSPNEA, VENOUS ENGORGEMENT, CYANOSIS AND EDEMA.



Clinical Investigational Plan
Protocol Number: 2010-03

AE CODE LIST	
CODE	DEFINITION
AE277	CARDIOGENIC SHOCK A CLINICAL STATE OF HYPOPERFUSION SUSTAINED FOR GREATER THAN 30 MINUTES, WITH EITHER SYSTOLIC BLOOD PRESSURE < 80 MM HG, AND /OR CARDIAC INDEX < 1.8 DESPITE MAXIMAL TREATMENT (FLUIDS) OR REQUIRING INTRAVENOUS INOTROPES AND/OR PRESSOR AGENT OR AN INTRA-AORTIC BALLOON PUMP (IABP).
AE.7	CARDIOVASCULAR - MISC (CONTINUED)
AE278	CHORDAE TENDINEAE DAMAGE
AE279	CORONARY ARTERY OSTIAL OBSTRUCTION OBSTRUCTION OF THE CORONARY OSTIA. SHOULD BE CONFIRMED BY IMAGING AND THE SOURCE OF THE OBSTRUCTION (AORTIC VALVE, THROMBUS, ETC. SHOULD BE REPORTED.
AE280	ENDOCARDITIS ANY INFECTION INVOLVING THE STUDY VALVE. THE DIAGNOSIS OF OPERATED VALVULAR ENDOCARDITIS IS BASED ON ONE OF THE FOLLOWING CRITERIA: (1) REOPERATION WITH EVIDENCE OF ABSCESS, PARAVALVULAR LEAK, PUS, OR VEGETATION CONFIRMED AS SECONDARY TO INFECTION BY HISTOLOGIC OR MICROBIOLOGIC STUDIES; (2) AUTOPSY FINDINGS OF ABSCESS, PUS, OR VEGETATION INVOLVING A REPAIRED OR REPLACED VALVE; OR (3) IN THE ABSENCE OF REOPERATION OR AUTOPSY, MEETING OF THE DUKE CRITERIA FOR ENDOCARDITIS [4]. MORBIDITIES ASSOCIATED WITH ACTIVE INFECTION, SUCH AS VALVE THROMBOSIS, THROMBOTIC EMBOLUS, BLEEDING EVENT, OR PARAVALVULAR LEAK, ARE INCLUDED UNDER THIS CATEGORY, BUT NOT COUNTED IN OTHER CATEGORIES OF MORBIDITY.
AE281	HEART FAILURE – ACUTE ACUTE HEART FAILURE DESCRIBES EXACERBATED OR DECOMPENSATED HEART FAILURE, REFERRING TO EPISODES IN WHICH A SUBJECT IS CHARACTERIZED AS HAVING A CHANGE IN HEART FAILURE SIGNS AND SYMPTOMS RESULTING IN A NEED FOR URGENT THERAPY OR HOSPITALIZATION.
AE282	HEART FAILURE – CHRONIC (CHF) AN EVENT IN WHICH THE HEART FAILS TO MEET THE CIRCULATORY REQUIREMENTS OF THE BODY UNDER DIFFERING PHYSIOLOGICAL CIRCUMSTANCES, AND/OR A STATE IN WHICH CARDIAC OUTPUT IS REDUCED RELATIVE TO THE DEMANDS OF THE BODY, ASSUMING THE EVIDENCE OF ADEQUATE VENOUS RETURN. EVENT IS CONFIRMED CLINICALLY OR BY DIAGNOSTIC TESTING.
AE283	HYPERTENSION – SYSTEMIC DEFINED AS BLOOD PRESSURE > 140 /90 MM HG FOR SUBJECT WITHOUT DIABETES OR KIDNEY DISEASE; >130/80 MMHG FOR SUBJECTS ON 2 OCCASIONS WITH DIABETES OR RENAL DISEASE. UNLESS DUE TO PRESENCE OF MEDICATION, E.G. BETA BLOCKERS FOR 10 YEARS
AE284	HYPERTENSION – PULMONARY MEAN PULMONARY ARTERY PRESSURE THAT IS GREATER THAN 25 MMHG AT REST AND/OR GREATER THAN 30 MMHG DURING EXERCISE CONFIRMED BY SWAN GANZ CATHETER OR DIAGNOSTIC PLACEMENT IN THE PULMONARY ARTERY BED AND CONDITION REQUIRES MEDICAL INTERVENTION TO RESOLVE OR TREAT THE CONDITION.
AE285	HYPOTENSION ABNORMALLY LOW BLOOD PRESSURE. FOR AN ADULT, HYPOTENSION IS DEFINED AS BLOOD PRESSURE LESS THAN 90/50 MMHG.

AE CODE LIST	
CODE	DEFINITION
AE.7	<p>CARDIOVASCULAR - MISC (CONTINUED)</p> <p>AN ACUTE MYOCARDIAL INFARCTION IS EVIDENCED BY ANY OF THE FOLLOWING:</p> <ol style="list-style-type: none"> 1. A RISE AND FALL OF CARDIAC BIOMARKERS (PREFERABLY TROPONIN) WITH AT LEAST ONE OF THE VALUES IN THE ABNORMAL RANGE (CK \geq 5X ULN) TOGETHER WITH AT LEAST ONE OF THE FOLLOWING MANIFESTATIONS OF MYOCARDIAL ISCHEMIA: <ol style="list-style-type: none"> A) ISCHEMIC SYMPTOMS; B) ECG CHANGES INDICATIVE OF NEW ISCHEMIA (NEW ST-T CHANGES, NEW LEFT BUNDLE BRANCH BLOCK, OR LOSS OF R WAVE VOLTAGE); C) DEVELOPMENT OF PATHOLOGICAL Q WAVES IN 2 OR MORE CONTIGUOUS LEADS IN THE ECG (OR EQUIVALENT FINDINGS FOR TRUE POSTERIOR MI); D. IMAGING EVIDENCE OF NEW LOSS OF VIABLE MYOCARDIUM OR NEW REGIONAL WALL MOTION ABNORMALITY. 2. DEVELOPMENT OF NEW PATHOLOGICAL Q WAVES IN 2 OR MORE CONTIGUOUS LEADS IN THE ECG, WITH OR WITHOUT SYMPTOMS. 3. IMAGING EVIDENCE OF A REGION WITH NEW LOSS OF VIABLE MYOCARDIUM AT REST IN THE ABSENCE OF A NON-ISCHEMIC CAUSE. THIS CAN BE MANIFEST AS: A. ECHOCARDIOGRAPHIC, CT, MR, VENTRICULOGRAPHIC OR NUCLEAR IMAGING EVIDENCE OF LEFT VENTRICULAR THINNING OR SCARRING AND FAILURE TO CONTRACT APPROPRIATELY (I.E., HYPOKINESIS, AKINESIS, OR DYSKINESIS); OR, B. FIXED (NON-REVERSIBLE) PERFUSION DEFECTS ON NUCLEAR RADIOISOTOPE IMAGING (E.G., MIBI, THALLIUM).
AE286	MYOCARDIAL INFARCTION
AE287	MYOCARDITIS
AE296	PERFORATION - ATRIAL
AE297	PERFORATION - VENTRICULAR
AE289	PERFORATION - OTHER
AE290	PERICARDIAL EFFUSION - MAJOR
AE291	PERICARDIAL EFFUSION - MINOR
AE292	PERICARDIAL TAMPONADE - MAJOR
AE294	PERICARDITIS
AE295	CARDIOVASCULAR - OTHER

Clinical Investigational Plan
Protocol Number: 2010-03

AE CODE LIST	
CODE	DEFINITION
AE.8	GASTROINTESTINAL/HEPATIC
AE350	GASTROINTESTINAL – ESOPHAGEAL RUPTURE/TEAR ANY EVIDENCE OF PUNCTURE/DISSECTION/PERFORATION, VARICES OR OTHER DAMAGE TO THE ESOPHAGUS REQUIRING INTERVENTION.
AE351	GASTROINTESTINAL – INFECTION SEVERE INFLAMMATION OF THE GASTROINTESTINAL TRACT INVOLVING BOTH THE STOMACH AND SMALL INTESTINE RESULTING IN ACUTE DIARRHEA AND VOMITING. SHOULD BE CONFIRMED BY CULTURE
AE352	GASTROINTESTINAL – OTHER OTHER GASTROINTESTINAL EVENT THAT DOES NOT FIT IN ONE OF THE OTHER GI/HEPATIC CATEGORIES.
AE353	LIVER FAILURE - ACUTE A SYNDROME DEFINED BY THE OCCURRENCE OF ENCEPHALOPATHY, COAGULOPATHY AND JAUNDICE IN AN INDIVIDUAL WITH A PREVIOUSLY NORMAL LIVER.
AE354	LIVER FAILURE - CHRONIC CHRONIC LIVER DISEASE CAUSES CAN BE ANY CONDITION THAT RESULTS IN THE GRADUAL DEGRADATION AND RENEWAL OF THE TISSUE CELLS WITH A BODY'S LIVER. THIS PROCESS USUALLY RESULTS IN FIBROSIS OR CIRRHOSIS. DIAGNOSIS MAY BE CONFIRMED BY ABNORMAL BLOOD ENZYMES AND/OR BIOPSY
AE355	HEPATIC COMPLICATION - OTHER OTHER LIVER EVENTS THAT DO NOT MEET THE DEFINITION OF LIVER FAILURE (E.G. LIVER DYSFUNCTION) REQUIRING HOSPITALIZATION OR MEDICAL INTERVENTION.
AE356	PANCREATIC COMPLICATION (PANCREAS) AN EVENT PERTAINING TO, CONNECTED WITH, OR AFFECTING THE PANCREAS REQUIRING HOSPITALIZATION OR MEDICAL INTERVENTION.
AE357	SPLENIC COMPLICATION (SPLEEN) AN EVENT PERTAINING TO, CONNECTED WITH, OR AFFECTING THE SPLEEN REQUIRING HOSPITALIZATION OR MEDICAL INTERVENTION.
AE358	BILIARY (GALLBLADDER) AN EVENT PERTAINING TO BILE OR TO THE GALLBLADDER AND BILE DUCTS, WHICH TRANSPORT BILE REQUIRING HOSPITALIZATION OR MEDICAL INTERVENTION.
AE359	ENDOCRINE COMPLICATIONS AN EVENT PERTAINING TO, CONNECTED WITH, OR AFFECTING THE ENDOCRINE SYSTEM REQUIRING HOSPITALIZATION OR MEDICAL INTERVENTION.
AE360	METABOLIC COMPLICATIONS AN EVENT PERTAINING TO, CONNECTED WITH, OR AFFECTING THE METABOLIC SYSTEM REQUIRING HOSPITALIZATION OR MEDICAL INTERVENTION.
AE.9	GENITOURINARY/RENAL
AE370	URINARY TRACT INFECTION (UTI) INFECTION THAT AFFECTS ANY PART OF THE URINARY TRACT THAT REQUIRE HOSPITALIZATION OR MEDICAL INTERVENTION.
AE371	VAGINAL INFECTION INFECTIONS AFFECTING THE VAGINAL AREA THAT REQUIRE HOSPITALIZATION OR MEDICAL INTERVENTION.
AE372	GENITOURINARY – OTHER OTHER GENITOURINARY EVENT NOT PREVIOUSLY DESCRIBED REQUIRING HOSPITALIZATION OR MEDICAL INTERVENTION.
AE373	RENAL DYSFUNCTION AN ACUTE EVENT OR WORSENING OF RENAL FUNCTION POST-OPERATIVELY (INCREASE OF SERUM CREATININE TO < 2.0 , AND < 2X MOST RECENT PREOPERATIVE CREATININE LEVEL) AND DOES NOT REQUIRE DIALYSIS.

Clinical Investigational Plan
Protocol Number: 2010-03



AE CODE LIST	
CODE	DEFINITION



AE CODE LIST	
CODE	DEFINITION
AE.9	GENITOURINARY/RENAL (CONTINUED)
AE374	RENAL FAILURE – ACUTE AN ACUTE EVENT OR WORSENING OF RENAL FUNCTION RESULTING IN ONE OR MORE OF THE FOLLOWING: 1) INCREASE OF SERUM CREATININE TO >2.0, AND 2X MOST RECENT PREOPERATIVE CREATININE LEVEL. 2) A NEW REQUIREMENT FOR DIALYSIS POSTOPERATIVELY.
AE375	RENAL FAILURE – CHRONIC A PROGRESSIVE LOSS IN RENAL FUNCTION OVER A PERIOD OF MONTHS OR YEARS RESULTING IN A DIAGNOSIS OF STAGE 5 - CHRONIC KIDNEY DISEASE.
AE376	RENAL – OTHER OTHER EVENT THAT IS NOT RENAL FAILURE OR RENAL DYSFUNCTION THAT REQUIRES HOSPITALIZATION OR MEDICAL INTERVENTION.
AE.10	PULMONARY/RESPIRATORY
AE380	ATELECTASIS COMPLETE OR PARTIAL COLLAPSE OF A PREVIOUSLY INFLATED LUNG; INABILITY OF LUNG TO FULLY EXPAND.
AE381	HYPOXEMIA DECREASED PARTIAL PRESSURE OF OXYGEN IN BLOOD SOMETIMES SPECIFICALLY AS LESS THAN 60 MMHG (8.0 KPA) OR CAUSING HEMOGLOBIN OXYGEN SATURATION OF LESS THAN 90%.
AE382	PLEURAL EFFUSION - RIGHT EXCESS ACCUMULATION OF FLUIDS, SOMETIMES BLOOD IN THE PLEURAL SPACE, WHICH IS COMMON AFTER CARDIAC SURGERY. REPORTABLE WHEN IT BECOMES SYMPTOMATIC AND REQUIRES FLUID TO BE INTERVENTIONALLY REMOVED.
AE383	PLEURAL EFFUSION - LEFT "
AE384	PLEURAL EFFUSION - BILATERAL "
AE385	PNEUMOTHORAX ACCUMULATION OF AIR OR GAS IN THE PLEURAL CAVITY, OCCURRING BECAUSE OF DISEASE OR INJURY AND REQUIRING SURGICAL INTERVENTION, HOSPITALIZATION OR MEDICAL INTERVENTION TO RESOLVE.
AE386	PULMONARY EDEMA AN ABNORMAL ACCUMULATION OF FLUID IN THE LUNGS REQUIRING HOSPITALIZATION OR MEDICAL INTERVENTION TO RESOLVE.
AE387	PULMONARY HYPERTENSION MEAN PULMONARY ARTERY PRESSURE THAT IS GREATER THAN 25 MMHG AT REST AND/OR GREATER THAN 30 MMHG DURING EXERCISE CONFIRMED BY SWAN GANZ CATHETER OR DIAGNOSTIC PLACEMENT IN THE PULMONARY ARTERY BED AND CONDITION REQUIRES HOSPITALIZATION OR MEDICAL INTERVENTION TO RESOLVE.
AE388	PULMONARY REGURGITATION THE BACKWARD FLOW OF BLOOD FROM THE PULMONARY ARTERY, THROUGH THE PULMONARY VALVE, AND INTO THE RIGHT VENTRICLE OF THE HEART DURING DIASTOLE.
AE389	PULMONARY EMBOLISM - RIGHT CLINICAL EVIDENCE OF NEW EMBOLISM WITH CONFIRMATION BY LUNG SCAN OR PULMONARY ANGIOGRAPHY.
AE390	PULMONARY EMBOLISM - LEFT "
AE391	PULMONARY EMBOLISM - BILATERAL "
AE392	PULMONARY/RESPIRATORY - OTHER OTHER RESPIRATORY EVENT THAT IS NOT RESPIRATORY FAILURE.
AE393	RESPIRATORY DYSFUNCTION/INSUFFICIENCY DETERIORATION OF SUBJECT'S RESPIRATORY EFFORTS LESS THAN 24 HRS AFTER COMPLETION OF THE INDEX PROCEDURE.

Clinical Investigational Plan
Protocol Number: 2010-03



AE CODE LIST	
CODE	DEFINITION



AE CODE LIST	
CODE	DEFINITION
AE.10	PULMONARY/RESPIRATORY
AE394	RESPIRATORY FAILURE -ASTHMA
AE395	RESPIRATORY FAILURE -EMPHYSEMA
AE396	RESPIRATORY FAILURE -COPD
AE397	RESPIRATORY FAILURE -PNEUMONIA
AE398	RESPIRATORY FAILURE -PNEUMOTHORAX
AE399	RESPIRATORY FAILURE -HEMOTHORAX
AE400	RESPIRATORY FAILURE - ARDS
AE401	RESPIRATORY FAILURE -OTHER
AE402	RESPIRATORY INFECTION – UPPER (URI)
AE403	RESPIRATORY INFECTION – PNEUMONIA
AE.11	PERIPHERAL VASCULAR
AE420	VASCULAR - ACCESS SITE COMPLICATION
AE421	VASCULAR - DEEP VEIN THROMBOSIS (DVT)
AE423	VASCULAR - OTHER
AE.12	PSYCHIATRIC
AE431	PSYCHIATRIC DISORDER
AE432	SUICIDE
AE433	TRANSIENT PSYCHOTIC SYNDROME

NEED FOR MECHANICAL VENTILATION REQUIRED GREATER THAN 24 HRS AFTER OF COMPLETION OF THE INDEX PROCEDURE (TIME 0 = WHEN THE SUBJECT LEAVES THE OR), OR NEED FOR RE-INTUBATION AND VENTILATOR SUPPORT OCCURRING ANY TIME WITHIN 30 DAY OF THE INDEX PROCEDURE WILL BE CONSIDERED RELATED TO THE INDEX PROCEDURE.

"

"

"

"

"

" ACUTE RESPIRATORY DISTRESS SYNDROME

"

THE ILLNESSES CAUSED BY AN ACUTE INFECTION WHICH INVOLVES THE UPPER RESPIRATORY TRACT: NOSE, SINUSES, PHARYNX OR LARYNX. THIS COMMONLY INCLUDES: TONSILLITIS, PHARYNGITIS, LARYNGITIS, SINUSITIS, OTITIS MEDIA, AND THE COMMON COLD.

LUNG INFECTION DOCUMENTED BY BLOOD STUDIES OR CHEST X-RAY, REQUIRING TREATMENT WITH ANTIBIOTICS, INHALATION THERAPY, INTUBATION OR SUCTIONING.

COMPLICATIONS OF BLEEDING OR INFECTION AT THE SITE OF CARDIOPULMONARY ACCESS AND OR PERCUTANEOUS CORONARY INTERVENTION OR DIAGNOSTICS THAT REQUIRE HOSPITALIZATION OR MEDICAL INTERVENTION.

FORMATION OF BLOOD CLOT (THROMBUS) IN THE LOWER EXTREMITIES (LEGS) CHARACTERIZED BY SWELLING, REDNESS, CLAUDICATION/PAIN IN AFFECTED LIMB. EVENT SHOULD BE CONFIRMED BY DOPPLER OR DUPLEX US STUDY, AND REQUIRES HOSPITALIZATION OR MEDICAL INTERVENTION TO RESOLVE.

OTHER VASCULAR COMPLICATIONS GENERALLY RELATED TO A DISEASE PROCESS AND NOT TRAUMA THAT REQUIRE HOSPITALIZATION OR MEDICAL INTERVENTION.

A PSYCHOLOGICAL OR BEHAVIORAL PATTERN GENERALLY ASSOCIATED WITH SUBJECTIVE DISTRESS OR DISABILITY THAT OCCURS IN AN INDIVIDUAL, AND WHICH IS NOT A PART OF NORMAL DEVELOPMENT OR CULTURE. SUCH A DISORDER MAY CONSIST OF A COMBINATION OF AFFECTIVE, BEHAVIORAL, COGNITIVE AND PERCEPTUAL COMPONENTS.

A PERSON WHO INTENTIONALLY TAKES HIS OR HER OWN LIFE.

A MENTAL STATE OFTEN DESCRIBED AS INVOLVING A "LOSS OF CONTACT WITH REALITY" THAT LASTS ONLY FOR A



AE CODE LIST	
CODE	DEFINITION
	SHORT TIME.
AE.12	PSYCHIATRIC (CONTINUED)
AE434	PSYCHIATRIC – OTHER
AE.13	MUSCULAR SKELETAL/ DERMATOLOGIC
AE450	STERNAL WOUND/THORACIC INFECTION
AE451	BONE FRACTURE/BREAK
AE452	WOUND INFECTION – OTHER
AE454	INFECTION/INFLAMMATION - OTHER
AE456	MUSCULAR SKELETAL / DERMATOLOGIC - OTHER
AE.14	NONSPECIFIC, UNKNOWN, OR OTHER BODY SYSTEM
AE470	ANAPHYLACTIC REACTION
AE471	ALLERGIC REACTION – MEDICATION RELATED
AE472	ALLERGIC REACTION – OTHER
AE473	CANCER – PROGRESSION OF UNDERLYING DISEASE
AE474	CANCER – NEWLY DIAGNOSED
AE475	HEARING DISORDER
AE476	MULTI-SYSTEM ORGAN FAILURE
AE477	SPEECH DISORDER
AE479	VISION DISORDER
AE480	FEVER - UNKNOWN ORIGIN



AE CODE LIST	
CODE	DEFINITION
AE481	NONSPECIFIC, UNKNOWN, OR OTHER BODY SYSTEM - OTHER COMPLICATION
AE.15	DEVICE DYSFUNCTION
AE500	SVD - STUDY VALVE WEAR
AE501	SVD - STUDY VALVE FRACTURE
AE502	SVD - STUDY VALVE POPPET ESCAPE
AE503	SVD - STUDY VALVE CALCIFICATION
AE504	SVD - STUDY VALVE LEAFLET TEAR
AE505	SVD - STUDY VALVE STENT CREEP
AE506	SVD - STUDY VALVE SUTURE LINE DISRUPTION
AE507	SVD - STRUCTURAL VALVE DETERIORATION, OTHER
AE525	SVD - ANNULAR FRAME DAMAGE
AE526	SVD - ANNULAR FRAME SEPARATION
AE527	SVD - STENT FRAME FRACTURE
AE528	SVD - STENT FRAME DEFORMATION
AE529	SVD - STENT FRAME SEPARATION
AE512	NSD - ENTRAPMENT BY PANNUS, TISSUE, OR SUTURE
AE164	NSD - PARAVALVULAR LEAK - +1
AE165	NSD - PARAVALVULAR LEAK - +2
AE166	NSD - PARAVALVULAR LEAK - +3
AE167	NSD - PARAVALVULAR LEAK - +4
AE176	NSD - STUDY VALVE STENOSIS - MILD

ANY COMPLICATION THAT CANNOT OTHERWISE BE CATEGORIZED REQUIRING HOSPITALIZATION OR MEDICAL INTERVENTION.

INCLUDES DYSFUNCTION OR DETERIORATION INVOLVING THE OPERATED VALVE (EXCLUSIVE OF INFECTION OR THROMBOSIS). THE TERM STRUCTURAL VALVE DETERIORATION REFERS TO CHANGES INTRINSIC TO THE VALVE SUCH AS: WEAR, FRACTURE, CALCIFICATION, LEAFLET TEAR, MANUFACTURED SUTURE LINE DISRUPTION

"

"

"

"

"

"

"

"

"

"

"

"

"

"

"

ANY ABNORMALITY NOT INTRINSIC TO THE VALVE (DO NOT DIRECTLY INVOLVE VALVE COMPONENTS) ITSELF THAT RESULTS IN STENOSIS OR REGURGITATION OF THE OPERATED VALVE OR HEMOLYSIS (EXCLUDES THROMBOSIS AND INFECTION). EXAMPLES INCLUDE: ENTRAPMENT BY PANNUS, TISSUE, OR SUTURE, PARAVALVULAR LEAK, INAPPROPRIATE SIZING, INAPPROPRIATE POSITIONING, REGURGITATION AS A RESULT OF TECHNICAL ERROR, STJ DILATION, DILATION OF THE VALVE ANNULUS, OBSTRUCTION OF THE CORONARY OSTIA BY THE STUDY VALVE.

LEAKAGE BETWEEN THE SEWING RING AND THE ANNULUS.

"

"

"

"

NSD "



Clinical Investigational Plan
 Protocol Number: 2010-03

AE CODE LIST		
CODE	LABEL/NAME	DEFINITION
AE177	NSD - STUDY VALVE STENOSIS - MODERATE	NSD "
AE178	NSD - STUDY VALVE STENOSIS - SEVERE	NSD "
AE121	NSD - PARAVALVULAR LEAK WITH HEMOLYSIS	NSD "
AE514	NSD - INAPPROPRIATE SIZING	NSD "
AE515	NSD - INAPPROPRIATE POSITIONING	NSD "
AE516	NSD - RESIDUAL LEAK OR OBSTRUCTION	NSD "
AE517	NSD - INTRAVASCULAR HEMOLYTIC ANEMIA	NSD " CLINICALLY IMPORTANT
AE518	NSD - DEVELOPMENT OF REGURGITATION	NSD " AS A RESULT OF TECHNICAL ERRORS
AE519	NSD - DILATATION OF THE SINOTUBULAR JUNCTION	NSD "
AE520	NSD - DILATION OF THE VALVE ANNULUS	NSD "
AE521	NSD - CORONARY OSTIAL OBSTRUCTION	NSD "
AE522	NSD - STUDY VALVE INSTABILITY	NSD "
AE523	NSD - STUDY VALVE MIGRATION	NSD "
AE524	NSD - LVOT DAMAGE	NSD "



15.2 SAMPLE INFORMED CONSENT FORM

Patient Information

CLINICAL STUDY # 2010-03:

“Clinical Study of the Edwards Pericardial Aortic Bioprosthesis, Model 11000”

You are invited to take part in a clinical research study. This information sheet tells you why the research is being done and what it would involve for you if you chose to take part. Please read the following information carefully and feel free to discuss this with your family or your Doctor. If you are unclear about anything or would like more information, please contact, <Name> on <Tel. number>. Take time to decide whether or not you wish to take part. Your participation in this research study is voluntary. If you decide to participate we will ask you to sign this consent document in order to state your agreement.

This study has been given a favorable opinion by the <Ethics Committee> and by the <Competent Authority>. It will be conducted according to the regulations governing clinical research.

INTRODUCTION

The heart is a muscle, that works like a pump, moving blood into the lungs and the entire body. In the heart there are 4 valves, whose role is to allow blood to flow in the correct direction. When a valve doesn't work properly, the heart muscle has to work harder to pump the normal amount of blood around the body. This may cause symptoms such as tiredness, difficulty in breathing, fainting or in some cases a condition called angina pectoris. The symptoms are different depending on the valve that is damaged and the amount of the damage. If the symptoms are serious the valve can be surgically removed and replaced with a new valve. There are different types of replacement valves that are used based on a patients condition and symptoms. One type is the biological valve, sometimes referred to as a tissue valve or bioprosthesis. Bioprostheses made with pericardial tissue have been used for many years.

WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this observational trial is to gather further clinical data to confirm the safety and performance of the Edwards Pericardial Aortic Bioprosthesis, Model 11000 (also referred to as the Model 11000).

WHY CAN YOU PARTICIPATE IN THIS RESEARCH STUDY?

You are being invited to participate in this clinical research study because it has been determined that your aortic heart valve needs replacement and your doctor believes that you may benefit from receiving a biological valve.

A variety of biological heart prostheses are available from different manufacturers. In this study we intend to test the Model 11000 aortic biological prosthesis. The Model 11000 prosthesis is a new CE marked product. This new aortic valve was developed to treat patients having aortic valve diseases called stenosis or insufficiency, like you.

STUDY DESIGN

This study will be conducted in up to 6 participating hospitals.

You may be one of approximately 200 participants invited to participate.

Your participation will last for 5 years. All participants will have to return to the hospital where the surgery was done and be checked by the study doctor or his colleagues on a regular basis. Following discharge you will be asked to return to the hospital at 3 months, 1 year, and annually until 5 years after the valve was implanted in your heart.

DESCRIPTION OF THE EDWARDS PERICARDIAL AORTIC BIOPROSTHESIS MODEL 11000

The Edwards Pericardial Aortic Bioprosthesis Model 11000A is a CE marked device. The Model 11000A is identical to the Model 11000.

The Model 11000 valve is a CE marked Carpentier-Edwards PERIMOUNT Magna Ease 3300TFX valve, with modifications in tissue processing and valve sterilization.

The Magna Ease valve consists of three tissue leaflets made of bovine (cow) pericardium (heart tissue). These leaflets have been treated with a new Edwards tissue process, built on the CE marked Edwards ThermaFix process to stabilize and preserve tissue. This process also allows the Model 11000 to be stored in non-liquid packaging and to not require rinsing prior to implant.

HOW WAS THE VALVE UNDER INVESTIGATION TESTED?

The valve was tested in conformity with European Regulations. The results of these tests have shown that the valve is suitable for implant in humans.

The technique used for implanting the valve is similar to the one your doctor uses with other biological heart valves. Each of the study doctors involved in this clinical study has been properly trained on how to implant the Model 11000.

WHAT WILL HAPPEN TO ME IF I TAKE PART?

If you agree to participate in this study, you receive the same treatment as any other patient having a similar operation, although you will also have some more tests (described below). The extra tests will enable us to collect more information about the valve and the surgery.

The decision about participating in this study is entirely yours.

Before your surgery, your doctor will discuss the study and answer any questions you may have. If you consent to participate you will be asked to sign and date an informed consent form. A copy of this form will be given to you.

The study doctor will then ask you questions and will run tests and procedures to see if you can participate in the study. These tests and procedures include:

- A screening assessment to see if you are eligible to participate in the study
- Your medical history will be reviewed
- You will be given a physical examination (a clinical evaluation of your condition), and any findings will be written down in the study chart

- The severity of your health will be graded using a standard scale called NYHA based on your ability to do physical activities.
- Your quality of life will be measured by two short health questionnaires
- You will have an echocardiogram (a machine that creates sound waves that can see the inside of your heart. The pictures are taken with a small probe that is put on the outside of your chest)
- You will have an electrocardiogram (a machine that records the electrical activity of your heart. The recording is done by putting self adhesive discs on your chest)
- Your blood will be collected for laboratory testing. The blood test will require a needle being inserted into a vein in your arm (or other area where a vein can be accessed). Approximately three teaspoons (15ml) of blood will be drawn at this visit for routine tests. Any remaining blood sample will be discarded according to hospital regulations.
- If you are a woman of child-bearing age (and are not sterile) a small amount of blood or urine will be obtained to check for pregnancy.

If the results of the tests and examinations do not meet the study requirements and your doctor assesses that you are not qualified to participate in the study, you will be excluded from the study and the study doctor will discuss with you an alternative treatment for your disease. No further commitments related to this study will be requested of you.

If, as a result of the above mentioned tests and examinations, your doctor assesses that you are eligible to participate in the study, you will be scheduled for your surgery.

This surgical procedure is performed under general anaesthesia as is normal for heart valve replacement. The cardiac surgeon will open the chest to enable access to the heart and will place your heart on a "heart-lung" machine while they operate on the valve. During your surgery and before the Model 11000 is implanted a small tube called a transesophageal ultrasound will be entered through your mouth and advanced down to the area of the heart. The doctor will use this ultrasound to take pictures of your heart and ensure it functions well once implanted. These are parts of every surgery to replace a heart valve.

If during surgery your study doctor finds a reason not to implant the Model 11000, you will receive another equivalent aortic Bioprosthesis approved in the market. You will be excluded from the study and you will not have any further commitments related to this study.

If your study doctor assesses that there are no further contraindications, you will receive the Model 11000 valve and will be considered enrolled in the study.

After your surgery and before you go home, you will have some more tests and examinations as described below:

- A physical examination will be performed
- Your blood will be collected for laboratory testing in order to determine the best pharmacological treatment for you
- An echocardiogram (a sound wave taking pictures of your heart) will be obtained to see that the newly implanted Model 11000 valve sits well in its position and that it works well
- You will have an electrocardiogram (recording of the electrical activity of your heart)

- You will be asked if you have experienced any unusual symptoms or side effects since the procedure – any finding will be recorded in order to control your health
- An appointment will be scheduled for you to return to the study center approximately 3 months after your procedure date.

During your 3 months and subsequent annual follow-up visits, you will be asked to provide information about your health status and you will undergo the following procedures:

- A physical examination
- An electrocardiogram (electrical recording of the heart)
- An echocardiogram (sound wave taking pictures of your heart)
- Your health condition will be graded based on your ability to perform physical activities (NYHA class)
- Your quality of life will be measured by two short health questionnaires (only at 1-year follow-up visit)
- Your blood will be collected for laboratory testing in order to determine the best pharmacological treatment for you
- You will be asked if you have experienced any unusual symptoms or side effects since your last assessment
- An appointment will be scheduled for you to return to the study center approximately at 1 year from your procedure date.

PARTICIPANT RESPONSIBILITIES

If you decide to participate in this research study, you will have to follow the instructions given by your study doctor and his colleagues and come back to the hospital for all the follow up visits until the fifth follow up year. Completing all study visits is important to make sure that the study results are complete and accurate. If you wish to stop participating in the study or if you find you have not followed instructions listed above, it is important that you notify the study doctor or study staff.

Your participation in this research study is **entirely 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. You are free to withdraw from the study at any time without giving any reason, even if you have confirmed in writing that you want to take part. Your decision to withdraw will not have any adverse effect whatsoever on your further treatment in our hospital.

Giving false, incomplete, or misleading information about your medical history, including past and present use of medications, could have a very serious effect on your health. It is very important that you give a true and complete medical history.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART?

There are no guaranteed benefits from participation in this clinical investigation. The potential benefit resulting from this clinical study beyond those afforded by a routine valve replacement may be a slightly shortened procedure time.

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 may include palliative medical therapy, aortic balloon valvuloplasty and surgical replacement of the aortic valve with another prosthesis.

WHAT ARE THE POSSIBLE RISKS OF TAKING PART?

You must understand that the treatment of choice for your condition is a heart valve replacement and that alternative valves are available.

As with all prosthetic heart valves, there is a possibility that serious complications, sometimes leading to death, could develop that were not anticipated. In addition, complications due to individual patient reaction to an implanted device, or to physical or chemical changes in the components, particularly those of biological origin, may occur at varying intervals (hours or days) necessitating reoperation and replacement of the prosthetic device. These risks will be explained to you by your study doctor. Should any side effects occur, they will be fully assessed and you will be monitored closely.

You may experience events and/or outcomes that may include, but are not necessarily limited to, the following:

- Allergic reaction or immunological response
- Angina (chest pain)
- Aortic wall and or annulus damage
- Cardiac arrhythmias / Conduction interference (change in the heartbeat rhythm)
- Chordae damage or trauma (damage to the mitral valve structure)
- Coronary ostia blockage (occlusion)
- Endocarditis (infection of the valve)
- Heart failure
- Hemolysis (Breaking open of red blood cells with release of hemoglobin)
- Hemolytic anemia
- Hemorrhage (bleeding related to the use of anticoagulant therapy)
- Myocardial infarction
- Prosthesis leaflet entrapment (Impingement)
- Prosthesis nonstructural dysfunction
- Prosthesis pannus (excessive tissues growth around the valve)
- Prosthesis Paravalvular leak (blood leaking around the valve when it is closed)
- Prosthesis regurgitation (blood leaking through the valve when it is closed)
- Prosthesis stenosis / Effective Orifice Area reduction (narrowing of the valve)
- Prosthesis structural deterioration (physical or chemical deterioration of valve components)
- Prosthesis thrombosis (blood clot attachment to the valve)
- Stroke or transient ischemic attack (TIA)
- Tissue deterioration including infection, calcification, thickening, perforation, de-generation, suture abrasion, instrument trauma, and leaflet detachment from the valve
- Thromboembolism
- Thrombotic obstruction

It is possible that these complications could lead to:

- Reoperation
- Explantation
- Permanent disability

- Death

WHAT HAPPENS IF I DECIDE AGAINST PARTICIPATING IN THE CLINICAL STUDY?

If you decide not to participate in the study you can discuss with your doctor which options of heart valve replacement best suit your requirements. This does not in any way affect your further medical care.

WHAT IF SOMETHING GOES WRONG?

Your doctor and the company that makes the valve (Edwards Lifesciences LLC (Irvine, CA)) will take all appropriate efforts to prevent you having any injury or illness which may occur as a result of your participation in this study. If you suffer any injury or illness as a direct result of participating in this study, you will receive medical care and treatment at this hospital. Signing this consent does not affect any legal rights you have.

As per the laws in your country, insurance has been taken out ([Insurance company details](#)).

Make sure you notify the insurance company without delay if you notice any deterioration in your state of health which may be related to the clinical study. Any such report may also be made by the study Investigator, your doctor.

WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

This section explains how your medical and health records might be used and disclosed if you agree to participate in this study.

All physicians involved in the study follow a strict clinical protocol. You have the right to determine who has access to your health records. Records collected in this study may include your medical history, the results of physical examinations, laboratory tests and other diagnostic or treatment procedures, as described above in this consent form, as well as basic demographic information.

By signing this form:

- You allow the study staff and/or the study doctor to use your medical records for the study and to disclose your health information to the sponsor, Edwards Lifesciences, LLC., or to the sponsor's representatives, in order to review the results of the study and to monitor the safety of participants.
- You allow the study doctor and/or sponsor to publish the results of the study or discuss the results at conferences. If this is done, no information will be included that would reveal your identity.

The information sent by the study doctor and/or study staff to the Sponsor will be anonymised, that means it will not include your name, address, or any other means of identification. Instead, the study doctor will use an assigned coded number to the records that are provided to the sponsor. However, your entire medical record may be reviewed at the study doctor's office and/or hospital by the Sponsor and/or Sponsor representatives, by regulatory/government agencies and the independent ethics committee (EC - is a group that has been formally designated to review and monitor research involving human subjects). The purpose of these reviews is to assure the quality of the study and patient safety.

The study doctor and/or study staff will make every effort to protect the privacy of your information. However, absolute confidentiality cannot be guaranteed because of the need to disclose information as described above.

You can cancel this authorization at any time by giving a written notice to the study doctor. If you cancel this authorization, then you will no longer be able to participate in the study, and the information that has been collected prior to canceling the authorization may still be used and disclosed to the above-mentioned parties. You will receive a signed copy of this consent for your records.

All data collected within the scope of the study may be forwarded to other persons or institutions not authorized for direct data inspection in an anonymized form only. We will inform your local doctor (general practitioner), only if you allow.

PARTICIPATION AND WITHDRAWAL

You have the right to choose not to participate in this study or to stop participating at any time, without any consequences. This means that there will be no penalty or loss of medical benefits to which you are entitled.

If you choose to stop being a part of this study, you must first notify the study doctor immediately so that a plan can be provided for your continued medical care. At the time you stop taking part in the study, you will be asked to return for a final safety evaluation that will include gathering information about your current medical condition and conducting any required procedures. For your own safety, you should go through the study exit procedures any time you leave the study and make arrangements for your follow up care.

It is possible that your participation in this study may be stopped at any time. This might happen if you do not follow the instructions given by the study doctor or if the study doctor believes it to be in your best interest. The study may also be stopped for administrative, medical, or other reasons as determined by the study doctor or Edwards Lifesciences, LLC., or the regulatory authorities of the counties where this clinical study is conducted. Any significant new findings developed during the course of this research that might affect your willingness to participate will be provided to you by your doctor.

While participating in this study, you should not take part in any other study. This is to protect you from possible unforeseen injuries that may arise.

WHO IS ORGANISING AND FUNDING THE RESEARCH?

This study/research is organized by Edwards Lifesciences, LLC. the medical device company manufacturing the Model 11000 valve and the Sponsor of this study.

1. The Sponsor reimburses the institution for tests and procedures needed for this study.
2. The study staff will not be paid to include you in this study but the hospital will be reimbursed for the costs incurred in conducting this research.

COSTS AND COMPENSATION

There will be neither charge, nor compensation, for your participation in this study. The investigational device, study-related procedures, and study visits will be provided at no charge.

You will be reimbursed for the travel expenses you face in order to come back to the hospital for the follow-up visits requested by this study

You will still be responsible for the cost of your usual ongoing medical care, including procedures and/or non-study drugs that are not required by this study. If you have any questions, please ask the study doctor, a member of the study staff.

CONTACT DETAILS FOR FURTHER INFORMATION

If you require any further information before or during the study, or if you have any questions after you have read this Patient Information, please contact the investigator responsible for you:

Telephone: _____

FURTHER INFORMATION

You consent to participate in a scientific study and in the statistical analysis of the results of that study. It is understood that your personal data continue to be subject to data protection and shall not be disclosed to any third parties. Participation in this study is voluntary, and you can discontinue participation at any time without giving reasons, and without penalty. The Principal Investigator or the sponsor may also decide on your premature discontinuation of this study.

CONSENT FORM

Title of the project: **Clinical study of an Edwards model 11000 aortic valve**

Name of the Principal Investigator: _____

Center number: _____

Study number: _____

Patient Identification Number: _____

Please initial box

1. I confirm that I have read and understand the information sheet dated _____ (version _____) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.
3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from Edwards Lifesciences, from regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
4. I agree to my GP being informed of my participation in the study. Yes No
5. I agree to take part in the above study.

Name of Patient

Signature

Date

Name of legal representative
(if applicable)

Signature

Date

I attest that I discussed this study with the above named participant. This person had enough time to consider the information, had an opportunity to ask questions, and voluntarily agreed to participate in this study.

Name of person taking consent

Signature

Date



15.3 CASE REPORT FORMS

PREOPERATIVE INCLUSION / EXCLUSION CRITERIA

Rev B

Please indicate whether or not the subject meets the following inclusion criterion

- No Yes Subject is 18 years or older
- No Yes Subject is diagnosed with aortic valve disease requiring a planned replacement as indicated in the preoperative evaluation
- No Yes Subject is scheduled to undergo planned aortic replacement with or without concomitant coronary bypass surgery
- No Yes Subject provided written informed consent prior to trial procedures

Please indicate when the subject signed the informed consent form:

Date: (DD/MMM/YYYY)Time: (HH:MM)

- No Yes Subject is geographically stable and agrees to attend follow-up assessments at the hospital of surgical services for up to 5 years

Please indicate whether or not the subject meets any of the following exclusion criterion

- No Yes Subject requires emergency surgery
- No Yes Subject has prior mitral, tricuspid or pulmonic valve surgery, which included implant of a bioprosthetic valve, mechanical valve, or annuloplasty ring that will remain in situ
- No Yes Subject requires multiple valve replacement/repair
- No Yes Subject requires a surgical procedure outside of the cardiac area (e.g. vascular bypass)
- No Yes Subject has aneurysm of the aortic root and/or ascending aorta requiring surgical intervention
- No Yes Subject has active endocarditis/myocarditis or endocarditis/myocarditis within 3 months to the scheduled aortic valve replacement (AVR) surgery
- No Yes Subject has renal insufficiency as determined by creatinine (S-Cr) level ≥ 2.5 mg/dL or end-stage renal disease requiring chronic dialysis at screening visit
- No Yes Subject has MRI or CT scan confirmed stroke, cerebrovascular accident (CVA) or transient ischemic attack (TIA) within 6 months (180 days) prior to AVR surgery
- No Yes Subject has acute myocardial infarction (MI) within 30 days prior to AVR surgery
- No Yes Subject has presence of non-cardiac disease limiting life expectancy to less than 12 months
- No Yes Subject is diagnosed with hypertrophic obstructive cardiomyopathy (HOCM)

Subject ID

Site

Visit Date

Status

Visit Name

Subevent#

CRF Name

Blank CRF

12. No Yes Subject is diagnosed with hyperparathyroidism
13. No Yes Subject exhibits left ventricular ejection fraction $\leq 30\%$ as validated by diagnostic procedure within 30 days prior to AVR surgery
14. No Yes Subject has echocardiographic evidence of an intra-cardiac mass, thrombus, or vegetation
15. No Yes Subject has hemodynamic or respiratory instability requiring inotropic support, mechanical circulatory support, or mechanical ventilation within 60 days prior to AVR surgery
16. No Yes Subject has documented leukopenia ($WBC < 3.5 \times 10^3/uL$), acute anemia ($Hgb < 10.0 \text{ gm/dL}$ or 6 mmol/L), thrombocytopenia (platelet count $< 50 \times 10^3/uL$) or history of bleeding diathesis or coagulopathy
17. No Yes Subject is diagnosed with myxomatous disease/connective tissue disorders (e.g. Marfan's Syndrome)
18. No Yes Subject has prior organ transplant
19. No Yes Current or recent participation (within 6 weeks prior to surgery) in an investigational drug or device trial
20. No Yes Subject was previously implanted with trial device
21. No Yes Subject is pregnant (female subject of childbearing potential only), lactating or planning to become pregnant during the duration of participation in trial
22. No Yes Subject is currently incarcerated or unable to give voluntary informed consent
23. No Yes Subject has documented history of substance (drug or alcohol) abuse within the last 5 years prior to implant

Based on the answers to the preoperative inclusion and exclusion criteria, is this subject eligible for intraoperative evaluation? No Yes

Has a surgery date for this subject been scheduled? No Yes

Please indicate the estimated surgery date: (DD/MMM/YYYY)

Study

Doc#

Subject ID

Site

Visit Date

Status

Visit Name

Subevent#

CRF Name

Blank CRF

INTRA-OPERATIVE EXCLUSION CRITERIA

Rev B

Does the subject have the following anatomic variances which contraindicate implant of the valve?

- 1. Position of the coronary ostia relative to the study valve that would result in obstruction of blood flow No Yes

- 2. The device is not available in the correct size for the subject No Yes

- 3. Subject is hemodynamically unstable during the procedure requiring the procedure to be aborted prior to implanting the study device No Yes

- 4. Surgeon determined that a trial valve cannot be implanted after intra-operative evaluation and prior to a trial valve implant attempt for any other reason No Yes

Please specify:

Was the subject enrolled in the study?

No Yes

Study

Doc#

Subject ID

Site

Visit Date

Status

Visit Name

Subevent#

CRF Name

Blank CRF

DEMOGRAPHICS

Rev B

Age:

What format will be used to indicate the subject's age?

- Birth date (DD/MMM/YYYY)

Birth date:

- Year (YYYY) and age

Year:

Age:

Gender:

- Male

- Female

Was a pregnancy test performed?

- Yes

What was the result?

- No

Why was the pregnancy test not performed?

Please specify:

Is the subject willing to identify their race/ethnicity? No Yes

Please indicate the subject's race:

Please specify:

Please indicate the subject's ethnicity:

Please specify:

E Edwards Lifesciences

Study

Doc#

Subject ID

Site

Visit Date

Status

Visit Name

Subevent#

CRF Name

Blank CRF

Subject height:

cm in

What is the subject's Canadian Cardiovascular Society (CCS) Angina Class?

What is the subject's current Left Ventricular Ejection Fraction (LVEF)?

%

What is the subject's baseline serum creatinine value (mg/dL)?

Is this value within the normal range? No Yes

Was this result clinically significant? No Yes

MEDICAL HISTORY (Part 1)

Rev B

CARDIOVASCULAR MEDICAL HISTORY / RISK FACTORS

Does the subject currently have or has the subject ever had the following diseases / conditions?

- No Yes Coronary Artery Disease (CAD)

Please indicate which native coronary vessels have $\geq 50\%$ narrowing:

- No Yes Left anterior descending (LAD) coronary artery
 No Yes Circumflex coronary artery
 No Yes Right coronary artery
 No Yes Left main coronary artery

- No Yes Carotid Artery Disease

Please indicate the severity of the disease:

- No Yes Peripheral Artery/Vascular Disease

Please indicate which symptoms the subject has experienced:

- No Yes Claudication
 No Yes $>50\%$ stenosis of any peripheral artery
 No Yes Aortic aneurysm

- No Yes Pulmonary Hypertension

What is the severity of the condition?

- No Yes Systemic Hypertension

Please indicate if the subject:

- No Yes Has a documented history of hypertension diagnosed and treated with medication, diet and/or exercise
 No Yes Has prior documentation of blood pressure >140 mmHg systolic or 90 mmHg diastolic for patient without diabetes or chronic kidney disease; or prior documentation of blood pressure > 130 mmHg systolic or 80 mmHg diastolic on at least 2 occasions for patients with diabetes or chronic kidney disease
 No Yes Is currently on pharmacologic therapy to control hypertension

- No Yes Cardiomyopathy

Please indicate the type of cardiomyopathy

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

No Yes Congestive Heart Failure (CHF)

No Yes Aortic Stenosis

No Yes Aortic Insufficiency

Please indicate the last known severity:

No Yes Mitral Stenosis

No Yes Mitral Insufficiency

Please indicate the last known severity:

No Yes Tricuspid Stenosis

No Yes Tricuspid Insufficiency

Please indicate the last known severity:

No Yes Myocardial Infarction (MI)

What types of myocardial infarction (MI) has the subject experienced?

No Yes ST elevation MI (STEMI)

No Yes Non ST-elevation MI (NSTEMI)

No Yes Other type of MI

Please specify:

No Yes Unknown type of MI

Is the date (DD/MMM/YYYY) when the last known MI occurred known? No Yes

Date of last known MI:

Is the approximate number of months since the occurrence of the last MI known?

No Yes

Number of months:

Did the event occur >5 years ago? No Yes

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

No Yes Cardiac rhythm abnormalities/conduction disturbances

Has the subject ever had the following cardiac rhythms?

No Yes Sinus tachycardia

No Yes Sinus bradycardia

No Yes Atrial fibrillation / Supraventricular tachycardia

Please indicate the episodic pattern:

Is this a permanent condition? No Yes

No Yes Atrial flutter

No Yes Tachycardia-bradycardia syndrome

No Yes Ventricular tachycardia

Please indicate the episodic pattern for VT

No Yes Other cardiac rhythm abnormality

Please specify:

Has the subject ever shown sign of the following conduction disturbances?

No Yes AV block

Indicate the last recorded degree of AV Block:

No Yes Bundle branch block

Indicate branch:

No Yes Other conduction disturbance

Please specify:

Study

Doc#

Subject ID

Site

Visit Date

Status

Visit Name

Subevent#

CRF Name

Blank CRF

No Yes Cerebrovascular Disease

Please indicate if the subject has experienced the following types of cerebrovascular events:

No Yes Transient ischemic attack (TIA; recovered within 24 hours)

Is the date when the last known TIA occurred known? No Yes

Date of last known TIA:

Is the approximate number of months since the occurrence of the last TIA known? No Yes

Number of months:

Did the event occur > 5 years ago? No Yes

No Yes Cardiovascular accident / Stroke (CVA; did not recover within 24 hours)

Is the date when the last known CVA occurred known? No Yes

Date of last known CVA:

Is the approximate number of weeks since the occurrence of the last CVA known? No Yes

Number of weeks:

Did the event occur > 5 years ago? No Yes

Does the subject have severe impairment of mobility as a result of a neurological dysfunction? No Yes

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

No Yes Endocarditis

When was the subject last being treated for endocarditis?

No Yes Myocarditis

When was the subject last being treated for myocarditis?

No Yes Hyperlipidemia or Hypercholesterolemia

No Yes Rheumatic fever

No Yes Pulmonary valve stenosis

No Yes Pulmonary valve insufficiency

Please indicate the last known severity:

Does the subject have a history of:

No Yes Smoking

Is the subject a current smoker? No Yes

When did the subject quit?

No Yes Alcohol/Drug Abuse

Subject ID

Site

Visit Date

Status

Visit Name

BASELINE

Subevent#

CRF Name

MEDICAL_HISTORY_P2

Blank CRF

MEDICAL HISTORY (Part 2)

Version A

PRIOR CARDIOVASCULAR SURGICAL INTERVENTIONS

How many previous cardiovascular surgeries has the subject had?

How many cardiac/heart surgeries has the subject previously had?

Has the subject required amputation of a limb due to arterial disease? No YesHas the subject been implanted with a permanent pacemaker or an implantable cardioverter defibrillator (ICD)? No Yes

Please specify the type of implant the subject has:

Is the date of the implant known? No Yes

Date of implant:

Is the approximate number of months since the implant known? No Yes

Approximately how many months ago was the subject implanted?

Did the event occur > 5 years ago? No Yes

Were surgical interventions performed on any of the following cardiovascular components?

 No Yes Carotid Arteries

What type of intervention was done on the carotids?

Please specify:

 No Yes Abdominal Aorta No Yes Thoracic Aorta No Yes Limb Arteries

No Yes Coronary Arteries

What type of interventions have been performed?

No Yes CABG

How many grafts were done?

No Yes Percutaneous transluminal coronary angioplasty (PTCA) /
Percutaneous coronary intervention (PCI)

Was a stent employed for any of the past PTCA / PCI procedures?

No Yes Unknown

No Yes Other intervention on the coronary arteries

Please specify:

No Yes Aortic Valve

Were the following interventions performed?

No Yes Valvuloplasty

No Yes Valve Replacement

No Yes Other repair

Please specify:

No Yes Mitral Valve

Were the following interventions performed?

No Yes Annuloplasty

No Yes Valvuloplasty

No Yes Valve replacement

No Yes Other repair

Please specify:

No Yes Pulmonary valve

Were the following interventions performed?

No Yes Valvuloplasty

No Yes Valve replacement

No Yes Other repair

Please specify:

No Yes Tricuspid valve

Were the following interventions performed?

No Yes Annuloplasty

No Yes Valvuloplasty

No Yes Valve replacement

No Yes Other repair

Please specify:

No Yes Other Cardiovascular Component

Please specify the location of the intervention and the type of surgical procedure performed

Subject ID

Site

Visit Date

Status

Visit Name

BASELINE

Subevent#

CRF Name

MEDICAL_HISTORY_P2

Blank CRF

NON-CARDIOVASCULAR RISK FACTORS

Does the subject currently have or has the subject ever had the following diseases?

 No Yes Blood Diatheses

Please specify the type:

Please specify:

 No Yes Calcium Metabolic Disorders No Yes Cancer

Please specify:

Has the subject received or will the subject receive chemotherapy within 30 days prior to the study procedure? No Yes No Yes Chronic obstructive pulmonary disease (COPD) / Chronic lung disease

Please indicate the FEV1/FVC value

What type of treatment did the subject receive for this condition?

 No Yes Chronic inhaled or oral bronchodilator therapy No Yes Chronic steroid therapy No Yes Oxygen or ventilation No Yes Other treatment

Please specify:

Subject ID

Site

Visit Date

Status

Visit Name

BASELINE

Subevent#

CRF Name

MEDICAL_HISTORY_P2

Blank CRF

No Yes Diabetes

Please indicate the type of diabetes:

Is the subject currently receiving the following treatments?

- No Yes Diet
 No Yes Oral
 No Yes Insulin

No Yes Obesity (BMI >=30)

No Yes Liver Disease

No Yes Musculoskeletal Dysfunction

Does the subject have severe impairment of mobility due to this condition? No Yes

No Yes Renal Failure/Insufficiency

Is the date when the subject was diagnosed known? No Yes

Date diagnosed

Is the approximate number of months since the subject was diagnosed known?

No Yes

Approximately how many months ago was the subject diagnosed?

Was the subject diagnosed > 5 years ago? No YesIs the subject currently on dialysis? No Yes

No Yes Other disease which requires immunosuppressive therapy inhaled or systemic steroid therapy or chemotherapy within 30 days of the study procedure

ASSESSMENT

Rev B

What was the primary method of contact with the subject?**PLEASE PROVIDE THE FOLLOWING PHYSICAL ASSESSMENT PARAMETERS:**

Weight:

 kg lb

Heart Rate:

BPM

Blood pressure:

/

mmHg

Systolic

Diastolic

NYHA Classification**Was an auscultation performed?**

- No
 Yes

Date of auscultation exam: (DD/MMM/YYYY)

Was an aortic murmur heard?

- No *If No, a transthoracic echocardiogram (TTE) is not needed for this visit (Applicable for 2 and 4 year visit)*
 Yes *If Yes, please complete transthoracic echocardiogram (TTE)*

Was information about the subject's current medications collected?

- No
 Yes *If Yes, please fill out a Medication form (MED)*

Was a transthoracic echocardiogram (TTE) performed?

- No
 Yes *If Yes, please fill out a Echocardiogram form (ECHO (S))*

Was an electrocardiogram (ECG) performed?

- No
 Yes *If Yes, please fill out a Electrocardiogram form (ECG)*

Was a blood test performed?

- No
 Yes *If Yes, please fill out a Blood Data form (LABS)*

Was Quality of Life assessed? (Required at Baseline and 1 Year only)

- No
 Yes *If Yes, please fill out a Quality of Life (QOL) form*

Study

Doc#

Subject ID

Site

Visit Date

Status

Visit Name

Subevent#

CRF Name

Blank CRF

Have any adverse events occurred that were not previously reported?

- No
- Not applicable at Baseline
- Yes If Yes, please ensure an adverse event form has been completed for each event.

Are the event(s) that occurred within the following AE classifications?

- No Yes Blood and Lymphatic (Including ALL Bleeding complications)
- No Yes Cardiovascular - Arrhythmia
- No Yes Cardiovascular - Regurgitation
- No Yes Cardiovascular - Stenosis
- No Yes Cardiovascular - Embolic Event/Valve Thrombosis
- No Yes Cardiovascular - Misc
- No Yes Device Dysfunction
- No Yes Gastrointestinal/Hepatic
- No Yes Genitourinary/Renal
- No Yes Pulmonary/Respiratory
- No Yes Peripheral Vascular
- No Yes Psychiatric
- No Yes Muscular Skeletal/Dermatologic
- No Yes Nonspecific or Unknown Body System

Comments

Subject ID

Site

Visit Date

Status

Visit Name

Subevent#

CRF Name

Blank CRF

SURGERY DATA

Rev B

Date of hospital admission: (DD/MMM/YYYY)Date of surgery: (DD/MMM/YYYY)Implanting surgeon: **PREOPERATIVE CONDITION****For Purposes of Risk Score Assessment, did a Myocardial Infarction (MI) occur within 21 days?** No Yes

Please indicate the time interval when the last MI occurred:

Within 2 weeks prior to the surgical procedure:Was the subject in congestive heart failure? No YesDid the subject experience an arrhythmia? No YesWas the observed arrhythmia considered Atrial fibrillation or Atrial flutter? No Yes**Did the subject experience cardiac/chest pain or angina after hospital admission?** No Yes

What is the likely cause of these symptoms?

Did the subject receive IV inotropic agents within 48 hours preceding surgery or was the administration of this medication documented as contraindicated? No Yes**On the day of surgery but prior to going under anesthesia, did the subject experience or require:** No Yes Ventricular fibrillation No Yes Ventricular tachycardia No Yes Cardiogenic shock No Yes Aborted sudden death No Yes Acute renal failure (anuria or oliguria <10 ml/hr) No Yes Cardiopulmonary resuscitation <1hr prior to surgery No Yes Ventilation before arrival in anesthetic room No Yes Inotropic support or IABP No Yes Another cardiac intervention <= 6 hours prior to scheduled surgery

What is the urgency of the surgery being performed?

- ELECTIVE (Admission for operation; subject's cardiac function is stable in the days/weeks prior to the operation)
- URGENT (Not admitted for the operation, but requires surgery on the current admission before they can be discharged)
- SALVAGE (Requires cardiopulmonary resuscitation prior to induction of anesthesia)
- EMERGENCY (Operation before the beginning of the next working day after the decision made to operate)

INTRA-OPERATIVE ETIOLOGY AND DIAGNOSIS

Were any of the following intraoperative diagnoses made concerning the etiology of the valve disease?

- No Yes Degenerative
- No Yes Dystrophic calcification
- No Yes Rheumatic
- No Yes Remote endocarditis
- No Yes Other etiology

Please specify:

Please confirm the diagnosis for the current replacement:

- Stenosis
- Stenosis with insufficiency
- Pure insufficiency
- Prosthetic valve dysfunction
- Other diagnosis

Please specify:

What surgical approach was used?

- Full sternotomy
- Mini upper sternotomy
- Right thoracotomy
- Other MIS approach

Please specify:

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

Is there evidence of the following conditions of the aortic valve, annulus, aortic wall, or coronary arteries?

No Yes Calcification

Was calcification observed in the following locations?

No Yes Annulus

No Yes Leaflets

No Yes Aortic wall

No Yes Coronary arteries

No Yes Leaflet fusion

No Yes Leaflet perforation

No Yes Myxomatous

No Yes Vegetation

No Yes Other disease condition

Please specify:

SURGICAL APPROACH AND ANNULUS PREPARATION

Were the following concomitant procedures performed?

No Yes Coronary artery bypass grafting (CABG)

How many grafts were done?

No Yes Permanent pacemaker implant

Was Cardiac Resynchronization Technique (CRT) used? No Yes

No Yes Automatic Implanted Cardioverter Defibrillator (AICD) implant

Was Cardiac Resynchronization Technique (CRT) used? No Yes

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

No Yes Atrial ablation

What type of ablation procedure was done?

Primarily epicardial

Primarily intracardiac

No Yes Aortic aneurysm/dissection repair

No Yes Occlusion / Removal of atrial appendage

Please indicate the appendage

Left

Right

No Yes Atrial septal defect (ASD) repair

What was the type of defect repaired?

No Yes Septal myectomy

No Yes Other procedure

Please specify:

Were any unplanned procedures performed during this operation? No Yes

Why was this procedure necessary?

Was the unplanned procedure a Ventricular Assist Device (VAD) insertion? No Yes

Was an intraaortic balloon pump (IABP) used in relation to this surgical procedure?

No

Yes

When was the IABP inserted?

Amount of Annular / Aortic Root Debridement

Study

Doc#

Subject ID

Site

Visit Date

Status

Visit Name

Subevent#

CRF Name

Blank CRF **What valve was implanted?**

- Model 11000 *(If selected, please complete **Model 11000** section below)*
- Commercial valve *(If selected, please complete *** Commercial Valve *** section below)*
- No valve implanted due to subject death *(If selected, please fill out a Study Exit form)*

**** If Model 11000 is selected, please complete the following questions: ****

On what attempt was the study valve implanted?

- 1 *(If '1' is selected, please fill out one (1) Device Performance form)*
- 2 *(If '2' is selected, please fill out two (2) Device Performance forms)*

Was a post-implant echocardiogram performed? No Yes

Please complete the following questions:

Time echocardiogram started: (HH:MM)

What type of echocardiogram was done?

What was the severity of central regurgitation for the study valve?

What was the severity of paravalvular leak for the study valve?

Was observed regurgitation clinically acceptable? No Yes***** If Commercial Valve is selected, please complete the following questions: *****

After which study valve attempt was a commercial valve implanted?

- 1 *(If '1' is selected, please fill out one (1) Device Performance form (PERF).*

Why was a second attempt to implant the study valve not performed?

Please specify:

- 2 *(If '2' is selected, please fill out two (2) Device Performance forms (PERF).*

Please provide the following information about the commercial valve:

Manufacturer and Model:

Valve size: (mm)

Study

Doc#

Subject ID

Site

Visit Date

Status

Visit Name

Subevent#

CRF Name

Blank CRF

Did any adverse events occur during the surgery?

No

Yes If Yes, please ensure an adverse event form has been completed for each event.

Are the event(s) that occurred within the following AE classifications?

No Yes Blood and Lymphatic (Including ALL Bleeding complications)

No Yes Cardiovascular - Arrhythmia

No Yes Cardiovascular - Regurgitation

No Yes Cardiovascular - Stenosis

No Yes Cardiovascular - Embolic Event/Valve Thrombosis

No Yes Cardiovascular - Misc

No Yes Device Dysfunction

No Yes Gastrointestinal/Hepatic

No Yes Genitourinary/Renal

No Yes Pulmonary/Respiratory

No Yes Peripheral Vascular

No Yes Psychiatric

No Yes Muscular Skeletal/Dermatologic

No Yes Nonspecific or Unknown Body System

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

Was there a bleeding-related reoperation within the first 24 hours after surgery? No Yes

Please provide the times at which the following procedural steps were performed:

Start skin incision: (HH:MM)

Start ECC (Pump): (HH:MM)

Start cross clamp: (HH:MM)

Start sizing: (HH:MM)

Remove cross clamp: (HH:MM)

End ECC (Pump): (HH:MM)

End Skin closure: (HH:MM)

Comments

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

DEVICE PERFORMANCE

Rev B

What study valve implant attempt was being performed?

Please provide the following information about the study valve:

Valve size:

Serial Number:

What type of sizer was used?

Please specify:

What was the barrel size of the valve sizer? mm

What suture technique was used to secure the valve?

Please specify:

How was the valve positioned?

Did the study valve perform as intended?

No

Please indicate the types of valve failures observed:

Failure type:

Please specify:

Failure type:

Please specify:

Failure type:

Please specify:

Failure type:

Please specify:

Yes

Study

Doc#

Subject ID

Site

Visit Date

Status

Visit Name

Subevent#

CRF Name

Blank CRF

DEVICE TECHNICAL SUCCESS:

Did the subject leave the operating room with the study valve in place for this attempt?

No

Why did the implant attempt fail?

Please specify:

Was the heart restarted after this implant attempt? No Yes

Yes

VALVE IMPLANT TIMES:

Start the study procedure (first stitch):

(HH:MM:SS)

Complete the study procedure (last stitch tied down on the valve):

(HH:MM:SS)

Comments

Subject ID

Site

Visit Date

Status

Visit Name

Subevent#

CRF Name

Blank CRF

DISCHARGE

Version A

Date of discharge (DD/MMM/YYYY)

Where was the subject discharged to?

Please provide the following information about the subject's hospitalization after the study valve procedure

Duration of time in the Intensive Care Unit (ICU)

Days and Hours

Duration of time in the Intermediate Care / High Dependency Unit

Days and Hours

Duration of time in the General Ward

Days and Hours

When was the transthoracic echocardiogram (TTE) performed?

Study

Doc#

Subject ID

Site

Visit Date

Status

Visit Name

Subevent#

CRF Name

Blank CRF

ADVERSE EVENT

Rev B

Event Onset Date

(DD/MMM/YYYY)

Site Awareness Date

(DD/MMM/YYYY)

Timing of Event Onset

Please select the AE Classification:

- Blood and Lymphatic (Including ALL Bleeding complications)

- Cardiovascular - Arrhythmia

- Cardiovascular - Regurgitation

- Cardiovascular - Stenosis

- Cardiovascular - Embolic Event/Valve Thrombosis

- Cardiovascular - Misc

- Device Dysfunction

- Gastrointestinal/Hepatic

- Genitourinary/Renal

- Pulmonary/Respiratory

- Peripheral Vascular

- Psychiatric

- Muscular Skeletal/ Dermatologic

- Nonspecific or Unknown Body System

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

Event Summary/Comments

Method of Detection

No Yes Lab finding

No Yes Echocardiogram

No Yes Angiogram

Date of Angiogram: (DD/MMM/YYYY)

No Yes MRI

Date of MRI: (DD/MMM/YYYY)

No Yes Electrocardiogram (ECG)

No Yes Autopsy

No Yes Observation

Date AE first observed: (DD/MMM/YYYY)

No Yes Clinical Exam

Date of Clinical Exam: (DD/MMM/YYYY)

No Yes Re-operation

Date of Re-operation: (DD/MMM/YYYY)

No Yes Other method

Please, specify:

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

Causality: Is this event related to any of the following?

- No Yes Indeterminate Surgical Procedure
- No Yes Indeterminate Study Valve
- No Yes Indeterminate User Error
- No Yes Indeterminate Deficiency in Instructions
- No Yes Indeterminate Underlying Condition

What was the underlying condition?

Did antithrombotic medication contribute to this event? No Yes

Was this medication prescribed due to study valve implant? No Yes

Please indicate what type(s) of medication contributed to this event:

- No Yes Anticoagulant medication
- No Yes Aspirin
- No Yes Other antiplatelet medication
- No Yes Other antithrombotic medication

Please, specify:

Did non-antithrombotic medication contribute to this event? No Yes

Please, specify:

Is this a serious adverse event (SAE)? No Yes

Please indicate all conditions of a SAE that apply:

- No Yes Resulted in death
- No Yes Resulted in life-threatening illness/injury
- No Yes Resulted in permanent impairment
- No Yes Resulted in hospitalization or prolongation or current hospitalization
- No Yes Resulted in surgical intervention to prevent permanent impairment to body structure or function
- No Yes Resulted in fetal distress or death, congenital abnormality or birth defect
- No Yes Resulted in a medical intervention to prevent permanent impairment to body structure or function

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

Is this an unanticipated device related adverse effect (UDAE)? No Yes

Was any intervention taken to treat this adverse event? No Yes

Please indicate whether the following interventions were needed:

No Yes Prolonged hospitalization

No Yes Re-hospitalization required

Hospital admission date: (DD/MMM/YYYY)

Was the subject discharged from the hospital? No Yes

Discharge date: (DD/MMM/YYYY)

No Yes Cardioversion

No Yes Transfusion

No Yes Medication given

What type of medication was given?

No Yes Permanent Pacemaker implanted (not planned prior to AVR)

Date of pacemaker implant: (DD/MMM/YYYY)

No Yes Surgical intervention - reoperation on the study valve

Date of surgical intervention: (DD/MMM/YYYY)

Was this adverse event the primary cause of reoperation on the study valve? No Yes

Did the reoperation result in removal/replacement of the study valve? No Yes

No Yes Surgical intervention - not reoperation on the study valve

Date of surgical intervention: (DD/MMM/YYYY)

No Yes Other intervention

Please, specify:

Indicate the outcome of the event:

Date resolved: (DD/MMM/YYYY)

BLOOD DATA (LABS)

Rev B

Date Blood Drawn: (DD/MMM/YYYY)

White Blood Cells (WBC)

Is this value within normal range? No Yes Not Applicable

Was the result clinically significant? No Yes

Red Blood Cells (RBC)

Is this value within normal range? No Yes Not Applicable

Was the result clinically significant? No Yes

Hemoglobin:

Is this value within normal range? No Yes Not Applicable

Was the result clinically significant? No Yes

Hematocrit:

Is this value within normal range? No Yes Not Applicable

Was the result clinically significant? No Yes

Platelet Count:

Is this value within normal range? No Yes Not Applicable

Was the result clinically significant? No Yes

Plasma Free Hemoglobin:

Is this value within normal range? No Yes Not Applicable

Was the result clinically significant? No Yes

Coagulation Profile

INR:

PTT:

PT (seconds):

Subject ID

Site

Visit Date

Status

Visit Name

BASELINE

Subevent#

CRF Name

MEDICATIONS

Blank CRF

MEDICATIONS

Version A

Date Information Collected: (DD/MMM/YYYY)

Please indicate what type of medications the subject is currently taking: No Yes Antithrombotics (Thrombolytics)Please indicate if the subject is taking anticoagulants: No Yes

Please indicate the type of anticoagulant(s):

 No Yes Warfarin - Coumadin (or derivatives) No Yes Heparin No Yes Low Molecular Weight Heparin No Yes Other anticoagulant

Please specify:

Please indicate if the subject is taking antiplatelets: No Yes

Please indicate the type of antiplatelet(s):

 No Yes Dipyridamole - Persantine No Yes Aspirin - Ecotrin or Entrophen No Yes Ticlopidine No Yes Clopidogrel-Plavix No Yes Other antiplatelet

Please specify:

Subject ID

Site

Visit Date

Status

Visit Name

Subevent#

CRF Name

Blank CRF

No Yes ACE or ARB Inhibitors

No Yes Antiarrhythmics

Please indicate if the subject is taking the following antiarrhythmics:

No Yes Beta Blockers (Propranolol, Esmolol)

No Yes Other (Sodium/Potassium channel blockers, i.e. Amiodarone)

No Yes Calcium Blocker

No Yes Diuretic

No Yes Lipid Lowering

No Yes Nitrates

No Yes Steroids

Subject ID

Site

Visit Date

Status

Visit Name

BASELINE

Subevent#

CRF Name

ECG

Blank CRF

ELECTROCARDIOGRAM (ECG) EXAM

Version A

Date of electrocardiogram (ECG) exam: (DD/MMM/YYYY)

Is the subject implanted with a permanent pacemaker? No Yes

Please specify the type:

Dose the subject have an implantable cardioverter defibrillator (ICD/AICD)? No Yes

Please indicate if the following cardiac rhythms were observed during the ECG:

- No Yes Sinus rhythm with no abnormalities
 No Yes Sinus tachycardia
 No Yes Sinus bradycardia
 No Yes Atrial fibrillation / Supraventricular tachycardia

Please indicate the episodic pattern:

- No Yes Atrial flutter
 No Yes Tachycardia-bradycardia syndrome
 No Yes Ventricular tachycardia

Please indicate the episodic pattern:

- No Yes Other cardiac arrhythmia

Please specify:

Please indicate if evidence of the following conduction disturbances was found during the ECG exam:

- No Yes AV block

Please indicate degree:

- No Yes Bundle branch block / Intraventricular block

Please indicate branch:

Left No YesRight No Yes

- No Yes Other conduction disturbance

Please specify:

QUALITY OF LIFE

Revision A

QUALITY OF LIFE (QOL) ASSESSMENT

Was an EQ-5D questionnaire completed? No Yes

EQ-5D Questionnaire

Date of assessment (DD/MMM/YYYY)

Indicate which statement the subject marked on the survey:

Mobility

Self-care

Usual Activities (*e.g. work, study, housework, family or leisure activities*)

Pain/Discomfort

Anxiety/Depression

Overall State (*Indicate how the subject rated their overall health today*)

Comments:

Subject ID

Site

Visit Date

Status

Visit Name

Subevent#

CRF Name

Blank CRF

Was an SF-12-v2 questionnaire completed? No Yes

SF-12 v2 QuestionnaireDate of assessment (DD/MMM/YYYY)**Indicate which statement the subject marked on the survey:**1. In general, would you say your health is:

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

a. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf. b. Climbing several flights of stairs

3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

a. Accomplished less than you would like b. Were limited in the kind of work or other activities

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

a. Accomplished less than you would like b. Did work or activities less carefully than usual?

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks.....

a. Have you felt calm and peaceful? b. Did you have a lot of energy? c. Have you felt downhearted and depressed?

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

Comments

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

SITE ECHO TRACKING FORM

Rev B

***** NOT A CRF *****

Date of ECHO Exam:

Name of the Echocardiographer:

ECHO Equipment used:

Please specify:

Please provide the following physical assessment parameters:

Weight: kg lb

Heart Rate (BPM):

Blood Pressure (mmHg): Systolic / Diastolic

Cardiac Rhythm:

Date echocardiographs were delivered to the Core Lab:

Delivery Method:

Please specify:

Shipment Tracking Number:

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

Did the echocardiographer assess the aortic valve? No Yes

Please indicate the results of the LVOT assessment

Peak Velocity

Peak Gradient

Mean Gradient

VTI

Please indicate the results of the aortic valve assessment

Peak Velocity

Peak Gradient

Mean Gradient

VTI

What was the annulus size (cm)?

What was the AV area (cm²)?

Please indicate the AR Severity:

Please indicate the MR Severity:

What was the LVEF?

What was the range of the LVEF? Max Value:

Min Value:

What method was used to determine the LVEF?

Please indicate the severity of paravalvular leak (PVL):

Please indicate the transvalvular leak severity:

What was the assessment of RV function?

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

ECHO CORE LAB RESULTS (Baseline)

Rev B

Date of ECHO Exam

Date ECHO Received by Core Lab

Date of Readability Assessment

Please indicate whether or not the images were readable:

Was a request sent to the site to resend the images? No Yes

Date of resend request:

Was the readability issue resolved? No Yes

Date readability issue resolved:

Was the ECHO Assessed by the Core Lab? No Yes

Physical Assessment

Height Unit

Weight Unit

Body Surface Area (BSA)

Heart Rate (BPM)

Blood pressure (mmHg) Systolic / Diastolic

Does the Echo indicate the subject has the following cardiac rhythm / conducting system disturbances?

Normal Sinus Rhythm No Yes Indeterminate

Atrial Fibrillation No Yes Indeterminate

Atrial Flutter No Yes Indeterminate

Ventricular Tachycardia No Yes Indeterminate

Ventricular Fibrillation No Yes Indeterminate

AV Block No Yes Indeterminate

Please indicate the degree:

Bundle Branch Block No Yes Indeterminate

Please indicate branch:

Aortic Valve Assessment: Stenosis

Please indicate the level of Aortic Stenosis:

LV Structure / Regional Function

Please indicate if any of the following abnormalities were observed:

LV aneurysm No Yes

Please specify the location:

Wall motion abnormality No Yes

Please specify:

Cavity dilation No YesApical and/or left atrial thrombi No YesOther abnormality No Yes

Please specify:

Global LV Structure / Function

What method of calculation was used for LV function assessment?

LVEDV (ml):

LVESV (ml):

LVEF (%):

LV Dimensions

Septal thickness (end-diastolic) (cm):

Posterior wall thickness (end-diastolic) (cm):

LV end-diastolic dimension (cm):

LV end-systolic dimension (cm):

LV Mass (g):

BSA corrected LV mass (g/m²):

Aortic DimensionsLVOT Diameter (cm): Aortic annulus (cm): Aortic root diameter (cm): STJ diameter (cm): **Aortic Valve Assessment: Measurements**VpeakAO (m/sec): TVI (AO) (cm): Peak systolic gradient of AV (by continuous wave) (mmHg): Mean systolic gradient of AV (by continuous wave) (mmHg): TVI (LVOT) (cm): Maximum V(LVOT) (m/sec): Mean V(LVOT) (m/sec): Stroke Volume (LVOT Derived) (ml): Transvalvular flow (ml/s): Cardiac Output (LVOT derived) (L/min): Cardiac Index (L/min/m²): Aortic EOA (continuity equation) (cm²): Aortic EOA Index (cm²/m²): Performance Index: **Aortic Valve Assessment: Regurgitation**

Please identify all the methods of calculation used:

Color Doppler No YesRegurgitant Fraction No YesProximal Convergent Flow No YesContinuous wave doppler (Pressure half-time) No YesAortic Flow Reversal No Yes

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

Please indicate the Paravalvular Leak Severity

Please indicate the Number of Jets:

Please specify:

Please indicate the location of the jets:

Please indicate the image views of the jets:

PLAX No Yes

PSAX No Yes

A5C No Yes

A3C No Yes

Please indicate the Transvalvular Leak Severity:

Please indicate the total regurgitation severity

Non-Aortic Valve Regurgitation

Please indicate the level of Tricuspid Valve Regurgitation:

Please indicate the level of Mitral Valve Regurgitation:

Was there Mitral Valve Stenosis? No Yes

Pericardial Effusion

Please indicate the level of Pericardial Effusion:

Please specify:

RV Function

Please indicate overall assessment of the Right Ventricle:

E Edwards Lifesciences

Study

Doc#

Subject ID

Site

Visit Date

Status

Visit Name

Subevent#

CRF Name

Blank CRF

ECHO Quality

Please indicate the overall Quality of the ECHOs:

Comments

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

ECHO CORE LAB RESULTS

Rev B

Date of ECHO Exam

Date ECHO Received by Core Lab

Date of Readability Assessment

Please indicate whether or not the images were readable:

Was a request sent to the site to resend the images? No Yes

Date of resend request:

Was the readability issue resolved? No Yes

Date readability issue resolved:

Was the ECHO Assessed by the Core Lab? No Yes

Physical Assessment

Height Unit

Weight Unit

Body Surface Area (BSA)

Heart Rate (BPM)

Blood pressure (mmHg) Systolic / Diastolic

Does the Echo indicate the subject has the following cardiac rhythm / conducting system disturbances?

Normal Sinus Rhythm No Yes Indeterminate

Atrial Fibrillation No Yes Indeterminate

Atrial Flutter No Yes Indeterminate

Ventricular Tachycardia No Yes Indeterminate

Ventricular Fibrillation No Yes Indeterminate

AV Block No Yes Indeterminate

Please indicate the degree:

Bundle Branch Block No Yes Indeterminate

Please indicate the branch:

Aortic Valve Assessment: Stenosis

Please indicate the level of Aortic Stenosis:

LV Structure / Regional Function

Please indicate if any of the following abnormalities were observed:

LV aneurysm No Yes

Please specify the location:

Wall motion abnormality No Yes

Please specify:

Cavity dilation No YesApical and/or left atrial thrombi No YesOther abnormality No Yes

Please specify:

Global LV Structure / Function

What method of calculation was used for LV function assessment?

LVEDV (ml):

LVESV (ml):

LVEF (%):

LV Dimensions

Septal thickness (end-diastolic) (cm):

Posterior wall thickness (end-diastolic) (cm):

LV end-diastolic dimension (cm):

LV end-systolic dimension (cm):

LV Mass (g):

BSA corrected LV mass (g/m²):

Aortic DimensionsLVOT Diameter (cm): Aortic annulus (cm): Aortic root diameter (cm): STJ diameter (cm): **Aortic Valve Assessment: Measurements**V_{peakAO} (m/sec): TVI (AO) (cm): Peak systolic gradient of AV (by continuous wave) (mmHg): Mean systolic gradient of AV (by continuous wave) (mmHg): TVI (LVOT) (cm): Maximum V(LVOT) (m/sec): Mean V(LVOT) (m/sec): Stroke Volume (LVOT Derived) (ml): Transvalvular flow (ml/s): Cardiac Output (LVOT derived) (L/min): Cardiac Index (L/min/m²): Aortic EOA (continuity equation) (cm²): Aortic EOA Index (cm²/m²): Performance Index : **Aortic Valve Assessment: Regurgitation**

Please identify all the methods of calculation used:

Color Doppler No YesRegurgitant Fraction No YesProximal Convergent Flow No YesContinuous wave doppler (Pressure half-time) No YesAortic Flow Reversal No Yes

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

Please indicate the Paravalvular Leak Severity:

Please indicate the Number of Jets:

Please specify:

Please indicate the location of the jets:

Please indicate the image views of the jets:

PLAX No Yes

PSAX No Yes

A5C No Yes

A3C No Yes

Please indicate the Transvalvular Leak Severity:

Please indicate the total regurgitation severity:

Aortic Valve Morphology

Please indicate the leaflet mobility:

Please indicate the leaflet thickening:

Please indicate the degree of calcification:

Please indicate whether the following morphologies were observed:

Cusp Perforation No Yes Indeterminate

Pannus Formation No Yes Indeterminate

Thrombus No Yes Indeterminate

Vegetation No Yes Indeterminate

Ring Abscess No Yes Indeterminate

Pseudoaneurysm No Yes Indeterminate

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

Non-Aortic Valve Regurgitation

Please indicate the level of Tricuspid Valve Regurgitation:

Please indicate the level of Mitral Valve Regurgitation:

Pericardial Effusion

Please indicate the level of Pericardial Effusion:

Please specify:

RV Function

Please indicate overall assessment of the Right Ventricle:

ECHO Quality

Please indicate the overall Quality of the ECHOs:

Comments

Study

Doc#

Subject ID

Site

Visit Date

Status

Visit Name

Subevent#

CRF Name

Blank CRF

PROTOCOL DEVIATION (Baseline)

Rev B

Date of Deviation

(DD/MMM/YYYY)

Please select type of deviation

Please describe the type of deviation

What was the reason for the deviation?

Please specify:

Please indicate the corrective action taken to prevent further deviations

Please specify:

Study

Doc#

Subject ID

Site

Visit Date

Status

Visit Name

Subevent#

CRF Name

Blank CRF

PROTOCOL DEVIATION (Discharge)

Version A

Date of Deviation

(DD/MMM/YYYY)

Please select type of deviation

Please describe the type of deviation

What was the reason for the deviation?

Please specify

Please indicate the corrective action taken to prevent further deviations

Please specify

Study

Doc#

Subject ID

Site

Visit Date

Status

Visit Name

Subevent#

CRF Name

Blank CRF

PROTOCOL DEVIATION (Procedure)

Version A

Date of Deviation (DD/MMM/YYYY)

Please select type of deviation

Please describe the type of deviation

What was the reason for the deviation?

Please specify

Please indicate the corrective action taken to prevent further deviations

Please specify

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

PROTOCOL DEVIATION (3 Month)

Version A

Date of Deviation (DD/MMM/YYYY)

Please select type of deviation

Was subject's family or friends contacted?

No

Please indicate the date when the last attempt to contact the subject was made

(DD/MMM/YYYY)

Can you confirm through any other sources if the subject is alive? No Yes

Yes

Date of Contact (DD/MMM/YYYY)

Was the subject alive based on the contact? No Yes

Please describe the type of deviation

What was the reason for the deviation?

Please specify

Please indicate the corrective action taken to prevent further deviations

Please specify

Study

Doc#

Subject ID

Site

Visit Date

Status

Visit Name

Subevent#

CRF Name

Blank CRF

PROTOCOL DEVIATION (1 Year)

Rev B

Date of Deviation (DD/MMM/YYYY)

Please select type of deviation

Was subject's family or friends contacted?

No

Please indicate the date when the last attempt to contact the subject was made

(DD/MMM/YYYY)

Can you confirm through any other sources if the subject is alive? No Yes

Yes

Date of Contact (DD/MMM/YYYY)

Was the subject alive based on the contact? No Yes

Please describe the type of deviation

What was the reason for the deviation?

Please specify:

Please indicate the corrective action taken to prevent further deviations

Please specify:

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

PROTOCOL DEVIATION (2 Year)

Version A

Date of Deviation (DD/MMM/YYYY)

Please select type of deviation

Was subject's family or friends contacted?

No

Please indicate the date when the last attempt to contact the subject was made

(DD/MMM/YYYY)

Can you confirm through any other sources if the subject is alive? No Yes

Yes

Date of Contact (DD/MMM/YYYY)

Was the subject alive based on the contact? No Yes

Please describe the type of deviation

What was the reason for the deviation?

Please specify

Please indicate the corrective action taken to prevent further deviations

Please specify

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

PROTOCOL DEVIATION (3 Year)

Version A

Date of Deviation (DD/MMM/YYYY)

Please select type of deviation

Was subject's family or friends contacted?

No

Please indicate the date when the last attempt to contact the subject was made

(DD/MMM/YYYY)

Can you confirm through any other sources if the subject is alive? No Yes

Yes

Date of Contact (DD/MMM/YYYY)

Was the subject alive based on the contact? No Yes

Please describe the type of deviation

What was the reason for the deviation?

Please specify

Please indicate the corrective action taken to prevent further deviations

Please specify

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

PROTOCOL DEVIATION (4 Year)

Version A

Date of Deviation (DD/MMM/YYYY)

Please select type of deviation

Was subject's family or friends contacted?

No

Please indicate the date when the last attempt to contact the subject was made

(DD/MMM/YYYY)

Can you confirm through any other sources if the subject is alive? No Yes

Yes

Date of Contact (DD/MMM/YYYY)

Was the subject alive based on the contact? No Yes

Please describe the type of deviation

What was the reason for the deviation?

Please specify

Please indicate the corrective action taken to prevent further deviations

Please specify

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

PROTOCOL DEVIATION (5 Year)

Version A

Date of Deviation (DD/MMM/YYYY)

Please select type of deviation

Was subject's family or friends contacted?

No

Please indicate the date when the last attempt to contact the subject was made

(DD/MMM/YYYY)

Can you confirm through any other sources if the subject is alive? No Yes

Yes

Date of Contact (DD/MMM/YYYY)

Was the subject alive based on the contact? No Yes

Please describe the type of deviation

What was the reason for the deviation?

Please specify

Please indicate the corrective action taken to prevent further deviations

Please specify

Study

Doc#

Subject ID

Site

Visit Date

Status

Visit Name

Subevent#

CRF Name

Blank CRF

PROTOCOL DEVIATION (Miscellaneous)

Version A

Date of Deviation

(DD/MMM/YYYY)

Please select type of deviation

Please describe the type of deviation

What was the reason for the deviation?

Please specify

Please indicate the corrective action taken to prevent further deviations

Please specify

Study

Doc#

Subject ID

Site

Visit Date

Status

Visit Name

Subevent#

CRF Name

Blank CRF

PROTOCOL DEVIATION (Adverse Event)

Version A

Date of Deviation

(DD/MMM/YYYY)

Please select type of deviation

Please describe the type of deviation

What was the reason for the deviation?

Please specify

Please indicate the corrective action taken to prevent further deviations

Please specify

REOP_EXP

Version A

Date of the study valve removal / replacement: (DD/MMM/YYYY)

Did the surgical procedure occur at the investigational center? No Yes

Please indicate the type of procedure that was performed:

If Valve-in-valve replacement or Other is the type of procedure that was performed, please answer questions at the bottom of the next page

EXPLANT

When was the device explanted?

Was information collected about the explant procedure? No Yes

What was the surgical approach used for the explant procedure?

What type of aortotomy was performed?
(Enter Type or Not Available)

Were study valve leaflets removed? No Yes Not Available

Was study valve sewing ring removed? No Yes Not Available

Ease of study valve explant (Rate ease on a scale of 1-5, 5 being the best)

1 2 3 4 5 N/A

Additional comments:

Was a replacement valve implanted? No Yes

Please provide the following information about the replacement valve:

Manufacturer and model:

Size (mm):

Subject ID

Site

Visit Date

Status

Visit Name

AE

Subevent#

CRF Name

REOPERATION

Blank CRF

Was information collected about the appearance of the valve prior to or immediately following explant? No Yes

Please indicate whether the following conditions were observed:

- No Yes Thrombus
- No Yes Vegetation
- No Yes Suture interference
- No Yes Calcification
- No Yes Fibrosis
- No Yes Dehiscence

Other observations

[Empty text box for other observations]

Did excision of the study valve require or result in structural changes?

- No Yes Not Available

Please specify:

[Empty text box for specifying structural changes]

Was the explanted study valve returned? No Yes

RGA #

[Empty text box for RGA #]

VALVE-IN-VALVE REPLACEMENT

Please provide the following information about the replacement valve:

Manufacturer and model:

[Empty text box for manufacturer and model]

Size (mm):

[Empty text box for size]

OTHER

Please specify:

[Empty text box for other replacement valve information]

STUDY EXIT

Version A

Date of Study Exit: (DD/MMM/YYYY)

Please indicate the reason for study exit:

Please indicate when the subject withdrew:

Please indicate the reason for withdrawal:

Date of Death: (DD/MMM/YYYY)

Did the subject die intraoperatively during the study procedure? No Yes

Did the subject die prior to discharge from the hospital after the study procedure? No Yes

Please provide the following information about the subject's hospitalization after the study valve procedure

Duration of time in the Intensive Care Unit (ICU)

Days: and Hours:

Duration of time in the Intermediate Care / High Dependency Unit

Days: and Hours:

Duration of time in the General Ward

Days: and Hours:

Cause of Death:

Date reported to the sponsor: (DD/MMM/YYYY)

Was an autopsy performed? No Yes

Date of autopsy: (DD/MMM/YYYY)

Was a study valve removed at autopsy? No Yes

If Yes, Please fill out the Study Valve Removal/Replacement form (REOP_EXP)

Please specify:

Study Doc#

Subject ID Site Visit Date Status

Visit Name Subevent# CRF Name Blank CRF

Comments:



15.4 PROTOCOL DEVIATION CODES



PROTOCOL DEVIATION CODES

SUBJECT SCREENING

- 1.01 SUBJECT DID NOT MEET INCLUSION CRITERION
- 1.02 SUBJECT MET EXCLUSION CRITERION
- 1.03 DATE OF INFORMED CONSENT IS AFTER DATE OF STUDY ENROLLMENT
- 1.04 INFORMED CONSENT WAS IMPROPERLY OBTAINED
- 1.05 PERSON OBTAINING INFORMED CONSENT DID NOT SIGN/DATE THE CONSENT FORM
- 1.06 OTHER SCREENING DEVIATION

BASELINE

- 2.01 BASELINE ECHOCARDIOGRAM NOT DONE
- 2.02 BASELINE ECHOCARDIOGRAM DONE > 30 DAYS PRIOR IMPLANT DATE
- 2.03 BASELINE BLOOD NOT DONE
- 2.04 BASELINE BLOOD DONE > 30 DAYS BEFORE IMPLANT
- 2.05 BASELINE BLOOD INCOMPLETE
- 2.06 BASELINE COAGULATION PROFILE NOT DONE
- 2.07 BASELINE COAGULATION PROFILE DONE > 30 DAYS BEFORE IMPLANT
- 2.08 BASELINE NYHA NOT DONE
- 2.09 BASELINE ELECTROCARDIOGRAM NOT DONE
- 2.10 BASELINE ELECTROCARDIOGRAM DONE > 30 DAYS BEFORE IMPLANT
- 2.11 BASELINE EQ-5D NOT DONE
- 2.12 BASELINE SF-12 NOT DONE
- 2.12 BASELINE PHYSICAL ASSESSMENT / VITAL SIGNS NOT DONE
- 2.13 PREGNACY TEST NOT DONE
- 2.14 MEDICAL HISTORY NOT COLLECTED
- 2.15 OTHER BASELINE DEVIATION

IMPLANT SURGERY

- 3.01 IMPLANTING SURGEON IS NOT ON APPROVED LIST
- 3.02 PROCEDURE DIAGNOSIS NOT DONE
- 3.03 INCORRECT SIZER USED
- 3.04 SKIN INCISION TIME NOT RECORDED
- 3.05 START TIME OF ECC (PUMP) NOT RECORDED
- 3.06 START CROSS CLAMP TIME NOT RECORDED
- 3.07 START OF SIZING TIME NOT RECORDED
- 3.08 REMOVAL CROSS CLAMP TIME NOT RECORDED
- 3.09 END ECC (PUMP) TIME NOT RECORDED
- 3.10 SKIN CLOSURE TIME NOT RECORDED
- 3.11 UNAPPROVED CONCOMITANT PROCEDURE PERFORMED
- 3.12 VALVE SERIAL NUMBER NOT RECORDED

- 3.13 MORE THAN 2 STUDY VALVES ATTEMPTED TO BE IMPLANTED
- 3.14 TIME FIST STITCH PLACED ON THE VALVE NOT RECORDED
- 3.15 COMPLETION TIME OF STUDY PROCEDURE (LAST STITCH TIED DOWN ON THE VALVE) NOT RECORDED
- 3.16 POST-IMPLANT ECHOCARDIOGRAM NOT DONE
- 3.17 POST-IMPLANT ECHOCARDIOGRAM NOT DONE WITHIN 1 HOUR OF REMOVING THE CROSS-CLAMP
- 3.18 OTHER PROCEDURE DEVIATION

DISCHARGE

- 4.01 DISCHARGE OR 10-DAY ECHOCARDIOGRAM NOT DONE
- 4.02 DISCHARGE OR 10-DAY ECHOCARDIOGRAM DONE > 10 DAYS POST IMPLANT DATE
- 4.03 DISCHARGE PHYSICAL ASSESSMENT / VITAL SIGNS NOT DONE
- 4.04 DISCHARGE ELECTROCARDIOGRAM NOT DONE
- 4.05 DISCHARGE COAGULATION PROFILE NOT DONE
- 4.06 DISCHARGE MEDICATIONS NOT ASSESSED
- 4.07 OTHER DISCHARGE DEVIATION

3 MONTHS

- 6.01 3 MONTHS - SUBJECT NOT CONTACTED
- 6.02 3 MONTHS - ASSESSMENT NOT DONE WITHIN FOLLOW-UP WINDOW
- 6.03 3 MONTHS - PHYSICAL ASSESSMENT / VITAL SIGNS NOT DONE
- 6.04 3 MONTHS - NYHA NOT DONE
- 6.05 3 MONTHS - ELECTROCARDIOGRAM NOT DONE
- 6.06 3 MONTHS - ELECTROCARDIOGRAM NOT DONE WITHIN FOLLOW-UP WINDOW
- 6.07 3 MONTHS - ECHOCARDIOGRAM NOT DONE
- 6.08 3 MONTHS - ECHOCARDIOGRAM NOT DONE WITHIN FOLLOW-UP WINDOW
- 6.09 3 MONTHS - BLOOD NOT DONE
- 6.10 3 MONTHS - BLOOD INCOMPLETE
- 6.11 3 MONTHS - COAGULATION PROFILE NOT DONE (ONLY REQUIRED FOR PATIENTS ON ANTICOAGULANT THERAPY)
- 6.12 3 MONTHS - BLOOD NOT DONE WITHIN FOLLOW-UP WINDOW
- 6.13 3 MONTHS - MEDICATIONS NOT ASSESSED
- 6.14 3 MONTHS - MEDICATIONS NOT ASSESSED WITHIN FOLLOW-UP WINDOW
- 6.15 3 MONTHS - OTHER DEVIATION

CONFIDENTIAL AND PROPRIETARY DATA: This document and the information contained herein may not be reproduced, used, or disclosed without written permission from Edwards Lifesciences LLC

1-YEAR

8.01 1 YEAR - SUBJECT NOT CONTACTED
8.02 1 YEAR - ASSESSMENT NOT DONE WITHIN FOLLOW-UP WINDOW
8.03 1 YEAR - PHYSICAL ASSESSMENT / VITAL SIGNS NOT DONE
8.04 1 YEAR - NYHA NOT DONE
8.05 1 YEAR - ELECTROCARDIOGRAM NOT DONE
8.06 1 YEAR - ELECTROCARDIOGRAM NOT DONE WITHIN FOLLOW-UP WINDOW
8.07 1 YEAR - ECHOCARDIOGRAM NOT DONE
8.08 1 YEAR - ECHOCARDIOGRAM NOT DONE WITHIN FOLLOW-UP WINDOW
8.09 1 YEAR - BLOOD NOT DONE
8.10 1 YEAR - BLOOD INCOMPLETE
8.11 1 YEAR - COAGULATION PROFILE NOT DONE (ONLY REQUIRED FOR PATIENTS ON ANTICOAGULANT THERAPY)
8.12 1 YEAR - BLOOD NOT DONE WITHIN FOLLOW-UP WINDOW
8.13 1 YEAR - MEDICATIONS NOT ASSESSED
8.14 1 YEAR - MEDICATIONS NOT ASSESSED WITHIN FOLLOW-UP WINDOW
8.15 1 YEAR - EQ-5D NOT DONE
8.16 1 YEAR - SF-12 NOT DONE
8.17 1 YEAR - OTHER DEVIATION

2 YEAR

9.01 2 YEAR - SUBJECT NOT CONTACTED
9.02 2 YEAR - ASSESSMENT NOT DONE WITHIN FOLLOW-UP WINDOW
9.03 2 YEAR - PHYSICAL ASSESSMENT / VITAL SIGNS NOT DONE
9.04 2 YEAR - NYHA NOT DONE
9.05 2 YEAR - ELECTROCARDIOGRAM NOT DONE
9.06 2 YEAR - ELECTROCARDIOGRAM NOT DONE WITHIN FOLLOW-UP WINDOW
9.07 2 YEAR - AUSCULTATION NOT DONE
9.08 2 YEAR - ECHOCARDIOGRAM NOT DONE (AUSCULTATION INDICATED AORTIC MURMUR)
9.09 2 YEAR - ECHOCARDIOGRAM NOT DONE WITHIN FOLLOW-UP WINDOW (AUSCULTATION INDICATED AORTIC MURMUR)
9.10 2 YEAR - BLOOD NOT DONE
9.11 2 YEAR - BLOOD INCOMPLETE
9.12 2 YEAR - BLOOD NOT DONE WITHIN FOLLOW-UP WINDOW
9.13 2 YEAR - MEDICATIONS NOT ASSESSED
9.14 2 YEAR - MEDICATIONS NOT ASSESSED WITHIN FOLLOW-UP WINDOW
9.15 2 YEAR - OTHER DEVIATION

3 YEAR

10.01 3 YEAR - SUBJECT NOT CONTACTED
10.02 3 YEAR - ASSESSMENT NOT DONE WITHIN FOLLOW-UP WINDOW
10.03 3 YEAR - PHYSICAL ASSESSMENT / VITAL SIGNS NOT DONE
10.04 3 YEAR - NYHA NOT DONE
10.05 3 YEAR - ELECTROCARDIOGRAM NOT DONE
10.06 3 YEAR - ELECTROCARDIOGRAM NOT DONE WITHIN FOLLOW-UP WINDOW
10.07 3 YEAR - ECHOCARDIOGRAM NOT DONE
10.08 3 YEAR - ECHOCARDIOGRAM NOT DONE WITHIN FOLLOW-UP WINDOW
10.09 3 YEAR - BLOOD NOT DONE
10.10 3 YEAR - BLOOD INCOMPLETE
10.11 3 YEAR - COAGULATION PROFILE NOT DONE (ONLY REQUIRED FOR PATIENTS ON ANTICOAGULANT THERAPY)
10.12 3 YEAR - BLOOD NOT DONE WITHIN FOLLOW-UP WINDOW
10.13 3 YEAR - MEDICATIONS NOT ASSESSED
10.14 3 YEAR - MEDICATIONS NOT ASSESSED WITHIN FOLLOW-UP WINDOW
10.15 3 YEAR - OTHER DEVIATION

4 YEAR

11.01 4 YEAR - SUBJECT NOT CONTACTED
11.02 4 YEAR - ASSESSMENT NOT DONE WITHIN FOLLOW-UP WINDOW
11.03 4 YEAR - PHYSICAL ASSESSMENT / VITAL SIGNS NOT DONE
11.04 4 YEAR - NYHA NOT DONE
11.05 4 YEAR - ELECTROCARDIOGRAM NOT DONE
11.06 4 YEAR - ELECTROCARDIOGRAM NOT DONE WITHIN FOLLOW-UP WINDOW
11.07 4 YEAR - AUSCULTATION NOT DONE
11.08 4 YEAR - ECHOCARDIOGRAM NOT DONE (AUSCULTATION INDICATED AORTIC MURMUR)
11.09 4 YEAR - ECHOCARDIOGRAM NOT DONE WITHIN FOLLOW-UP WINDOW (AUSCULTATION INDICATED AORTIC MURMUR)
11.10 4 YEAR - BLOOD NOT DONE
11.11 4 YEAR - BLOOD INCOMPLETE
11.12 4 YEAR - BLOOD NOT DONE WITHIN FOLLOW-UP WINDOW
11.13 4 YEAR - MEDICATIONS NOT ASSESSED
11.14 4 YEAR - MEDICATIONS NOT ASSESSED WITHIN FOLLOW-UP WINDOW
11.15 4 YEAR - OTHER DEVIATION

5 YEAR

- 12.01 5 YEAR - SUBJECT NOT CONTACTED
- 12.02 5 YEAR - ASSESSMENT NOT DONE WITHIN FOLLOW-UP WINDOW
- 12.03 5 YEAR - PHYSICAL ASSESSMENT / VITAL SIGNS NOT DONE
- 12.04 5 YEAR - NYHA NOT DONE
- 12.05 5 YEAR - ELECTROCARDIOGRAM NOT DONE
- 12.06 5 YEAR - ELECTROCARDIOGRAM NOT DONE WITHIN FOLLOW-UP WINDOW
- 12.07 5 YEAR - ECHOCARDIOGRAM NOT DONE
- 12.08 5 YEAR - ECHOCARDIOGRAM NOT DONE WITHIN FOLLOW-UP WINDOW
- 12.09 5 YEAR - BLOOD NOT DONE
- 12.10 5 YEAR - BLOOD INCOMPLETE
- 12.11 5 YEAR - COAGULATION PROFILE NOT DONE (ONLY REQUIRED FOR PATIENTS ON ANTICOAGULANT THERAPY)
- 12.12 5 YEAR - BLOOD NOT DONE WITHIN FOLLOW-UP WINDOW
- 12.13 5 YEAR - MEDICATIONS NOT ASSESSED
- 12.14 5 YEAR - MEDICATIONS NOT ASSESSED WITHIN FOLLOW-UP WINDOW
- 12.15 5 YEAR - OTHER DEVIATION



15.5 DEVICE DEFICIENCY CODES

DEVICE DEFICIENCY CODES

Code	Label
DD.2	Valve / Holder
DD.2.01	Device function, packaging not intact
DD.2.02	Device function, component contamination
DD.2.03	Device function, unable to remove from jar
DD.2.04	Device function, unable to place sutures through sewing ring
DD.2.05	Device function, unable to position on the aortic annulus
DD.2.06	Device function, bioprosthesis and holder separate during procedure
DD.2.07	Device function, other, specify
DD.2.08	Device use, sizing technique
DD.2.09	Device use, sterility compromised
DD.2.10	Device use, used expired product
DD.2.11	Device use, component damaged by operator
DD.2.12	Device use, improper positioning
DD.2.13	Device use, other specify



15.6 ECHO MANUAL

Table of Contents

1	Purpose	2
2	Introduction	2
3	Transthoracic echocardiogram (TTE)	2
3.1	Performing the exam	2
3.2	Exam view sequence	2
3.3	Data collection	2
4	Transesophageal echocardiogram (TEE).....	4
4.1	Performing the exam	4
4.2	Exam view	4
4.3	Data collection	4
5	Abbreviated Transthoracic Echocardiogram (aTTE)	4
5.1	Performing the exam	4
5.2	Exam view sequence.....	5
5.3	Data collection	5

1 Purpose

The purpose of this Echo Manual is to provide instruction on study echocardiograms for clinical sites participating in the #2010-03 clinical study.

2 Introduction

There are three types of echocardiographic exams required in the #2010-03 clinical study protocol:

- Transthoracic echocardiogram (TTE)
- Transesophageal echocardiogram (TEE)
- Abbreviated transthoracic echocardiogram (aTTE)

Investigation Procedure	Baseline	Implant	Discharge	3 month	1, 3, 5 year	2 & 4 years
TTE	X		X	X	X	
TEE		X				
aTTE		X				X

3 Transthoracic echocardiogram (TTE)

3.1 Performing the exam

Study subjects are typically examined in the left lateral decubitus or supine position. All views are to be acquired twice for 3 beats.

The sweep speed for all spectral Doppler and M-mode recordings should be 100 mm/sec. Nyquist settings for color Doppler assessment of the cardiac valves should be >50 cm/sec.

3.2 Exam view sequence

View	2-D	Pulse wave	Continuous wave	Color
Parasternal long axis	X			AV
Parasternal short axis	X	AV		AV
Apical 4-chamber	X			
Apical 5-chamber	X	LVOT	AV	LVOT / AV
Apical 2-chamber	X			
Apical 3-chamber	X	AV	AV	LVOT / AV

3.3 Data collection

The clinical site is to provide the following data for each TTE:

- Study subject identification number
- Heart rate (bpm)
- Height (cm)
- Weight (kg)
- Cardiac rhythm

Data from TTE exams is to include the following measurements/calculations by a Core Lab:

- Aortic bioprosthesis assessment
 - Flow velocities and gradients
 - Mean gradient
 - Peak gradient
 - Effective orifice area
 - Time velocity integral left ventricular outflow tract
 - Time velocity integral aortic valve
 - Maximum velocity aortic valve
 - Maximum velocity left ventricular outflow tract
 - Aortic insufficiency
 - Central leak grade
 - Paravalvular / perivalvular leak grade
 - Aortic stenosis grade
- Left ventricle measurements
 - Dimension
 - Left ventricle end-systolic
 - Left ventricle end-diastolic
 - Septal wall thickness (end-diastolic)
 - Posterior wall thickness (end-diastolic)
 - Volume
 - Left ventricle end-systolic
 - Left ventricle end-diastolic
 - Ejection fraction
- Calculated cardiac performance parameters
 - Cardiac Output
 - Stroke Volume

4 Transesophageal echocardiogram (TEE)

4.1 Performing the exam

Study subjects are typically examined within 1 hour after aortic valve replacement with the study device (after the aortic cross clamp is removed).

4.2 Exam view

The exact position of the TEE probe may vary from patient to patient, but should be aligned at the level of the aortic annulus.

Doppler requirements in this view:

- Continuous wave through the aortic valve
- Color of AV

4.3 Data collection

The clinical site is to provide the following data for each TEE:

- Study subject identification number
- Heart rate (bpm)
- Height (cm)
- Weight (kg)
- Cardiac rhythm

Data from TEE exams is to include the following measurements/calculations by a Core Lab:

- Aortic bioprosthesis assessment
 - Aortic insufficiency
 - Central leak grade
 - Paravalvular / perivalvular leak grade

5 Abbreviated transthoracic echocardiogram (aTTE)

5.1 Performing the exam

Study subjects are typically examined in the left lateral decubitus or supine position. This exam may be performed while the subject is still in the Operating Room. All views are to be taken with 2 captures, the length of which will vary under the following clinical conditions:

- Sinus rhythm with up to 90bpm: 3 beat capture
- Sinus rhythm with more than 90bpm: 5 beat capture

- Frequent atrial or ventricular ectopy: 3 second capture
- Atrial fibrillation or atrial flutter: 5 second capture
- Paced rhythm: 5 second capture

The sweep speed for all spectral Doppler and M-mode recordings should be 100 mm/sec. Nyquist settings for color Doppler assessment of the aortic valve should be >50 cm/sec.

5.2 Exam view sequence

View	2-D	Pulse wave	Continuous wave	Color
Parasternal short axis	X	AV		AV
Apical 4-chamber	X			
Apical 3-chamber	X	AV	AV	LVOT / AV

5.3 Data collection

The clinical site is to provide the following data for each aTTE:

- Study subject identification number
- Heart rate (bpm)
- Height (cm)
- Weight (kg)
- Cardiac rhythm

Data from aTTE exams is to include the following measurements/calculations by a Core Lab:

- Aortic bioprosthesis assessment
 - Aortic insufficiency
 - Central leak grade
 - Paravalvular / perivalvular leak grade
 - Aortic stenosis grade



15.7 EQ-5D QUESTIONNAIRE



Kwestionariusz Dotyczący Zdrowia

wersja polska do użytku w Polsce

(Polish version for Poland)

Poprzez zaznaczenie symbolem (☑) jednego kwadratu w każdej grupie podanej poniżej, proszę wybrać zdanie najlepiej określające stan Pana/Pani zdrowia dzisiaj.

Zdolność poruszania się

- Nie mam problemów z chodzeniem
- Mam trochę problemów z chodzeniem
- Jestem zmuszony/a pozostawać w łóżku

Samoopieka

- Nie mam żadnych problemów z samoopieką
- Mam trochę problemów z myciem i ubieraniem się
- Nie mogę sam/a się umyć ani ubrać

Zwykła działalność (np. praca, nauka, zajęcia domowe, aktywności rodzinne, zajęcia w czasie wolnym)

- Nie mam problemów z wykonywaniem moich zwykłych czynności
- Mam trochę problemów z wykonywaniem moich zwykłych czynności
- Nie mogę wykonywać moich zwykłych czynności

Ból/Dyskomfort

- Nie odczuwam bólu ani dyskomfortu
- Odczuwam umiarkowany ból lub dyskomfort
- Odczuwam krańcowy ból lub dyskomfort

Niepokój/Przygnębienie

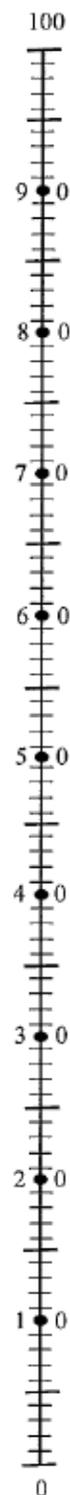
- Nie jestem niespokojny/a ani przygnębiony/a
- Jestem umiarkowanie niespokojny/a lub przygnębiony/a
- Jestem krańcowo niespokojny/a lub przygnębiony/a

Aby umożliwić badanym ocenę jak dobry lub zły jest ich stan zdrowia przygotowaliśmy skalę (podobną do skali termometru), na której najlepszy stan zdrowia jaki można sobie wyobrazić jest oznaczony liczbą 100, a najgorszy stan zdrowia jaki można sobie wyobrazić jest oznaczony jako 0.

Prosimy o wskazanie na skali, jak dobry lub zły jest w państwa opinii stan Pana/Pani zdrowia dzisiaj. Proszę zrobić to rysując linię z kostki poniżej do jakiegokolwiek punktu na skali, określającego jak dobry lub zły jest Pana/Pani dzisiejszy stan zdrowia.

**Twój stan
zdrowia
dzisiaj**

Najlepszy
wyobrażalny stan
zdrowia



Najgorszy
wyobrażalny s
tan zdrowia



15.8 SF-12 V2 QUESTIONNAIRE



STUDY NUMBER 2010-03
CLINICAL STUDY OF THE EDWARDS PERICARDIAL AORTIC BIOPROSTHESIS,
MODEL 11000

Subject Study ID #	<input type="text" value="2"/> <input type="text" value="0"/> <input type="text" value="1"/> <input type="text" value="0"/> <input type="text" value="0"/> <input type="text" value="3"/> <input type="text" value="-"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Site#	<input type="text"/> <input type="text"/> <input type="text"/>
--------------------	--	-------	--

QualityMetric's SF-12v2[®] Health Survey¹ is a shorter version of the SF-36v2[®] Health Survey that uses just 12 questions to measure functional health and well-being from the subject's point of view. It takes only 2-3 minutes to complete. The SF-12v2 is a practical, reliable, and valid measure of physical and mental health and covers the same [eight health domains](#) as the SF-36v2 with one or two questions per domain.

VISIT INTERVAL: SCREENING 1 YEAR

Date of Assessment: / /
D D M M M Y Y Y Y

1. In general, would you say your health is:

- | | | | | |
|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|
| Excellent | Very good | Good | Fair | Poor |
| <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ | <input type="checkbox"/> ₃ | <input type="checkbox"/> ₄ | <input type="checkbox"/> ₅ |

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

- | | Yes, limited a lot | Yes, limited a little | No, not limited at all |
|---|---------------------------------------|---------------------------------------|---------------------------------------|
| a. <u>Moderate activities</u> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf. | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ | <input type="checkbox"/> ₃ |
| b. Climbing <u>several</u> flights of stairs. | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ | <input type="checkbox"/> ₃ |

3. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

- | | All of the time | Most of the time | Some of the time | A little of the time | None of the time |
|--|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|
| a. <u>Accomplished less</u> than you would like. | <input type="checkbox"/> ₁ | <input type="checkbox"/> ₂ | <input type="checkbox"/> ₃ | <input type="checkbox"/> ₄ | <input type="checkbox"/> ₅ |

¹SF-12v2[™] Health Survey[®] 1994, 2002 by QualityMetric incorporated and Medical Outcomes Trust. SF-12[®] a registered trademark of Medical Outcomes Trust. (SF12v2 Standard, US version 2.0).



STUDY NUMBER 2010-03
CLINICAL STUDY OF THE EDWARDS PERICARDIAL AORTIC BIOPROSTHESIS,
MODEL 11000

Subject Study ID #	<table border="1" style="display: inline-table; border-collapse: collapse;"> <tr> <td style="width: 20px; text-align: center;">2</td> <td style="width: 20px; text-align: center;">0</td> <td style="width: 20px; text-align: center;">1</td> <td style="width: 20px; text-align: center;">0</td> <td style="width: 20px; text-align: center;">0</td> <td style="width: 20px; text-align: center;">3</td> <td style="width: 20px; text-align: center;">-</td> <td style="width: 20px;"></td> <td style="width: 20px;"></td> <td style="width: 20px;"></td> <td style="width: 20px;"></td> </tr> </table>	2	0	1	0	0	3	-					Site#			
2	0	1	0	0	3	-										

b. Were limited in the kind of work or other activities. ₁ ₂ ₃ ₄ ₅

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

All of the Most of Some of A little of None of
time the time the time the time the time

a. Accomplished less than you would like. ₁ ₂ ₃ ₄ ₅

b. Did work or activities less carefully than usual? ₁ ₂ ₃ ₄ ₅

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all A little bit Moderately Quite a bit Extremely
₁ ₂ ₃ ₄ ₅

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks

All of the Most of Some of A little of None of
time the time the time the time the time

a. Have you felt calm and peaceful? ₁ ₂ ₃ ₄ ₅

b. Did you have a lot of energy? ₁ ₂ ₃ ₄ ₅

c. Have you felt downhearted and depressed? ₁ ₂ ₃ ₄ ₅

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

¹SF-12v2™ Health Survey® 1994, 2002 by QualityMetric incorporated and Medical Outcomes Trust. SF-12® a registered trademark of Medical Outcomes Trust. (SF12v2 Standard, US version 2.0).



STUDY NUMBER 2010-03
CLINICAL STUDY OF THE EDWARDS PERICARDIAL AORTIC BIOPROSTHESIS,
MODEL 11000

Subject Study ID #	<table border="1" style="width:100%; border-collapse: collapse;"> <tr> <td style="width:10%; text-align:center;">2</td> <td style="width:10%; text-align:center;">0</td> <td style="width:10%; text-align:center;">1</td> <td style="width:10%; text-align:center;">0</td> <td style="width:10%; text-align:center;">0</td> <td style="width:10%; text-align:center;">0</td> <td style="width:10%; text-align:center;">3</td> <td style="width:10%; text-align:center;">-</td> <td style="width:10%;"></td> <td style="width:10%;"></td> <td style="width:10%;"></td> <td style="width:10%;"></td> </tr> </table>	2	0	1	0	0	0	3	-					Site#	<table border="1" style="width:100%; border-collapse: collapse;"> <tr> <td style="width:25%;"></td> <td style="width:25%;"></td> <td style="width:25%;"></td> <td style="width:25%;"></td> </tr> </table>				
2	0	1	0	0	0	3	-												

All of the time <input type="checkbox"/> ₁	Most of the time <input type="checkbox"/> ₂	Some of the time <input type="checkbox"/> ₃	A little of the time <input type="checkbox"/> ₄	None of the time <input type="checkbox"/> ₅
---	--	--	--	--

I HAVE REVIEWED AND AGREE WITH ALL DATA ENTERED ON THIS FORM

INVESTIGATOR SIGNATURE	DATE SIGNED	<table border="1" style="width:100%; border-collapse: collapse;"> <tr> <td style="width:25%;"></td> <td style="width:25%;"></td> </tr> <tr> <td align="center">D</td> <td align="center">D</td> </tr> </table>			D	D	<table border="1" style="width:100%; border-collapse: collapse;"> <tr> <td style="width:25%;"></td> <td style="width:25%;"></td> <td style="width:25%;"></td> </tr> <tr> <td align="center">M</td> <td align="center">M</td> <td align="center">M</td> </tr> </table>				M	M	M	<table border="1" style="width:100%; border-collapse: collapse;"> <tr> <td style="width:25%;"></td> <td style="width:25%;"></td> <td style="width:25%;"></td> <td style="width:25%;"></td> </tr> <tr> <td align="center">Y</td> <td align="center">Y</td> <td align="center">Y</td> <td align="center">Y</td> </tr> </table>					Y	Y	Y	Y
D	D																					
M	M	M																				
Y	Y	Y	Y																			

¹SF-12v2™ Health Survey® 1994, 2002 by QualityMetric incorporated and Medical Outcomes Trust.
SF-12® a registered trademark of Medical Outcomes Trust. (SF12v2 Standard, US version 2.0).