COMMENCE Trial

ProspeCtive, nOn‑randoMized, MulticENter Clinical evaluation of the Edwards Pericardial Aortic & Mitral Bioprostheses (Models 11000A & 11000M) with a new tissue treatment platform

NCT01757665

August 14, 2018

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Protocol Number 2012-02

CLINICAL INVESTIGATIONAL PLAN

Revision I

14 August 2018

ProspeCtive, nOn-randoMized, MulticENter Clinical evaluation of the Edwards Pericardial Aortic & Mitral Bioprostheses (Models 11000A & 11000M) with a new tissue treatment platform (COMMENCE TRIAL)

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

1.0 INVESTIGATOR SIGNATURE PAGE

Trial Title:	*ProspeCtive, nOn-randoMized, MulticENter Clinical evaluation of the Edwards Pericardial Aortic & Mitral Bioprostheses(Models 11000A and 11000M) with a new tissue treatment platform (COMMENCE TRIAL)*
Protocol Number:	**2012-02**
Version Number:	**Rev. I**
Date:	**14 August 2018**

I have read this protocol and agree to participate in the clinical investigation of the Model 11000A and Model 11000M 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

2.0 TRIAL CONTACT PERSONNEL

2.1 SPONSOR CONTACT

TRIAL DIRECTOR

[redacted]

TRIAL LEAD / MONITORING

[redacted]

2.2 TRIAL CONTACT

NATIONAL PI

[redacted]

ECHOCARDIOGRAPHY CORE LAB

[redacted]

CLINICAL EVENTS COMMITTEE

[redacted]

GLYCEROL ASSESSMENT CORE LAB

[redacted]

DATA MONITORING COMMITTEE

[redacted]

3.0 PROTOCOL SYNOPSIS

Title:	*ProspeCtive, nOn-randoMized, MulticENter Clinical evaluation of the Edwards Pericardial Aortic & Mitral Bioprostheses(Models 11000A and 11000M) with a new tissue treatment platform (COMMENCE TRIAL)*
Protocol Number	2012-02
Trial Sponsor:	Edwards Lifesciences One Edwards Way Irvine, CA 92614 Contact: [redacted]
Trial Device:	Edwards Pericardial Aortic Bioprosthesis, Model 11000A Edwards Pericardial Mitral Bioprosthesis, Model 11000M
Indication for Use:	The Edwards Pericardial Aortic Bioprosthesis, Model 11000A, is indicated for patients who require replacement of their native or prosthetic aortic valve. The Edwards Pericardial Mitral Bioprosthesis, Model 11000M, is indicated for patients who require replacement of their native or prosthetic mitral valve.
Trial Objective:	The objective of this trial is to confirm that the modifications to tissue processing, valve sterilization, and packaging of the FDA-approved (P860057/S042) Carpentier-Edwards PERIMOUNT Magna Ease Pericardial Aortic Bioprosthesis, Model 3300TFX, which will be designated as the Edwards Pericardial Aortic Bioprosthesis Model 11000A, and the Carpentier-Edwards PERIMOUNT Magna Mitral Ease Pericardial Bioprosthesis, Model 7300TFX, which will be designated as the Edwards Pericardial Mitral Bioprosthesis Model 11000M do not raise any new questions of safety and effectiveness in subjects who require replacement of their native or prosthetic aortic or mitral valve. The only differences between the Model 3300TFX and the Model 11000A and between the Model 7300TFX and the Model 11000M are modifications in tissue processing, valve sterilization, and packaging.
Trial Design:	Multicenter, prospective, double arm trial – Up to seven hundred (700) aortic valve replacement (AVR) subjects and up to one hundred seventy five (175) mitral valve replacement (MVR) subjects at up to forty (40) clinical sites will be enrolled. An enrollment rate of three (3) to four (4) subjects per site per month is anticipated. At least eight (8) centers will implant and follow for at least 1 year,

	thirty (30) or more AVR or thirty (30) or more AVR/MVR subjects. Analysis for the aortic arm will be performed when at least three hundred (300) AVR subjects have completed the POD 390 follow-up visit and at least eight hundred (800) AVR patient-years of cumulative follow-up have been reached. Analysis for the mitral arm will be completed when at least three hundred (300) combined aortic and mitral subjects have completed the POD 390 follow-up visit and at least eight hundred (800) AVR and at least one hundred (100) MVR patient-years of cumulative follow-up have been reached. The tests for the trial endpoints were performed and the trial data was submitted to FDA for the PMA approval of the devices evaluated under the aortic and mitral arms. All IDE Subjects (aortic and mitral arms) who are currently enrolled and alive will be followed to 5 years. In addition, as a condition of approval of the PMA (P150048, approved June 29, 2017) all Subjects implanted with the Model 11000A valve at the top 3 enrolling sites (n=222) who have consented to continued follow-up will be followed annually through 10 years post-procedure. As a condition of approval of the PMA supplement for the mitral arm (approved 09Aug2018) all Subjects implanted with the Model 11000M valve at 3 sites (n=25) who have consented to continued follow-up will be followed annually through 10 years post procedure.
Trial Sites:	Participating sites are chosen based on their experience in conducting clinical trials, their surgical experience implanting bioprosthetic valves, as well as their ability to maintain robust subject enrollment and follow-up. The investigational sites will be selected throughout the United States, Canada, Europe and Asia Pacific.
Trial Duration:	Total enrollment period for this trial is estimated to be 1095 days or 3 years. Subject duration in the trial is estimated to be no longer than 1825 days (5 years) or 3650 days (10 years) for those who have consented to continued follow-up. Overall duration of the trial is estimated to be 3833 days or 10.5 years, and will involve at least 800 AVR patient-years and at least 100 MVR patient-years of cumulative follow-up. The trial begins with the enrollment of the first subject and ends after the last subject is exited from the trial after completing the last follow-up visit at approximately postoperative day (POD) 3650, all subjects are fully monitored, all outstanding data queries are resolved and all trial sites are closed to follow-up.

Trial Follow-Up Visits:	**Visit**	**Visit Window (Days)**	**Timing from Implant (Day 0)**
	Screening/Baseline		Day -60 to Day 0
	Discharge[1]		Prior to Discharge
	POD 30	-5/+10	Day 25 to 40
	POD 105	- 15/+30	Day 90 to 135
	POD 390 (1 yr)	-25/+45	Day 365 to 435
	POD 730 (2 yr)	-25/+45	Day 705 to 775
	POD 1095 (3 yr)	-25/+45	Day 1070 to 1140
	POD 1460 (4 yr)	-25/+45	Day 1435 to 1505
	POD 1825 (5 yr)	-25/+45	Day 1800 to 1870
	POD 2190 (6 yr)*	-55/+75	Day 2135 to 2265
	POD 2555 (7 yr)*	-55/+75	Day 2500 to 2630
	POD 2920 (8 yr)*	-55/+75	Day 2865 to 2995
	POD 3285 (9 yr)*	-55/+75	Day 3230 to 3360
	POD 3650 (10yr)*	-55/+75	Day 3595 to 3725

[1] Subjects who are not discharged within 10 days post procedure must have an echocardiogram to assess performance of the trial valve. Those subjects will not require an additional echocardiogram at discharge.
*Subjects who have consented to continued follow up with the Model 11000A or Model 11000M valve.

Trial Endpoints:

Primary Safety Endpoint (up to 390 days post-implant):

The primary safety endpoint for the trial is the rate of implanted subjects that experience structural deterioration of the trial valve by the time of the POD 390 follow-up visit. The null hypothesis is that the rate of structural valve deterioration at one year is greater than 1%. The alternative hypothesis is that this rate is less than 1%.

Primary Safety Endpoint (Continued follow-up):

For continued follow-up of Subjects, the primary safety endpoint for the trial is the rate of implanted subjects that experience structural deterioration of the trial valve as determined by a Clinical Events Committee (CEC).

***Secondary Safety Endpoints (Pre-approval)*:**

Safety is established by comparing the occurrence of specific safety endpoints to the objective performance criteria (OPC) reported in Table R.1 in ISO 5840:2009, Annex R.1 as recommended by the FDA in the Draft Guidance involving Heart Valves – Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications (2010).

***Secondary Safety Endpoints (Continued follow-up)*:**

For continued follow-up of Subjects, linearized rates will be used to summarize the following safety endpoints for the late (>30 days) post-operative period.

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

***Effectiveness Endpoints*:**

- 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 questionnaire Short Form 12 version 2 (SF-12v2) from baseline/screening to POD 390

Additional Data in support of analysis:

- Blood Data

Subject Enrollment:

Inclusion Criteria:

Each subject is required to meet all of the following inclusion criteria:

1. Is 18 years or older
2. Provides written informed consent prior to trial procedures
3. Agrees to attend all follow-up assessments for up to 5 years and is willing to comply with specified follow-up evaluations at clinical investigational sites that are participating in the COMMENCE trial and/or obtain the protocol-specified diagnostic tests at centers that are under the same IRB or the same healthcare system
4. Diagnosed with aortic or mitral valve disease requiring valve replacement based on pre- operative evaluation
5. Scheduled to undergo planned aortic or mitral valve replacement with or without concomitant bypass surgery
6. Scheduled to undergo planned aortic valve replacement with or without resection and replacement of the ascending aorta from the sinotubular junction and without the need for circulatory arrest for hemi arch or arch replacement

Exclusion criteria: A subject meeting any of the following criteria shall be excluded:

1. Requires emergency surgery
2. Requires planned multiple valve replacement/ repair (with the exception of mitral valve replacement with tricuspid valve repair)
3. Has prior valve surgery, which included implant of a bioprosthetic valve, mechanical valve, or annuloplasty ring that will remain *in situ*
4. Requires a surgical procedure outside of the cardiac area (e.g. vascular bypass)
5. Requires surgical replacement of the aortic root
6. Has active endocarditis/myocarditis or endocarditis/myocarditis within 3 months to the scheduled aortic or mitral valve replacement surgery
7. 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
8. Has MRI or CT scan confirmed stroke, cerebrovascular accident (CVA) or transient ischemic attack (TIA) within 6 months (180 days) prior to planned valve surgery
9. Has acute myocardial infarction (MI) within 30 days prior to planned valve surgery
10. Has presence of non-cardiac disease limiting life expectancy to less than 12 months
11. Diagnosed with hypertrophic obstructive cardiomyopathy (HOCM)
12. Diagnosed with abnormal calcium metabolism and hyperparathyroidism
13. Exhibits left ventricular ejection fraction ≤ 20% as validated by diagnostic procedure prior to planned valve surgery
14. Echocardiographic evidence of an intra-cardiac mass, thrombus, or vegetation
15. Hemodynamic or respiratory instability requiring inotropic support, mechanical circulatory support, or mechanical ventilation within 30 days prior to planned valve surgery
16. Documented leukopenia (WBC < 3.5x 10^3/µL), acute anemia (Hgb < 10.0 gm/dL or 6 mmol/L), or thrombocytopenia (platelet count < 50x10^3/µL) accompanied by history of bleeding diathesis or coagulopathy
17. Has prior organ transplant or is currently an organ transplant candidate
18. Current or recent participation (within 6 weeks prior to surgery) in another drug or device trial
19. Was previously implanted with trial device (Model 11000A or Model 11000M)[1]
20. Pregnant (female subject of childbearing potential only), lactating or planning to become pregnant during the duration of participation in trial
21. Currently incarcerated or unable to give voluntary informed consent
22. Documented history of substance (drug or alcohol) abuse within the last 5 years prior to implant
23. Requires concomitant left ventricular assist device (LVAD) placement

4.0 ABBREVIATIONS

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

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5.0 TRIAL OVERVIEW

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 AORTIC AND MITRAL 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 of 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.

Stenosis of the mitral valve is the narrowing of the valve opening that causes lower blood flow through the valve. In over 99% of stenotic mitral valves, the etiology is rheumatic disease.[3] Other rare causes of mitral stenosis include congenital malformed valves, active infective endocarditis, massive annular calcium, and metabolic or enzymatic abnormalities.[3] Regurgitation of the mitral valve occurs when blood flows back into the valve as the leaflets close or leaks through the leaflets after they are closed. Mitral regurgitation has multiple etiologies including: floppy mitral valves, active or healed infective endocarditis, papillary muscle dysfunction, annular calcium, idiopathic chordae tendineae rupture, rheumatic disease, dilated and hypertrophic cardiomyopathies, endocardial fibrosis, and collagen-vascular disorders (lupus, scleroderma), or Marfan's or Marfan-like disorders. Edward et al reviewed data collected from 1648 patients between January 1990 and December 1999 in northern New England, and noted that mitral valve replacements and repair procedures have substantially increased and indications for these procedures have expanded to also include older and sicker patients with less rheumatic and more degenerative and coronary artery-related mitral valve problems.[4] As the incidence of rheumatic mitral stenosis and regurgitation has decreased, mitral regurgitation caused by degenerative disease of

the mitral apparatus and caused by the left ventricular dysfunction associated with coronary artery disease has become the predominant hemodynamic lesion of the mitral valve.[5]

5.1.2 TREATMENT OF AORTIC AND MITRAL 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.[6,7] Aortic valve repair for stenosis does not show good clinical results.[8] Replacement of the aortic valve is indicated for symptomatic subjects and asymptomatic subjects with left ventricular dysfunction.

Diseased mitral valves can be treated by medication, surgical repair and surgical replacement. Repairing the native valve is generally preferred over replacing it. Surgical repair can involve modifying the valve tissue or underlying structures. This procedure can be performed with or without implantation of an annuloplasty ring that provides support to the native valve so that it closes completely and functions normally. If the native valve cannot be repaired, it is replaced by either a mechanical valve (constructed from synthetic material) or a tissue bioprosthetic valve (made primarily from animal tissue including bovine pericardium, or human valves from cadavers.

5.1.3 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

Edwards Pericardial Aortic Bioprosthesis

The Edwards Pericardial Aortic Bioprosthesis, Model 11000A (also referred to as the Model 11000A) is a bioprosthesis comprised of bovine pericardium. It is based on the same design as the Carpentier-Edwards PERIMOUNT Magna Ease Pericardial Aortic Bioprosthesis, Model 3300TFX, which was approved under P860057/S042 on 07 May 2009.

The physical structure and design of the Model 11000A is identical to the Model 3300TFX, except for tissue processing, sterilization and packaging. The Edwards Pericardial Aortic Bioprosthesis, Model 11000A, is a trileaflet bioprosthesis comprised of treated bovine pericardium that is mounted on a flexible frame. It is available in sizes 19, 21, 23, 25, 27, and 29 mm. The bioprosthesis is stored in non-aqueous packaging, and does not require rinsing prior to implantation.

The wireform is made of a cobalt-chromium alloy and is covered with a woven polyester fabric. A cobalt-chromium alloy/polyester film laminate band surrounds the base of the wireform frame. A silicone sewing ring that is covered with a porous polytetrafluoroethylene (PTFE) cloth is attached to the wireform frame. 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 11000A valve is treated with a new tissue process that builds on Edwards' existing tissue process, ThermaFix (TFX). The new process allows the valve to be stored in non-aqueous packaging and the valve is ethylene oxide sterilized.

Edwards Pericardial Mitral Bioprosthesis

The Edwards Pericardial Mitral Bioprosthesis, Model 11000M is a bioprosthesis comprised of bovine pericardium. It is based on the same design as the Carpentier-Edwards PERIMOUNT Magna Mitral Ease Pericardial Bioprosthesis, Model 7300TFX, which was approved under P860057/S068 on 24 June 2010.

The physical structure and design of the Model 11000M is identical to the Model 7300TFX, except for tissue processing, sterilization and packaging. The Edwards Pericardial Mitral Bioprosthesis, Model 11000M, is a trileaflet bioprosthesis comprised of treated bovine pericardium that is mounted on a flexible frame. It is available in sizes 25, 27, 29, 31, and 33 mm. The bioprosthesis is stored in non-aqueous packaging, and does not require rinsing prior to implantation.

The wireform is made of a cobalt-chromium alloy and is covered with a woven polyester fabric. A cobalt chromium alloy/polyester film laminate band surrounds the base of the wireform frame. A waffled silicone sewing ring that is covered with a porous polytetrafluoroethylene (PTFE) cloth is attached to the wireform frame. The sewing ring is scalloped along its anterior portion. Black silk suture markers on the anterior portion facilitate the orientation of the bioprosthesis and help avoid obstruction of the left ventricular outflow tract by a strut. A black silk suture guide line circles the sewing ring.

The Model 11000M valve is treated with a new tissue process that builds on Edwards' existing tissue process, ThermaFix (TFX). The new process allows the valve to be stored in non-aqueous packaging and the valve is ethylene oxide sterilized.

5.2.1 DEVICE INDICATION FOR USE

The Edwards Pericardial Aortic Bioprosthesis, Model 11000A, is indicated for patients who require replacement of their native or prosthetic aortic valve. The device is contraindicated only if the implanting surgeon decides the anatomy and pathology pose unwarranted risk.

The Edwards Pericardial Mitral Bioprosthesis, Model 11000M, is indicated for patients who require replacement of their native or prosthetic mitral valve. The device is contraindicated only if the implanting surgeon decides the anatomy and pathology pose unwarranted risk.

5.2.2 DEVICE TRAINING

[redacted] The implant technique for the Model 11000A and Model 11000M is the same as other supraannular bioprosthetic valves. The only usage difference in Model 11000A and Model 11000M from other tissue valves is that Models 11000A and 11000M do not require rinsing prior to implantation. If the bioprosthesis is rinsed prior to implantation, the valve must then be kept hydrated with sterile physiological saline irrigation on both sides of the leaflets until the heart is closed.

5.3 REPORT OF PRIOR INVESTIGATIONS

A clinical trial (Protocol Number 2010-03) initiated in Europe in July 2011 is underway to gather data on the Model 11000A. This is a prospective, non-randomized clinical trial of the investigational valve for subjects undergoing aortic valve replacement (AVR). This trial is an observational, confirmatory trial and not powered for statistical analysis. To date, the trial has enrolled one hundred thirty three (133) subjects at two (2) investigational sites in Poland. There are three (3) early deaths, of which two (2) deaths were adjudicated by the CEC as not related to the valve, and one (1) death was adjudicated as valve related.

There are sixteen (16) late deaths, of which three (3) have been adjudicated as valve related. One (1) incident of late study valve related mortality was adjudicated to be due to valve thrombosis, one (1) was adjudicated as to be due to nonspecific/unknown cause, and one (1) valve-related late death was adjudicated to be due to cardiac arrest. As of 7 April 2017, 100% of the eligible subjects completed the discharge, 99.2% completed the 3 month, 97.6% completed the 1 year follow-up, 92.5% completed the 2 year follow-up, 93.8% completed the 3 year follow-up, 92.7% of eligible subjects completed the 4 year follow-up, and 100% completed the 5 year follow up visits. At the time of this interim report there are no occurrences of study valve related bleeding, hemolysis, structural valve deterioration or unanticipated adverse device effects.

Clinical Follow-up

Clinical follow-up endpoints are listed in **Table 1** for the first 133 subjects implanted.

Table 1: Safety endpoints Events (2010-03 Cohort)

	Early Events (≤30 POD) N = 133	Late Events (>30 POD) Late pt-yrs = 495.29	
Safety Endpoint	**% (n)**	**%/pt-yr (m)**	**95% CL**
Mortality	2.3 (3)	3.2 (16)	4.8
Valve-related mortality	0.8 (1)	0.6 (3)	1.4
Thromboembolism	2.3 (3)	0.2 (1)	0.8
Valve thrombosis	0.0 (0)	0.2 (1)	0.8
Major bleeding events	6.8 (9)	0.4 (2)	1.1
Major paravalvular leakage[§]	0.8 (1)	0 (0)	0.5
Endocarditis	0.0 (0)	0.2 (1)	0.8
Structural valve deterioration	0.0 (0)	0 (0)	0.5
Hemolysis	0.0 (0)	0 (0)	0.5
Nonstructural valve dysfunction	0.0 (0)	0.2 (1)	0.8
Reoperation (trial valve)	0.0 (0)	0.2 (1)	0.8
Explant (trial valve)	0.0 (0)	0.2 (1)	0.8

'n' is the number of subjects who experienced the event; 'm' is the number of events observed.
Early event rates are described as simple proportions (n/N); late event rates utilize linearized rates (m/ late pt-yrs).
One-sided upper 95% confidence limit for the linearized rate (CI: Confidence Interval).
[§]Major paravalvular leak is defined as paravalvular leak graded as +3 Moderate or +4 Severe by the Echo Core Lab or any paravalvular leak requiring intervention. Previous report included one late major PVL (+3) and one early minor PVL (+2) in Subject 201003-330 which was reassessed by the Core Lab to be minor late PVL (+2) and no early PVL (0/None).

The investigational valve, Model 11000 is the same design as Model 11000A, and was later renamed as Model 11000A.

6.0 BENEFITS AND RISKS

6.1 BENEFITS

The benefits of the Models 11000A and 11000M are the same as other bioprosthetic valves including improved valvular function, acute alleviation of symptoms related to valve stenosis or insufficiency, and/or improved morbidity and mortality.

The anticipated additional benefits of aortic valve Model 11000A, and mitral valve Model 11000M are to eliminate the need for rinsing the bioprosthesis prior to implantation, 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
- 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

- Hematoma
- Heparin induced thrombocytopenia (HITs)
- Hypotension
- Hypertension
- Thromboembolism
  - Venous, peripheral or central
  - Arterial, peripheral or central
  - Pulmonary, thrombus or other

Risks associated with Models 11000A and 11000M are anticipated to be the same as those listed above for other aortic or mitral bioprosthetic valves and valve replacement surgery. Based on pre-clinical testing, it is not anticipated that any new risks associated with the Model 11000A and Model 11000M tissue process, sterilization method, or packaging will be observed.

6.3 MINIMIZING SUBJECT RISK

Several safeguards are incorporated into the trial to minimize subject risk. The pre-clinical device testing for the implantable valve was performed in accordance with FDA guidance, ISO 5840:2009 and recognized product standards. All test results met or passed the required specifications supporting reasonable safety for this investigational product.

This clinical trial is conducted under the direction of qualified physicians experienced with cardiac surgery including aortic and mitral valve repair/replacement and the use of investigational devices. All participating investigators and sites are screened and qualified. They must be experienced in conducting clinical research and have adequate personnel to assure compliance to the trial protocol. No special training is required to implant the Models 11000A and 11000M. [redacted]

7.0 TRIAL DESIGN

This trial design methodology is based on a one year structural valve deterioration primary endpoint, as discussed in Sections 7.3.1 and 9.0. Based on the results of a pre-clinical assessment and OUS clinical trial, the use of the investigational valve is justified.

7.1 OBJECTIVE

The objective of this trial is to confirm that the modifications to tissue processing, valve sterilization, and packaging of the FDA-approved (P860057/S042) Carpentier-Edwards PERIMOUNT Magna Ease Pericardial Aortic Bioprosthesis, Model 3300TFX, which will be designated as the Edwards Pericardial Aortic Bioprosthesis Model 11000A, and the Carpentier-Edwards PERIMOUNT Magna Mitral Pericardial Bioprosthesis, Model 7300TFX, which will be designated as the Edwards Pericardial Mitral Bioprosthesis Model 11000M do not raise any new questions of safety and effectiveness in subjects who require replacement of their native or prosthetic aortic or mitral valve. The only differences between the Model 3300TFX and Model 11000A, and Model 7300TFX and 11000M are modifications in tissue processing,

valve sterilization, and packaging. The primary safety hypothesis to be accepted or rejected by statistical data is provided in **Statistical Methods Section 9.0**.

7.2 DESIGN

The trial is a multicenter, prospective, double arm trial to be conducted throughout the United States, Canada, Europe and Asia Pacific. It will include subjects with valve stenosis or insufficiency, or stenosis plus insufficiency requiring a planned valve replacement of their native or prosthetic valve. Final analysis for the aortic arm will be performed when at least three hundred (300) AVR subjects have completed the POD 390 follow-up visit, and at least 800 AVR patient-years of cumulative follow-up have been reached. Analysis for the mitral arm will be completed when at least three hundred (300) combined aortic and mitral subjects have completed the POD 390 follow-up visit and at least eight hundred (800) AVR and at least one hundred (100) MVR patient-years of cumulative follow-up have been reached. The tests for the trial endpoints were performed and the trial data was submitted to FDA for the PMA approval of the devices evaluated under the aortic and mitral arms. All IDE Subjects (aortic and mitral arms) who are currently enrolled and alive will be followed to 5 years. In addition, as a condition of approval of the PMA (P150048, approved June 29, 2017) all Subjects implanted with the Model 11000A valve at the top 3 enrolling sites (n=222) who have consented to continued follow-up will be followed annually through 10 years post-procedure. As a condition of approval of the PMA supplement for the mitral arm (approved 09Aug2018) all Subjects implanted with the Model 11000M valve at 3 sites (n=25) who have consented to continued follow-up will be followed annually through 10 years post-procedure.

7.3 ENDPOINTS

All safety and effectiveness data for the Model 11000A and Model 11000M valves will be compared to control data published in articles in the prosthetic heart valve literature.

7.3.1 SAFETY

Primary Safety Endpoint (up to 390 days post-implant):

The primary safety endpoint for the trial is the rate of implanted subjects that experience structural deterioration of the trial valve by the time of the POD 390 follow-up visit. The null hypothesis is that the rate of structural valve deterioration at one year is greater than 1%. The alternative hypothesis is that this rate is less than 1%.

Primary Safety Endpoint (Continued follow-up):

For continued follow-up of Subjects, the primary safety endpoint for the trial is the rate of implanted subjects that experience structural deterioration of the trial valve as determined by a Clinical Events Committee (CEC).

***Secondary Safety Endpoints (Pre-approval)*:**

Safety will be established by comparing the occurrence of specific safety endpoints to the objective performance criteria (OPC) reported in Table R.1 in ISO 5840:2009, Annex R.1 as recommended by the FDA in the Draft Guidance involving Heart Valves – Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications issued January 20, 2010.

***Secondary Safety Endpoints (Continued follow-up)*:**

For continued follow-up of Subjects, linearized rates will be used to summarize the following safety endpoints for the late (>30 days) post-operative period.

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

The Data Monitoring Committee (DMC) will review aggregate safety and hemodynamic data to determine if the trial is being conducted safely and in accordance to the protocol. The DMC will decide if the clinical investigation should be modified, suspended and or stopped.

The Clinical Events Committee (CEC) evaluates the adverse events that are endpoint related as well as those resulting in death. The CEC adjudicates early and late events for their relatedness to the investigational device and/or the surgical procedure.

[redacted]

[redacted]

7.3.2 EFFECTIVENESS

Effectiveness endpoints include the following:

- Clinically acceptable hemodynamic performance confirmed by echocardiography and core lab evaluation which will include the following parameters:
  - Mean gradient
  - Peak gradient
  - Effective orifice area [EOA]
  - EOA index
  - Performance index
  - Cardiac Output [CO]
  - Cardiac index
  - Valvular regurgitation including paravalvular leak
- New York Heart Association (NYHA) functional class compared to baseline
- Change in Quality of Life assessment – Short Form 12 version 2 (SF-12v2) score from baseline to POD 390.

7.4 ADDITIONAL CLINICAL MEASURES

Additional Data in support of analysis:

- Blood Data
  - White Blood Cell Count
  - Red Blood Cell Count
  - Hemoglobin
  - Hematocrit
  - Platelet Count
  - Plasma free hemoglobin or haptoglobin or serum LDH
  - Coagulation profile (If collected per standard of care dependent on anticoagulation regimen)
  - Serum Glycerol (See Section 10.4.1 for details)

7.5 NUMBER OF SUBJECTS

Up to seven hundred (700) aortic valve replacement (AVR) subjects and up to one hundred seventy five (175) mitral valve replacement (MVR) subjects at up to forty (40) clinical sites will be enrolled. At least eight (8) centers will implant thirty (30) or more AVR or thirty (30) or more AVR/MVR subjects with one year follow-up. An enrollment rate of three (3) to four (4) subjects per site per month is anticipated. Sites with less than ten (10) subjects enrolled will have data combined and reported. Enrollment period completion is anticipated within 1095 days or three (3) years.

7.6 METHODS OF FOLLOW-UP

Following informed consent and determination of eligibility, subjects undergo a pre-operative echocardiogram to document the function of their current valve prior to surgery. Evaluation of the echocardiogram (echo) is performed by a qualified cardiologist/sonographer at the site and over read by an independent core lab. Other baseline exams include physical assessment, recording of pertinent medical history, electrocardiogram (ECG), NYHA classification, Canadian Cardiovascular Society (CCS) Angina classification, quality of life (QOL) assessment, and selected hematological variables.

During the procedure, a transesophageal echo (TEE) and blood collection (if applicable, see Section 10.4.1) will be completed, and a post-operative ECG/rhythm strip will be conducted upon admission to the intensive care unit. In addition, follow-up will occur at or prior to hospital discharge where physical assessment, NYHA classification, CCS Angina classification, ECG, echo and evaluation of selected hematological variables will occur. A post-op echocardiogram must be completed on or prior to post-operative Day 10. At POD 30, a phone follow-up will assess NYHA classification and information on any adverse events that have occurred since discharge. At POD 105 follow-up visit, a physical assessment, NYHA classification, ECG, echocardiogram, and selected hematological variables will be evaluated. The subsequent follow-up visits will be made at POD 390, and annually thereafter up to POD 1825 or 3650. **Table 2** lists the follow-up visit time points and visit windows.

Adverse events and anti-thromboembolic therapy/medications are collected from the time of the index procedure until the subject exits the clinical trial.

Table 2. Visit Follow-Up Schedule

Visit	Visit Window (Days)	Timing from Implant (Day 0)
Screening/Baseline		Day -60 to Day 0
Discharge[1]		Prior to Discharge
POD 30	-5/+10	Day 25 to 40
POD 105	-15/+30	Day 90 to 135
POD 390 (1 yr)	-25/+45	Day 365 to 435
POD 730 (2 yr)	-25/+45	Day 705 to 775
POD 1095 (3 yr)	-25/+45	Day 1070 to 1140
POD 1460 (4 yr)	-25/+45	Day 1435 to 1505
POD 1825 (5 yr)	-25/+45	Day 1800 to 1870
POD 2190 (6 yr)*	-55/+75	Day 2135 to 2265
POD 2555 (7 yr)*	-55/+75	Day 2500 to 2630
POD 2920 (8 yr)*	-55/+75	Day 2865 to 2995
POD 3285 (9 yr)*	-55/+75	Day 3230 to 3360
POD 3650 (10yr)*	-55/+75	Day 3595 to 3725

[1] Subjects who are not discharged within 10 days post procedure must have an echocardiogram to assess performance of the trial valve. Those subjects will not require an additional echocardiogram at discharge.
*Subjects who have consented to continued follow up with the Model 11000A or Model 11000M valve.

8.0 TRIAL POPULATION

8.1 SUBJECT INCLUSION CRITERIA

A subject who meets ***all of the following criteria*** potentially ***may be included*** in the trial:

1. Is 18 years or older
2. Provides written informed consent prior to trial procedures
3. Agrees to attend follow-up assessments for up to 5 years and is willing to comply with specified follow-up evaluations at clinical investigational sites that are participating in the COMMENCE trial and/or obtain the protocol-specified diagnostic tests at centers that are under the same IRB or the same healthcare system
4. Diagnosed with aortic or mitral valve disease requiring valve replacement based on pre- operative evaluation
5. Scheduled to undergo planned aortic or mitral valve replacement with or without concomitant bypass surgery
6. Scheduled to undergo planned aortic valve replacement with or without resection and replacement of the ascending aorta from the sinotubular junction and without the need for circulatory arrest for hemi arch or arch replacement

8.2 SUBJECT EXCLUSION CRITERIA

A subject who meets ***any of the following criteria will not be included*** in the trial:

1. Requires emergency surgery
2. Requires planned multiple valve replacement/repair (with the exception of mitral valve replacement with tricuspid valve repair)
3. Has prior valve surgery, which included implant of a bioprosthetic valve, mechanical valve, or annuloplasty ring that will remain *in situ*

4. Requires a surgical procedure outside of the cardiac area (e.g. vascular bypass)
5. Requires surgical replacement of the aortic root
6. Has active endocarditis/myocarditis or endocarditis/myocarditis within 3 months to the scheduled aortic or mitral valve replacement surgery
7. 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
8. Has MRI or CT scan confirmed stroke, cerebrovascular accident (CVA) or transient ischemic attack (TIA) within 6 months (180 days) prior to planned valve surgery
9. Has acute myocardial infarction (MI) within 30 days prior to planned valve surgery
10. Has presence of non-cardiac disease limiting life expectancy to less than 12 months
11. Diagnosed with hypertrophic obstructive cardiomyopathy (HOCM)
12. Diagnosed with abnormal calcium metabolism and hyperparathyroidism
13. Exhibits left ventricular ejection fraction ≤ 20% as validated by diagnostic procedure prior to planned valve surgery
14. Echocardiographic evidence of an intra-cardiac mass, thrombus, or vegetation
15. Hemodynamic or respiratory instability requiring inotropic support, mechanical circulatory support, or mechanical ventilation within 30 days prior to planned valve surgery
16. Documented leukopenia (WBC < 3.5x 10^3/µL), acute anemia (Hgb < 10.0 gm/dL or 6 mmol/L), or thrombocytopenia (platelet count < 50x10^3/µL) accompanied by history of bleeding diathesis or coagulopathy
17. Has prior organ transplant or is currently an organ transplant candidate
18. Current or recent participation (within 6 weeks prior to surgery) in another drug or device trial
19. Was previously implanted with investigational device (Model 11000A or Model 11000M)[2]
20. Pregnant (female subject of childbearing potential only), lactating or planning to become pregnant during the duration of participation in trial
21. Currently incarcerated or unable to give voluntary informed consent
22. Documented history of substance (drug or alcohol) abuse within the last 5 years prior to implant
23. Requires concomitant left ventricular assist device (LVAD) placement

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

8.3 ENROLLED POPULATION

Subjects will be included in the enrolled population after meeting all the enrollment criteria, signing the informed consent, and after the surgeon assesses the subject's anatomy, sizes the annulus, and determines that the trial valve can be implanted. If the surgeon is unable to complete the implant procedure, the subject is considered "intent to treat" and will be followed for safety (adverse event collection) for 30 days or until any adverse events experienced by subject are resolved. No protocol-specified tests during this period will be required.

Each investigator screens subjects for potential inclusion into the trial. Screening results are used to make a final determination as to subject suitability for enrollment. Early and late results from this trial (i.e., immediate post-operative and up to one year) serve as the basis for determining the safety and effectiveness of the Edwards Pericardial Aortic Bioprosthesis, Model 11000A and the Edwards Pericardial Mitral Bioprosthesis, Model 11000M. Subjects must meet **all** applicable inclusion criteria and **no** pre-operative exclusion criteria at the time of enrollment evaluation in order to participate.

8.4 INDEX VALVE POPULATION

The investigational valve population includes all enrolled subjects that receive and retain the index valve. The analysis of the effectiveness endpoints and of the primary safety endpoint will be based on the investigational valve population.

8.5 SUBJECT AND TRIAL DURATION

Total enrollment period for this trial is estimated to be 1095 days or 3 years. Subject duration in the trial is estimated to be no longer than 1825 days (5 years) or 3650 days (10 years) for those who have consented to continued follow-up. Overall duration of the trial is estimated to be 3833 days or 10.5 years, and will involve at least eight hundred (800) AVR patient-years and at least one hundred (100) mitral valve replacement (MVR) patient-years of follow-up. Trial begins with the enrollment of the first subject and ends after the last subject is exited from the trial after completing the last follow-up visit at approximately POD 3650, all subjects are fully monitored, all outstanding data queries are resolved and all trial sites are closed to follow-up.

8.6 SUBJECT TERMINATION OR WITHDRAWAL

Once enrolled, subjects may discontinue participation at any time by withdrawing informed consent or meeting the requirement for termination. Participation in the trial is entirely voluntary. Subject participation for any explanted patient will be terminated at either 30 days post-explant (followed for safety only) or when all post-explant adverse events are resolved (whichever comes last). If the surgeon is unable to complete the implant procedure, those subjects are considered enrolled as "intent to treat" and will be followed for safety (adverse event collection) for 30 days or until any adverse events experienced by this cohort are resolved and then will be exited from the trial.

9.0 STATISTICAL METHODS

9.1 ANALYSIS POPULATION

The analysis populations will include the enrolled population and the index valve population. The index valve population will include all subjects who meet enrollment criteria, provide written informed consent, those deemed able to implant in the operating room and who receive the index valve. The enrolled population will include the index valve population and the "intent to treat" population[3]. For the enrolled population, the number of patients enrolled per site will be reported. Summaries of baseline and procedural data will be based on the enrolled population. The analysis of mortality and all safety data, including the primary endpoint, shall in general be based on the index valve population; however, the analysis will also be provided using the enrolled cohort. For the investigational valve population, the number of subjects implanted per site will be reported, stratified by implant position and valve size within each position.

9.2 SAMPLE SIZE

The sample size for this study follows the recommendation from the FDA in the Draft Guidance involving Heart Valves – Investigational Device Exemption (IDE) and Premarket (PMA) Applications (2010).

Assuming the Poisson distribution and the true rate being equal to its OPC, and with probabilities of Type I error of 0.05 and Type II error of 0.20, the amount of data necessary to achieve the smallest OPC of 1.2% per patient-year (excluding the OPCs for valve thrombosis, major hemorrhage, and major paravalvular leak, which are all less than 1.2% per patient-year) is 800 patient-years.

9.3 STATISTICAL ANALYSIS

9.3.1 SAFETY ANALYSIS

9.3.1.1 Primary Safety Endpoint (up to 390 days post-implant)

The primary safety endpoint for the trial is the rate of structural deterioration of the study valve at the time of the POD 390 visit. If we let p denote the probability that an implanted subject will experience structural valve deterioration by the time of the POD 390 visit, then the null and alternative hypotheses for the primary safety endpoint are:

$$H_0: p \geq 1\%$$

$$H_a: p < 1\%$$

[3] If the surgeon is unable to complete the implant procedure, those subjects are considered enrolled as "intent to treat" and 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.

The statistical test of the null hypothesis for the primary safety endpoint is based on a one-sided, upper 95% confidence interval calculated by the method of Clopper and Pearson[9]:

$$B(0.95; x + 1, n - x)$$

Here x is the number of structural valve deteriorations occurring by the POD 390 visit, n is the number of patients completing the POD 390 visit, and $B(0.95; x + 1, n - x)$ is the 95% upper quantile of the Beta distribution with parameters $x + 1$ and $n - x$. If the confidence interval above is less than 1%, then it will be concluded with 95% confidence that p is less than 1% and the acceptance criterion for the primary safety endpoint will be met. For the purposes of this hypothesis test, both aortic and mitral patients will be combined; however, results for the primary safety endpoint also will be reported separately for each implant position.

Based on a simulation, the power of the confidence interval above to reject the null hypothesis is greater than 80% for the sample size of 300 patients receiving the POD 390 visit. The simulation assumed for the purposes of power calculation a rate of SVD at the POD 390 visit of 0.05%; if a smaller rate is assumed, the power of the statistical test would of course be higher. [redacted]

9.3.1.2 PRIMARY SAFETY ENDPOINT (CONTINUED FOLLOW-UP):

For continued follow-up of Subjects, the primary safety endpoint for the trial is the rate of implanted subjects that experience structural deterioration of the trial valve as determined by a Clinical Events Committee (CEC). The linearized rate will be calculated as the number of late events divided by the total number of late-subject years. These results will be reported for both implant positions combined and separately for each position.

9.3.1.3 Secondary Safety Endpoints (Pre-approval)

The secondary safety endpoints listed in **Section 7.3.1** will be analyzed using the enrolled population. 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. In addition, a one-sided upper 95% confidence limit will be calculated for the linearized rate.

The hypotheses for the secondary safety endpoints are:

$$H_0 : p \geq 2 \times OPC \quad vs. \quad H_A : p < 2 \times OPC$$

where *p* is the complication rate for a given valve-related event. If the one-sided sided upper 95% confidence limit for *p* for a given secondary endpoint is less than $2 \times OPC$ then the trial will be considered a success with regards to that secondary endpoint. These hypotheses will be tested based on the combined aortic and mitral populations; however the results will also be reported separately for each implant position.

Percentages for the early events and linearized rates for the late events also will be calculated for all other complications observed in the trial, including structural deterioration. These results will be reported for both implant positions combined and separately for each position.

Actuarial rates based on the method of Kaplan - Meier will be calculated for SVD and for each of the safety events in Section 7.3.1 at each of the follow-up time points; the number of subjects at risk for the event will be reported at each of these intervals. These results will be reported for both implant positions combined and separately for each position.

9.3.1.4 SECONDARY SAFETY ENDPOINTS (CONTINUED FOLLOW-UP):

For continued follow-up of Subjects, percentages for the early events and linearized rates for the late events also will be calculated for all other complications observed in the trial, including structural deterioration.

Actuarial rates based on the method of Kaplan - Meier will be calculated for SVD and for each of the safety events in Section 7.3.1 at each of the follow-up time points; the number of subjects at risk for the event will be reported at each of these intervals. These results will be reported for both implant positions combined and separately for each position.

9.3.2 EFFECTIVENESS ANALYSIS

The following effectiveness endpoints will be analyzed using the investigational valve population. The analysis for valve performance will be performed separately for each implant position, and the analyses for NYHA Class and Quality of Life will be performed for both implant positions combined, separately for each position, and for isolated mitral valve replacement and mitral valve replacement with concomitant tricuspid valve repair.

9.3.2.1 VALVE PERFORMANCE

The following parameters will be summarized at baseline and at each follow-up visit for all subjects in the investigational valve population

- Peak pressure gradient
- Mean pressure gradient
- Effective orifice area index
- Performance index

- Effective orifice area
- Valvular regurgitation
- Cardiac output
- Cardiac index

Valvular regurgitation will be summarized by the number and percentage of subjects in each level of regurgitation. All other parameters will be summarized by N, mean, and standard deviation, and a 95% confidence interval. These summaries will be stratified by valve size.

9.3.2.2 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. POD 390 NYHA will be presented for all subjects in the investigational valve population with both baseline and POD 390 NYHA data.

9.3.2.3 QUALITY OF LIFE

The N, mean and standard deviation for the SF-12 physical and mental health summary measures (PCS-12 and MCS-12, respectively) will be calculated for baseline and POD 390. In addition, the N and mean for the change from baseline to POD 390 in PCS-12 and MCS-12 will be presented with a 95% confidence interval. These summaries will be based on the investigational valve population.

9.4 ADDITIONAL MEASURES

9.4.1.1 BLOOD DATA

For all measured blood parameters, individual results will be compared to documented normal ranges. The Investigator will determine for each parameter that is out-of-range whether the value is not clinically significant and summary statistics will be provided.

Summary statistics (N, mean, and standard deviation) will be calculated preoperatively and post-operatively. In addition, the percentage of patient within the normal range preoperatively and post-operatively will be calculated. The percentage of patients within the normal range post-operatively will be reported separately for patients within and without the normal range preoperatively and for all patients combined.

Analyses of blood data will be performed for both implant positions combined and separately for each position.

9.5 POOLABILITY

Subject baseline risk will be statistically compared between the regions (US, Canada, Europe and Asia Pacific) and among centers for the implanted population. Chi-square tests will be used to compare categorical risk factors while analysis of variance will be used to compare continuous risk factors. Comparisons will be based on the following demographic and pre-operative variables: age, sex, etiology, pre-operative NYHA, and concomitant CABG procedures, and any other baseline risk factors as deemed appropriate.

One-year Kaplan Meier estimates for the implanted population will be compared between the regions (US, Canada, Europe and Asia Pacific) and among sites for the following events: thromboembolism, valve thrombosis, major bleeding/ hemorrhage, all paravalvular leak, endocarditis, explant, and death. Estimates will be compared via a log-rank test. The primary safety endpoint will not be compared between regions or sites as it is expected that no structural valve deteriorations will be observed within the first year at any site or within any region.

9.6 ANALYSIS OF COVARIATES

A hazard regression analysis will be performed to test for the effect of gender, age at implant, pre-operative NYHA functional classification, previous valve surgery, concomitant coronary artery bypass surgery, implant position, and implant size on survival. This analysis will be performed by using a Cox proportional hazards model and will be based on the implanted population. Additionally, one-year Kaplan Meier estimates for each of the adverse events listed in the **Safety Endpoints Section 7.3.1** will be compared between the genders via a log-rank test.

Finally, the effect of gender on each of the following effectiveness endpoints at POD 390 (1 year) will be investigated with a linear regression model: peak gradient, mean gradient, effective orifice area (EOA) index. These linear regression models will be adjusted by BSA (to adjust for the effect of body size), implant position, and by valve size. The effect of gender on all valvular regurgitation at POD 390 (1 year) will be investigated via an ordinal logistic regression; this model also will be adjusted by BSA, implant position, and by valve size. All analyses will be based on the implanted population.

9.7 MISSING DATA

All statistical tests on the effectiveness endpoints will be performed using only those subjects with available data required for endpoint analysis. No missing value imputation will be performed.

9.8 FOLLOW-UP AND COMPLIANCE DATA

The number of valve population subjects followed to 390 days post-implant will be reported stratified by site and valve size; follow-up duration information, including mean follow-up, standard deviation and range of follow-up, and cumulative follow-up in subject-years will be reported for the valve population.

Subject compliance will be calculated and reported as the following four percentages: the number of subjects a) having completed follow-up visits; b) with NYHA functional classification data; c) with echocardiographic data; and d) with clinical laboratory results at each follow-up time-point, divided by the total number of implanted subjects available (i.e., who have not died or had their valve explanted) and eligible (i.e., who have reached the given time-point) for follow-up at that particular time-point. Compliance will be reported for each follow-up visit and will be based on the investigational valve population.

10.0 TRIAL PROCEDURES

10.1 SUBJECT SCREENING

All subjects diagnosed with aortic or mitral stenosis, insufficiency or stenosis-insufficiency requiring valve replacement as assessed by cardiac surgeons participating in this clinical trial, should be screened for eligibility. All subjects who may meet eligibility requirements will be asked to participate.

A "Screening Log" is provided to the investigational sites to maintain a cumulative log of all screened subjects. For subjects who are ineligible for participation in the clinical investigation, a reason supporting the disqualification of the subject must be entered on the Screening Log. Sites are not required to enter data into the EDC system for any preoperative or intraoperative screen failures. Any subject deemed ineligible due to active or recent endocarditis/myocarditis, recent myocardial infarction, pregnancy or lactation, or participation in another clinical investigation may be re-screened later. Re-screened subjects must be re-entered on the Screening Log.

10.2 INFORMED CONSENT

Written informed consent, in accordance with applicable international standards and trial center regulations, shall be obtained from each subject, prior to the trial procedures. The investigator retains a copy of the signed informed consent document in each subject's record, and provides a copy to the subject.

The Investigator must obtain the written informed consent of all subjects, and must not allow any subject to participate in the investigation prior to obtaining governing institutional review board (IRB), research ethics board (REB) approval, or Ethics Committee (EC) approval. Before starting the trial, the investigator provides trial Sponsor with a copy of the sample Informed Consent document approved by the IRB, REB, or EC with documented evidence that the IRB, REB, or EC approved the protocol and the informed consent.

[redacted]

[redacted]

10.3 BASELINE ASSESSMENT

After a written informed consent is obtained from the subject, the following baseline data is obtained as noted in **Table 3** below. This data includes physical assessment, demographic and medical history, 12-lead electrocardiogram (ECG), transthoracic echocardiogram (TTE) or transesophageal echocardiogram (TEE) per protocol, blood studies, an assessment of NYHA Functional Classification, CCS Angina Classification, an assessment of quality of life (QoL), and coagulation profile (via INR or PTT). Test results conducted within **60 days** before planned valve surgery may be used for this trial if all values are available and are no significant changes in the subject's condition would invalidate the test results.

Table 3. Baseline Assessment

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

10.4 VALVE REPLACEMENT PROCEDURE

All procedures are performed in an operating room, or a surgical suite having cardiac surgery and anesthesia services. The surgical approach used is at the discretion of the Investigator's routine surgical practice. At the time of valve replacement, transesophageal echocardiography (TEE) is recommended to assess the subject's anatomy. After performing the aortotomy, the native valve and surrounding anatomy will be examined for compatibility with the investigational device.

Note: The Edwards Pericardial Bioprostheses, Models 11000A and 11000M do not require rinsing prior to implant. ***Note:*** If the valve is rinsed prior to implant, it must be kept hydrated with sterile physiological solution throughout the remainder of the surgical procedure. Rinsing every 1-2 minutes is recommended. ***Caution:*** Contact of the leaflet tissue with any articles or sources of particulate matter should be avoided.

Transesophageal echocardiography (TEE) should be performed within 1 hour after the bioprosthesis is implanted (from cross-clamp removal) to assess placement and bioprosthesis function. [redacted] A post-operative ECG or rhythm strip should also be performed upon arrival to the intensive care unit (ICU).

10.4.1 SERUM GLYCEROL ANALYSIS

In order to obtain serum glycerol levels in a minimum of 100 subjects, the first 15 subjects enrolled at each of 8 sites will be evaluated. Two (2) blood samples for this assay will be collected from each of these subjects, one (1) pre-operatively (post-heparinization) and one (1) between 60 and 120 minutes after the heart has been restarted. The time that each sample is drawn will be recorded, as will the time the heart was restarted.

[redacted] Any subject who becomes an intra-operative screen failure will be replaced with next consecutively enrolled subject until up to 15 subject samples are achieved at each of the 8 sites.

Procedural information, findings, results and device identification information to be recorded are identified in **Table 4.**

Table 4. Procedural Information

General Information	Clinical Information	Device Information
Date of Admission Date of Procedure Implanting Surgeon Type of Operation	Etiology Diagnosis for Replacement Valve Implant/ Valve Position Sizing Condition of the Native Valve Concomitant Procedures Intra-operative Adverse Events Post-operative Cardiac Rhythm upon arrival to ICU *Blood collection for Glycerol Analysis (See Section 10.4.1) **REFER TO SERUM GLYCEROL SAMPLE COLLECTION MANUAL**	Valve Size and Serial Number Valve Performance Post-operative TEE (within 1 hour) **REFER TO ECHO MANUAL**

10.5 POST INDEX VALVE IMPLANT

At the discretion of the investigator, bioprosthetic heart valve recipients should be maintained on anticoagulant therapy (except when contraindicated) during the initial healing stage after implant, in accordance with the ACC/AHA 2006 Guidelines for the Management of Subjects with Valvular Heart Disease. However, the appropriate anticoagulation therapy must be determined by the physician on an individual basis.

10.6 DISCHARGE

The medical information and clinical evaluation of trial subjects prior to discharge is identified in **Table 5.** Subjects not discharged within 10 days post procedure, must have an echocardiogram to assess placement and performance of the index valve. This echocardiogram is required to complete the evaluation of short-term valve function. Those subjects will not require an additional echocardiogram at

discharge.

Table 5. Discharge Information

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

10.7 POST DISCHARGE FOLLOW-UP ASSESSMENTS

[redacted]

A telephone follow-up visit is conducted at POD 30 (-5/+10 days) to document anti-thromboembolic therapy (medications), adverse events and determine NYHA and CCS Angina functional classification.

Post-procedure clinical evaluation is performed on all trial subjects at the investigational site. Information to be recorded at scheduled visits is further detailed in **Table 6.**

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, and the data will be recorded as an interim visit, and any applicable data pertinent to the visit will be collected. Coagulation profile is only required if collected per standard of care dependent on anticoagulation regimen (i.e. non-Vitamin K oral anticoagulants (NOAC's) do not require monitoring of coagulation profile).

Table 6. Follow-Up Information at all Post-Discharge Visits

Clinical/Physical Assessment	Blood Studies	Echocardiography (TTE)
Date of Discharge Weight Heart Rate Blood Pressure Cardiac Rhythm (12-lead ECG) NYHA Classification CCS Angina Classification Quality of Life (SF-12)* Anti-thromboembolic Therapy (medications) Adverse Events	Blood Draw Date White Blood Cell Count Red Blood Cell Count Hemoglobin Hematocrit Platelet Count Plasma Free Hemoglobin or haptoglobin or serum LDH Coagulation Profile**	Date of Exam **REFER TO ECHO MANUAL**

*Conducted only at the POD 390 visit **Only required if collected per standard of care dependent on anticoagulation regimen

All efforts should be taken by the Investigator and the research staff to encourage subjects to return for required follow-up visits. If a subject cannot return for follow-up visits, all attempts will be made to collect the protocol-specified data from outside hospitals or clinics. [redacted]

10.8 MISSED FOLLOW-UP

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

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 three (3) attempts of telephone contact at separate dates and times, and a registered letter sent before the end of the follow-up window (telephone attempts may include a family member if available). 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 make three (3) attempts of telephone contact at separate dates and times, and a registered letter sent before the end of the follow-up window (telephone attempts may include a family member if available). Subjects who miss two (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.

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:

- Fails enrollment criteria after written consent
- Is Lost-to-follow-up (LTFU)
- Voluntarily withdraws from the trial
- Death
- Explant (after 30 days for safety endpoints only; or after adverse events from explant are resolved, whichever comes later)
- Does not retain trial valve after attempt to implant (after 30 days for safety endpoints only; or after adverse events from explant are resolved, whichever comes later)
- Completes last trial follow-up visit (at POD 1825 or POD 3650 for Continued Follow-Up Subjects)
- Investigator withdraws the subject from the trial

10.9 DEVICE REMOVAL OR EXPLANT

Index valve 'removal' is the excision of the investigational valve, before implant of the investigational valve is complete, i.e., the subject does not leave the OR with the investigational valve. 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 subject leaves the OR with the investigational valve in place, 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.

11.0 ADVERSE EVENTS

11.1 REPORTING

Adverse event information is reported throughout the clinical investigation. Adverse events are followed until they are adequately resolved. [redacted]

11.1.1 UNANTICIPATED ADVERSE DEVICE EFFECT

An ***unanticipated adverse device effect (UADE)*** is any serious adverse effect on health or safety or any life threatening problem or death caused by or associated with the device, if that effect, problem, or death was not previously identified in nature, severity, degree of incidence in this Investigational Plan. Additionally, an unanticipated adverse event includes any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects.

Investigator(s) are required to submit to the reviewing IRB/REB/EC and the trial Sponsor a report of any ***unanticipated adverse device effect (UADE)*** occurring during this investigation as soon as possible, but in no event later than two (2) business days after the investigator(s) first learns of the effect (21CFR 812.150(a)(l)). The trial Sponsor must immediately conduct an evaluation of an UADE, and must report the results of the evaluation to FDA, all reviewing IRB/REB/ECs, and participating investigators within ten (10) business days after the trial Sponsor first receives notice of the effect (21CFR 812.46(b), 812.150(b)(l)).

If it is determined that an UADE occurred, the trial Sponsor will notify the Data Monitoring Committee (DMC) within five (5) business days after the trial Sponsor or its designee first receives notice of the event. If the trial Sponsor and/or the DMC determines an event or event rate presents an unreasonable risk to a

subject, all investigations or parts of investigations presenting that risk are terminated, as soon as possible. Termination of the investigation shall occur no later than five (5) working days after the trial Sponsor makes this determination and no later than fifteen (15) days after trial Sponsor or its designee first receives notice of the event.

11.1.2 ADVERSE DEVICE EFFECTS

An adverse event is any undesirable experience associated with the use of a medical product in a patient. The event is serious and should be reported to FDA (and other relevant regulatory agencies) when the subject outcome is/led to:

- Death
- Life-threatening
- Hospitalization or prolonged hospitalization
- Disability or permanent damage
- Congenital Anomaly or birth defect
- Intervention to prevent permanent impairment or damage
- Other serious or important medical events – medical or surgical intervention to prevent one of the above outcomes

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Investigational sites report all applicable serious adverse events in accordance with the reviewing IRB/REB/EC committee's requirements.

Trial Sponsor or its designee determines reportability of applicable adverse events according to its responsibilities for European vigilance reporting.

11.2 NOTIFICATION OF UADE AND/OR SERIOUS DEVICE RELATED ADVERSE EFFECTS

Notification of UADE and serious device related adverse effects should be done via email to HVTClinicalResearch@edwards.com or faxed to 949-809-5610.

11.3 DEATH AND EXPLANTS

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 investigator(s). 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 by the trial Sponsor.

11.4 DATA MONITORING COMMITTEE

The trial Sponsor will appoint a Data Monitoring Committee (DMC) composed of two or more independent physicians including a cardiothoracic surgeon and a cardiologist, and a statistician. Members of the DMC will not have scientific, financial, or other conflict of interest related to the trial Sponsor or the Investigators. Curricula Vitae for the DMC members are maintained by the trial Sponsor, and are available for regulatory review. These individuals may not participate in this trial as investigators, and may not hold significant material, financial or other interests, which create a potential conflict with respect to this role. DMC members must sign a non-conflict-of-interest statement in this regard.

The primary purpose of the DMC is to ensure a consistent, independent review of events and their clinical significance using standardized criteria and definitions. The DMC will be tasked with identifying any issues such as higher than expected AE and/or death rates, UADEs or hemodynamic performance that is substantially worse than expected, to determine if the trial should be stopped, suspended, or modified at any time. The DMC will establish guideline criteria for recommending trial termination.

The DMC will meet at least yearly or more often as determined by the Chairperson and possibly on an *ad hoc* basis to evaluate trial progress and results during the enrollment phase. The Chairperson of the DMC will be informed of all UADEs within five (5) business days of these events being reported to the trial Sponsor or its designee. This requirement, in addition to the guideline criteria for recommending trial termination, will be incorporated into the DMC charter.

11.5 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 and 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. The 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.

12.0 TRIAL AND DATA MANAGEMENT

12.1 TRIAL CORE LABS

12.1.1 ECHOCARDIOGRAPHY CORE LAB

The Echocardiography 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. The purpose of the Echocardiography Core Lab is to ensure unbiased, timely and consistent analysis of the diagnostic data, and for evaluating changes in subject status over the course of the trial based on serial echocardiographic studies conducted on the same subject.

Personnel at the Echocardiography Core Lab must demonstrate appropriate training and experience for analyzing Doppler Echocardiography data. The trial Sponsor or its designee periodically will audit the Echocardiography Core Lab. Echocardiograms will be sent directly from the investigational sites to the Echocardiography Core Lab. The Echocardiography Core Lab reviews the Doppler echocardiograms upon receipt, and promptly notifies the site and the trial Sponsor if the quality of the echocardiograph is insufficient for analysis. The Echocardiography Core Lab will enter the data into the eCRF. [redacted]

12.1.2 GLYCEROL ASSESSMENT CORE LAB

The Glycerol Assessment Core Lab is responsible for independently analyzing all blood samples collected for measurement of serum glycerol. The purpose is to ensure unbiased, timely and consistent analysis of the data. [redacted]

12.2 DEVICE ACCOUNTABILITY

An initial set of Edwards Pericardial Bioprostheses Models 11000A and/or 11000M, is shipped to the clinical site once the following conditions are met: the site obtained regulatory approval (Institutional Review Board, Ethics Committee approval or Research Ethics Board), a signed Clinical Trial Agreement is in place, and the Site Initiation Visit, including Principal Investigator training, is complete. Additional devices are sent to the clinical site as devices are used or as needed.

12.2.1 INVENTORY AND ACCOUNTABILITY RECORDS

A Device Accountability Log is maintained by the Investigator noting all investigational devices received for use during this clinical trial. The log is kept with the documents for the clinical trial and is available for review during trial Sponsor monitoring visits.

All device shipments include inventory and shipment records (packing slip). The Principal Investigator or designee will take inventory of the product, note the condition of the device, and attest to accuracy of the valve shipment by signing the packing slip. Both the investigational site and the trial Sponsor retain copies of the packing slips and the Device Accountability Log.

12.2.2 DEVICE STORAGE

The device inventory is to be stored in a locked, controlled, cool, dry and clean area. This storage area shall be accessible only to the Principal Investigator(s), Co-Investigator(s) or approved designee(s). Only cardiac surgeons identified in the Clinical Trial Agreement and/or on the Delegation of Authority form on file may implant the investigational device.

12.2.3 DEVICE RETURN

The Principal Investigator(s) is notified in writing upon termination of the clinical trial. All unused devices in original package and/or those in opened packages 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 are returned. The trial Sponsor will provide shipping instructions.

12.3 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 adhere to procedures for reporting trial deviations to the IRB/EC/REB in accordance with their specific reporting policies and procedures.

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

- **Major deviations** – will be reported to the trial Sponsor within 48 hours but no later than 3 business days of awareness of the major deviation and document on the appropriate case report form provided; and to the IRB/REB/EC per their guidelines
  - Any deviation from subject inclusion and exclusion criteria
  - Any deviation from subject informed consent procedures
  - Unauthorized use of an investigational device outside the trial
  - Unauthorized use of an investigational device by a physician who is not listed in the Clinical Trial Agreement

- **Minor deviations** – will be reported to the trial Sponsor in writing on the appropriate form provided
  - Deviation from a protocol requirement such as incomplete/inadequate testing procedures;
  - Follow-up performed outside specified time windows in the protocol

  NOTE: Information that is not essential to the trial endpoints is not considered a deviation if absent.

12.4 TRIAL SITE INITIATION AND MONITORING PLAN

12.4.1 SITE INITIATION AND TRAINING

Site staff will be trained and experienced to perform their delegated tasks. Training may be in person, webinar, read and review, or other methods as deemed appropriate.

Training is documented on a "Training Log". A "Delegation of Authority Form" is completed at each 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.

New research staff members may be trained by previously trained personnel on the Delegation of Authority Form.

12.4.2 MONITORING

Written procedures have been established by the trial Sponsor for monitoring clinical investigations, to assure the quality of the trial and to assure that each person involved in the monitoring process carries out his or her duties. Standardized written procedures, sufficiently detailed to cover the general aspects of clinical investigations, will be used as a basic monitoring plan and will be supplemented by more specific / additional procedures specific to this clinical investigation.

A pre-trial monitoring visit or meeting will be conducted to ensure that the Investigator clearly understands and accepts the obligations incurred in undertaking the clinical investigation as listed in **Table 7** (Regulations and Guidelines), and that the facilities are acceptable. Periodic monitoring visits will be conducted with adequate frequency to ensure that the Investigator's obligations as set forth in 21 CFR Part 56 and 21 CFR Part 812 are being fulfilled and that the facilities continue to be acceptable.

The trial Sponsor will assign a monitor to oversee the progress of the clinical investigation at each investigational center. The monitor will remain in close contact with each investigational center throughout the duration of the investigation to provide any needed materials, (i.e., investigation forms) and answer any questions. The monitor will be responsible for verifying that the subject signed the consent, reviewing all data recorded on the eCRFs, and visiting each investigational center periodically to observe trial progress and compliance with clinical protocol and regulations applicable to this clinical investigation. Additionally, the monitor will provide assurance that complete records are being maintained, appropriate timely reports are made to the trial Sponsor and IRB/REB/EC, device inventory is controlled, and that the Investigator is carrying out all agreed upon activities. Any personnel changes must be reported to the monitor immediately and a training program must be scheduled and documented. A trial termination monitoring visit will be conducted at the completion of the clinical trial to ensure that all data are properly documented and reported.

Site Termination: If a clinical monitor becomes aware that an Investigator is not complying with the signed Investigator's Agreement, the Investigational Plan, the requirements of applicable health authority regulations, or any conditions of approval imposed by the reviewing IRB/REB/EC or health authority, trial Sponsor will immediately either secure compliance or terminate the Investigator's participation in the trial. The final action will be taken with the goal of assuring the rights, safety and welfare of the patients.

12.5 DOCUMENTATION REQUIREMENTS

12.5.1 SOURCE DOCUMENTS

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 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 trial Sponsor e.g. for reporting serious adverse device effects (SADE), 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.

Site monitoring will include 100% primary source verification of events contributing to the safety and effectiveness endpoints and unanticipated adverse device effects (UADE).

12.5.2 TRIAL DOCUMENTS

The trial Sponsor will provide pre-printed forms to each trial site for documentation of:

- Investigator and site training to the protocol (Training Log)
- Authorized trial site personnel (Delegation of Authority)

- Subject consent and screening (Screening and Enrollment Log)
- Monitoring visit tracking (Site Visit Log)
- Investigational Device Accountability (Investigational Device Accountability Log)

The site visit is recorded on the appropriate site visit report. All tasks and action items noted during the visit should be documented with detailed findings and comments provided as appropriate. The monitor provides a visit follow-up letter to the investigator and other appropriate trial staff briefly summarizing the visit and specifically addressing any outstanding issues and/or action items from the visit, any incidents of noncompliance with the protocol or applicable regulations noted during the visit, and any necessary corrective actions.

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 regulatory binder provided by the trial Sponsor. This binder must be made available for monitoring visits and audits.

12.6 DATA COLLECTION

[redacted] Electronic CRF (eCRF) will be utilized for this trial. Each eCRF must be signed electronically by the Principal Investigator listed in the Clinical Trial Agreement and Delegation of Authority Log. If for any reason an eCRF is unavailable and/or inaccessible, a 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.

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

The Sponsor's data management group is responsible for database development, validation, control and management of input from each monitored CRF, issuance and resolution of queries, database maintenance, and statistical support. Data Management personnel will employ a full-featured relational Oracle database application (or equivalent) on a central server that is 21 CFR Part 11 compliant. 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 trial Sponsor's internal network.

12.7 DATA AND DOCUMENT RETENTION

Trial-related correspondence, subject records, consent forms, records of device implant, and source document worksheets are to be maintained on file by the trial site. The trial Sponsor requires that it be notified in writing if the Principal Investigator wishes to relinquish ownership of the data and information

so that mutually agreed upon arrangements can be made for transfer of ownership to a qualified entity. Per FDA regulation 21 CFR 812.140, records of each subject's participation in the trial must be maintained for a period of two (2) years after trial closure and submission of the final report to the IRB/REB/EC.

12.8 TRIAL PROTOCOL AMENDMENTS

Changes in the protocol are made only by written amendment agreed upon by the trial Sponsor, the applicable regulatory agency, including the United States Food and Drug Administration, and if pertinent, the IRB/REB/EC. As appropriate, the trial Sponsor will submit changes in the protocol to the applicable regulatory agencies, including the United States Food and Drug Administration and investigators to obtain IRB/REB/EC re-approval. A report of withdrawal of IRB, REB or EC approval must be submitted to the trial Sponsor **within five (5) business days**. Any revisions to the protocol, including the Informed Consent Form and the Case Report Forms, other than very minor revisions must be approved by trial Sponsor, the IRB/EC/REB and the FDA and/or other regulatory agencies.

12.9 TRIAL COMPLETION

The principal investigator will be notified in writing upon termination/conclusion of the clinical trial. The trial Sponsor retains the right to suspend or terminate this clinical trial at any time.

A final clinical report shall be compiled once data collection is complete. Such reports include all information required and outlined in this protocol. The final report will be provided to regulatory agencies and/or institutional review boards/independent ethics committees and other regulatory agencies as per applicable laws. The final clinical report will be filed in the clinical trial master file.

12.10 FUTURE PLANS

No changes are planned at this time.

13.0 STATEMENTS OF COMPLIANCE, CONFIDENTIALITY AND RESPONSIBILITIES

13.1 GOOD CLINICAL PRACTICE STATEMENT

This trial will be conducted in compliance with all applicable US Federal regulations pertaining to investigational devices including but not limited to: 21 CFR Part 50, Part 54, Part 56, Part 812, Good Clinical Practice (GCP) standards, and Health and Insurance Portability and Accountability Act (HIPAA). The protocol and supporting documents for this trial will be reviewed and approved by an appropriately constituted IRB, REB or EC prior to trial initiation. All reviews and approvals will be in accordance with Good Clinical Practice (GCP) and all other applicable standards, regulations (local and national), guidelines and institutional policies.

13.1.1 PROTECTION OF SUBJECT CONFIDENTIALITY

Subject confidentiality will be maintained in accordance with GCP, the HIPAA and all other applicable standards, regulations (local and national), guidelines and institutional policies.

13.2 REGULATIONS AND GUIDELINES

The regulations listed in **Table 7** must be observed to comply with the trial Sponsor's policy for conduct of clinical studies; they represent good clinical practice. It is the responsibility of the investigator(s) to comply with the requirements set forth in their country specific regulations.

Table 7. Regulations and Guidelines

Country or Region	Regulation / Guideline
US	- Investigational Device Exemption (IDE), 21 CFR Part 812 - Institutional Review Board (IRB), 21 CFR Part 56 - Protection of Human Subjects, 21 CFR Part 50 - Financial Disclosure, 21 CFR part 54 - Draft Guidance for Industry and FDA Staff - Heart Valves – Investigational Device Exemption (IDE) and Premarket Approval (PMA) Applications, January 20, 2010
Europe	- 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	- Canadian Medical Device Regulations (CMDR) - Canadian Investigational Testing Authorization as defined in the Medical Devices Regulation, May 1998
Asia Pacific	- Regional requirements will be added in an Appendix as required.

13.3 INVESTIGATOR RESPONSIBILITIES

The trial Investigator(s) will adhere to the trial protocol, Good Clinical Practice, HIPAA, and compliance with applicable government and institutional regulations. The trial Investigator(s) is responsible for obtaining proper regulatory approvals, and reporting to regulatory authorities per all applicable regulations. [redacted]

13.4 SPONSOR RESPONSIBILITIES

The trial Sponsor will adhere to the trial protocol, Good Clinical Practice, HIPAA, and compliance with applicable government and institutional regulations. The trial Sponsor is responsible for obtaining proper regulatory approvals, and reporting to regulatory authorities per all applicable regulations. [redacted]

14.0 PUBLICATIONS

Edwards Lifesciences, as the trial Sponsor of record, has a proprietary interest in this trial. Authorship and manuscript composition will reflect cooperation between multiple investigators and sites, core laboratories, and Edwards Lifesciences. Authorship will be established prior to writing of the manuscript. No individual publications will be allowed prior to the completion of the final report for this trial and as agreed in writing by Edwards Lifesciences.

15.0 REFERENCES

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