



Edwards

Carpentier-Edwards PERIMOUNT Magna Ease  
Pericardial Bioprosthesis in the Aortic Position,  
Model 3300TFX

NCT01171625

September 15, 2009

**POST APPROVAL STUDY # 2007-08**  
**CARPENTIER-EDWARDS® PERIMOUNT® MAGNA EASE™ PERICARDIAL**  
**BIOPROSTHESIS in the AORTIC POSITION, MODEL 3300TFX**

**Prepared by:**

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**CLINICAL PROTOCOL STUDY # 2007-08**  
**CARPENTIER-EDWARDS PERIMOUNT MAGNA EASE**  
**PERICARDIAL BIOPROSTHESIS in the AORTIC POSITION,**  
**MODEL 3300TFX**

**Revision E**

**September 15, 2009**

**Protocol Change Status**

<b>Protocol Revision #</b>	<b>Revision Date</b>
Revision A (Never implemented)	January 23, 2007
Revision B (Implemented in Europe)	September, 2007
Draft Revision C (US and OUS)	March 16, 2009
Revision D (US and OUS)	May 27, 2009
Revision E (US and OUS)	September 15, 2009

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# 1. CARPENTIER-EDWARDS® PERIMOUNT® MAGNA EASE™ PERICARDIAL BIOPROSTHESES STUDY SUMMARY

<b>Protocol No:</b>	2007-08
<b>Study Title</b>	Carpentier-Edwards Perimount Magna Ease Pericardial Bioprosthesis in the Aortic Position, Model 3300TFX
<b>Study Purpose:</b>	To evaluate the long term safety and effectiveness of the Carpentier-Edwards® PERIMOUNT® Magna Ease™ Valves in patients undergoing isolated aortic valve replacement.
<b>Study Device:</b>	Carpentier-Edwards® PERIMOUNT® Magna Ease™, Model 3300TFX.
<b>Study Design:</b>	This is a prospective, single-arm, multi-center study to be conducted in the US, and outside the US (OUS). This study will enroll a minimum of 225 patients implanted with the study valve in order to achieve 101 aortic valve replacement subjects each followed for a minimum of 8 years.
<b>Study Population:</b>	Male and female patients, 18 years or older, requiring replacement for a diseased, damaged, or malfunctioning natural or prosthetic aortic valve.
<b>Entry Criteria:</b>	Patients will preoperatively sign the patient informed consent form, and meet all inclusion criteria and none of the exclusion criteria to participate in this clinical study.
<b>Duration of Participation:</b>	After valve implantation, patients will be followed and assessed at discharge, 6-months, one year, and annually thereafter for a minimum of 8 years.
<b>Clinical Endpoints:</b>	<p><u>Primary Safety</u></p> <p>Linearized yearly rates of:</p> <ul style="list-style-type: none"> <li>• Thromboembolism</li> <li>• All hemorrhage</li> <li>• All perivalvular leak</li> <li>• Endocarditis</li> </ul> <p><u>Secondary Safety</u></p> <p>Early rates, late linearized rates, and actuarial rates of:</p> <ul style="list-style-type: none"> <li>• Thromboembolism</li> <li>• Valve thrombosis</li> <li>• All hemorrhage</li> <li>• Major hemorrhage</li> </ul>

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	<ul style="list-style-type: none"> <li>• All perivalvular leak</li> <li>• Major perivalvular leak</li> <li>• Endocarditis</li> <li>• Hemolysis</li> <li>• Structural valve deterioration</li> <li>• Non-structural valve dysfunction</li> <li>• Reoperation</li> <li>• Explant</li> <li>• Death</li> <li>• Valve-related death</li> </ul> <p>Blood Data</p> <p><u>Primary Effectiveness:</u></p> <p>Percent of subjects in NYHA Functional Class I and II at 8 years post implant.</p> <p><u>Secondary Effectiveness:</u></p> <p>Hemodynamic Performance at 8 years post implant:</p> <ul style="list-style-type: none"> <li>• Peak gradient</li> <li>• Mean gradient</li> <li>• Effective orifice area (EOA)</li> <li>• EOA index</li> <li>• Performance index</li> <li>• Cardiac output</li> <li>• Cardiac index</li> <li>• Severity of aortic regurgitation</li> </ul> <p>Quality of Life survey (EQ-5D)</p>
<p><b>Study Sponsor:</b></p>	<p>Edwards Lifesciences LLC                  One Edwards Way                  Irvine, CA 92614 USA</p>

## 2. Carpentier-Edwards Perimount Magna Ease Pericardial Bioprosthesis in the Aortic Position Study Procedures Chart

Required information or Procedure	Assessments					
	Pre-op	Operative	Discharge	6-Month	1 Year, annually thereafter	Unscheduled visit
Subject Informed Consent	X					
Inclusion/Exclusion Criteria	X					
Subject Demographics	X					
History	X					
Diagnosis for Implant		X				
Operative Information		X				
Implant Data Card			X			
Physical Assessment <sup>1</sup>	X		X	X	X	X
Cardiac Rhythm by EKG	X			X	X	X
Antithromboembolic Therapies	X		X	X	X	X
Coagulation Profile	X		X	X	X	X
NYHA Functional Class	X			X	X	X
Echocardiography	X <sup>4</sup>	X <sup>2</sup>	X	X	X <sup>3</sup>	X <sup>4</sup>
Blood Data	X			X	X	X
Adverse Events		X	X	X	X	X
Visit / Subject Status			X	X	X	X
QOL <span style="background-color: black; color: black;">XXXXXXXXXX</span>	X			X		

<sup>1</sup> Physical Assessment includes measurement of heart rate, height (initial assessment only), weight and blood pressure

<sup>2</sup> If Intra-operative TEE is conducted, echocardiography data should be collected

<sup>3</sup> Full Echocardiography data is required at 1, 5 and 8 Year follow-up visits.  
 At 2, 4 and 6 Year follow-up visits, an echocardiography with regurgitation data, if present; ejection fractions, gradients EOA, LV Mass and perivalvular leaks.

<sup>4</sup> Optional

### **3. INTRODUCTION**

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 [1]. Diseased heart valves can be treated by medication, surgical repair and surgical replacement.

The Carpentier-Edwards PERIMOUNT Magna Ease Pericardial Bioprosthesis Model 3300TFX is a trileaflet valve comprised of bovine pericardium that has been preserved in a buffered glutaraldehyde solution and mounted on a flexible cobalt-chromium alloy frame. It is intended for patients who require replacement of their diseased, damaged or malfunctioning native or prosthetic aortic valve and whose prognosis without aortic valve replacement is unacceptably poor in terms of survival, quality of life, or both in the opinion of the attending physicians.

## **4. STUDY OVERVIEW**

### **4.1 PURPOSE**

The primary objective of the investigation is to obtain long-term human clinical data in order to demonstrate that the Carpentier-Edwards PERIMOUNT Magna Ease is a safe and effective replacement aortic bioprosthesis.

### **4.2 ENDPOINTS**

#### **4.2.1 PRIMARY SAFETY ENDPOINTS**

Long term safety performance will be evaluated by comparing the linearized yearly rates listed below to the objective performance criteria (OPC) referenced in the Food and Drug Administration (FDA) 1994 Draft Heart Valve Guidance [2].

OPC's from the Heart Valve Guidance are:

- Thromboembolism
- All Hemorrhage
- All Perivalvular Leak
- Endocarditis

#### **4.2.2 SECONDARY SAFETY ENDPOINTS**

Descriptive information of early rates, late linearized rates and actuarial analysis of the following:

- Thromboembolism
- Valve thrombosis
- All hemorrhage
- Major hemorrhage
- All perivalvular leak
- Major perivalvular leak
- Endocarditis
- Hemolysis
- Structural valve deterioration

- Non-structural valve dysfunction
- Reoperation
- Explant
- Death
- Valve-related death

Blood Data (white blood count, red blood count, hematocrit, hemoglobin, platelet count, serum lactate dehydrogenase, haptoglobin and reticulocytes).

#### 4.2.3 PRIMARY EFFECTIVENESS ENDPOINTS

The primary effectiveness endpoint will be:

Proportion of subjects in NYHA Functional Classification I and II at 8 years post-implant.

#### 4.2.4 SECONDARY EFFECTIVENESS ENDPOINTS

The secondary effectiveness endpoints will be:

Hemodynamic Performance by echocardiography at 8 years post implant, which includes:

- Peak Gradient
- Mean Gradient
- Effective Orifice Area
- Effective Orifice Area Index
- Performance Index
- Cardiac Output
- Cardiac Index
- Severity of aortic regurgitation

Quality of Life Survey (EQ-5D)

## 5. STUDY DESIGN

This is a prospective, single-arm, multi-center study to be conducted in the US and outside the US (OUS). A minimum of 225 subjects will be implanted (Section 11.1 Sample Size) to obtain long term data from 101 subjects at 8 years post implant of the Carpentier-Edwards PERIMOUNT

Magna Ease Pericardial Aortic Bioprosthesis, Model 3300TFX (Magna Ease valve). Subject enrollment will not start in the US before obtaining FDA approval of this post approval study.

## 5.1. STUDY SITE SELECTION

Up to 20 sites will enroll subjects in this study. Participating sites will be chosen based on their experience in conducting clinical studies, their experience implanting bioprostheses, excellent academic and medical reputation, as well as their ability to obtain a robust patient population. Each of the centers is required to have a study coordinator to assist the primary investigator(s). In addition, each participating center must have the time and resources available to participate in this study.

Study sites will be in the United States, and outside the US (OUS). On average, each site is expected to implant the Magna Ease valve in at least 15 subjects until enrollment requirements are met. It is anticipated that each of the participating sites will have a Principal Investigator, and there will be up to six Co-Investigators per site, for a total of up to 140 investigators. Each of the operating investigators will be experienced in aortic valve replacement surgery.

## 5.2. STUDY TIMELINE

Expected timeline for study implementation:

**Table 1: Expected timeline for study implementation**

Study Milestone	Timeframe in Quarters (3 months)	Cumulative Subject Enrollment
FDA protocol approval	Q0	0
Study Site Start-up • 1-2 IRB approvals / month	Q1 – Q3 (3 months – 9 months)	40 - 86*
First subject enrolled	Q1 – Q2 (3 months – 6 months)	87
Enrollment Phase • 1-3 subjects / quarter / site	Q2	107
	Q3	123
	Q4	143
	Q5	170
	Q6	194
	Q7	218
Completion of Subject Enrollment	Q8	225
Completion of Follow-up	101 subjects complete 8 year assessment	
Final Study Report Submission	Q1 after last subject completes follow-up	

\* Subjects already enrolled outside U.S. (OUS)

## 6. PATIENT POPULATION

Patients undergoing valve replacement of the diseased native aortic valve or previously implanted prosthesis will be considered for this study if they sign the subject informed consent form preoperatively, and meet all inclusion criteria and none of the exclusion criteria.

The routine practice of cardiovascular surgery employed by the principal investigator will determine the indications for replacement of a patient's natural valve or previously implanted prosthesis. Due to the complexity and variations in surgical procedures, and the individual anatomy and other patient related factors, the choice of surgical technique and approach is left to the discretion of the individual surgeon.

### 6.1 ENTRY CRITERIA

Patients will have to preoperatively sign the subject informed consent form, and meet all inclusion criteria and none of the exclusion criteria as indicated below to participate in this clinical study. The investigator will determine and document whether each patient meets the selection criteria before enrollment into the study. Subjects will be considered enrolled for study participation at the time the patient signs the subject informed consent form. A subject identification number will be assigned to each enrolled subject. If an enrolled subject does not receive the study valve an explanation will be indicated on the Case Report Form (CRF). The subject will be discontinued from the study and no further CRFs will be completed for these subjects. If a non-study tissue valve or a mechanical valve is implanted in an otherwise eligible subject, the reason for implanting the non-study valve must be documented in the Subject Screening Log. Reasons for implant of a non-study tissue valve in the aortic position include the subject's refusal to participate, withdrawal from the study, etc. Documentation of these cases is important to prevent bias in subject selection. Subjects censored from the study will be identified and the reason for censorship will be indicated.

### 6.2 INCLUSION CRITERIA

1. The patient requires, as indicated in the preoperative evaluation, a replacement aortic valve.

2. The patient is an average or better operative risk.
3. The patient is geographically stable and agrees to attend follow-up assessments at the hospital of surgical services for at least 8 years.
4. The patient is 18 years or older.
5. The patient has signed and dated the subject informed consent form prior to surgery.

### 6.3 EXCLUSION CRITERIA

1. The patient has any known non-cardiac life-threatening disease, which will limit the patient's life expectancy below 1 year.
2. The patient presents with active endocarditis within the last 3 months.
3. The patient has an abnormal calcium metabolism (e.g., chronic renal failure, hyperparathyroidism).
4. The patient has an aneurismal aortic degenerative condition (e.g., cystic medial necrosis, Marfan's syndrome).
5. The patient is pregnant or lactating.
6. The patient is an intravenous drug abuser.
7. The patient is currently a prison inmate.
8. The patient is currently participating in a study of an investigational drug or device.
9. The patient requires replacement of a native or prosthetic mitral, tricuspid or pulmonic valve.
10. The patient requires a repair of the mitral or tricuspid valve with the use of an annuloplasty device.
11. The patient was previously enrolled in the study.
12. The patient had a prior mitral, tricuspid or pulmonic valve surgery, which included implantation of a bioprosthetic valve, mechanical valve, or annuloplasty ring that will remain *in situ*.

## 7. STUDY MATERIALS

### 7.1. DEVICE DESCRIPTION

The Carpentier-Edwards PERIMOUNT Magna Ease Pericardial Bioprosthesis Model 3300TFX is a trileaflet bioprosthesis comprised of bovine pericardium that has been preserved in a buffered glutaraldehyde solution and mounted on a flexible frame. The bioprosthesis is treated according to the Edwards ThermaFix® process, which involves heat treatment of the tissue in glutaraldehyde and uses ethanol and polysorbate 80. The frame is designed to be compliant at the orifice and commissures. The lightweight frame is made of cobalt-chromium alloy, a corrosion-resistant alloy chosen because of its superior spring efficiency and fatigue-resistant characteristics, and is covered with a woven polyester fabric [REDACTED].

A thin cobalt-chromium alloy /polyester film laminate surrounds the base of the wireform frame providing structural support for the orifice. A silicone rubber suture ring is attached to the cobalt-chromium alloy frame that is covered with a porous, polytetrafluoroethylene cloth to facilitate tissue ingrowth and encapsulation. The aortic sewing ring has been scalloped to conform to the natural aortic annulus. The compliant nature of the suture ring also facilitates coaptation between the bioprosthesis and an often irregular calcified tissue bed.

The original aortic Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis, Model 2700, has been commercially available in the US since 1981 and the Model 2900 has been commercially available on the international market since 1983, Model 2800 (RSR) has been commercially available in the US since 1996 and Model PERIMOUNT Magna 3000TFX has been CE marked since 2004 and was launched in the US in 2005. The aortic Carpentier-Edwards PERIMOUNT Magna Ease obtained CE marking in December 2006.

The modifications resulting in Carpentier-Edwards PERIMOUNT Magna Ease Pericardial Bioprosthesis, Model 3300TFX is based on the continuing clinical experience in pericardial valves. The profile height on the Magna Ease bioprosthesis has been reduced to facilitate implantation in patients with small aortic roots.

The Model 3300TFX Magna Ease valve is available in the following sizes: 19 mm, 21 mm, 23 mm, 25 mm, 27 mm and 29 mm.

## **Pre-Clinical Studies**

Pre-clinical bench studies included sewing ring integrity testing, valve hydrodynamic, durability, shelf life & packaging, sterility, biocompatibility testing and structural component fatigue analysis. The design validation data demonstrate that the Magna Ease valves are designed to perform safely and effectively.

## **8. STUDY PROCEDURES**

Edwards will provide the study sites with the post approval study clinical protocol, Case Report Forms (CRFs, ██████████), Quality of Life survey ██████████ and all other necessary study related documentation. Edwards' Clinical Affairs Department will conduct all aspects of data quality assurance (data review and monitoring of study sites) per departmental Standard Operating Procedures.

Each study site will adhere to all the requirements specified in this protocol. Assessments for each patient will be obtained for the preoperative and operative visits, and postoperatively at discharge, 6-months, 1-year and annually thereafter for a minimum of 8 years (see tables 1, 2, 3 and 4).

The investigator will make every attempt to follow the subjects and will document the information gathered during the above mentioned study visits on the CRFs. The subjects will be encouraged by the investigator to report any address or telephone number changes. They will also be informed of the importance of returning for scheduled follow-up visits even if they are not having any problems. If a subject is lost to follow-up the efforts undertaken to locate the subject should be documented.

Each site will provide a list of normal blood values and a certificate, or equivalent documentation, outlining the quality level of their laboratory prior to study initiation.

## 8.1 PREOPERATIVE PROCEDURES

The investigator will determine and record each subject's demographics (date of birth, sex), physical assessment (heart rate, height, weight and blood pressure), New York Heart Association (NYHA) functional class, cardiac rhythm, cardiovascular medical history/risk factors, non-cardiovascular conditions, previous cardiovascular procedures/interventions, anti-thromboembolic medications and coagulation profile.

Blood data is required for each subject preoperatively and should be collected within 30 days prior to valve replacement. The following parameters will be collected: white blood cell count (WBC), red blood cell count (RBC), hemoglobin, hematocrit, reticulocytes, platelet count, haptoglobin and serum lactic dehydrogenase (SLDH). Should the serum LDH be elevated, it should be fractionated. Preoperative data is indicated on the CRF and is outlined in Table 2. The investigator or designee will also indicate if the parameters are within normal ranges or not and whether the change is clinically significant. A QOL survey (EQ-5D) will be completed by the subject pre operatively.

In addition, pre-operative echocardiographic evaluation is optional for this study; however if performed, the investigator should document the findings. The echocardiography information will be indicated on the CRF.

**Table 2: Preoperative Evaluation**

Clinical information	Blood Studies	Echocardiography Data
Date of Birth	White Blood Cell Count	Echo Date & Interval
Sex	Red Blood Cell Count	Reason for Echocardiography
Physical Assessment	Hemoglobin	Echo Variables <sup>1</sup>
• Heart Rate	Hematocrit	Cardiac Output Calculation
• Height (cm)	Reticulocytes	LV Measurements <sup>2</sup>
• Weight (kg)	Platelet Count	Transducer Position
• Blood Pressure (mmHg)	Haptoglobin	Peak & Mean Gradients Method
NYHA Functional Classification	Serum Lactate Dehydrogenase	Stenosis
Antithromboembolic Therapy	(fractionated, if elevated)	Regurgitation
Cardiac Rhythm by EKG		LV Structure/Function
Cardiovascular Medical history/Risk Factors		
Cardiovascular Conditions (past and present)		
Previous Cardiovascular Operations		
Non Cardiovascular Conditions (past and present)		
Coagulation Profile		
QOL survey		

## 8.2 OPERATIVE PROCEDURES

The surgical technique employed will be that developed and perfected by the Investigator in his or her normal practice of cardiac surgery. Special attention should be given to proper sizing,

<sup>1</sup>Echo Variables include:  $V_{\text{peakLVOT}}$ ,  $V_{\text{peakAO}}$ , Peak systolic gradient, mean systolic gradient, Stroke volume, cardiac output, LVOT diameter,  $TVI_{\text{LVOT}}$ ,  $TVI_{\text{AO}}$ , ejection fraction, aortic EOA).

<sup>2</sup> LV Measurements include: LV Mass and LV Mass Index.

orientation and irrigation of the valve during surgery as indicated in the Instructions For Use (IFU)



The investigator will record the implant date, implanting surgeon, etiology, diagnosis for current replacement, information regarding the particular valve implanted (including valve size, serial number, valve position, suture technique, whether pledgets were used or not) and other details concerning the surgery such as condition of the valve being replaced, condition of the annulus, debridement procedures, annulus diameter (Hegar sizer) after debridement procedure, surgical approach, concomitant procedures and intra-operative adverse events.

An intra-operative echocardiographic evaluation is not required for this study, however if performed, the echocardiography information will be indicated on the CRF.

**Table 3: Operative Evaluation**

<b>Clinical information</b>	
Date of Implant	Study valve
Implanting Surgeon	Valve Size
Etiology	Serial number
Diagnosis for Valve Replacement	Suture technique
Total Cross clamp time	Condition of the Valve being replaced
Pump Time	Debridement procedure
Surgical Approach	Tissue Annulus Diameter of Subject (Hegar sizer)
Condition of the Annulus	Concomitant procedures
Placement of Valve	Intra-operative Adverse Events
	Seating the Valve in Annulus
	Valve Position
	Pledgets

## 8.3 POSTOPERATIVE PROCEDURES

### 8.3.1 DISCHARGE

At discharge, the investigator or designee will provide the subject with an Implant Data Card (See Section 17.4 and [REDACTED]). The Implant Data Card must be filled with the required information (i.e., the name of the investigator, the contact information and the name of the facility). The investigator or designee should also obtain from the device package two stickers with the implanted Magna Ease serial number and affix one sticker on the back of the Implant Data Card and the second sticker on the front page of the subject's operations notes. In addition, the investigator or designee must explain to the subject the purpose of this Implant Data Card.

The investigator or designee will record the subject's status, physical assessment date, cardiac rhythm, anti-thromboembolic therapy, coagulation profile, and adverse events on the CRF. Echo/Doppler evaluation is required early postoperatively (within 30 days from implant date) or at discharge whichever comes first (Echo CRF). The requested clinical and echocardiographic variables at discharge are outlined below. The echocardiography information will be indicated on the CRF.

**Table 4: Postoperative Evaluation at Discharge**

Clinical information	Echocardiography Data (TTE)
Subject status	Echo Date & Interval
Physical Assessment: Heart Rate Weight (kg) Blood Pressure (mmHg)	Reason for Echocardiography Transducer Position Echo Variable <sup>3</sup>
Cardiac Rhythm	LV Measurements <sup>4</sup>
Anti-Thromboembolic Therapy	Stenosis
Coagulation Profile	Regurgitation
Adverse Events	LV Structure/Function
Provide subject with Implant Data Card	

<sup>3</sup> Echo Variables include:  $V_{\text{peakLVOT}}$ ,  $V_{\text{peakAO}}$ , Peak systolic gradient, mean systolic gradient, Stroke volume, cardiac output, LVOT diameter,  $TVI_{\text{LVOT}}$ ,  $TVI_{\text{AO}}$ , ejection fraction, aortic EOA).

<sup>4</sup> LV Measurements include: LV Mass and LV Mass Index

### 8.3.2 POSTOPERATIVE FOLLOW-UP VISITS

Post operative follow-up visits are required at 6 months, 1 year, and annually thereafter for a minimum of 8 years. In addition to the requested data at discharge, the New York Heart Association (NYHA) functional class will be assessed at subsequent postoperative assessments at 6-months (between 3-6 months) and annually post implant ( $\pm$  1 month of annual follow-up evaluations).

Postoperative blood studies are also required at 6- months (between 3-6 months), Blood data will support the absence/presence of related adverse events; in particular hemolysis. Should the serum LDH be elevated, it should be fractionated. The investigator or designee will also indicate if the parameters are within normal ranges or not and whether this poses a clinically significant event. The investigator will document all clinically significant events by completing the appropriate adverse event CRF.

Full Doppler/echocardiography is required for all subjects at 6-months (between 3-6 months) at 1, 5 and 8 year follow-up visits. At 2, 4 and 6 year follow-up visits, an echocardiography with regurgitation data, if present; ejection fractions, gradients, EOA, LV Mass and perivalvular leaks will be obtained. The echocardiography information will be indicated on the CRF. The investigator will document all clinically significant regurgitation and stenosis that need intervention by completing the appropriate adverse event CRF.

A QOL survey (EQ-5D) will be completed by the subject preoperatively and at the 6-month follow-up visit.

The assessment of cardiovascular adverse events will be conducted in accordance with the revised "Guidelines for Reporting Morbidity and Mortality after Cardiac Valvular Operations" (STS guidelines) published by the Society for Thoracic Surgeons (STS) in September 1988 [3] and revised in 2008 [4] [REDACTED]. All pertinent details related to the adverse event and evaluation of valve relatedness will be completed in accordance with the revised STS guidelines. In reporting adverse events, the clinical investigator will assess all cardiovascular related

symptoms including abnormal heart murmur, shortness of breath, exercise intolerance, dyspnea, orthopnea, anemia, fever, arrhythmia, transient ischemic attack, stroke, paralysis, low cardiac output, pulmonary edema, congestive heart failure and myocardial infarction as to their relation to the valve and will complete the appropriate adverse event data form as needed.

The investigator will record adverse events on the adverse event CRF. The different adverse event CRFs are designed to capture relevant information for thromboembolism, valvular thrombosis, non-structural valve dysfunction, structural valve deterioration, bleeding events, endocarditis, hemolysis and all other adverse events respectively. Perivalvular leaks will be captured as part of the non-structural valve dysfunction adverse event data form. The outcome/resolution status of the adverse event will also be indicated as part of the adverse event data form. If an event results in death, copies of the autopsy report and/or death summary must be sent to Edwards, as permitted by local laws. Details of expiration and re-operation / explant data will be documented on CRFs. The investigator will make every effort to return the explanted valve(s) (at autopsy or explantation) to Edwards (Section 10.5).

It is recommended to maintain bioprosthetic heart valve recipients on anticoagulant therapy during the initial healing stages after implantation (approximately two to three months) except where contraindicated. The appropriate anticoagulation therapy must be determined by the physician on an individual basis and based on current ACC/AHA guidelines [5].

At each postoperative assessment, the investigator should determine the subject's availability for future follow-ups. The requested clinical, blood data and echocardiography variables postoperatively are collected on the CRFs provided and are outlined in Table 5 below.

**Table 5: Postoperative Evaluations (6 Month, 1 Year, Annual)**

Clinical information	Blood Studies	Echocardiography Data †
Date of Assessment	White Blood Cell Count	Echo Date & Interval
Follow-Up Interval	Red Blood Cell Count	Reason for Echocardiography
Visit Status	Hemoglobin	Echo Variables <sup>5</sup>
Subject Status	Hematocrit	LV Measurements <sup>6</sup>
Physical Assessment: Heart Rate	Reticulocytes	Transducer Position
Weight (kg)	Platelet Count	Peak & Mean Gradients Method
Blood Pressure (mmHg)	Haptoglobin	Stenosis
Cardiac Rhythm by EKG	Serum Lactate Dehydrogenase	Regurgitation
NYHA Functional Class	(fractionated, if elevated)	LV Structure/Function
Anti-thromboembolic Therapy	Coagulation profile	
Coagulation Profile		
QOL Survey*		
Adverse Events		

\* At the 6-month follow-up visit only.

† Full Doppler echo was required at 6 months, 1, 5 and 8 years and a more limited study at 2, 4 and 6 years.

### 8.3.3 UNSCHEDULED VISIT

If any subject needs to be seen at other than a regularly scheduled follow-up visit for assessment of cardiac symptoms, the obtained information will be documented by the investigator on the CRF and follow-up interval is indicated as an “Other” visit. If blood studies are performed at these visits in response to symptoms, the investigator should document these studies on the CRF. Should the serum LDH be elevated, it should be fractionated. Doppler/echocardiography performed at these visits is optional, however if performed, the investigator should record echo parameters on the echo CRF. The echocardiography information will be indicated on the CRF.

<sup>5</sup> Echo Variables include:  $V_{\text{peak}}\text{LVOT}$ ,  $V_{\text{peak}}\text{AO}$ , Peak systolic gradient, mean systolic gradient, Stroke volume, cardiac output, LVOT diameter,  $\text{TVI}_{\text{LVOT}}$ ,  $\text{TVI}_{\text{AO}}$ , ejection fraction, aortic EOA).

<sup>6</sup> LV Measurements include: LV Mass and LV Mass Index.

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## 9. RISKS AND BENEFITS

The subjects for whom this device is intended are those seriously or critically ill whose prognosis without surgery for replacement of the diseased natural valve or previously implanted prosthesis is unacceptably poor in terms of survival, quality of life, or both in the opinion of the attending physicians. For this special subset of patients there are a number of widely accepted prosthetic heart valves in common use; however, none are without risk of serious complications related to thrombogenicity, hemodynamics, and durability.

Patients with mechanical valves are generally considered to have a serious threat of thromboembolic complications unless they are on an adequate anti-thromboembolic therapy. Even with adequate anti-thromboembolic therapy, the risk of complications is significant, particularly when the risk of serious hemorrhage is considered. Bioprostheses, on the other hand, pose a reduced risk of thromboembolism and serious hemorrhage since they do not require anti-thromboembolic therapy.

Although the proven longevity of bioprosthesis is not as extensive as for some of the currently available mechanical valves, Banbury et al. [6] reported on the durability of the Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis, Model 2700, in the aortic position. The mean age of this patient population at implant was  $65 \pm 12$  years. The risk-unadjusted freedom from structural valve deterioration was 77.0% at fifteen years [4]. A study conducted by Frater et al [7] on a patient cohort of 267 patients reported the valve related survival rate was  $78.8\% \pm 3.2\%$  and overall freedom from explant due to valve dysfunction was  $85.1\% \pm 3.0\%$  at 14 years [5]. Freedom from valve failure was  $68\% \pm 12\%$  at 18 years in a study conducted by Aupart [8] et al. with the Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis. Among patients > 60 years, the actuarial freedom of valve failure at 18 years was  $85\% \pm 8\%$  [6].

As with any patient undergoing heart valve replacement, patients in this study may experience adverse events which may include, but are not limited to, the following: angina, hemorrhage, arrhythmia, cardiac arrest, endocarditis, heart failure, hemolysis, myocardial infarction, prosthesis pannus, (non)-structural valve dysfunction, perivalvular leak, stenosis, stroke, regurgitation,

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reoperation or explant, thromboembolism, valve thrombosis and/or death. All cardiovascular adverse events will be evaluated in relationship to the valve using the revised STS guidelines [3]

██████████.

No procedures in this study are experimental. Participating in this study is thought not to induce any additional risk to patient undergoing aortic valve replacement.

## 10. CLINICAL ADVERSE EVENTS

### 10.1 OVERVIEW AND DEFINITIONS

Adverse events associated with Magna Ease valve will be recorded and analyzed. An appropriate adverse event data form will be completed as per revised STS guidelines 3] ██████████ and submitted to Edwards.

**Consideration of Adverse Events will hereafter consist of Adverse Events and Adverse Device Effects, including Serious Adverse Events, Serious Adverse Device Effects, Anticipated Adverse Device Effects, and Unanticipated Adverse Device Effects.**

**Adverse Event (AE):**

Any unfavorable and/or unintended sign symptom, or disease, temporally associated with the use of a device product, whether or not the event is considered related to the device product.

**Adverse Device Effects (ADE):**

An untoward or unintended response to the device. This definition includes any event resulting from insufficiencies or inadequacies in the Instructions For Use or the deployment of the device or any event that is a result of user error.

**Anticipated Adverse Device Effect (AADE):**

Any adverse effect related to the device, which is identified in the protocol prior to study commencement.

**Serious Adverse Event (SAE):**

Includes any of the following events that may or may not be considered related to the device.

- Death due to any cause
- Life threatening or permanently disabling events
- Any event resulting in additional treatment (intervention to prevent permanent impairment/ damage), hospitalization or prolonged hospitalization

Hospitalization for diagnostic or elective surgical procedures for a pre-existing condition is not considered an SAE

**Serious Adverse Device Effect (SADE):**

Adverse Device Effect that resulted in any of the consequences characteristics of a SAE or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

**Unanticipated Adverse Device Effect (UADE):**

Any SAE on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity or degree of incidence in the protocol or application (including a supplementary plan or application) or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

The occurrence of any UADE must be reported to Edwards within 2 business days of discovery by the investigator or his or her designee

## 10.2 ADVERSE EXPERIENCE REPORTING

The investigator(s) shall report any device related adverse event and any unexpected adverse device effect occurring during the study to the sponsor within **24 hours**; submit a written summary of the event to the Heart Valve Therapy Clinical Affairs department either via email to HVTClinicalResearch@edwards.com, or by fax to +1-949-809-5610. Edwards will report the event according to the country specific regulations and respective reporting requirements The

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Investigator is responsible for notifying their Institutional Review Board / Ethics Committee (IRB /EC).

### 10.3 MEDICAL DEVICE REPORTING (MDR)

The Sponsor will be responsible for reporting events to the Food and Drug Administration in accordance with 21 CFR 803 Medical Device Reporting. Examples of MDR events include the Safety Endpoints listed in section 4.2.1 and section 4.2.2.

### 10.4 AUTOPSY/DEATH

Copies of the autopsy report and/or death summary must be sent to Edwards as permitted by local laws. This information should be redacted at the site to remove any identifying information (i.e. subject full name, personal identification numbers, address, etc.). Information on the cause of death and valve relatedness will be evaluated by the Principal Investigator.

Deaths which must be reported to Edwards Clinical Affairs Department include:

- All deaths while participating in the study.
- All deaths up to 30 days post study valve explantation.

### 10.5 EXPLANTED VALVES

Every effort should be made to return the explanted valve(s), at autopsy or explantation to Edwards. The explanted valve should be placed in a container with a suitable histological fixative such as 10% formalin or 2% glutaraldehyde immediately after excision and returned to Edwards. Refrigeration is not necessary under these circumstances. Contact Edwards Clinical Research for additional instructions.

Any pertinent information, e.g. operative notes, autopsy report etc should be sent to Edwards. This information should be redacted at the site to remove any identifying information (i.e. subject full name, personal identification numbers, address, etc.).

After the study valve is explanted, the subject will be followed for either an additional 30 days to monitor for any new adverse events or until all study device related serious adverse events (see section 9.1) are resolved. After that point the subject will be discontinued from the study. No further evaluations and/or case report forms are needed after study exit. Data from these subjects will be included in analysis.

## 10.6 PATIENT WITHDRAWAL

The investigator should make every attempt to follow the patient at each of the required assessment periods. This information needs to be indicated on the CRF. Patients may withdraw from the study without penalty or loss of benefits to which they are otherwise entitled. A study patient that has been withdrawn from the study will not be replaced.

## 10.7 MISSED VISIT/ LOST TO FOLLOW-UP

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 3 attempts of telephone contacts at separate dates and times, and a registered letter before the end of the follow-up window. If a subject cannot be reached for the follow-up visit and misses the scheduled visit, the visit will be recorded as a missed visit on the date of last attempted contact. At the next visit interval, the investigator and/or designee will attempt to contact the subject again for follow-up. Should this attempt to contact the subject fail, a family member should be contacted in addition to the subject. Subjects who miss 2 sequential follow-up visits will be considered lost to follow-up at the second missed visit and exempt from future study follow-up visits. After the subject is terminated from the study, the investigator will attempt to determine if the subject is alive; including searching national mortality registries when available and as permitted by local laws.

# 11. STATISTICAL ANALYSIS

## 11.1 SAMPLE SIZE

Sections 11.1 – 11.3 detail the sample size calculation for the trial as well as the analysis approach for each of the study outcomes. Sections 11.4 and 11.5 address the issues of data

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poolability and missing data. Unless otherwise noted, all statistical tests will be performed at 0.05 level.

The sample size calculation for the trial is based on the primary safety endpoints. The linearized yearly rates for thromboembolism, all hemorrhage, all perivalvular leak, and endocarditis will be compared to the OPC provided in FDA's Replacement Heart Valve Guidance. These OPC are presented in Table 6.

**Table 6: Safety OPC**

<b>Adverse Event</b>	<b>OPC</b>
Thromboembolism	2.5
All Hemorrhage	1.4
All Perivalvular Leak	1.2
Endocarditis	1.2

More specifically, a statistical test based on the Poisson [9] distribution will be performed for each of these adverse event rates to evaluate whether it is less than 2 times the appropriate OPC. Thus, the null and alternative hypotheses for each adverse event are as follows:

$$H_0: \lambda \geq 2 \cdot OPC$$

$$H_A: \lambda < 2 \cdot OPC$$

where  $\lambda$  is the linearized yearly rate for the given adverse event (thromboembolism, valve thrombosis, all hemorrhage, all perivalvular leak, and endocarditis) computed when the total subject years reaches 808 and *OPC* denotes the relevant OPC. The test statistic for each adverse event is of the form:

$$Z = (\lambda - 2 \cdot OPC) / \sqrt{\lambda} .$$

$H_0$  is rejected in favor of  $H_A$  if  $Z$  is less than -1.645, the lower 5% percentile of the standard normal distribution. Grunkemeier, et al. [10] have demonstrated that 800 subject life-years is adequate to test against the smallest OPC of 1.2% per subject year (excluding valve thrombosis, and

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stratification for major versus minor hemorrhage, and perivalvular leak) with Type I and Type II error controlled at the .05 and .20 levels, respectively.

The proposed subject enrollment is calculated to ensure that at least 101 subjects survive to 8 years post implant. These  $8 \times 101 = 808$  life years in addition to the life years from those subjects not surviving to 8 years will more than fulfill the 800 life-years required by Grunkemeier, et al [10].

Sample size calculation for primary effectiveness endpoint is based on a test of the hypothesis:

$$H_0: p \leq 75\%$$

$$H_A: p > 75\%$$

where  $p$  is the proportion of the subjects in NYHA Class I or Class II at 8 years post implant. The expected proportion of the alive subjects in NYHA class I or II at eight years is above 90%, based on 8 year follow up data for the Carpentier-Edwards PERIMOUNT 2700/2800/2900 valve (this proportion is above 90% within the subjects with valid NYHA assessment at each annual visit till 8 years follow up). Based on this expected proportion, a sample size of 45 subjects provides 85% power to test the hypothesis that the true proportion is greater than 75% using an exact binomial test. Thus, the sample size of 101 subjects with NYHA data at 8 year post implant is more than adequate to provide sufficient power.

The calculated number of subjects ( $n$ ) that must be enrolled in order to have 101 subjects survive to 8 years post implant with 99% probability is based on the binomial distribution. Specifically,  $n$  is such that

$$1 - \sum_{x=1}^{101} \binom{n}{x} p^x (1-p)^{n-x} > 99\%$$

where  $p$  is the probability that a subject will survive for 8 years post implant. This calculation can be performed using standard statistical software. Based on the reported 8-year survival of 60% from Aupart, et al. (2006) [8], a sample size of 195 subjects fulfills the requirements of the equation above. Based on the data collected in a previous post approval study conducted by

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Edwards (Study 98-1), a lost to follow-up rate of 7.8% was observed among subjects who reached 5 or more years of follow-up post implant. The sample size is further inflated to 225 to account for up to a 15% rate of lost to follow up.

## 11.2 ANALYSIS POPULATION

All the data collected up to the point of the explant or expirations will be included in the safety and effectiveness analyses. The primary safety analysis will include all the enrolled subjects. The primary effectiveness analysis will include the subjects who survived post implant and have at least one post-implant NYHA assessment.

## 11.3 SAFETY ANALYSIS

### 11.3.1 PRIMARY SAFETY ENDPOINT

As described above a statistical test based on the Poisson distribution will be performed to investigate whether the linearized yearly rate for each cardiovascular adverse event (thromboembolism, all hemorrhage, all perivalvular leak, and endocarditis) is less than 2 times the appropriate OPC from the 1994 Draft Heart Valve guidance.

For reporting purposes, the percent of subjects who experience an early adverse event within 30 days of implant will be summarized. Linearized rates will be used to summarize adverse events for the late (>30 days) post-operative period. The linearized rates will be reported as the number of events occurring after the early post-operative period per year of subject survival. In addition, the linearized rate and 30-day frequency for thromboembolism will be stratified by concomitant cardiac problems (atrial fibrillation, sinus rhythm, pacemakers, etc.).

Accounting for both early and late post-operative events, actuarial analysis according to Kaplan-Meier will be used to show estimated probability of freedom from each adverse event.

### 11.3.2 SECONDARY SAFETY ENDPOINTS

#### **Blood Data**

Blood data (red blood count, white blood count, hematocrit, hemoglobin, platelet count, serum lactate dehydrogenase, haptoglobin, and reticulocytes) will be collected preoperatively, at 6-months and annually post implant. This blood data will support the absence / presence of related adverse events; in particular hemolysis. Data will be reported as the percent of subjects with results within the normal ranges at each time interval. The percent of subjects with hemolysis at each point will also be reported. Summaries will be presented for the entire study cohort and will also be stratified by valve size.

### **Time to Death, Reoperation, and Explant**

Time to death from the date of operation will be analyzed by the method of Kaplan and Meier. Time to reoperation from the date of operation as well as time to explant from the date of reoperation will be similarly analyzed. For time to explant and time to reoperation, the time to *first* explant or reoperation will be calculated for those subjects requiring explant or reoperation. These analyses will also be reported stratified by valve size. Analyses for time to explant and time to reoperation will also be stratified by fatal versus non-fatal events.

### **Nonstructural Valve Dysfunction and Structural Valve Deterioration**

The percentage of subjects experiencing nonstructural valve dysfunction and structural valve deterioration within the early post-operative period (within 30 days of implant) will be reported. Linearized rates will be used to summarize nonstructural valve dysfunction and structural valve deterioration for the late (>30 days) post-operative period. The linearized rates will be reported as the number of nonstructural valve dysfunctions and structural valve deteriorations occurring after the early post-operative period per year of subject exposure. The 30-day frequency and linearized rate for nonstructural deterioration and structural dysfunction will be stratified by the nature of the dysfunction.

## **11.4 EFFECTIVENESS ANALYSIS**

### **Subject functional classification**

Subjects will be stratified according to the NYHA classification preoperatively, at 6 months and annually post implant for 8 years. The distribution (numbers of subjects and percentages) in the various NYHA classes will be tabulated at each follow-up interval.

The primary effectiveness analysis will include all the subjects who survived the implant procedure and have at least one post-implant NYHA assessment. The proportion of the subjects in NYHA Classes I and II at 8 years post implant will be calculated to determine if it is  $\geq 75\%$  using a one-sided Binomial exact test. For subjects who die, withdraw or are lost to follow-up before reaching the 8 year follow-up visit, the last observed NYHA classes will be used in this analysis. As a consequence, those subjects will be counted as failures if they were in NYHA Classes III or IV at the time those events occurred. Subjects whose status at the time of the events is not known will be counted as failures if they were in NYHA Classes III or IV during their last assessment prior to the time of the events.

The proportion of subjects in NYHA Classes I and II and proportion of subjects who died and were in NYHA Classes III and IV at death or at their last known NYHA classification will also be calculated at each annual report.

### **Hemodynamic Performance**

Echocardiography data will be obtained preoperatively, early postoperatively and/or discharge, at 6-months and at 1, 5 and 8 year follow-ups. Descriptive statistics for the continuous echo variables and change from baseline (e.g. mean, standard deviation, and range) will be categorized by time interval and size. Regurgitation data will be summarized using frequency at each severity level.

Improvement in regurgitation at one year will be analyzed via the Jonckheere-Terpstra [11] test. Change at one year from baseline for all other hemodynamic outcomes will be analyzed using paired *t*-tests.

## 11.5 POOLABILITY

Subject baseline risk will be statistically compared between centers and regions (i.e. United States vs. OUS). 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, previous heart valve replacement surgery, valvular lesion, pre-operative NYHA, concomitant cardiac procedures, and coexisting cardiovascular conditions. Also included in the analysis will be the size of implant. Furthermore, time to event for the following events will be compared between centers via a log-rank statistic: thromboembolism, all hemorrhage, death or explant, and death. Additional analyses may be performed if the need arises.

## 11.6 MISSING DATA

All statistical tests on the effectiveness endpoints will be performed in two ways: (1) using only those subjects with available required for endpoint analysis and (2) by using the method of last observation carried forward (LOCF). Both methods of analyses will then be compared. However, both methods will be used for the comparison of NYHA classification at 8 year post implant to OPC (75%) and for the comparison of hemodynamic performance one year to baseline for the purpose of investigating the effect of loss-to-follow-up.

NYHA classification and hemodynamic performance will be summarized at each of the follow-up interval. In addition, the NYHA classification will only be statistically compared to OPC at 8 years post implant and only the one year post implant hemodynamic performance will be statistically compared to baseline.

## 12. ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed in order to comply with the sponsor's policy for conduct and monitoring of clinical investigations; they also represent sound research practice.

A written subject informed consent form will be obtained preoperatively from all subjects. The subject must be adequately informed of his or her participation in the clinical study and what will be required of him or her in order to comply with the protocol requirements. In addition, a subject informed consent form is required to allow appropriate data collection and data monitoring including access to medical records by the sponsor and regulatory agencies [REDACTED].

If an Institutional Review Board (IRB) or Ethics Committee (EC) exists for an institution, this board/committee must approve the subject informed consent form and protocol for use at its institution. A written statement by the IRB / EC indicating approval of the subject informed consent form and protocol must be submitted to the sponsor prior to study initiation.

### **13. HEALTH ECONOMIC INFORMATION**

In the United States only, the Sponsor may choose to obtain billing information such as charges associated with the Intensive Care Unit (ICU) and hospital stays to evaluate hospital costs for the initial implant hospitalization and subsequent readmissions, as necessary. For each subject, hospital charge data will be obtained from form UB-04 or similar report provided by the hospital.

### **14. CASE REPORT FORMS**

CRFs for individual subjects will be provided by Edwards [REDACTED]. The principal investigator or designee must keep a separate log of subject names and current addresses to facilitate record keeping and his or her ability to contact subjects for future follow-up.

CRFs are used to record study data and are an integral part of the study and subsequent reports. Therefore, the reports must be legible and complete. In order to comply with the HIPAA regulations and European data protection laws, any information related to the subject's identity must be redacted. All forms should be filled out using a ballpoint pen. Errors should be corrected by drawing a single strikethrough in ink, initialed and dated by the person who makes the change on the day the change is made. Copies of the changed form must be provided to the sponsor and retained in the subject study file.

A CRF must be completed and signed by the principal investigator, co-investigator or his or her designee listed in the Delegation of Authority form for each subject receiving a study valve, including subjects withdrawn from the study for any reason. The reason for withdrawal must be noted on the CRF, by the investigator.

Since there is a potential for errors, inaccuracies, and illegibility in transcribing data onto CRFs, originals or photocopies of all relevant operative records and reports, postoperative examinations, laboratory and other test results must be kept on file. CRFs and copies of test results must be available at all times for inspection by the study sponsor, the study monitor, and authorized regulatory bodies.

CRF's must be kept current to reflect subject status at each phase during the course of the study. Instructions for CRF collection or submission are provided in the CRF synopsis.

Electronic data capture (EDC) may be used for part or all of the data collection in this study. Edwards will provide training in the use of EDC to all necessary site personnel. Each investigator and staff participant will be assigned a unique password and only that individual should access subject records under that password. Changes made to the electronic record after a report has been saved or "committed" will be tracked in an electronic audit file linked to the date the change was made and the password of the individual who opened the record. Regardless of the type of CRF used, the sponsor will monitor subject CRFs for agreement with source documents on an ongoing basis.

## **15. STUDY TERMINATION**

The principal investigator will be notified in writing upon termination of the study. Edwards retains the right to suspend or terminate this clinical investigation at any time.

## **16. RECORD RETENTION**

Study files must be maintained at the clinical site for a minimum of two years after the study is either completed or terminated or until Edwards notifies the investigator that the records may be destroyed or in accordance with country specific regulations.

## **17. STUDY RESPONSIBILITIES**

### **17.1 INVESTIGATOR RESPONSIBILITIES**

The principal investigator is responsible for obtaining IRB/EC approval for the study at his or her institution.

Study records including CRFs, signed Agreement, originals of all blood and hemodynamic studies, signed informed consents, a copy of the implant data card, IRB/EC approval letters, the log of IRB/EC submissions, and other documents pertaining to the conduct of the study should be kept on file by the investigator.

The investigator(s) will adhere to the regulations that provide the greatest protection to the subject. The investigator is responsible to comply with the following regulations:

US Code of Federal Regulations:

- 21 CFR part 50: Protection of Human Subjects
- 21 CFR part 54: Financial Disclosure
- 21 CFR part 56: Institutional Review Boards
- 21 CFR part 814, subpart E: Post Approval Requirements

In Europe, EU Medical Device Vigilance System

and the:

- ICH Good Clinical Practice Guidelines
- Declaration of Helsinki
- US Department of Health and Human Services: Health Insurance Portability and Accountability Act of 1996 (HIPAA)
- Local and Regional Laws of the Country including Data Protection and ISO 14155 Part 1 and 2: 2003 Clinical Investigation of Medical Devices for Human Subjects, where appropriate for commercially available products

All protocol deviations must be fully documented and explained on the CRF. These include noncompliance related to inclusion/exclusion criteria, consent form, blood data, echo and follow-up visits.

Although the risks to the subject are felt to be the same as those reported for other available bioprostheses, the subjects receiving the Magna Ease valve will be closely followed. Any unusual or unanticipated adverse events will be reported immediately to the sponsor (see 10.1) and if applicable, to the IRB/EC as outlined in the Investigator's Statement and Agreement. If deemed necessary by the investigator, the IRB/EC, or the sponsor, the investigation may be suspended pending a thorough study of the incident.

If the investigator wishes to assign the files to someone else or move them to another location, he or she should consult with the sponsor in writing as to this change. If there is a change or addition of co-investigators, an amended agreement must be completed promptly. Any other personnel changes should be reported immediately to the monitor and a training program scheduled.

Monitoring visits will be scheduled throughout the course of the study. It is essential that the investigator set aside a sufficient amount of time for these visits to permit an adequate review of the study's progress, completed CRFs and original records.

## 17.2 SPONSOR/ STUDY MONITOR RESPONSIBILITIES

A study monitor assigned to the study by the sponsor will monitor the progress of the study. The study monitor must be acquainted with the investigator and other key people involved in the study. The study monitor will remain in close contact with the site throughout the duration of the study to answer any questions and provide any needed materials, e.g. CRFs.

The study monitor will be responsible for monitoring CRFs and visiting the site periodically to monitor study progress and compliance with the study protocol. The local data protection laws will be followed. Monitoring visits will be scheduled throughout the duration of the study at a mutually convenient time for the monitor and principal investigator or designee.

The sponsor will provide results of the ongoing study to the Food and Drug Administration, including a comparison to the available data in the heart valve literature regarding other FDA-approved bioprosthetic valves implanted in the aortic position. An Interim Post-Approval Study Status Report will be submitted every 6 months during the first two years of the study and annually thereafter. A Final Clinical Study Report will be prepared as early as 3 months after the last study subject completes follow-up.

## 17.3 STUDY CHANGES

Changes in the protocol may be made only by written amendment submitted to and agreed upon by FDA. Following written approval of a protocol amendment by FDA, the sponsor will submit the amended protocol and associated document to the IRB/EC. The above changes shall be implemented upon written approval by the respective IRB/EC. Administrative changes may be communicated to FDA and to the IRB/EC via the Annual Report.

## 17.4 IMPLANT DATA CARD

After implantation, subjects will be given the Implant Data Card by the Investigator prior to discharge [REDACTED]. This identification card allows subjects to inform healthcare providers what type of implant they have when they seek care.

## 17.5 STUDY PUBLICATION

Investigators shall submit to Edwards early drafts of all abstracts, manuscripts or presentations authored by investigators and collaborators based on data generated from the clinical study at least sixty days prior to submission of the abstract, manuscript for publication or presentation. Edwards shall have the right to advise investigators regarding proprietary information which shall not be divulged or the patentability of any inventions disclosed in the manuscripts. If requested by Edwards, investigators shall delay submission of manuscripts for publication up to ninety days to permit preparation and filing of related patent applications. In addition, Edwards shall have the right to require that any publication concerning the work performed hereunder acknowledges Edwards' financial support.

It is understood, however, that no press releases, literature, advertising, publicity, or written statements in connection with work under the Clinical Studies Agreement having or containing any reference to Edwards shall be made by the clinical site and/or the investigator without the prior written consent of Edwards. The clinical site and the investigator reserve the right to acknowledge the source of sponsorship in response to any legitimate inquiry.

Neither party will use the name of the other in any form of advertising or publicity without the written permission of the other party.

## 18. REFERENCES

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- 1 Yoganathan AP *et al.* Fluid Mechanics of Heart Valves. Annual Review of Biomedical Engineering 2004; 6:331-362.
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