Magna Mitral - 23mm

Clinical Evaluation of the Size 23mm Carpentier-Edwards PERIMOUNT Magna Mitral Bioprosthesis, Model 7000TFX

NCT01312779

November 11, 2011

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Edwards

Magna Mitral 23

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IDE CLINICAL PROTOCOL

Study Number: 2008-07
Revision: F
Effective Date: November 11, 2011

Written by:

[redacted] Date

Approved by:

[redacted] Date

[redacted] Date

[redacted] Date

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Protocol Change Status

Protocol Revision #	Revision Date
Revision A	December 21, 2009
Revision B	February 25, 2010
Revision C	May 13, 2010
Revision D	March 14, 2011
Revision E	July 8, 2011
Revision F	November 11, 2011

Study Sponsor:
Edwards Lifesciences LLC
One Edwards Way
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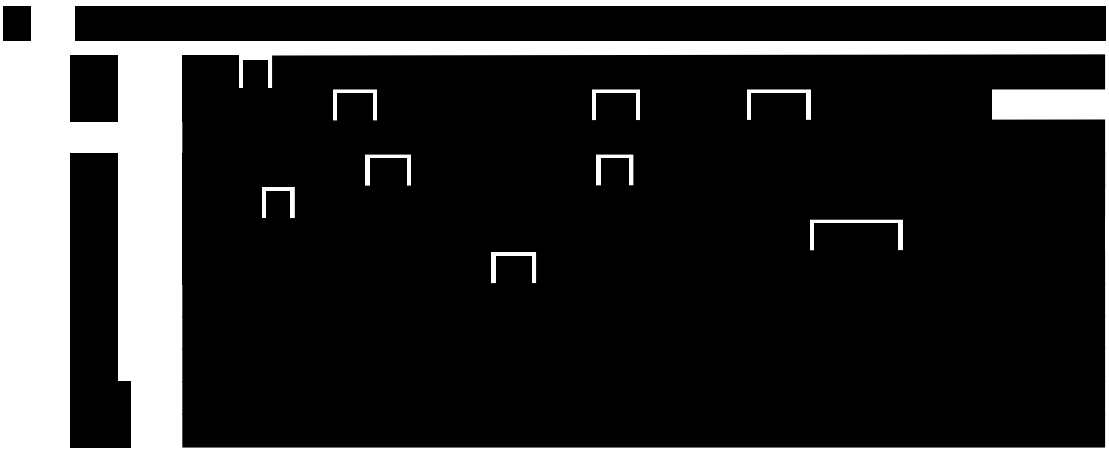

1 SYNOPSIS

<table>
<tr><td>Study Number:</td><td>2008-07</td></tr>
<tr><td>Title:</td><td>Magna Mitral 23

Clinical Evaluation of the size 23 mm Carpentier–Edwards PERIMOUNT Magna Mitral Bioprosthesis, Model 7000TFX</td></tr>
<tr><td>Purpose:</td><td>The purpose of this clinical study is to obtain human clinical data that demonstrates that the size 23 mm Carpentier–Edwards PERIMOUNT Magna mitral pericardial valve, model 7000TFX, is a safe and effective replacement heart valve.</td></tr>
<tr><td>Study Device:</td><td>Carpentier–Edwards PERIMOUNT Magna mitral pericardial valve, model 7000TFX, size 23 mm (Magna mitral valve, size 23 mm)

The size 23 mm Magna mitral valve is one size smaller than the Magna mitral valve, size 25 mm approved by FDA in August 2008. The Magna mitral valve, size 23 mm would be implanted in same size mitral annulus as the size 27 mm porcine Carpentier–Edwards Duraflex mitral low pressure valve, model 6625LP, as shown below in Table A. The Duraflex valve was approved by FDA in September 1991.

Table A: Valve dimension comparison
<table>
<tr><th>Dimension</th><th>Model 7000TFX, 23 mm</th><th>Model 6625LP, 27 mm</th></tr>
<tr><td>Tissue Annulus diameter (TAD)*</td><td>27 mm</td><td>27 mm</td></tr>
<tr><td>External Sewing Ring Diameter</td><td>34 mm</td><td>36 mm</td></tr>
</table>
* Note TAD corresponds to the “External Stent Post Diameter (Base)” in the Model 7000TFX, size 23 mm IFU and the “Mounting Diameter (Annulus)” in the Model 6625LP IFU.</td></tr>
<tr><td>Intended Use:</td><td>The Carpentier–Edwards PERIMOUNT Magna mitral pericardial valve, model 7000TFX, is indicated for patients who require replacement of their native or prosthetic mitral valve.</td></tr>
</table>

Study Objective:	The objective of this study is to evaluate the safety and effectiveness of the size 23 mm Magna mitral valve in subjects with mitral heart valve disease requiring replacement with a valve. Data collected in this study will be used to support the premarket application for approval in the United States. This study may also be used to support device approval in other countries as applicable.
Overall Design and Duration:	This is a prospective, non-randomized, multi-site, descriptive study. A minimum of 15 and up to 20 subjects will be implanted at a minimum of 2 and up to 8 participating investigational sites, within the US and internationally. Subject participation will last for 5 years. Subjects will be assessed for clinical follow-up at the following intervals: pre-study procedure, at implant, index hospitalization discharge, 6 months post procedure, 1 year post procedure and annually thereafter until 5 years post procedure or death, whichever occurs first. Safety and effectiveness data for Edwards Lifesciences Carpentier-Edwards PERIMOUNT Plus Pericardial Bioprosthesis, Mitral Model 6900P from Protocol 98-1 will be used to generate a general comparison with the size 23mm Magna mitral valve data from this IDE protocol.
Study Population:	Male and female diagnosed with mitral heart valve disease and scheduled to undergo elective mitral valve replacement with a smaller bioprosthetic are eligible for participation in the study. Key Inclusion Criteria - Patient is 13 years of age or older; - Patient has mitral valve disease requiring planned surgical replacement; - Patient has provided written informed consent prior to mitral valve surgery; - Patient is willing to comply with specified follow-up evaluations. Key Exclusion Criteria - Patient has life expectancy < 12 months due to non-cardiac co-morbid conditions; - Patient has/had active endocarditis within the last 3 months; - Patient has a body surface area (BSA) >1.9 m^2; - Patient requires replacement of a native or previously

	implanted prosthetic tricuspid, pulmonic, or aortic valve; - Patient has/had prior aortic, tricuspid and/or pulmonary valve surgery, which included implant of a bioprosthetic valve or mechanical valve that will remain in situ.
Safety Endpoints:	The following adverse events will be reported for the safety analysis: - 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 to evaluate valve-related hemolysis collected preoperatively, at 6-month, 1-year, and every yearly follow-up visit will be analyzed and presented by time period.
Effectiveness Endpoints:	The following are the effectiveness endpoints: - Mean effective orifice area (EOA) at 1 year post-implant - Number and percentages of subjects in NYHA functional class I or II at 1 year post-implant Hemodynamic Performance The pre-procedure and 1-year post-procedure NYHA distribution (numbers and percentages of subjects) will be tabulated. Number and percentage of subjects in NYHA functional class I or II at 1 year post-implant will be reported. NYHA functional class will be obtained at each follow-up time-point, and the numbers and percentages of subjects who have improved in class, not changed in class, and worsened in class will be reported. Hemodynamic Performance at 1 year post implant:

	- Peak gradient - Mean gradient - Effective orifice area (EOA) index - Performance index - Cardiac output - Cardiac index - Severity of mitral regurgitation - Left ventricular mass regression(data collected for research; not required for endpoint evaluation) Quality of Life Survey (EQ-5D) at 6 and 12 months post-implant as compared to baseline measurements prior to implant.
General Statistical Methods	The format used to support the 3/26/02 approval of the size 29mm Edwards Lifesciences Prima Plus aortic valve, via P00007/S002 will serve as a guide for data presentation.
Principal Investigator:	[redacted]
Study Sponsor	[redacted]
Study Monitor	Edwards Lifesciences, LLC One Edwards Way, Irvine, CA 92614
DMC Chair:	[redacted]
Core Lab:	[redacted]

2 INTRODUCTION

2.1 CLINICAL BACKGROUND

2.1.1 DISEASE PROCESS

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] Mitral valvular heart disease is a condition that may include stenosis, regurgitation, or combination of the two, sometimes referred to as mixed disease.

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.[2] Other rare causes of mitral stenosis include congenital malformed valves, active infective endocarditis, massive annular calcium, and metabolic or enzymatic abnormalities.[2] 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, collagen-vascular disorders (lupus, scleroderma), or Marfan's or Marfan-like disorders.[3] 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.[4] 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]

2.1.2 ALTERNATIVE THERAPIES/TECHNIQUES

Diseased heart 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 implant 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 (constructed from synthetic material) or a tissue bioprosthetic valve (made primarily from animal tissue including bovine pericardium, or human valves from cadavers).

The Society of Thoracic Surgeons (STS) published an Executive Summary quantifying major cardiac surgical procedures performed in the United States throughout a 10 year period from 1998 to 2007. The data showed an average of 4,339 isolated mitral valve replacements are performed per year.[5] The Starr-Edwards ball-and-cage mitral valve was the first commercially available reliable device for mitral valve replacement.[6] This device was first implanted in a 52 year old patient in 1960. Since then, many generations of both mechanical and bioprosthetic valves have emerged. As the first, second and third generations of mechanical prosthetic valves were being developed; bioprosthetic replacement valves were simultaneously being developed. The advantages of bioprosthetic valves include a much lower frequency of thromboembolism; subsequently, long-term anticoagulation therapy can be avoided.[7] The third generation of these valves included pericardial valves which incorporated new technology aimed at improving valve longevity and hemodynamic function.[6]

Currently, there are no commercially approved bovine pericardial tissue mitral valves with the same or similar dimensions as the size 23 mm Magna mitral valve.

2.1.3 CONCOMITANT VALVE THERAPIES

Simultaneous replacement of the aortic valve is recommended by the ACC/AHA 2006 Guidelines for the Management of Patients with Valvular Heart Disease when patients are diagnosed with regurgitation or stenosis in the aortic valve when treatment by repair or valvuloplasty would not or did not have a therapeutic effect.[8] When both aortic and mitral valves are replaced, the prostheses chosen should both be tissue or mechanical to balance the need for anticoagulation and projected longevity.[9] Studies have shown that the implant of simultaneous tissue versus mechanical valves has no reduction in risk of valve-related morbidity, thromboembolism, or late death.[10, 11] The STS Executive Summary [redacted] indicated that 15% of patients undergoing mitral valve surgery in 2007 in the United States underwent simultaneous mitral and aortic valve replacement (1205/7883).[5]

2.2 STUDY PURPOSE

The purpose of this clinical trial is to obtain human clinical data in order to demonstrate that the size 23 mm Carpentier-Edwards PERIMOUNT Magna mitral pericardial valve, model 7000TFX, is a safe and effective replacement heart valve. Edwards has a successful commercial line and is introducing a smaller valve. This valve will herein be referred to as the "size 23 mm Magna mitral valve."

2.3 STUDY DEVICE

2.3.1 DEVICE DESCRIPTION

Edwards currently markets the Magna mitral valve in sizes 25 - 33 mm and has internationally sold more than 11,400 valves as of September 30, 2009. The Magna mitral valve has received the following approvals for sizes 25 - 33 mm as summarized in Table 1.

Table 1: Device Approvals

Region	Date of Approval
Europe	August 2005
Canada	November 2005
Australia	July 2008
US[1]	August 2008[2]

1 Currently being evaluated in a post-approval study
2 (P860057/S029)

The device to be studied in this investigation is the size 23 mm valve which is pictured below in Figure 1. The size 23 mm Magna mitral valve has the same design as the other currently approved model 7000TFX sizes. The size 23 mm Magna mitral valve is one size smaller than the size 25 mm Magna mitral valve approved by FDA in August 2008. The size 23 mm Magna mitral valve would be implanted in same size mitral annulus as the size 27 mm porcine Carpentier-Edwards Duraflex mitral low pressure valve, model 6625LP, as shown below in Table 2. The Duraflex valve was approved by FDA in September 1991.

Table 2: Valve dimension comparison

Dimension	Model 7000TFX, 23 mm	Model 6625LP, 27 mm
Tissue Annulus diameter (TAD)*	27 mm	27 mm
External Sewing Ring Diameter	34 mm	36 mm

* Note TAD corresponds to the "External Stent Post Diameter (Base)" in the size 23 mm Magna mitral valve IFU and the "Mounting Diameter (Annulus)" in the model 6625LP IFU.

Figure 1: Size 23 mm Magna mitral valve

The leaflets, of the size 23 mm Magna mitral valve, are composed of bovine pericardium. The valve leaflets are treated using the ThermaFix process. Bovine pericardium was selected for its superior intrinsic properties for valve manufacture, notably collagen content[12] and tolerance to high bending curvatures.[13] The bovine pericardium tissue is cross-linked using the Neutralogic fixation process in which the tissue is placed in a stress-free bath of buffered glutaraldehyde solution. The valve is then further treated using the Edwards ThermaFix process, which involves heat treatment of the tissue in glutaraldehyde, as well as exposure to ethanol and Polysorbate-80 (a surfactant). Glutaraldehyde is shown to both reduce the antigenicity of tissue xenograft valves and increase tissue stability.[14,15] During manufacturing, leaflet thickness is measured and leaflet deflection testing is conducted to characterize each leaflet for elasticity. Three leaflets matched for similar thickness and elasticity are then assembled by mounting them underneath the wireform frame to minimize commissural stress points.

The lightweight wireform frame is made of cobalt-chromium alloy chosen because of its superior spring efficiency, corrosion-resistance, and fatigue-resistance characteristics. The frame is designed to be compliant at the orifice as well as at the commissures. The frame is covered with a woven polyester fabric. The wireform frame of the size 23 mm Magna mitral valve is symmetrical and the three commissure supports (struts) are equally spaced.

The cobalt-chromium alloy band attached to a polyester film band surrounds the base of the wireform frame providing structural support for the orifice and enhancing radiological identification. In addition to maintaining the orifice shape during implant, the cobalt-chromium alloy band serves as a point of attachment for the sewing ring.

The model 7000TFX valve incorporate a sewing ring specifically designed for the mitral position. The sewing ring is uniquely scalloped along its anterior portion and

mimics the natural saddle shape of the native mitral valve anatomy. The ring is made of waffled silicone-rubber and is covered with a porous polytetrafluoroethylene cloth to facilitate tissue in-growth and encapsulation. Black suture markers on the anterior portion facilitate the orientation of the valve and help avoid obstruction of the left ventricular outflow tract by a strut. The design of the silicone waffle eases needle penetration and provides variable compliance. The waffle has wider cells along the posterior portion, where calcification or irregularities of the native mitral annulus are more frequent.[16] This results in a very compliant sewing ring that facilitates coaptation between the sewing ring and the mitral tissue bed. The width of the sewing ring allows for coverage of an irregular or calcified mitral annulus.

The valve is terminally sterilized in glutaraldehyde and packaged in a sealed jar packaging system consisting of the jar, sleeve, and clip. The finished valve with holder is suspended by a clip and a sleeve within the sealed jar containing glutaraldehyde.

2.3.2 Principle of Operation

The Magna mitral valve, with three leaflets, operates similarly to the native mitral valve, thereby preventing backflow from the left ventricle to the left atrium during systole. During normal valve functioning, the mitral valve leaflets open as a result of decreased ventricular pressure due to ventricular dilatation at diastole and increased pressure due to contraction of the left atrium and flow from the lungs. Blood flows through the open mitral valve from the left atrium to the left ventricle. Following the contraction of the left ventricle (ventricular systole), the mitral valve closes and prevents backflow of blood to the left atrium.

The asymmetric design of the Magna mitral valve mimics the mitral anatomy of the heart. This asymmetry optimizes annular conformity while reference markers delineate the outflow tract for hemodynamic positioning in the mitral annulus. The

valve has a wide sewing cuff with variable compliance that enhances the coaptive interface between cuff and mitral annular tissue while accommodating variability in suture technique.

2.3.3 ANCILLARY PRODUCTS

The ancillary instruments for use with the size 23 mm Magna mitral valve are the same as the ancillary instruments used for the Magna mitral valve, model 7000TFX, sizes 25-33 mm:

- Tricentrix holder system
- Carpentier-Edwards PERIMOUNT Magna mitral sizers, model 1177HP
- Sterilization trays, model TRAY1177HP
- Handles, models 1111 (universal), 1117 (mitral) and 1126 (single use)

All accessories are supplied non-sterile, except for the Tricentrix holder system which is supplied sterile attached to the sterile valve, and the handle, model 1126, that is supplied sterile and is for single use only. For information on sterilization of the other devices, reference the Instructions for Use included in the clinical protocol.

Only model 1177HP sizers in conjunction with an attached handle (model 1111, 1117 or 1126) must be used to determine the appropriate Magna mitral valve size. Model 1177HP sizers permit direct observation of their fit within the annulus and are provided for each available Magna mitral valve size. The barrel of the sizers indicates the external stent diameter at the tip. The lip of the sizers replicates the sewing ring of the valve, with its scalloped anterior portion and black markings, to better determine the outcomes of specific suture or subvalvular apparatus preservation techniques. The black marks on the lip replicate the black suture markers on the sewing ring. They delimit the anterior portion of the valve sewing ring which should be positioned across the anterior intercommissural portion of the native annulus, in order to avoid potential obstruction of the left ventricular outflow

tract area. Further details on use of the sizers are available in the Instructions for Use included in the clinical protocol.

The holder/handle assembly consists of two components: the Tricentrix holder system that is mounted to the valve, and a handle (model 1111, 1117 or 1126) that is attached to the Tricentrix holder system at the time of surgery. The Tricentrix holder is designed to minimize suture or chordae entrapment, ease insertion and increase leaflet visibility. Handle model 1111 is a universal stainless steel handle that can be used with other Edwards Lifesciences prostheses. Handle model 1117 has been designed specifically for the mitral position: it is longer to provide an easier access to the mitral valve in the case of a difficult exposure, a deep thoracic cage or a minimally invasive access. It's nitinol shaft is more flexible than stainless steel. With each sterilization cycle, it returns to its original straight shape, for an easier attachment to the sizer or holder. Models 1111 and 1117 are both reusable handles. Handle 1126 has a long and thin stainless steel shaft and is intended for single use only.

The Magna mitral valve with the attached Tricentrix holder and handle model 1117 is shown in **Figure 2**.

Figure 2 – Carpentier-Edwards PERIMOUNT Magna mitral pericardial valve, model 7000TFX, with attached Tricentrix holder and handle model 1117.

2.3.4 Clinical Utility

The size 23 mm Magna mitral valve is indicated for patients who require replacement of their native or prosthetic mitral valve. Replacement of a diseased mitral valve restores left heart function.

2.3.5 Prior Testing

Information is available in the Clinical Investigator's Brochure (Report of Prior Investigations).

2.3.6 Prior Clinical Studies

Information is available in the Clinical Investigator's Brochure (Report of Prior Investigations).

2.3.7 Anticipated Changes to the Device

Minor changes may be made to the device or packaging components that may have minimal effect on the safety and effectiveness. These changes will be evaluated for their impact, if any, on the study.

3 RISK ANALYSIS

3.1 RISKS

3.1.1 PATIENT POPULATION

Refer to sections 5 "Study Design" and 6.1 "Demographic and Clinical Characteristics."

3.1.2 RISKS ASSOCIATED WITH THE SIZE 23 MM MAGNA MITRAL VALVE

The following risks, compiled from the literature, are potentially associated with the use of bioprosthetic heart valves include, including the size 23 mm Magna mitral valve:

- Endocarditis
- Fracture of the cobalt-chromium alloy wireform frame
- Malfunctions of the valve due to distortion at implant
- Myocardial infarction
- Prosthesis leaflet entrapment
- Prosthesis nonstructural dysfunction
- Prosthesis pannus
- Prosthesis perivalvular leak
- Prosthesis regurgitation
- Prosthesis stenosis
- Prosthesis structural deterioration
- Prosthesis thrombosis
- Stroke
- Thromboembolism
- Ventricular perforation by stent posts

It is possible that these risks could lead to:

- Reoperation
- Explantation
- Permanent disability
- Death

3.1.3 RISKS ASSOCIATED WITH MITRAL VALVE REPLACEMENT

The following risks, compiled from the literature, are potentially associated with mitral valve replacement surgery:

- Angina
- Bleeding
- Cardiac Arrest
- Cardiac arrhythmias, which may include conduction disturbances
- Diabetes,
- Heart failure
- Hemolysis
- Hemolytic anemia
- Hypertension / Hypotension
- Infection,
- Myocardial failure,
- Multisystem organ failure,
- Non-cerebral blood clot
- Pericardial effusion or cardiac tamponade
- Respiratory failure in the chronically ill, debilitated individual,
- Stroke,
- Transient Ischemic Attack
- Ventricular rupture

It is possible that these risks could lead to:

- Reoperation
- Explantation
- Permanent disability
- Death

3.2 MINIMIZING RISKS

The design risk management process, according to EN ISO 14971, used for the model 7000TFX valve identified design, manufacturing process, and application risks. These risks were mitigated to be as low as reasonably possible. Further risks may be identified during the post market surveillance of the valve and similar valves, and necessary mitigations will be taken.

During the clinical study, there are strict inclusion/exclusion criteria for patient participation. In addition, a sizer for the size 23 mm Magna mitral valve is available. This sizer is marked for both size and EOA to provide clinical relevant information during surgery and to help avoid oversizing. To evaluate the actual risk of 23 mm

Magna mitral valve, this study will gather data to trend the relationship between the valve size and complication rate.

An analysis of the relationship between valve size and the occurrence of various complications was made to assess the potential risk of the size 23 mm Magna mitral valve. Since very limited Magna mitral valve data are available, this analysis studied the relationship between complication rates and valve size from historical studies of similar valves. Data from the following three studies were used:

- Study 89-17: *Carpentier-Edwards Duraflex Low Pressure (CELP) Porcine Mitral Heart Valve* models *6625 LP* and *6625-ESR-LP.*
- Study 98-1: *Carpentier-Edwards PERIMOUNT Plus Pericardial Mitral Heart Valve* model *6900P.*
- Study 2000-05 *Carpentier-Edwards PERIMOUNT Pericardial Mitral Heart Valve* model *6900.*

[redacted]

The logistic regression analyses indicate that none of the complications shows a significantly increased trend as the valve size (TAD) decreased. The estimated complication rates decrease for most of the complications. Therefore, there is minimal risk that the complication rates on the size 23 mm Magna mitral valve will be significantly increased from that of approved Magna mitral valve sizes.

In order to further minimize risks, the valve will be implanted only by trained cardiac surgeons, familiar with mitral valve replacement. Qualified personnel from Edwards will provide training to the physicians and OR staff regarding the use of this valve and the details of the clinical protocol prior to enrollment of the first patient. During the clinical study, there are strict inclusion/exclusion criteria for patient participation developed in accordance with the risk analysis, valve size and intended use. In addition, a sizer for the 23 mm Magna mitral valve is provided. This sizer, like the

sizers for the Magna mitral valve sizes 25 through 33 mm, is marked for both size and EOA to provide clinically relevant information during surgery and to ensure correct sizing. If a patient who has been consented through the preoperative screening process is found, during the procedure, to require a different size valve, the patient will be terminated from the study and will receive the valve size most appropriate for their anatomy. Finally, all data will be reviewed by a Data Safety Monitoring Board at regular intervals throughout the study to ensure patient safety.

3.3 BENEFITS

As mentioned above, the size 23 mm Magna mitral valve is one size smaller than the size 25 mm Magna mitral valve approved by FDA in August 2008. The size 23 mm Magna mitral valve would be implanted in same size mitral annulus as the size 27 mm porcine Carpentier-Edwards Duraflex mitral low pressure valve, model 6625LP. The Duraflex valve was approved by FDA in September 1991.

Based on Edwards implant data, 29% of model 6625LP bioprostheses implanted from 1991 to 2004 were size 27 mm. The availability of the size 23 mm Magna mitral valve would directly benefit these patients by offering the long-term durability of a pericardial valve.[17, 23]

There are no guaranteed benefits from participation in this study. Study subjects may benefit from participation and it is possible that future subjects may benefit based upon the results of the study.

3.4 STUDY JUSTIFICATION AND SCIENTIFIC SOUNDNESS

The benefits identified in Section 3.3 outweigh the potential risks identified in Section 3.1 to participating subjects.

4 STUDY OBJECTIVES

The objective of this study is to evaluate the safety and effectiveness of the size 23 mm Magna mitral valve in subjects with mitral heart valve disease requiring

replacement with a valve. Data collected in this study will be used to support the premarket application supplement to P860057 for approval of the 23 mm size in the United States. This study may also be used to support device approval in other countries as applicable.

4.1 SAFETY ENDPOINTS

Safety Endpoints include 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

Rates of the above referenced adverse events within the early (within 30 days of implant) post-operative period, calculated as the number of events divided by the number of subjects, will be reported.

The calculation of late rates and standard errors for the safety endpoints will be based on actuarial (Kaplan-Meier) methods in addition to rates based on cumulative patient-years.
Blood Data to evaluate valve-related hemolysis collected preoperatively, at 6-month, 1-year, and every yearly follow-up visit will be analyzed and presented by time period.

4.2 EFFECTIVENESS ENDPOINTS

Effectiveness Endpoints include the following:

- Mean effective orifice area (EOA) at 1 year post-implant, and

- Number and percentage of subjects in NYHA functional class I or II at 1 year post-implant will be reported

Hemodynamic Performance

The following hemodynamic performance parameters, measured 1 year post implant:

- Peak gradient
- Mean gradient
- Effective orifice area (EOA) index
- Performance index
- Cardiac output
- Cardiac index
- Severity of mitral regurgitation
- Left ventricular mass regression

The pre-procedure and 1 year post-procedure NYHA distribution (numbers and percentages of subjects) will be tabulated. Number and percentage of subjects in NYHA functional class I or II at 1year post-implant will be reported. NYHA functional class will be obtained at each follow-up time-point, and the numbers and percentages of subjects who have improved in class, not changed in class, and worsened in class will be reported.

Quality of Life Survey (EQ-5D) [redacted] at 6 and 12 months post implant will be compared to baseline measurements prior to implant.

5 STUDY DESIGN

This is a prospective, non-randomized, multi-site descriptive study. A minimum of 15 and up to 20 subjects will be implanted at a minimum of 2 and up to 8 participating investigational sites, within the US and internationally. Subject participation will last for 5 years. Subjects will be assessed for clinical follow-up at the following intervals: pre study procedure, at implant, index hospitalization discharge or within 30 days of implant, whichever comes first, 6 months post

procedure, 1 year post procedure, and annually thereafter until 5 years post procedure or death, whichever occurs first.

6 SUBJECT POPULATION

6.1 DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Male and female subjects aged 13 and older diagnosed with mitral heart valve disease and scheduled to undergo elective mitral valve replacement with a smaller bioprosthetic are eligible for participation in the study.

6.2 INCLUSION CRITERIA

The Principal Investigator at the site has the responsibility of screening potential subjects to determine if the patients meet all the inclusion criteria. The following are requirements for entry into the study:

1. Patient has mitral valve disease requiring a planned surgical replacement;
2. Patient has provided written informed consent prior to mitral valve surgery;
3. Patient is expected to survive surgery and be discharged;
4. Patient is willing to comply with specified follow-up evaluations;
5. Patient is 13 years of age or older.

6.3 EXCLUSION CRITERIA

Potential subjects must be excluded if any of the exclusion criteria is present. The following are the criteria for exclusion from participating in the study:

1. Patient has life expectancy < 12 months due to non-cardiac co-morbid conditions;
2. Patient has/had active endocarditis within the last 3 months*;
3. Patient requires replacement of a native or previously implanted prosthetic tricuspid, pulmonic or aortic valve;
4. Patient was previously enrolled and implanted in the study;

5. Patient has/had prior aortic, tricuspid and/or pulmonary valve surgery, which included implant of a bioprosthetic valve or mechanical valve that will remain in situ;
6. Patient has a body surface area (BSA) > 1.9 m^2 **
7. Female patients who are pregnant, planning to become pregnant, or lactating;
8. Patient has a documented history of substance (drug or alcohol) abuse within the 5 years prior to scheduled implant ;
9. Patient is currently a prison inmate;
10. Patient is currently participating in an investigational drug or another device study;
11. Patient is undergoing renal dialysis for chronic renal failure or has hyperparathyroidism;
12. Patient has active myocarditis;
13. Patient has had an acute preoperative neurological deficit, myocardial infarction, or cardiac event and has not returned to baseline or stabilized $\geq$ 30 days prior to the planned valve implant surgery;
14. Patient has an abnormality such as an aortic aneurysm (e.g. due to cystic medial necrosis or Marfan's syndrome), aortic dissection, or ventricular aneurysm that might place the patient at high risk for surgical complications.

* Note: The 3 month window for active endocarditis is determined from the implant date.

** Note: BSA (m^2) The Mosteller formula will be used as the Standard to calculate body surface area.

$$BSA\ (m)^2 = \left(\frac{Height\ (cm)\ x\ Weight\ (kg)}{3600}\right)^{1/2}$$

6.4 WITHDRAWAL CRITERIA AND PROCEDURES

Subjects may voluntarily withdraw consent at any time during the study with no loss of benefits or penalty. Subjects will be exempt from follow-up after withdrawing from the study. The Investigator may withdraw any subject due to any of the following conditions:

1. Participation in the study may be contrary to the subject's medical treatment;
2. It is discovered that the subject is participating in another investigational study.

The Investigator will document the withdrawal of study subjects and notify Edwards Lifesciences (the Sponsor) within 5 working days. Additional subjects may be enrolled and implanted with the device to replace those who withdraw from the study.

7 INVESTIGATIONAL DEVICE MANAGEMENT

7.1 DEVICE SHIPMENTS

Once Edwards's has obtained FDA clearance to proceed with the study, the site has obtained IRB approval, a signed Investigator Study Agreement and Clinical Study Agreement is in place, and the Site Initiation Visit, including Principal Investigator training, has been completed the initial size 23 mm Magna mitral valve will be shipped to the site. Additional valves will be sent to the site as valves are used or as needed.

7.2 INVENTORY AND ACCOUNTABILITY RECORDS

All size 23 mm Magna mitral valve shipments will have inventory and shipment records. Devices may be hand carried to participating sites by Edwards' personnel and will be accompanied by delivery of investigational product documentation. The Principal Investigator(s) or designee will account for and monitor inventory of the

device. Both the investigational site and Edwards Lifesciences will have copies of device shipment records.

The Investigator will maintain a Device Accountability log on all size 23 mm Magna mitral valve received for use during this study. The log will be kept with the study documents and will be available for review during sponsor monitoring visits. Documentation on the log will include:

1. Serial number
2. Lot number
3. Date of receipt
4. Device Disposition
5. Date Device Implanted
6. Subject study identification number
7. Returned goods authorization (RGA) number (if applicable).

7.3 DEVICE STORAGE

The size 23 mm Magna mitral valve inventory will be stored in a controlled, cool, dry and clean area. This area must be secure and only accessible to the Principal Investigator(s), his/her co-Investigators or approved designee. Only surgeons identified in the Clinical Study Agreement and Delegation of Authority Log on file may implant this investigational device.

7.4 DEVICE RETURN

The Principal Investigator(s) will be notified in writing upon termination of the study. All unused size 23 mm Magna mitral valve will be returned upon receipt of this notice. In the event that a device package is opened, but the device is not used, the Principal Investigator is to return the product. The Investigator's copy of the Device Accountability log must document any unused devices that have been returned. The valve should be placed in a container with a suitable histological fixative such as 10% formalin or 2% glutaraldehyde immediately and returned to Edwards. Refrigeration

is not necessary under these circumstances. Contact Edwards Clinical Research for additional instructions.

8 PROCEDURES AND METHODS

8.1 ORIENTATION OF INVESTIGATIONAL SITE PERSONNEL

Principal Investigator(s) and support staff will be trained by an Edwards Lifesciences representative on the use of the device, the Protocol, Case Report Forms , GCP and ICH Guidelines and other study documents as applicable. Training will be documented on a training form provided by Edwards Lifesciences, which all trainees must sign and date. In addition, a "Delegation of Authority Form" will be completed at each investigational site designating which individuals are allowed to perform specific study related tasks.

8.2 INFORMED CONSENT

Subjects who are eligible for the study should be explained the following:

1. the background of the study;
2. the potential benefits and risks of the procedures involved;
3. study follow-up requirements

The subject should be given the opportunity and ample time to read and understand the Informed Consent in its entirety to make an informed decision. The subject must sign and date the institution's Institutional Review Board (IRB) approved Informed Consent prior to participation or according to regulations regarding Informed Consent for subjects unable to sign a consent form. The Investigator or designee must sign and date the consent as well. Failure to provide written Informed Consent renders the subject ineligible for the study. [redacted]

8.3 SUBJECT SCREENING

All patients admitted for mitral valve replacement should be screened for study eligibility. A Screening Log will be provided to the investigational sites to maintain a cumulative log of all screened patients admitted for mitral valve replacement. A member of the research team at the investigational site should review the subject's eligibility prior to enrolling potential subjects. If it is deemed that a subject is not eligible for participation in the study, a reason supporting the disqualification of the subject must be entered on the screening log. Any patients that are screen failures due to the need of mitral valve repair may be re-screened at a later time should mitral valve replacement be needed. Re-screened patients must be re-entered on the Screening Log. The Screening Log should be duly completed and is to be sent to the Sponsor on a regular basis.

8.4 SUBJECT ENROLLMENT

All subjects who meet eligibility requirements will be asked to participate. A subject will be considered enrolled into the study and assigned a subject number after signing the informed consent.

8.5 BASELINE – PRIOR TO PROCEDURE

A baseline evaluation is to be conducted within 1 month prior to device implant. The baseline evaluation will include:

1. History and physical examination
2. Screening for clinical inclusion and exclusion criteria
3. Baseline blood studies (Complete blood count and Plasma Free Hemoglobin)
4. Baseline echocardiography per protocol **
5. Baseline 12 lead electrocardiogram
6. NYHA Functional Class
7. Quality of Life Survey (EQ-5D)

** Baseline echocardiography must be completed within 6 months of study procedure.

Baseline information, findings, and results to be recorded are identified in Table 3.

Table 3: Baseline Evaluation

General Information	Clinical Information	Blood Studies	Echocardiography
Subject ID Number Subject Initials Birth Date Subject Sex Physical Assessment	Cardiac Rhythm Cardiovascular Risk Factors Cardiovascular Conditions Non-Cardiovascular Conditions Previous Procedures / Interventions	Blood Draw Date White Blood Cell Count Red Blood Cell Count Hemoglobin Hematocrit Platelet Count Plasma Free Hemoglobin	Date of exam 2D measurements[1] Ejection fraction Mitral valve assessment[2] LVOT assessment Aortic Valve assessment[3] Other Variables[4] Left Ventricular Assessment[5]

Subjects who are enrolled in the study (signed an informed consent) but do not receive a device may be exited from the study and exempt from data collection after the baseline evaluation. The investigational site must retain the subject's signed informed consent and all other source documents regarding the Baseline procedures. Verification that the subject(s) signed the informed consent will occur during the on-site monitoring visit.

8.6 PROCEDURE

The surgical technique employed will be that developed and perfected by the Investigator in his/her normal practice of cardiac surgery. The Magna mitral sizer must be used intra-operatively to confirm that the size 23 mm Magna mitral valve

[1] 2-Dimensional measurements are Interventricular Septal thickness (IVS), Left Ventricular Internal Diameter in diastole (LVEDD), end diastolic Posterior Wall thickness (PW), Left Ventricular Internal Diameter in systole (LVESD), Left Atrium (LA), Left Ventricular Outflow Tract (LVOT)
[2] Mitral valve assessment includes the following parameters Mitral Valve Peak Flow Velocity (VmaxMV), Mean Pressure Gradient: Mitral Valve (MPG MV), Peak Pressure Gradient: Mitral Valve (PPG MV), Mitral Valve Time Velocity Integral (TVI MV), presence of Stenosis, presence and degree of Regurgitation
[3] Aortic valve assessment includes the following parameters Aortic Valve Peak Flow Velocity (VmaxAV), Mean Pressure Gradient: Aortic Valve (MPG AV), Aortic Valve Time Velocity Integral (TVI AV)
[4] Other variables includes the following parameters which are calculated by the echo machine Stroke Volume (SV), Cardiac Output (CO), Cardiac Index (CI), Effective Orifice Area: Mitral Valve (EOA MV)
[5] Left ventricular Assessment includes presence of wall motion abnormality, thrombi, pericardial effusion and other relevant clinical findings

can be implanted (TAD of valve is 27 mm). If the operator determines during the procedure that the subject is ineligible to receive the study valve, the subject will not be considered part of the study cohort and data after baseline evaluation will not be collected. Special attention should be given to proper orientation of the size 23 mm Magna mitral valve. Investigators are expected to be familiar with Precautions and Technique information described in the Instructions for Use [redacted] prior to use of the size 23 mm Magna mitral valve.

Procedural information, findings, results and size23mmMagna mitral valve identification information to be recorded is identified in Table 4.

Table 4: Procedural Information

General Information	Clinical Information
Subject ID Number Subject Initials Date of Procedure Implanting surgeon Device serial number	Etiology Surgical approach Diagnosis for replacement Valve implant Condition of the annulus Debridement procedure Condition of the valve being replaced Preservation of Subvalvular apparatus Concomitant procedures Intraoperative Adverse Events

8.7 POST-PROCEDURE

8.7.1 POST-PROCEDURE CARE

Bioprosthetic heart valve recipients should be maintained on anticoagulant therapy (except when contraindicated) during the initial healing stages after implant, approximately 2 to 3 months. Anticoagulants should then be discontinued over a period of 10 days, except in those patients for whom indefinite anticoagulant protection is indicated, i.e., in the absence of sinus rhythm and in patients with a dilated left atrium, calcification of the atrial wall, or history of previous atrial

thrombus. However, the appropriate anticoagulation therapy must be determined on an individual basis.[18]

8.7.2 DISCHARGE

At discharge, the Investigator or designee will provide the subject with an Implant Data Card [redacted]. The Implant Data Card must be completed with the required information (i.e., the name of the Investigator, the contact information and the name of the investigational site). The Investigator or designee should also obtain from the device package two stickers with the implanted Magna mitral serial number and affix one sticker on 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.

Documentation of alternate contact information such as referring physicians, and relatives should be collected in the event that the subject cannot be reached at his/her primary residence. The research coordinator of the study should record any planned extended or seasonal absence from the subject's place of residence and take into consideration when planning follow up visits. A clinical evaluation including echocardiography of the subject will be performed at discharge from the hospital or within 30 days from implant, whichever comes first. Echocardiography will be sent to the Core Lab for analysis [redacted]. Medical information, findings, and results information to be recorded is identified in Table 5.

Table 5: Discharge Evaluation

General Information	Clinical Information	Echocardiography
Subject ID Number Subject Initials	Subject status Cardiac Rhythm Physical Assessment Coagulation Profile Antithromboembolic therapy Adverse Events	Date of exam 2D measurements[6] Ejection fraction Mitral valve assessment[7] LVOT assessment Aortic Valve assessment[8] Other Variables[9] Left Ventricular Assessment[10]

DISCHARGE ECHCARDIOGRAPHY

Subjects, who are not discharged within 10 days post procedure must have an echocardiogram to further assess placement and performance of the bioprosthesis. This echocardiogram is required to complete the evaluation of procedural success. Those subjects will not require an additional echocardiogram at discharge.

8.7.3 FOLLOW-UP ASSESSMENTS

Post-procedure clinical evaluation will be performed on all subjects at 6 months post procedure, 1 year post procedure, and annually thereafter until 5 years post procedure, adhering to the visit windows in Table 6.

Table 6: Visit windows

Interval	Window
6 months post procedure	3-6 months
1 year post procedure	± 1 month of annual visit
Subsequent annual post procedure	± 2 month of annual visit

During the clinical evaluation of the subject, medical information, findings, and results will be recorded. Blood will be drawn at 6 months post procedure, 1 year

[6] 2-Dimensional measurements are Interventricular Septal thickness (IVS), Left Ventricular Internal Diameter in diastole (LVEDD), end diastolic Posterior Wall thickness (PW), Left Ventricular Internal Diameter in systole (LVESD), Left Atrium (LA), Left Ventricular Outflow Tract (LVOT)
[7] Mitral valve assessment includes the following parameters Mitral Valve Peak Flow Velocity (VmaxMV), Mean Pressure Gradient: Mitral Valve (MPG MV), Peak Pressure Gradient: Mitral Valve (PPG MV), Mitral Valve Time Velocity Integral (TVI MV), presence of Stenosis, presence and degree of Regurgitation
[8] Aortic valve assessment includes the following parameters Aortic Valve Peak Flow Velocity (VmaxAV), Mean Pressure Gradient: Aortic Valve (MPG AV), Aortic Valve Time Velocity Integral (TVI AV)
[9] Other variables includes the following parameters which are calculated by the echo machine Stroke Volume (SV), Cardiac Output (CO), Cardiac Index (CI), Effective Orifice Area: Mitral Valve (EOA MV)
[10] Left ventricular Assessment includes presence of wall motion abnormality, thrombi, pericardial effusion and other relevant clinical findings

post procedure, and annually thereafter until 5 years post procedure. A Quality of Life survey will be required at 6 month and 12 month post procedure. Echocardiography will be required 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years post procedure and will be evaluated by an independent Core Lab. Information to be recorded is identified in Table 7.

Table 7: Follow-up Evaluation

General Information	Clinical Information	Blood Studies	Echocardiography
Subject ID Number Subject Initials Date of Evaluation Visit Status	Patient Status Physical Assessment Cardiac Rhythm NYHA Functional Class Antithromboembolic therapy Adverse Events	Blood Draw Date White Blood Cell Count Red Blood Cell Count Hemoglobin Hematocrit Platelet Count Plasma Free Hemoglobin	Date of exam 2D measurements[11] Ejection fraction Mitral valve assessment[12] LVOT assessment Aortic Valve assessment[13] Other Variables[14] Left Ventricular Assessment[15]

At each postoperative assessment, the Investigator(s) will need to determine the subject's availability for future follow-up. If any subject needs to be seen at a time other than a regularly scheduled follow-up visit, the same information as described above will be documented by the Investigator and indicated as an interim visit. Follow-up information obtained by physicians outside of the investigational site should be obtained by the Investigator.

[11] 2-Dimensional measurements are Interventricular Septal thickness (IVS), Left Ventricular Internal Diameter in diastole (LVEDD), end diastolic Posterior Wall thickness (PW), Left Ventricular Internal Diameter in systole (LVESD), Left Atrium (LA), Left Ventricular Outflow Tract (LVOT)
[12] Mitral valve assessment includes the following parameters Mitral Valve Peak Flow Velocity (VmaxMV), Mean Pressure Gradient: Mitral Valve (MPG MV), Peak Pressure Gradient: Mitral Valve (PPG MV), Mitral Valve Time Velocity Integral (TVI MV), presence of Stenosis, presence and degree of Regurgitation
[13] Aortic valve assessment includes the following parameters Aortic Valve Peak Flow Velocity (VmaxAV), Mean Pressure Gradient: Aortic Valve (MPG AV), Aortic Valve Time Velocity Integral (TVI AV)
[14] Other variables includes the following parameters which are calculated by the echo machine Stroke Volume (SV), Cardiac Output (CO), Cardiac Index (CI), Effective Orifice Area: Mitral Valve (EOA MV)
[15] Left ventricular Assessment includes presence of wall motion abnormality, thrombi, pericardial effusion and other relevant clinical findings

The Investigator(s) will make every attempt to follow the subjects and will document the information gathered during the follow-up visits on the Case Report Forms [redacted]. Subjects will be informed by the Investigator(s) about the importance of returning for scheduled follow-up visits even if they are not having any problems. Subjects will also be directed to communicate any address or telephone number changes.

8.8 ECHOCARDIOGRAM EVALUATION

Echocardiograms will be evaluated as described in the Echo Protocol (Section 17.8).

8.9 MISSED SUBJECT VISITS

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

If a subject cannot be reached for a follow-up visit, the Investigator will document on the CRF, the efforts undertaken to contact the subject or the subject's primary health care provider. These efforts should include 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. Subjects who miss a visit will not be considered withdrawn. At the next visit interval, the Investigator and/or designee will attempt to contact the subject again for follow-up. Should this attempt to contact the subject fail, a family member should be contacted in addition to the subject. Subjects who miss 2 sequential follow-up visits will be considered lost to follow-up at the second missed visit and exempt from 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 as permitted by local laws.

8.10 CLINICAL STUDY TERMINATION

The Principal Investigator(s) will be notified in writing upon termination of the study. Edwards retains the right to suspend or terminate this clinical study at any time. Safety and review committees associated with the study may recommend termination should safety concerns warrant such action. Upon study termination, the Investigator will contact the study subjects to perform a final follow-up assessment. Subjects should continue seeing their physicians as part of routine clinical follow-up after heart valve replacement surgery.

9 DATA COLLECTION AND REPORTING

9.1 DATA COLLECTION METHODS

All required data for this study are to be collected with standardized Case Report Forms (CRFs) for individual subjects; [redacted]. The paper CRF forms must be completed, signed by the Principal Investigator or designee and submitted to the Sponsor.

Research coordinators at each clinical site will perform primary data collection drawn from hospital chart and operator worksheet (source document) reviews. CRFs must be kept current to reflect subject status during the course of the study.

Case Report Form Instructions will be provided assist the Investigator(s) and appropriate site staff in the completion of the required CRFs.

9.2 SOURCE DOCUMENTATION REQUIREMENTS

Regulations require that Investigators maintain information in the study subject's medical records that corroborate data collected on the CRFs. In order to comply with these regulatory requirements, all required data for this study is to be recorded in the subject's medical chart for source documentation and data verification as follows:

1. Medical history and physical condition of the study subject before involvement in the study sufficient to verify protocol entry criteria
2. Dated and signed notes in the subject's medical record on the date of entry into the study.
3. Dated and signed notes from each study subject visit with reference to the CRFs for further information, if appropriate (for specific results of procedures and exams).
4. Notations on abnormal lab results and adverse events reported and their resolution.
5. Notes regarding concomitant medications taken during the study.
6. Study subject's condition upon completion of or withdrawal from the study.

9.3 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

Because of the potential for errors, inaccuracies, and illegibility in transcribing data into CRFs, originals or photocopies of all relevant procedural records and reports, post-procedural examinations, laboratory and other test results may be kept on file in the Investigator's subject study files. CRFs and copies of test results must be available at all times for inspection by the study monitor.

Data Management personnel will employ a full-featured relational Oracle database on a central server, networked to data entry and data analytical workstations. Conventional data verification sub-routines will be extensively programmed to test entry and logical errors, while all individual (Subject-based) CRFs will be linked for cross-reference. Periodic analysis of each data field (across cases) will be performed in order to examine the expected distributions of data and to identify outliers for possible data entry errors.

10 ADVERSE EVENT REPORTING

All types of adverse events (AEs) will be reported by the Investigator and reviewed by the Sponsor in compliance with applicable regulations. Adverse event information will be collected from the point of implant. Adverse event information including but not limited to, a description event, date of onset, and relationship to device will be recorded on the CRF by the Investigator or research coordinator. Adverse events will be followed until they are adequately resolved or explained.

10.1 ADVERSE EVENT

An adverse event is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

10.2 SERIOUS ADVERSE EVENT

A serious adverse event is defined as any untoward medical occurrence that:

- Leads to death,
- Leads to a serious deterioration in the health of the subject that:
    - Results in life-threatening illness or injury;
    - Results in permanent impairment of a body structure or a body function;
    - Requires inpatient hospitalization or prolongation of existing hospitalization;
    - Results in medical or surgical intervention to prevent permanent impairment to body structure or a body function;
- Leads to fetal distress, fetal death, or a congenital abnormality or birth defect.

All Serious Adverse Events (SAE) must be reported to the Sponsor within one business day of the Investigator becoming aware of the event. **Notification should be done via email to HVTClinicalResearch@edwards.com or faxed to 949-809-5610.** SAE reports must include but are not limited to the following information:

- Identifiable subject number;
- Identifiable reporter;
- Adverse event description;
- Date of onset;
- Relationship to device.
- Relationship to procedure

SAEs will be followed until they are adequately resolved or explained. The Investigator(s) will report any SAEs to their local Institutional Review Board (IRB) in accordance with the IRB's requirements.

10.3 UNANTICIPATED ADVERSE DEVICE EFFECT

Unanticipated adverse device effect (UADE) is defined in 21 CFR 812 as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the Clinical Investigator's Brochure (Report of Prior Investigations), Clinical Protocol, or Instructions for Use, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

The Investigator(s) will report any UADEs to Edwards Clinical Research within one business day of occurrence or knowledge of the device related event. **Notification should be done via email to HVTClinicalResearch@edwards.com or faxed to 949-809-5610.** In addition, sites will report all UADEs to their local Institutional Review Board (IRB) in accordance with the IRB's requirements.

UADE reports must include but are not limited to the following information:

- Identifiable subject number;
- Identifiable reporter;
- A description of the event;
- Date of onset;
- Relationship to device.

UADEs will be followed until they are adequately resolved or explained. The Investigator(s) will report any UADE to their local Institutional Review Board (IRB) in accordance with the IRB's requirements.

10.4 DEATHS AND DEVICE EXPLANTS

10.4.1 SUBJECT DEATHS

In the event of subject death, every effort must 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 study device will be determined by the Principal Investigator. Copies of available autopsy report and/or a death summary must be sent to Edwards.

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

10.4.2 DEVICE EXPLANTS

In the event a device is explanted, every effort must be made to obtain a copy of the explant procedure report, as applicable. Information on the cause of explant and its relationship to the study device will be determined by the Principal Investigator and recorded. Copies of an available explant report must be sent to Edwards.

Explanted devices should be returned to Edwards for analysis. Return kits for devices will be provided upon request by the clinical monitor.

The explanted valve will be evaluated according to Edwards' quality procedure QCOPG3009: Implantable Products Evaluation Procedure [redacted].

11 STATISTICAL ANALYSIS

The safety and effectiveness endpoints of the data obtained from this study will be summarized using descriptive statistics. Safety and effectiveness data for Edwards Lifesciences Carpentier-Edwards PERIMOUNT Plus Pericardial Bioprosthesis, Mitral Model 6900P from Protocol 98-1 will be used to generate a general comparison with the size 23mm Magna mitral valve data from this IDE protocol.

ANALYSIS POPULATION

The primary safety and effectiveness analyses will include all the implanted subjects. All the data collected up to the point of the explant or expirations will be included in the safety and effectiveness analyses.

11.1 SAFETY ANALYSIS

11.1.1 SAFETY ENDPOINTS

The following adverse events will be reported for the safety analysis:

- Thromboembolism
- Valve thrombosis
- All hemorrhage
- Major hemorrhage
- All perivalvular leaks
- Major perivalvular leak
- Endocarditis
- Hemolysis
- Structural valve deterioration
- Non-structural valve dysfunction

- Reoperation
- Explant
- Death
- Valve-related death.

Rates of the above referenced adverse events within the early (within 30 days of implant) post-operative period, calculated as the number of events divided by the number of subjects, will be reported.

The calculation of late rates and standard errors for the safety endpoints will be based on actuarial (Kaplan-Meier) methods in addition to rates based on cumulative patient-years.

11.1.1.1 Time to Death, Re-operation, and Explant
Times to re-operation, explants and death are listed in Table 8below:

Table 8: Times to Re-operation, Explants and Deaths

Event	Starting point	End point
Re-operation	Implant Date	Re-operation Date*
Explant	Implant Date	Explant Date*
Death	Implant Date	Expiration Date

* Time to first explant or re-operation will be calculated for those subjects requiring multiple explants or re-operations. Analyses of “time to explants” and “time to re-operation” will also be stratified by outcomes--fatal versus non-fatal events.

11.1.1.2 Blood Data
Blood data (red blood count, white blood count, hematocrit, hemoglobin, platelet count, and plasma free hemoglobin) 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 interval will also be reported.

11.2 EFFECTIVENESS ANALYSIS

11.2.1 EFFECTIVENESS ENDPOINTS

Mean effective orifice area (EOA) at 1 year post-implant will be reported. The pre-procedure and 1 year post-procedure NYHA distribution (numbers and percentages of subjects) will be tabulated. Number and percentage of subjects in NYHA functional class I or II at 1 year post-implant will be reported. NYHA functional class will be obtained at each follow-up time-point, and the numbers and percentages of subjects who have improved in class, not changed in class, and worsened in class will be reported.

11.2.1.1 Hemodynamic Performance

Echocardiography data will be obtained preoperatively, at discharge, 6-months and 1 year, 2 year, 4 year, and 5 year follow-up visits. The echocardiographic hemodynamic parameters to be evaluated are peak gradient, mean gradient, effective orifice area (EOA), EOA index, performance index, cardiac output, cardiac index, left ventricular mass regression (data collected for research; not required for endpoint evaluation), and valvular regurgitation. Descriptive statistics for the continuous echo variables and change from baseline (e.g. mean, standard deviation, and range) categorized by follow up time intervals will be reported. Regurgitation data will be summarized by frequencies at each pre-procedure severity level.

11.2.1.2 Quality of Life

The pre-procedure, 6 months, and 12 months post-procedure EQ-D5 survey will be summarized.

11.3 ANALYSIS SOFTWARE

Unless otherwise specified, the analyses will be performed using SAS version 9.0 or the latest release generally available at the time of analysis.

12 MONITORING

12.1 MONITORING METHODS

A study monitor will be assigned to monitor the progress of the study by Edwards. The study monitor will remain in close contact with each investigational site throughout the duration of the study to provide any needed materials, or answer any questions. The study monitor will be responsible for reviewing CRFs and visiting each investigational site periodically to observe study progress and compliance with study protocol.

Monitoring visits will be scheduled throughout the duration of the study between the monitor and the Principal Investigator at a mutually convenient and available time. These visits will assure that the facilities are still acceptable, the protocol and investigational plan are being followed, the IRB has been notified of approved protocol changes and adverse events as required, complete records are being maintained, appropriate timely reports to the sponsor and the IRB have been made, device inventory is controlled, and the Investigator is carrying out all agreed upon activities. Any personnel changes must be reported to the monitor immediately and training of new personnel participating in the study scheduled and documented.

To protect subject confidentiality, all subject identifiers, (i.e. medical record number, social security number, subject name) are to be redacted on imaging media sent to the core laboratory, CRFs or supporting documentation submitted to Edwards. Each page should be identified with the subject's study ID number and initials only.

12.2 MONITORING PLAN

Prior to subject enrollment, a study initiation visit will be completed at each investigational site to ensure the following:

1. IRB approval has been obtained and documented,
2. The Investigators and study personnel are appropriately trained and clearly understand the study,
3. The Investigators and study personnel accept the obligations incurred in undertaking this clinical investigation.

Periodic monitoring visits will be made at all enrolling investigational sites in accordance with site enrollment rates. Investigational sites should be visited a minimum of once each year by the study monitor.

Upon termination or conclusion of the study, the study monitor will perform a close-out visit.

12.3 PROTOCOL DEVIATION

A protocol deviation is defined as an event where the Investigator or site personnel did not conduct the study according to the clinical protocol or the Clinical Study Agreement. Investigators shall contact Edwards clinical study management to obtain prior approval for a change to the study requirements, which does not limit or interfere with the authority of a physician to provide **emergency medical treatment** for patients

Deviations shall be reported to Edwards regardless of whether medically justifiable, pre-approved by Edwards, or taken to protect the subject in an emergency. Subject specific deviations and non-subject specific deviations, (e.g. unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a physician who is not listed in the Clinical Study Agreement, etc.) will be reported in writing. Investigators will also adhere to procedures for reporting study

deviations to their IRB in accordance with their specific IRB's reporting policies and procedures.

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

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

12.4 COMMUNICATION PROCEDURES

During the course of the study, all correspondence (letters, telephone call, emails and faxes) regarding the study must be maintained in the study binder provided by Edwards. This binder must be made available for monitoring visits or audits.

13 STUDY COMMITTEES

13.1 DATA MONITORING COMMITTEE

The sponsor will appoint a Data Monitoring Committee (DMC) whose members will be independent of both Edwards Lifesciences and the study Investigators. The DMC will consist of a minimum of 3 members, a statistician and two physicians; one the physicians will be a cardiothoracic surgeons. The DMC data review is to detect evidence of early dramatic benefit or harm for subjects while the trial is in progress. Accordingly, at least one committee member will review each adverse event, unanticipated adverse event, re-operation, explants and death on an ongoing basis.

In addition, after the initial meeting, the DMC will meet a minimum of twice yearly or more often as determined by the Chairperson and possibly on an *ad hoc* basis to evaluate study progress and results..

The DMC will be responsible for:

1. Monitoring and evaluating the safety of subjects;
2. Identify issues and solutions regarding trial design;
3. Recommending if the trial is to be terminated prior to study completion due to clinical adverse events outweighing clinical benefit.

Additional duties may be assigned during execution of the study that are unforeseen (i.e. adverse event adjudication, protocol modifications). The DMC may establish further criteria for recommending study termination before the proposed study begins. [redacted]

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 APPLICABLE REGULATIONS AND GUIDELINES

The regulations listed in **Table 9** must be observed to comply with Edwards' policy for conduct of clinical investigations; they also represent sound research practices. It is the responsibilities of the Investigator(s) comply with the requirements set forth in the United States.

Table 9: Applicable Regulations and Guidelines

Region	Regulation / Guideline
United States	- Investigational Device Exemption (IDE) regulations, 21 CFR Part 812 - Institutional Review Board (IRB) regulations, 21 CFR Part 56 - Protection of Human Subjects regulations, 21 CFR Part 50 - Financial Disclosure, 21 CFR part 54 - Medical Device Tracking Requirements, 21 CFR Part 821 - Draft Heart Valve Guidance

Furthermore, the Investigator must comply with the requirements of the Declaration of Helsinki (Seoul 2008) to ensure protection to the subject.

14.2 DATA PROTECTION AND SUBJECT CONFIDENTIALITY

Edwards is dedicated to maintaining the confidentiality and privacy of subjects who volunteer to participate in the study. Passwords are issued to appropriate personnel to insure confidentiality and protection of the database by allowing variable levels of access to the computer system. In addition, the Principal Investigator is responsible for maintaining confidentiality throughout the clinical study. All subject identifiers will be obliterated from all photocopies of source documents that have been removed from the site. Subject identifiers include, but are not limited to: subject's name, social security number, and medical / hospital number. All study documents will identify the subject only by a subject study identification number assigned by the Sponsor.

14.3 INFORMED CONSENT AND IRB APPROVAL

All subjects must provide written informed consent in accordance with the investigational site's IRB and the Code of Federal Regulations. A copy of the consent form from each site must be forwarded to Edwards Lifesciences for review and approval prior to submitting it to the IRB. Each site must provide Edwards with a copy of the investigational site's IRB approval letter (stating the study name, protocol revision being approved and an approval date) and the informed consent. Yearly approvals for the continuation of the study at each clinical site must also be forwarded to Edwards Clinical Research.

14.4 HEALTH ECONOMIC INFORMATION

In the United States only Sponsor may opt to obtain billing information such as, ICU stay, hospital stay, and 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.

14.5 INVESTIGATOR RESPONSIBILITIES

14.5.1 GENERAL DUTIES

The Principal Investigator shall ensure that all work and services described herein, or incidental to those described herein, shall be conducted in accordance with the highest standards of medical and clinical research practice and the applicable regulations. The Principal Investigator will provide copies of the current study protocol to all staff responsible for study conduct. The Principal Investigator will affirm by his/her signature on the Investigator's Agreement that he/she will fulfill his/her responsibilities relative to this clinical study, and maintain compliance with 21 CFR 812.100 and ICH guidelines on Good Clinical Practice (E6)

The Principal Investigator is responsible for obtaining and maintaining IRB approval for the study at his/her site.

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

14.5.2 INVESTIGATOR RECORDS

The Principal Investigator will maintain the accurate, complete, and current records relating to participation in this clinical study. Study records including CRFs and supporting data, signed Clinical Study Agreement, protocols and protocol amendments, signed informed consents, device use, IRB approval letters, IRB submissions, correspondence, including required reports, and other documents pertaining to the conduct of the study must be kept on file by the Principal Investigator. If the Principal Investigator(s) wish(es) to assign the files to someone else or move them to another location, he/she should consult with the sponsor in writing as to this change. Study files must be maintained in a known location until Edwards notifies the Principal Investigator in writing that he/she may discard them.

14.5.3 INVESTIGATOR REPORTS

The Principal Investigator will prepare and submit the following accurate and complete reports to the sponsor and IRB in a timely manner:

- Unanticipated adverse device effects occurring during the study will be reported within 24 hours of the event, but no later than 5 working days after the Principal Investigator first learns of the event.
- Withdrawal of IRB approval will be reported to the sponsor within 5 working days or review withdrawal. Annual progress reports will be submitted to the IRB.
- Deviation from the clinical protocol (investigational plan) to protect the subject's life or physical well-being in an emergency will be reported to Edwards Clinical Research and the IRB within 5 working days.
- Use of the study device without informed consent will be reported to Edwards and IRB within 2 working days after the use occurs.
- Progress reports on the investigation to the sponsor, the monitor and reviewing IRB at regular intervals, but in no event less often than yearly.
- Upon request by a reviewing IRB or the pertinent regulatory agencies, the Principal Investigator will provide current information about any aspect of the investigation.

14.6 SPONSOR RESPONSIBILITIES

14.6.1 GENERAL DUTIES

As the study sponsor of this clinical study, Edwards Lifesciences has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the pertinent regulatory agencies. The clinical investigation will be conducted under a protocol that complies with US Food and Drug Administration (FDA) regulations (e.g., 21 CFR 812, *Investigational device exemptions*) and with ISO 14155-1:2003 and ISO 14155-2:2003, *Clinical Investigation*

of Medical Devices for Human Subjects – Part 1: General Requirements, and Part 2: Clinical Investigation Plans). The investigation will also be conducted per site-specific requirements regarding Institutional Review Board (21 CFR 56), protection of human subjects (21 CFR 50), general device labeling, Financial Disclosure by Clinical Investigators (21 CFR 54) and other applicable regulations.

14.6.2 Selection of Investigators

Edwards Lifesciences will select Investigators, a study coordinator and supporting staff qualified by education and/experience to perform tasks and duties as required by this clinical study. Edwards Lifesciences will ship investigational devices to participating Investigators once Edwards's has obtained FDA approval to proceed with the study and the site has obtained IRB approval. Edwards will obtain signed study agreements and provide the Investigators with the information and supplies necessary to conduct the study.

14.6.3 Monitoring the Study

Edwards will ensure compliance with the signed Clinical Study Agreement, the protocol (investigational plan), the requirements of applicable regulations stated in Table 10, and any conditions of study approval by the IRB or Food and Drug Administration (FDA).

Edwards will protect the rights, heath, safety and welfare of study subjects in accordance with 21 CFR 50 and ISO 14155-2:2003.

Edwards will conduct and immediate investigation of any unanticipated adverse device effects (UADE) to determine if an event is found to present an unreasonable risk to study subjects in accordance with 21 CFR 812.46(b)(1&2). Edwards will inform the Investigator of any new information about the study that may affect the health, safety or welfare of the subjects or which may influence their decision to continue participating in the study.

14.6.4 SPONSOR RECORDS

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

14.6.5 SPONSOR REPORTS

Edwards Clinical Research will prepare and submit the following accurate and complete reports to the IRBs and FDA in a timely manner:

- Unanticipated adverse device effects reported by an investigational site will be evaluated and the IRB and the pertinent regulatory agencies will be informed of the results of the evaluation no later than 10 working days after Edwards first learns of the event.
- Withdrawal of IRB approval will be reported to all IRBs and FDA within 5 working days of receipt of withdrawal of approval.
- Withdraw of the FDA approval will be reported to investigational sites and IRBs within 5 working days after receiving the notice of approval withdrawal.
- Current Investigator list will be submitted to FDA at 6-month intervals.
- Progress reports to the FDA and IRBs annually or as defined by in 21 CFR 812.150(b)(5).
- Instances of return, repair, or disposition of any units of a device will be sent to IRBs and FDA within 30 days after the request was made and should include the reason for the device recall.

- A final written report is to be completed and submitted to the IRB and the pertinent regulatory agencies within six months after completion or termination of the trial.
- Use of the study device without informed consent will be reported to regulatory authorities within 5 working days after notification of device use.
- Upon request by a reviewing IRB or FDA, Edwards will provide current information about any aspect of the investigation.

14.7 STUDY CHANGES

Changes in the protocol may be made only by written amendment agreed upon by the sponsor, and if pertinent, the IRB. As appropriate, Edwards Lifesciences will submit changes in the protocol to FDA and Investigators to obtain IRB re-approval.

14.8 STUDY COMPLETION OR TERMINATION AND CLOSE-OUT

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

14.9 AUDITS AND INSPECTIONS

In the event that audits are initiated by the Sponsor or FDA, the Investigator shall allow access to the original medical records and provide all requested information, as required by law.

14.10 PUBLICATION POLICY

At the conclusion of the Magna Mitral 23 trial, a multi-site publication may be prepared for publication in a reputable scientific journal. The publication of the Principal results from any single site experience within the trial is not allowed until the preparation and publication of the multi-site results. Exceptions to this rule require prior approval from Edwards Lifesciences. For purposes of abstract

presentation and publication, any secondary publications will be delegated to the appropriate Principal authors, and final analyses and manuscript review for all multi-site data will require the approval of Edwards Lifesciences.

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