POST-APPROVAL STUDY PROTOCOL
STUDY# 2006-05

CARPENTIER-EDWARDS® PERIMOUNT MAGNA® MITRAL PERICARDIAL BIOPROSTHESES MODELS 7000/7000TFX and CARPENTIER-EDWARDS® PERIMOUNT® MAGNA MITRAL EASE™ PERICARDIAL BIOPROSTHESIS MODEL 7200TFX and 7300/7300TFX

Protocol Change Status

Protocol Revision #	Revision Date
Revision A (Not implemented)	January 23, 2007
Revision B (Implemented in the European Community)	May 23, 2007
Revision C (Not implemented)	July 17, 2007
Revision D (United States and European Community)	September 25, 2008
Revision E (United States and European Community)	January 23, 2009
Revision F (United States only)	November 24, 2009
Revision G (Not implemented)	September 17, 2010
Revision H (United States and European Community)	May 24, 2011
Revision I (United States and European Community)	November 18 , 2013

Sponsor
Edwards Lifesciences, LLC
One Edwards Way
Irvine, CA 92656
Tel: 001-949-250-0500
Fax: 001-949-250-3630

TABLE OF CONTENTS

1.0 STUDY SUMMARY 6

2.0 INTRODUCTION 9

2. 1 BACKGROUND 9
2.1 MITRAL VALVE REPLACEMENT 10
2.2 MULTIPLE VALVE REPLACEMENT 10
2.3 TRICUSPID VALVE REPAIR 11
2.4 STUDY VALVES 11

3.0 STUDY OVERVIEW 13

3.1 PURPOSE 13
3.2 INDICATIONS FOR USE 13
3.3 ENDPOINTS 13
3.3.1 Primary Safety Endpoints 13
3.3.2 Secondary Safety Endpoints 13
3.3.3 Primary Effectiveness Endpoints 14
3.3.4 Secondary Effectiveness Endpoints 14

4.0 STUDY DESIGN 16

4.1 SITE SELECTION 16
4.2 STUDY TIMELINE 16
4.4 STUDY POPULATION 18
4.5 STUDY ELIGIBILITY AND ENROLLMENT 19
4.6 TIMING OF INFORMED CONSENT 19
4.7 INCLUSION CRITERIA 20
4.8 EXCLUSION CRITERIA 20

5.0 STUDY MATERIALS 22

5.1 DEVICE DESCRIPTION 22
5.2 PRE-CLINICAL STUDIES 24

6.0 STUDY PROCEDURES 25

6.1 PREOPERATIVE PROCEDURES 25
6.2 OPERATIVE PROCEDURES 26
6.3 POSTOPERATIVE PROCEDURES 27
6.1.1 Hospital Discharge 27
6.1.2 Late Post-Operative Follow- Up 29
6.4 UNSCHEDULED VISITS 31
6.5 MISSED VISIT 31
6.6 LOST TO FOLLOW-UP 31
6.7 TIME PERIODS FOR COMPLETING STUDY VISITS 32
6.8 VALVE EXPLANTS 32
6.9 DEATHS/AUTOPSY REPORTS 33
6.10 SUBJECT WITHDRAWAL 33
6.11 CORE LABORATORY 34

7.0 ADVERSE EVENTS 35

7.1 ADVERSE EVENT REPORTS 37

7.2 MEDICAL DEVICE REPORTING (MDR) 38
7.3 MEDICAL DEVICE REPORTING OUTSIDE THE UNITED STATES 38

8.0 RISK ANALYSIS 38

8.1 POTENTIAL RISKS 39
8.2 MINIMIZATION OF RISKS 40
8.2.1 Physician Training 40
8.2.2 Clinical Events Review Committee 41
8.2.3 Echocardiography Core Laboratory 41
8.2.4 Data Quality Assurance 42
8.3 POTENTIAL BENEFITS 42
8.4 RISK /BENEFIT ANALYSIS 44

9.0 STATISTICAL ANALYSIS 45

9.1 SAMPLE SIZE CALCULATION 45
9.2 ANALYSIS POPULATION 47

9.3 SAFETY ANALYSIS 47

9.3.1 Primary Safety Endpoint 47
9.4 SECONDARY SAFETY ENDPOINTS 48
9.4.1 Blood Data 48
9.4.2 Time to Death, Reoperation, and Explant 49
9.5 EFFECTIVENESS ANALYSIS 49
9.5.1 Subject Functional Classification 50
9.5.2 Hemodynamic Performance 50
9.6 POOLABILITY 50
9.7 MISSING DATA 51

10.0 ETHICAL AND REGULATORY CONSIDERATIONS 52

10.1 SUBJECT INFORMED CONSENT AND INSTITUTIONAL REVIEW BOARD/ETHICAL REVIEW COMMITTEE 52
10.2 HEALTH ECONOMIC INFORMATION 53
10.3 CASE REPORT FORMS (CRFS) 53
10.4 STUDY TERMINATION 54
10. 5 RECORD RETENTION 54
10.6 STUDY RESPONSIBILITIES 55
10.6.1 Investigator Responsibilities 55
10.6.2 Study Monitor/Sponsor Responsibilities 57
10.6.3 Clinical Monitor 57
10. 7 STUDY CHANGES 58
10. 8 IMPLANT DATA CARD 58
10.9 STUDY PUBLICATION 59

11.0 REFERENCES 60

12.0 APPENDIX 1- STS GUIDELINES FOR REPORTING MORBIDITY AND MORTALITY AFTER CARDIAC VALVULAR OPERATIONS 63

13.0 APPENDIX 2: SAMPLE SUBJECT INFORMED CONSENT FORM AND HIPAA AUTHORIZATION 64

14.0 APPENDIX 3: ECHO CORE LAB PROTOCOL 72

15.0 APPENDIX 4: INSTRUCTIONS FOR USE 73
16.0 APPENDIX 5: CASE REPORT FORMS 74
17.0 APPENDIX 6: QUALITY OF LIFE SURVEY 75
18.0 APPENDIX 7: IMPLANT DATA CARD 76
19.0 APPENDIX 8: ADVERSE EVENT DEFINITIONS 79
20.0 APPENDIX 9: CLINICAL RISK ASSESSMENT 80

1.0 STUDY SUMMARY

Protocol No:	2006-05
Study Title	Post Approval Study 2006-05 Carpentier-Edwards® PERIMOUNT® Magna Mitral Pericardial Bioprostheses Models 7000/7000TFX and Carpentier-Edwards® PERIMOUNT® Magna Mitral Ease™ Pericardial Bioprostheses Models 7200TFX and 7300/7300TFX
Study Purpose:	To evaluate the long term safety and effectiveness of the Carpentier-Edwards® PERIMOUNT® Magna Mitral Bioprostheses Models 7000/7000TFX and the Carpentier-Edwards® PERIMOUNT® Magna Mitral Ease™ Pericardial Bioprostheses Models 7200TFX and 7300/7300TFX in patients undergoing mitral valve replacement with or without concomitant procedures requiring cardiopulmonary bypass.
Study Device:	Carpentier-Edwards® PERIMOUNT® Magna Mitral Pericardial Bioprostheses, Models 7000/7000TFX and Carpentier-Edwards® PERIMOUNT® Magna Mitral Ease™ Pericardial Bioprostheses Models 7200TFX and 7300/7300TFX
Study Design:	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 250 subjects implanted with the study valve in order to achieve 101 mitral valve replacement subjects who complete follow-up for a minimum of 8 years.
Study Population:	Male and female patients, 18 years or older, requiring replacement for a diseased, damaged, or malfunctioning native or prosthetic mitral valve.
Entry Criteria:	Patients will preoperatively sign the subject informed consent form, and meet all inclusion criteria and none of the exclusion criteria to participate in this clinical study.
Duration of Participation:	After the valve implantation, subjects will be followed and assessed at discharge, 6-months, one year, and annually thereafter for a minimum of 8 years.

Clinical Endpoints:	Primary Safety Linearized rates of: • Thromboembolism • All hemorrhage • All perivalvular leak • Endocarditis Secondary Safety Early and late linearized and actuarial rates of: • 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 Studies to assess hemolysis and adverse events. • white blood count • red blood count • hematocrit • plasma free hemoglobin (or haptoglobin and SLDH) • platelet count • reticulocyte counts

	Primary Effectiveness: Percentage of subjects in NYHA Functional Class I or II at 8 years post implant. Secondary Effectiveness: Hemodynamic Performance at 8 years post implant: • Peak gradient • Mean gradient • Effective orifice area (EOA) • EOA index • Performance index • Cardiac output • Cardiac index • Severity of mitral regurgitation • Left ventricular mass regression Quality of Life Survey (EQ-5D)
Study Sponsor:	Edwards Lifesciences LLC One Edwards Way Irvine, CA 92614 USA Telephone: 001 949-250-2500 Facsimile: 001 949-250-3630

2.0 INTRODUCTION

2. 1 Background

Valvular heart disease is a life-threatening disease that afflicts millions of people worldwide and leads to approximately 250,000 valve repairs and/or replacements each year[1]. Mitral valvular heart disease is a condition that involves obstruction of the blood flow through the mitral heart valve or stenosis, leakage of the mitral valve, known as regurgitation, incompetence, or insufficiency; and combination of the two, sometimes referred to as mixed disease. It may be caused by any number of factors, including congenital abnormalities, infection by various microorganisms, degenerative calcification, and rheumatic heart disease.

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 implantation of an annuloplasty ring that provides support to the native valve so that it closes completely and functions normally. If the native valve cannot be repaired, it is replaced by either a mechanical (constructed from synthetic material) or a tissue bioprosthetic valve (made primarily from animal tissue including bovine pericardium, or human valves from cadavers).

Since Carpentier introduced improved techniques for mitral valve repair in 1971[2], the etiology and treatment of mitral valve disease have changed[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 3.7 times increase in mitral valve repair (from 2.4 to 8.9 cases/100,000/year) whereas mitral valve replacement increased 1.9 times from (4.3 to 8.0

cases/100,000/year). Based on the regional data they concluded 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 Mitral Valve Replacement

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 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 and 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.

2.2 Multiple Valve Replacement

Simultaneous replacement of the mitral and aortic valves 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 both the mitral and aortic valves 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 implantation 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 indicated that 15% of patients

undergoing mitral valve surgery in 2007 in the United States underwent simultaneous mitral and aortic valve replacement (1205/7883).

2.3 Tricuspid Valve Repair

The most common Tricuspid Valve disease etiology in North America is tricuspid regurgitation secondary to left heart pathology, such as mitral valve disease and left heart failure[12]. Tricuspid regurgitation may be functional or organic. Functional tricuspid regurgitation is commonly caused by severe mitral valve stenosis or regurgitation, both of which lead to dilatation of the right ventricle and the tricuspid annulus[13.] Tricuspid regurgitation is a significant clinical problem that may be undertreated by cardiologists and surgeons[14]. Tricuspid dilation secondary to mitral regurgitation is often unrecognized as tricuspid regurgitation[15,16,17]. The ACC/AHA 2006 Guidelines for the Management of Patients with Valvular Heart Disease recommend concomitant tricuspid annuloplasty to be considered at time of mitral valve surgery, especially if there are preoperative signs or symptoms of right-sided heart failure. This would alleviate the risk of severe persistent TR and the need for another surgery. The European Society of Cardiology 2007 Guidelines on the Management of Valvular Heart Disease point out that the relative simplicity of tricuspid valve repair along with the high risk of secondary surgical correction are incentives for earlier tricuspid repair. Furthermore, reoperation on the tricuspid valve after mitral valve surgery in persistent tricuspid regurgitation carries a high risk due to the clinical condition of the patients, including advanced age and the number of previous cardiac interventions, and may result in poor long-term results due to irreversible right ventricular dysfunction[18].

2.4 Study Valves

The Carpentier-Edwards® PERIMOUNT® Magna Mitral pericardial bioprostheses, models 7000/7000TFX and Carpentier-Edwards® PERIMOUNT® Magna Mitral Ease™ Pericardial Bioprostheses Models 7200TFX and 7300/7300TFX (also referred to as the Magna Mitral valves) are built upon the same proven wireform frame and leaflet attachment as the Carpentier-Edwards PERIMOUNT mitral pericardial bioprostheses

models 6900, 6900P and 6900PTFX. Valves are available in the sewing ring diameters and sizes shown below in Section 5, Table 3.

The Magna Mitral valve model 7000TFX received European CE marking in August 2005 and Canadian approval in November 2005. Models 7000 and 7000TFX, received Australian approval in July 2008 and FDA approval in August 2008 (sizes 25 mm – 33 mm (P860057/S029). More than 4000 Magna Mitral 7000TFX valves had been sold worldwide as of August 2008.The Magna Mitral model 7200TFX received FDA approval on July 09, 2009 (P860057/S56). Models 7300/7300TFX received FDA approval in June 24,2010 (P860057/S68).

Table 1: Magna Mitral Device Approvals by Region

Region	Approval Date	Valve Model(s)
European Community	August 2005	7000 TFX
Canada	November 2005	7000 TFX
Australia	July 2008	7000/7000 TFX
United States	July 2009	7200TFX
European Community	August 2010	7300/7300 TFX
United States	June 2010	7300/7300 TFX

3.0 STUDY OVERVIEW

3.1 Purpose

The purpose of this study is to evaluate the long term safety and effectiveness of the Magna Mitral valves in patients undergoing mitral valve replacement with or without concomitant procedures requiring cardiopulmonary bypass.

3.2 Indications for Use

The Carpentier-Edward PERIMOUNT Magna Mitral and Magna Mitral Ease bioprostheses are indicated for use in patients who require replacement of their native or prosthetic mitral valve.

3.3 Endpoints

3.3.1 Primary Safety Endpoints

Long term safety performance will be evaluated by comparing the linearized rates listed below to the objective performance criteria referenced in ISO 5840-2005, Cardiovascular Implants-Cardiac Valve Prostheses

- Thromboembolism
- All Hemorrhage
- All Perivalvular Leak
- Endocarditis

3.3.2 Secondary Safety Endpoints

Secondary safety endpoints will include early and late linearized 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 studies including white blood count, red blood count, hematocrit, plasma free hemoglobin (or haptoglobin and SLDH), platelet and reticulocyte counts will be used to evaluate the rate of hemolysis and adverse events at the 6 month, 1 year and annual follow-up visits.

3.3.3 Primary Effectiveness Endpoints

The primary effectiveness endpoint will be the percentage of subjects in NYHA functional classification I or II at 8 years post-implant

3.3.4 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 Valvular Regurgitation
- LV Mass Regression

Quality of Life Survey (EQ-5D) at 6 month post index procedure as compared to preoperative baseline.

4.0 STUDY DESIGN

This study has been designed as a prospective, multi-center post-approval study to be conducted in the United States (US) and outside the United States (OUS). A minimum of 250 subjects will be enrolled to obtain long term data from at least 101 subjects who have completed 8 years of post-implant follow-up. Of these 250, approximately 38 (15%) are anticipated to be simultaneous aortic and mitral replacements. Subject enrollment will not start in the US before obtaining FDA approval.

4.1 Site Selection

Up to 25 sites will enroll subjects in this study. Participating sites will be chosen based on their experience in conducting clinical studies, implanting bioprostheses, academic and medical reputation, and their ability to enroll the required study subject population. Study centers will be required to have a study coordinator to assist the primary investigator(s), and study participating center must have the time and resources available to participate in this study.

Study sites will be in the United States, and OUS (Outside the US, i.e. Canada, Europe, Asia Pacific, Israel). On average, each site is expected to enroll at least 15 subjects. 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 mitral valve replacement.

4.2 Study Timeline

Subject enrollment in this study was initiated with the Magna Mitral Model 7000/7000TFX in Europe under protocol revision B as of May 23, 2007 and in the United States under protocol version D as of September 25, 2008. Internal revisions A and C were not reviewed or approved by FDA and were never implemented. Internal revision G was submitted to FDA to request inclusion of the Magna Mitral valve model 7300 in the study. Revision H was submitted in response to FDA requests to update the

statistical analysis plan to address the inclusion of double valve replacement recipients in the study population and include a comparison of the subject data separating the various valve models covered under this post approval study .

The Study Timeline is revised to reflect the final study report date of December 31, 2020.

Table 2 which follows shows the report schedule listing the original and revised scheduled report dates:

Table 2: Revised Study Reporting Time

Report Schedule	Original Schedule Report Date	Scheduled Report Date
6-Year Interim Report	Remains the same	August 28, 2014
7-year Interim Report	Remains the same	August 28, 2015
8-year Interim Report	Remains the same	August 27, 2016
9-Year Interim Report	This was originally intended to be the final report, and was to be submitted November 27, 2017.	August 27, 2017
10-Year Interim Report	None	August 27, 2018
11-Year Interim Report	None	August 27, 2019
Final Report, minimum 101 patients with 8 year follow-up	August 27, 2017	December 31, 2020

Justification for Change in the Study Reporting Time

As of November 4, 2013, a total of 249 patients had a study valve in place at discharge. Therefore, only one (1) additional subject must be implanted between now and December 31, 2014, to meet the protocol requirement of 250 subjects implanted. Of the minimum 250 implanted subjects required per revision H of study protocol (2006-05), a minimum of 101 subjects must be followed for eight (8) years. As of November 4, 2013, we have lost the ability to follow 55 patients either due to death, withdrawal or removal of the study valve. This leaves 203 who can potentially make it to the eight (8) year follow up. Currently, the longest recorded follow-up is five (5) years. Therefore, it will be another three (3) years before the first patient reaches the 8-year follow-up visit and up to six (6) years to achieve 101 patients with eight (8)

year follow-up data. As a result, Edwards anticipates the **final study report** will be submitted in December 2020.

Table 3. Study Enrollment by Protocol Revision by Valve Model

Location	Protocol Revision	Revision Date	Valve Model No(s).
United States/Europe (Not implemented)	Revision A	January 23, 2007	7000/7000TFX
Europe	Revision B.	May 23, 2007	7000/7000TFX
United States/Europe (Not implemented)	Revision C	July 17, 2007	7000/7000TFX
United States/Europe	Revision D	September 25, 2008	7000/7000TFX
United States/Europe	Revision E	January 23, 2009	7000/7000TFX
United States (Northwestern University only)	Revision F	November 24, 2009	7200TFX
United States (Not implemented)	Revision G	September 17, 2010	7300/7300TFX
United States/Europe	Revision H	May 24, 2011	7000/7000TFX/ 7300/7300TFX

Edwards continues to actively review study recruitment procedures in an ongoing effort to improve study enrollment rates and complete the study in a timely fashion.

4.4 Study Population

The Carpentier-Edward PERIMOUNT Magna Mitral bioprostheses is indicated for patients who require replacement of a native or prosthetic mitral valve. Therefore this post-approval study population may include patients age 18 or older who have been identified as a potential candidates for mitral valve replacement based on the pre-

operative diagnosis and intraoperative anatomical and pathological considerations as determined by the implanting surgeon.

4.5 Study Eligibility and Enrollment

Patients who have been diagnosed with mitral valve disease for which valve replacement surgery is indicated may be considered for study participation at qualified study sites. Patients who have been considered for study inclusion by the study investigator shall be listed on the Subject Screening Log. Patients who agree to participate in the study and have completed approved written informed consent will be considered enrolled in the study and will be assigned a unique site specific sequential study identification numbers defined by Edwards Lifesciences.

4.6 Timing of Informed Consent

Informed consent must be obtained from any potential study subject prior to conducting any preoperative assessments that are not part of the routine preparation and evaluation of a study subject for mitral valve replacement.

Study subjects who complete informed consent but are found to be ineligible for study inclusion, shall be notified and the reason for study exclusion shall be documented on the Subject Screening Log. A Patient Selection case report form shall be used to document subject ineligibility and a Study Withdrawal case report form shall be completed to document the reason for subject withdrawal. No further CRFs need to be completed for these subjects.

For subjects who are eligible for the study but who do not receive the study valve, the reason the subject did not receive a study valve shall be recorded on the Subject Screening Log. A Patient Selection case report form and Study Withdrawal form shall

also be completed to document the reason for subject withdrawal. No further CRFs need to be completed for these subjects.

For subjects who are eligible for the study, but who ultimately receive a non-study valve, the reason for use of a non-study valve shall be documented on the Subject Screening Log, and Patient Selection and Study Withdrawal case report forms completed. No other CRFs need to be completed for these subjects.

Documentation of all potential study subjects is required in order to reduce the potential for study subject selection bias. Subjects who are censored from the study will be identified and the reason for censorship will be indicated in the data analysis.

4.7 Inclusion Criteria

1. The patient requires, as indicated in the preoperative evaluation, a replacement mitral valve.
2. The patient has signed and dated the subject informed consent form prior to surgery.
3. The patient is expected to survive the surgery and be discharged.
4. The patient is geographically stable and agrees to attend follow-up assessments.
5. The patient is 18 years or older.

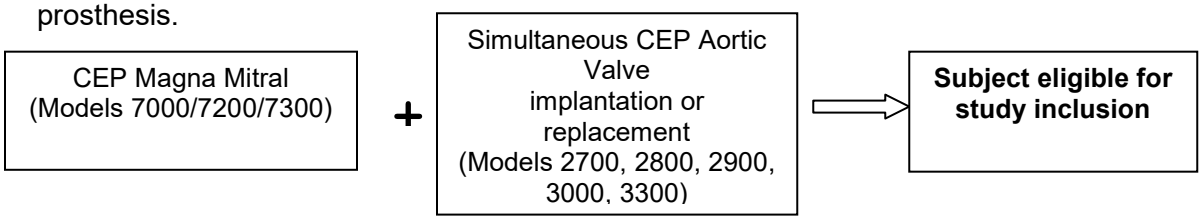
4.8 Exclusion Criteria

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 is pregnant or lactating.
4. The patient is an intravenous drug abuser.
5. The patient is currently a prison inmate.
6. The patient is currently participating in a study of an investigational drug or device.

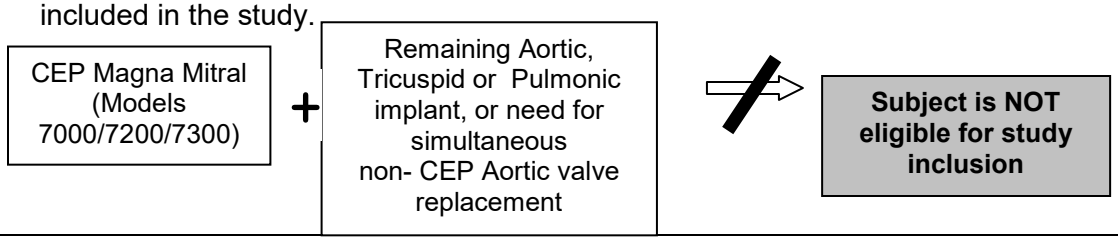
7. The patient requires replacement of a native or prosthetic tricuspid or pulmonic valve.
8. The patient requires replacement of a native or prosthetic aortic valve with a prosthesis other than a commercially available Carpentier-Edwards PERIMOUNT Valve (i.e. models 2700, 2700TFX, 2800, 2800TFX, 2900, 3000, 3000TFX, 3300TFX)*.
9. The patient was previously enrolled in the study.
10. The patient has had prior aortic, tricuspid and/or pulmonary valve surgery, which included implantation of a bioprosthetic valve or mechanical valve that will remain *in situ*.

NOTE: Commercial availability may vary by region. At the time of this protocol, the model 2900 is not available in the United States.

As of Protocol revision D, this study allows simultaneous implantation of the Magna Mitral valve with a concomitant replacement of the aortic valve, if the aortic valve replacement is performed using a commercially available Carpentier Edwards aortic prosthesis.



However, if the study subject already has a valve prosthesis in the aortic, tricuspid or pulmonic position or requires a valve replacement of the native valve or replacement of a prior prosthesis in one of these positions, and this valve is intended to remain in the subject at the time of mitral valve replacement, the study subject should NOT be included in the study.



5.0 STUDY MATERIALS

5.1 Device Description

The Carpentier-Edwards PERIMOUNT Magna Mitral and Magna Mitral Ease valves included in this study are modified versions of the Carpentier-Edwards PERIMOUNT mitral valve models 6900, 6900P and 6900PTFX. All study valves are built upon the same proven wireform frame and leaflet attachment as the Model 6900 and are available in various sewing ring diameters and sizes shown below in Table 3.

Table 4. Valve Size by Tissue Annulus Diameter (mm)

Tissue Annulus Diameter (TAD)	28	29.5	31.5	33.5	33.5
Model 7000/7000TFX	25	27	29	31	33
Model 7200TFX	27	29	31	33	35
Model 7300/7300TFX	25	27	29	31	33

These bioprostheses incorporate a sewing ring specifically designed for the mitral position and are the first bioengineered mitral valve design with three selected bovine pericardial leaflet mounted on a flexible metal alloy frame.

Bovine pericardium was selected for its intrinsic properties for valve manufacture, notably in terms of collagen content and tolerance to high bending curvatures. Bovine pericardium is cross-linked using a Neutralogic fixation process in which tissue is treated in a stress-free bath of buffered glutaraldehyde solution. Magna Mitral valve models 7000TFX, 7200TFX and 7300TFX are treated according to the ThermaFix process, which involves heat treat of the tissue in glutaraldehyde and uses ethanol and Polysorbate-80 (a surfactant). Glutaraldehyde has been shown to reduce the antigenicity

of tissue xenograft valves and increase tissue stability. Glutaradehyde alone has not been shown to affect or reduce the calcification rate of the valve. [23, 24].

Tissue thickness is measured for each valve size and leaflets are die-cut in selected areas of the pericardial sheet. Three leaflets matched for similar thickness and elasticity are then assembled and mounted underneath the lightweight wireform frame, to minimize commissural stress points. The lightweight wireform frame is made of corrosion resistant cobalt-chromium ally, chosen for its spring efficiency and fatigue properties. 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 sewn with polyfluoroethylene thread. The wireform frame is symmetrical and the three commissure supports (struts) are equally spaced. Detailed instructions for use of the valve including a description of the sewing ring and valve holder system can be found for each Magna mitral valve model in Appendix 4.

Comparison of Mitral Valve and Packaging Systems

System Feature	Carpentier-Edwards PERIMOUNT Magna Mitral 7000 / 7000TFX	Carpentier-Edwards PERIMOUNT Magna Mitral Ease 7200TFX	Carpentier-Edwards PERIMOUNT Magna Mitral Ease 7300 / 7300TFX

System Feature	Carpentier-Edwards PERIMOUNT Magna Mitral 7000 / 7000TFX	Carpentier-Edwards PERIMOUNT Magna Mitral Ease 7200TFX	Carpentier-Edwards PERIMOUNT Magna Mitral Ease 7300 / 7300TFX
Valve	Carpentier-Edwards PERIMOUNT Magna Mitral pericardial bioprosthesis, model 7000TFX sizes 25 – 33 mm	Valve is identical to the model 7000TFX Valve, but has a different sizing convention; sizes 27 – 35	Valve is identical to the model 7000TFX valve, sizes 25 – 33 mm. A black silk suture guide line is added to the sewing ring
Clip	Acetal Homopolymer	Acetal Homopolymer	Acetal Homopolymer Clip contains new features for sleeve engagement and blue arrow molded into material.
Jar	3.8 oz Jar	3.8 oz Jar	3.8 oz Ribbed Jar Internal Ribs added to 3.8 oz Jar
Sleeve	Polypropylene Sleeve	Polypropylene Sleeve	Polypropylene Ribbed Sleeve External Ribs added to Sleeve
Holder System	Tricentrix Holder System: White* Holder White Post White Adapter *White also referred to as Natural	Grey Tricentrix Holder System: Grey Holder Grey Post White Adapter	Tri-color Tricentrix Holder System: Grey Holder White Post Blue Adapter Component color changed to provide additional contrast
Accessories **Handle Class I** **Sizers Class IIa** **Tray Class I** **NB: TÜV SÜD Product Service GmbH CE 0123**	Handles 1111, 1117 Sizer 1177HP Tray TRAY1177HP	Flex Handle 1172 Replica Sizer 1171R Barrel Sizer 1171B Tray SET 1171	Flex Handle 1173 Replica Sizer 1173R Barrel Sizer 1173B Tray SET 1173 Updated graphics and size markings on sizers and tray

5.2 Pre-Clinical Studies

Pre-clinical bench studies included sewing ring integrity testing, spot weld pull test and chromium-cobalt band compression resistance testing, valve hydrodynamic, durability and structural integrity testing, shelf life & packaging and biocompatibility testing. All testing met acceptance criteria per ISO 5840 and FDA Heart Valve Guidance 1996.

6.0 STUDY PROCEDURES

Edwards will provide the study sites with the post approval study clinical protocol, case report forms (CRFs) (Appendix 5), Quality of Life survey (Appendix 6) and all other necessary study related documentation. Edwards' Clinical Affairs Department or authorized designee will conduct all aspects of data quality assurance (data monitoring, and monitoring of study sites) per departmental Standard Operating Procedures.

Each study site will adhere to all the requirements specified in this protocol. Assessments will be obtained for the preoperative and operative visits, and postoperatively at discharge, six months, 1-year and annually thereafter for a minimum of 8 years (see Tables 4, 5, 6 and 7).

The investigator will make every attempt to follow the subjects and will document the information gathered during the required study follow-up visits on the standardized 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.

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.

6.1 Preoperative Procedures

All procedures shall be documented on the applicable visit case report forms (see Appendix 5). Compact discs or electronic copies of Doppler echocardiographic examinations will be sent directly to the Core Laboratory according to the procedures outlined in Appendix 3 - Echo Core Lab Protocol. A summary of all required treatment procedures can be found in Table - Study Schedule.

Table 5: Pre- Operative Evaluations and Data Requirements

Patient Status	Date of birth, gender, demographics
Physical Assessment	Height, Weight, Heart Rate, Blood Pressure, NYHA classification
Medical History	Non cardiac conditions, cardiac conditions, previous cardiac surgery
Electrocardiogram	Cardiac Rhythm
Blood studies [1]	RBC, WBC, HCT, Plasma Free HGB, (or Haptoglobin and SLDH) Platelet and Reticulocyte counts
Pregnancy Test	Blood or Urine
Medication Use	Antiplatelet, Antithrombolytic Therapies
Coagulation Profile	PTT or INR
Echocardiography [2]	Exam Date/Interval
Echo Core Lab	Cardiac output, Ejection fraction, Peak and mean valve gradients, assessment of stenosis or regurgitation, LV structure and function, LV mass, jet velocities
Quality of Life Survey [3]	EQ-5D

[1] Pre-procedure blood studies to be performed within 30 days of the planned valve replacement procedure.

[2] Pre- procedure echocardiography to be performed within 6 months of the planned valve replacement procedure

[3] Quality of Life survey to be completed within 3 months of planned valve replacement procedure

6.2 Operative Procedures

Investigators shall use routine surgical technique for mitral valve replacement surgery in accordance with the relevant IFUs and carefully following the valve sizing, and valve

orientation Tricentrix valve holder system instructions, (See Appendix 4 for Instructions for Use).

Required operative evaluations and data requirements are listed below in Table 6. An intra-operative transesophageal echo (TEE) is not required for this study, however if an echo is performed, the investigator should send a copy of the examination to the Echo Core Lab for evaluation.

Table 6: Operative Evaluations and Data Requirements

Valve Implant Procedure	Implant date, implanting surgeon name
Valvular Lesion Assessment	Diagnosis for valve replacement, current condition of valve, condition of annulus, (debridement procedures) condition of leaflets and preservation of subvalvular apparatus
Study Valve Implant Data	Valve size, model and serial number, bypass pump time, total cross clamp time, suture technique, use of pledgets, valve seating leaflet coaptation
Surgical Approach	Full or mini-sternotomy
Concomitant Procedures	CABG, AVR, tricuspid repair, etc.
Echocardiography	TEE is optional, If TEE is performed, site shall send to exam to Core Lab for evaluation
Adverse Events	All adverse events or complications regardless of relationship to the device or valve replacement procedure

6.3 Postoperative Procedures

6.1.1 Hospital Discharge

Prior to hospital discharge, the investigator or designee will provide the study subject with an Implant Data Card (See Section 10.8 and Appendix 7).

The Investigator or designee will explain the use and importance of the implant card and shall ensure that all required information (Investigator Name, Facility Name and contact information) has been included on the card. The Investigator or designed shall also ensure that one of the valve serial number serial number stickers provided with the implant packaging is firmly attached to the back side of the Implant Data Card. The second implant serial number sticker should be placed either on the front page of the subject's operations notes, or scanned into the subject's hospital electronic records.

Hospital discharge evaluations and data requirements are listed in Table 7.

Table 7: Early Post-Operative / Discharge Procedures and Data Requirements (30 days or discharge, whichever is later)

Patient Status	Complete Implant Card
Physical Assessment	Heart Rate, Blood Pressure, NYHA

	classification
Electrocardiogram	Cardiac Rhythm
Medication Use	Antiplatelet, Antithrombolytic Therapies
Coagulation Profile	PTT or INR
Echocardiography	Exam Date/Interval, clinical evidence of PV leak or regurgitation
Echo Core Lab	Cardiac output, Ejection fraction, Peak and mean valve gradients, assessment of stenosis or regurgitation, LV structure and function, LV mass, jet velocities
Adverse Events	All adverse events or complications that have occurred since the valve replacement procedure

6.1.2 Late Post-Operative Follow- Up

Postoperative follow-up visits are required between 3-6-months, at one year, and annually thereafter for a minimum of 8 years. Required evaluations and data requirements are listed below in Table 8.

Table 8. Late Post-Operative Procedures and Data Requirements

Patient Status	Visit Date, Type of Visit

Physical Assessment	Heart Rate, Blood Pressure, NYHA classification
Electrocardiogram	Cardiac Rhythm
Blood studies	RBC, WBC, HCT, Plasma Free HGB (or Haptoglobin and SLDH), Platelet and Reticulocyte counts
Medication Use	Antiplatelet, Antithrombolytic Therapies
Coagulation Profile	PTT or INR
Echocardiography (6 mo, 1. **2, 4 6, and 8 year follow-up visits)**	Exam Date/Interval, clinical evidence of PV leak or regurgitation
Echo Core Lab	Cardiac output, Ejection fraction, Peak and mean valve gradients, assessment of stenosis or regurgitation, LV structure and function, LV mass, jet velocities
Quality of Life Survey (6 month visit only)	EQ-5D
Adverse Events	All adverse events or complications that have occurred since the last visit

Echocardiography exams are required at the 6-month visit (between 3-6 months), and at 1, 2, 4, 6, and 8 year follow-ups (± 1 month). A QOL survey (EQ-5D) will be completed for the 6-month follow-up visit.

Use of anticoagulant therapy is recommended for two to three months post-operatively except where contraindicated. The appropriate anticoagulation therapy must be determined by the physician on an individual basis and based on current ACC/AHA guidelines.

Clinical assessment of adverse events shall be conducted per revised STS guidelines (Appendix 1) and reported per the event classifications and definitions provided in Section 7.0 and Appendix 8 respectively.

6.4 Unscheduled Visits

If a subject needs to be seen at other than a regularly scheduled follow-up visit for assessment of cardiac symptoms, all visit information shall be recorded on the appropriate follow-up visit CRF. If blood studies are performed the investigator shall document these studies on the CRF. Doppler/echocardiography performed at these visits is optional, however if performed, the investigator should send the echo exam to the Core Lab for evaluation.

6.5 Missed Visit

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. The study site shall document the efforts made to contact the study subject or the subject's primary health care provider for each required follow-up visit.

6.6 Lost To Follow-Up

A subject will be considered "lost to follow-up" and terminated from the study when all of the following criteria have been met:

- Failure to complete two consecutive visits without due cause; and
- Documentation of three unsuccessful attempts on three different days over a period of 3 months by the Investigator or his/her designee to contact the subject or next of kin; and
- A letter from the Investigator to Edwards requesting subject removal from the study, and
- Prior agreement of Edwards to remove the subject from the study.

6.7 Time Periods for Completing Study Visits

Follow-up visits are scheduled for appointed times after the date of the procedure. It is important that this schedule be maintained as closely as possible for all study subjects. Edwards recognizes that subjects may not be able to return for all scheduled visits at precisely the date required, and therefore, a period of time in which each visit is allowed is described in Table 9 below. Studies not completed within these windows will be considered missed visits. Study visits should be scheduled as close to the early part of the visit time period as possible so that if it is necessary to cancel and reschedule the visit, the visit could still be conducted in the required time period.

Table 9. Schedule of Follow-up Visits and Time Periods

Follow-up Visit	Time Period
Discharge/30 Days	Day before or Day of Discharge or 30 days post implant (whichever is later)
Early Postoperative	3 - 6 months
Late Postoperative	12 months ± 1 month
Late Postoperative	Annually from procedure date ± 1 month

6.8 Valve Explants

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. All supporting data should be de-identified at the site to protect the privacy of the study subject.

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 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

6.9 Deaths/Autopsy Reports

All deaths that occur during study participation and deaths that occur 30 days post-study valve explantation shall be reported to the Edwards Clinical Affairs Department. The Investigator shall provide a written summary of the subject death including the cause of death and relationship of the death to the study valve or procedure. Copies of an autopsy report and/or death certificate shall be submitted to Edwards as permitted by local law. Death notifications shall be de-identified in order to protect the privacy of the subject.

6.10 Subject Withdrawal

Although all subjects are informed of their right to withdraw from the clinical study at any time, it is anticipated that such withdrawals will be infrequent. All measures should be taken by the Investigator and their staff to encourage subjects to return for required follow-up visits. The clinical study objective may be jeopardized if large numbers of subjects are lost to follow-up.

All subjects are expected to continue in the study until Edwards notifies the Investigator, in writing that further follow-up is no longer required, except in the event of death or upon the subject's written request for early withdrawal from the clinical study. A copy of any request for subject withdrawal shall should sent to Edwards via the study monitor and a Subject Withdrawal case report form completed.

Table 10. Study Schedule

Time Period						
Data Collection	**Pre-Operative**	**Operative**	**Early Post-Operative /Hospital Discharge**	**Late Postoperative (3-6 Months)**	**1 Year (11-13 months) Annually**	**Unscheduled Visit**
Informed Consent	X					
Study Eligibility	X					
Patient Status	X		X	X	X	
Physical Assessment	X		X	X	X	
Electrocardiogram	X		X		X	
Blood Studies	X			X	X	
Pregnancy Test	X					
Medication Use	X		X	X	X	
Coagulation Profile	X		X	X	X	
Echocardiography	X		X	X [2]	X [2]	X [3]
Quality of Life Survey (EQ-5D)	X [1]			X [1]		
Implant Procedure		X				
Concomitant Procedures		X				
Adverse Events		X	X	X	X	X

[1] QOL surveys are required pre-operatively and at the 3-6 month visit.
[2] Echocardiograms are required at 6 months, 1 year, 2, 4, 6 and 8 year follow- up visits.
[3] If blood studies or echocardiograms performed at unscheduled visits, they should be recorded on the appropriate CRF, Echo data should be submitted to the Core Lab for evaluation.

6.11 Core Laboratory

Independent Core Laboratory evaluation of all Doppler echocardiograms will be performed using common protocols and CRFs. The purpose of a Core Laboratory is to ensure unbiased, timely and consistent analysis of this diagnostic data. A Core Lab is responsible for evaluating changes in study subject status over the course of the study based on serial studies in the same study subject. Core Lab personnel shall be qualified

by training and experience in Doppler echocardiography data analysis. Edwards will ensure that Core Lab personnel are familiar with the study valve. Edwards or its designee will monitor Core Labs periodically to ensure adherence to data review schedules. Clinical Affairs will also perform audits of Core Labs at least once per year to ensure compliance with applicable study requirements

Doppler Echocardiograms

Echocardiographic studies shall be performed per the Core Lab Protocol found in Appendix 3. Sites shall send properly labeled compact discs or electronic copies of echocardiograms directly from the Study Sites to the Core Lab. The Core Laboratory will review the echocardiograms upon receipt and notify the Edwards promptly if the exam is of insufficient quality for analysis. Edwards will contact the site and request additional echocardiograms for analysis.

7.0 ADVERSE EVENTS

An adverse event has been defined as any side effect, complication or medical consequence that has adverse health implications for the study subject receiving the study product/ treatment. Adverse events may be considered anticipated or unanticipated and shall be classified per the applicable definitions for the countries in which the study is being conducted.

The Investigator at each participating center is responsible for reporting adverse events (complications) to the Edwards or its designee regardless of whether they are considered to be related to the study procedure or study device. The Investigator shall complete the appropriate adverse event case report forms (See CRFs in Attachment 5) at each study visit, indicating the relationship of the event to the study device or procedure. The adverse event CRF for a given visit must report all adverse events that have occurred since the last documented visit. For example, all adverse events occurring after the Discharge visit, but prior to the 3-6 months postoperative visit should be reported on the 6 month follow-up CRF.

Anticipated Adverse Events

A variety of device and procedure related complications are expected to occur in subjects undergoing mitral valve replacement These predefined complications are considered adverse events. (See Appendix 8 for definitions of anticipated adverse events).

Unanticipated Adverse Device Effect (*US CFR 21-812.3)*

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

NOTE: By definition a UADE is considered Serious, therefore for the purposes of reporting at European sites under ISO 14155, all UADEs should be reported as Serious Adverse Device Effects (SADEs).

This study will also report adverse events from non-US sites under the following additional classifications:

Adverse Device Effect (ADE): *(ISO14155-1:2009)*

An Adverse Device Effect is defined per ISO 14155 as “Any untoward and unintended response to a medical device”, including events that result from insufficiencies or inadequacies in the Instructions for Use, the deployment of the device, as a result of user error. Both the study subject or user may experience an adverse device effect if the event is due to user error. (Meddev 2.12)

Serious Adverse Event (SAE): *(ISO 14155-1:2009)*

An serious adverse event is defined as an event that:

a) led to death

b) led to a serious deterioration in the health of a subject that

   1) resulted in a life-threatening illness or injury,

   2) resulted in a permanent impairment of a body structure or a body function,

   3) required in-patient hospitalization or prolongation of existing hospitalization, or

   4) resulted in-patient medical or surgical intervention to prevent permanent impairment to body structure or a body function

c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

Serious Adverse Device Effect (SADE): *(ISO 14155-1:2009)*

As Serious Adverse Device Effect is defined as an "adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune".

7.1 Adverse Event Reports

All adverse events regardless of device relationship shall be recorded and reported to Edwards Lifesciences.

Adverse events related to the study device, unanticipated adverse device effects (UADEs) and serious adverse events (SAEs) or adverse device effects (SADEs) must be reported to Edwards within 2 business days of knowledge of the event.

Following initial notification, the Investigator shall submit a written summary of the event (including the time and date of onset, complete description of the event, severity, duration, actions taken and outcome) to the Heart Valve Therapy Clinical Research department either via email to HVTClinicalResearch@edwards.com, or by fax to +1-949-809-5610 and to the reviewing IRB or Ethics Committee.

Edwards shall report the event to the appropriate regulatory authorities per country specific regulations and respective adverse event classifications.

7.2 Medical Device Reporting (MDR)

Edwards 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 3.3 above.

7.3 Medical Device Reporting Outside the United States

Edwards will be responsible for reporting events to the Country Competent Authorities and EU Notified Bodies in accordance with MedDev 2.7.1 Dec 2009. Guidelines on Medical Devices.

8.0 RISK ANALYSIS

The purpose of this study is to confirm reasonable safety and effectiveness for the use of the Magna Mitral valve when compared to the Objective Performance Criteria from Annex R, Table R.1 per ISO 5840 as proposed by the US FDA in the Heart Valve Guidance draft 2009.

8.1 Potential Risks

Risks known to be associated with the use of bioprothestic heart valves and valve replacement procedures may include, but are not limited to the following: angina, cardiac arrhythmia, endocarditis, heart failure, hemolysis, hemolytic anemia, hemorrhage (bleeding), local and/or systemic infection, myocardial infarction, prothetic leaflet entrapment, prosthetic nonstructural dysfunction, prosthetic pannus, prosthesis perivalvular leak, prosthetic regurgitation, prosthetic structural deterioration, prosthesis thrombosis, thromboembolism, multi-system organ failure, non-cerebral blood clot, pericardial effusion or cardiac tamponade, respiratory failure, stroke or transient ischemic attack

Additional risks associated with the use of Carpentier-Edwards PERIMOUNT mitral valve models have been compiled from critical literature reviews and from reports received through the Edwards Lifesciences complaint handling system. These risks may include but are not limited to the following: stenosis, regurgitation through an incompetent valve, ventricular perforation by stent posts, malfunctions of the valve due to distortion at implant, and fracture of the wireform frame.

As a result of these complications, a study subject may require:

- reoperation or
- explant and replacement of the Edwards Magna Mitral valve,

OR may experience:

- permanent disability
- death

Although the Magna Mitral valve models have undergone extensive bench top and animal testing in accordance with the FDA guidance document, not all models required clinical trial data due to minor modifications.

8.2 Minimization of Risks

Potential study subjects will undergo thorough preoperative assessments and only subjects who meet the study eligibility criteria will be allowed to participate in the study. Subjects will be closely followed intraoperatively and carefully monitored in the early post-operative period through hospital discharge. Study subjects will undergo regular clinical examinations including serial blood studies to assess for hemolysis and anemia, and Doppler echocardiography examinations to assess hemodyamic performance of the valve throughout the duration of the study.

The study devices were developed, designed and manufactured under an ISO compliant quality system and in accordance with applicable guidelines and international standards including the ISO14971 Medical Design Risk Management process. The biocompatibility of all components of the valve has been established in compliance with international standards (ISO10993-1), and designed to provide hemodynamic performance similar to other commercially available valves. The sewing ring has been designed to facilitate sewing to and seating in the mitral annulus and valve materials have been selected for their durability and resistance to wear and fatigue.

The study device should be used with caution in the presence of severe systemic hypertension or when the anticipated subject longevity is longer than the known longevity of the prosthesis. Subjects undergoing dental procedures should receive prophylactic antibiotic therapy to minimize the possibility of prosthetic infection.

8.2.1 Physician Training

Each investigator will have received appropriate product training in the study protocol and investigational plan requirements by the sponsor or sponsor representative.

Data from all study sites will be monitored as it is submitted to Edwards. Qualified employees of Edwards, or a designated contract research organization (CRO), under contract with Edwards will conduct monitoring visits at the initiation of the study, periodically during the course of the study and upon study completion to assess ongoing compliance with the study protocol and adherence to protocol requirements.

8.2.2 Clinical Events Review Committee

A Clinical Events Committee (CEC) will be responsible for the ongoing review of all reported adverse events and will serve to adjudicate the relationship of the event and the study device or surgical procedure. The CEC will be composed of independent physicians familiar with the treatment of valvular heart disease and cardiac surgery and a statistician will evaluate the rates of complications, including deaths and explants for all subjects in the study as well as the hemodynamic performance of the Magna Mitral valve. The CEC will be tasked with identifying any issues such as higher than expected complication and/or death rates or unanticipated adverse events or hemodynamic performance that is substantially better or worse than expected, to determine if the study should be stopped or changed at any time.

8.2.3 Echocardiography Core Laboratory

An Echo Core Lab will provide unbiased independent review of valve hemodynamics and potential valve complications over time.

8.2.4 Data Quality Assurance

Edwards has designed quality assurance procedures to ensure that complete, accurate and timely data are collected, all Study Protocol requirements are followed and that all complications and adverse events are reported in a timely manner.

Standardized case report forms (CRFs) will be used for the collection and recording of data at all study sites. Investigators are responsible for the timely completion and submission of these forms to the Clinical Monitor.

Incoming data are reviewed to identify inconsistent or missing data and adverse events. Data problems will be addressed by telephone or written communication with the study sites and/or during site visits. All hard copy forms and data files will be secured to ensure confidentiality.

Pre-operative diagnostic tests will be evaluated by the Investigator and other appropriate professionals at the study sites to determine the study subject's suitability for the clinical study.

Investigators shall maintain all source documents required by regulation, including diagnostic test reports, laboratory results, completed case report forms, supporting medical records and informed consents. The source documents will be referenced during regular monitoring visits to verify the information documented on the case report forms.

8.3 Potential Benefits

In general, young patients, patients with chronic atrial fibrillation and who require long-term anticoagulation and patients who wish to minimize the chance of re-operation

should chose a mechanical valve[6]. Patients with implanted mechanical valves are generally considered to have a serious threat of thromboembolic adverse events thus requiring a lifelong anti-thromboembolic therapy. Even with adequate anti-thromboembolic therapy, the risk of adverse events is significant, particularly when the risk of serious hemorrhage is considered.

For patients in whom anticoagulation therapy is contraindicated and for patients who are in sinus rhythm and who wish to avoid anticoagulation therapy, a bioprosthetic (tissue) valve is preferred[6]. The ACC/AHA Guidelines for Management of Patients with Valvular Heart Disease states that it is reasonable to implant a mitral bioprostheses in patients age 65 years and older with long standing atrial fibrillation. A mitral valve replacement may be also considered appropriate for patients less than 65 years of age who are in sinus rhythm with lifestyle considerations who have been informed of the risks of reoperation vs. anticoagulation.

Bioprosthetic valves have the advantage of low thrombogenicity, which must be weighed against limited long term durability and subsequent hemodynamic deterioration and the risk of reoperation[6]. Hemodynamically, the bovine pericardial valves maximize use of the flow area and minimize flow resistance, thus providing a better solution to flow problems than the porcine valves. The bovine pericardium has superior intrinsic properties to porcine aortic valve, notably in terms of collagen content[20] and tolerance to high bending curvatures which can favorably influence the long-term mechanical durability of pericardial valves.

Although the proven longevity of bioprostheses is not as long as that of some of the currently available mechanical valves, results from a multi-center study involving the original Carpentier-Edwards PERIMOUNT mitral valve model 6900 showed actuarial freedom from explant due to structural valve deterioration (SVD) to be 68.8% $\pm$ 4.7%. Results from the same study showed overall actuarial survival rate to be 37.1% $\pm$ 3.3% and valve related survival rate to be 63.1% $\pm$ 4.4% at 14 years. Actuarial freedom from

adverse events at 14 years was as follows: thromboembolism, 83.8% ± 3.2% and hemorrhage, 86.6% ± 3.2%[20]. Subjects participating in this study will be closely followed to monitor their health and safety.

8.4 Risk /Benefit Analysis

The Clinical Risk Assessment has been revise to consider the Model 7300/7300TFX. Please refer to Appendix 9 attached.

9.0 STATISTICAL ANALYSIS

Please refer to Sections 11.1 – 11.3 for study sample size calculations, and a summary of the study analysis plan . Sections 11.4 and 11.5 address the issues of data poolability and missing data. Unless otherwise noted, all statistical tests will be performed at the $\alpha = 0.05$ level.

9.1 Sample Size Calculation

The sample size calculation for the trial is based on the primary safety endpoints. The linearized rates for thromboembolism, all hemorrhage, all perivalvular leak, and endocarditis will be compared to the Objective Performance Criteria from Annex R, Table R.1 per ISO 5840 as proposed by the US FDA in the Heart Valve Guidance draft 2009. These OPC are presented in Table 11.

Table 11: Safety OPC

Adverse Event	OPC
Thromboembolism	2.5
All Hemorrhage	1.4
All Perivalvular Leak	1.2
Endocarditis	1.2

More specifically, a statistical test based on the Poisson 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 λ is the linearized 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:

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

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.[32] 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 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*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.[32].

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 approximately 90%, based on 7 year follow up data for the Carpentier-Edwards PERIMOUNT 6900/6900P valve (this proportion is essentially constant across each annual visit). 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

$$1-\sum_{x=1}^{101}\binom{n}{x}p^{x}(1-p)^{n-x}>98.7\%$$

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 56% from Thourani, et al. [33], a sample size of 212 subjects fulfills the requirements of the equation above. Based on the data collected in a previous post approval study conducted by 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 250 to account for up to a 15% rate of lost to follow up.

The STS Executive Summary 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]. In order to reflect actual market use of the Carpentier-Edwards PERIMOUNT Magna Mitral valve, of the 250 subjects enrolled in the study, approximately 38 are anticipated to be those patients eligible for simultaneous aortic and mitral valve replacement.

9.2 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 and have NYHA assessment at 8 years post implant.

9.3 Safety Analysis

9.3.1 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 Objective Performance Criteria from Annex R, Table R.1 per ISO 5840 as proposed by the US FDA in the Heart Valve Guidance draft 2009.

For reporting purposes, the percent of subjects who experience an early adverse events 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.

9.4 Secondary Safety Endpoints

The analysis of secondary safety endpoints will be presented for the entire study cohort and also stratified by valve size according to the Tissue Annulus Diameter (TAD) and by valve model (7000/7000 TFX, 7200 and 7300/7300TFX).

9.4.1 Blood Data

Blood data (red blood count, white blood count, hematocrit, plasma free hemoglobin (or Haptoglobin and SLDH), reticulocyte and platelet counts) 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 and valve model.

9.4.2 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 for the entire study cohort and also stratified by valve size and valve model. Analyses for time to explant and time to reoperation will also be stratified by fatal versus non-fatal events.

9.4.3 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. These analyses will be reported for the entire study cohort and also stratified by valve size and valve model.

9.5 Effectiveness Analysis

The effectiveness analyses will be reported for the entire study cohort and also stratified by valve size according to the Tissue Annulus Diameter (TAD) and valve model (7000/7000 TFX ,7200 and 7300/7300 TFX).

9.5.1 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 with be tabulated at each follow-up interval. The percentage of the subjects in NYHA Classes I or II at 8 years post implant will be calculated to determine if it is≥ 75% using a one - sided Binomial exact test. This analysis will also be reported stratified by valve size and valve model**.**

9.5.2 Hemodynamic Performance

Echocardiography data will be obtained preoperatively, early postoperatively and/or discharge, at 6-months and at 1, 2, 4, 6 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 valve size. Regurgitation data will be summarized using frequency at each severity level by time interval and valve size. Improvement in regurgitation at one year will be analyzed via the Jonckheere-Terpstra test[34]. Change at one year from baseline for all other hemodynamic outcomes will be analyzed using paired *t*-tests. These analyses will also be reported for the entire study cohort and also stratified by valve model.

9.6 Poolability

Subject baseline risk will be statistically compared between centers and regions (ie,. United States vs. Canada, United States vs. Europe, United States vs. Asia Pacific, and United States vs. Israel). 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 adjusted for both model 7000/7000TFX, model 7200TFX and models 7300/7300TFX according to the TAD. 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.

9.7 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.

To further demonstrate the impact of lost of the follow-up on the effectiveness calculation; a bootstrapped simulation for missing data imputation will be generated as described below:
For each subject who is alive and for whom NYHA assessment is not available at the 8 year post implant follow up visit (Subject A), the last year for which NYHA data is available will be identified (year X).

Separately, a sub group (Group A) of subjects with the same pre-operative and year X NYHA information as Subject A, available data at 8 year post-implant will be identified.

Subsequently, an observed value from the pool of subjects in sub group A will be selected randomly and used to impute the NYHA classification for subject A at 8 years post implant.

The above steps (1-3) will be performed for each subject who is lost to follow up before the 8 year post implant follow-up visit.

Lastly, steps 1 – 4 above will be repeated 999 times to generate 1000 estimated percentages of subjects with NYHA in classes I or II at 8 years post implant. The central 95th percentile for the 1000 estimated percentages will be calculated.

The central 95th percentile generated by the simulation will reflect the variability in the primary effectiveness endpoint estimate caused by lost to follow up.

10.0 ETHICAL AND REGULATORY CONSIDERATIONS

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

10.1 Subject Informed Consent and Institutional Review Board/Ethical Review Committee

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 (Appendix 2).

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. If an IRB or EC does not exist, the head of surgery or medical director of the institution must approve the use of the subject informed consent form and protocol. A written statement by the IRB/ERC or head of surgery / medical director

indicating approval of the subject informed consent form and protocol must be submitted to the sponsor prior to study initiation.

10.2 Health Economic Information

In the United States only, the Sponsor may choose to obtain billing information such as charges associated with the 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.

10.3 Case Report Forms (CRFs)

Case report forms (CRFs) for individual subjects will be provided by Edwards (Appendix 5). 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.

Stadardized CRFs will be used to record all study data. All data should be recorded accurately and completely. Paper CRFs should be filled out using a blue or black ball point pen, and all handwritten comments must be legible for monitoring review and data entry purposes. Errors should be corrected by drawing a single line through the erroneous data, and recording the correction next to the data field. All corrections must be initialed and dated by the person who makes the change. Copies of the changed paper form must be provided to the sponsor and retained in the subject study file.

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 as completed 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.

CRFs 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.

Completed CRFs must be signed by the principal investigator, co-investigator or his or her designee as listed in the Designation of Authority form for each subject receiving a study valve.

Source data (including originals or copies of pre-operative assessments, operative records, reports, postoperative examinations, laboratory and other test results) shall be retained at the study center and shall be made available for inspection by the study sponsor, the study monitor, and authorized regulatory bodies upon request.

Source data shall be de-identified in order to protect the privacy of the study subject and comply with HIPAA regulations in the US and European data protection laws.

10.4 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 study at any time.

10. 5 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.

10.6 Study Responsibilities

10.6.1 Investigator Responsibilities

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

Study records including CRFs, signed Agreement, originals of all blood and hemodynamic studies, signed subject informed consent forms, a copy of the implant data card, IRB/Ethics Committee approval letters, the log of IRB/Ethics Committee submissions, and other documents pertaining to the conduct of the study must 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
- US Department of Health and Human Services: Health Insurance Portability and Accountability Act of 1996 (HIPAA)

In Europe, study sites are responsible for complying with all applicable regulations including:

- EU Medical Device Vigilance System
- Declaration of Helsinki
- Local and Regional Privacy Laws

- Local and Regional Laws of the Country including Data Protection and ISO 14155 parts 1 & 2: Clinical Investigation of Medical Devices in 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 Mitral valves will be closely followed. Any unusual or unanticipated adverse events will be reported immediately to the sponsor (see section 9.2) and if applicable, to the IRB/Ethics Committee as outlined in the Investigator's Statement and Agreement. If deemed necessary by the investigator, the IRB/Ethics Committee or the sponsor, the study may be suspended pending a thorough study of the incident.

If the investigator wishes to assign the files to someone else or remove 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-investigator, an amended agreement must be completed promptly. Any other personnel changes must 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.

10.6.2 Study Monitor/Sponsor 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 individuals 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.

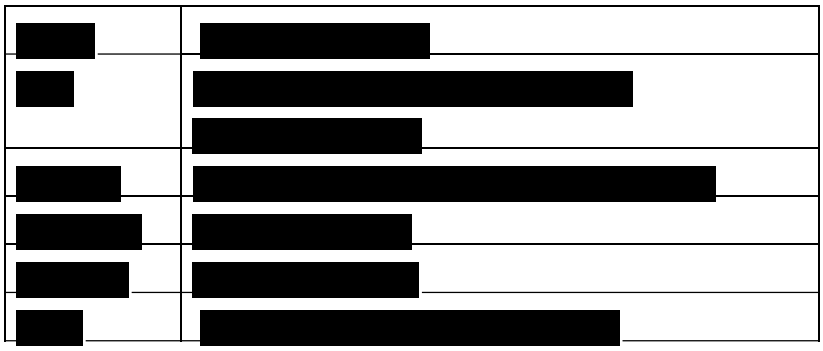
The study monitor will be responsible for monitoring CRFs and visiting the site periodically to monitor study progress and compliance with the study protocol. Monitoring visits will be scheduled throughout the duration of the study at a mutually convenient time for the monitor and principal investigator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

10.6.3 Clinical Monitor

The clinical monitor(s) is responsible for the conduct and administration of this clinical study. These responsibilities include maintaining regular contact with each study site and conducting on-site monitoring visits at each study site at least once per year to ensure compliance with this study protocol, to verify that accurate and complete data are being submitted in a timely manner and to verify that the study site facilities continue to be adequate.

The primary contact for this study is:



10. 7 Study Changes

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

10. 8 Implant Data Card

After implantation, subjects will be given the Implant Data Card by the Investigator prior to discharge (See Section 8.3.1 and Appendix 7). This identification card allows subjects to inform healthcare providers what type of implant they have when they seek care.

10.9 Study Publication

Investigator shall submit to Edwards early drafts of all abstracts, manuscripts or presentations authored by investigator 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 investigator regarding proprietary information which shall not be divulged or the patentability of any inventions disclosed in the manuscripts. If requested by Edwards, investigator 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.

11.0 REFERENCES

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

2. Carpentier A. Cardiac Valve Surgery—the "French Correction". *Journal of Thoracic Cardiovascular Surgery* 1983; 86:323-337.

3. Olson LJ *et. al.,* Surgical pathology of the mitral valve: a study of 712 cases spanning 21 years. *Mayo Clin Proc.* 1987; 62:22-34.
4. Edward NR *et. al.,* Mitral valve repair and replacement in northern New England. *American Heart Journal* 2003; 145(6): 1058-1062.

5. Executive Summary STS 10 year Report, December 2007.

6. Gudbjartsson T. *et. al*., Mechanical/Bioprosthetic mitral valve replacement. In: Cohn LH eds. Cardiac Surgery in the Adult. New York: McGraw-Hill, 2003:951-986.

7. Chikwe J *et. al.,* The surgical management of mitral valve disease. *British Journal of Cardiology* 2004; 11(1): 42-48.

8. The American College of Cardiology/American Heart Association 2006 Guidelines for the Management of Study subjects with Valvular Heart Disease.

9. Schaff H Vi , Suri R Mi . Multiple Valve Disease. Cohn Lh, ed. Cardiac Surgery in the Adult. New York: McGraw-Hill, 2008:1129-1158.

10. Bortolotti U, Milano A, Testolin L, et al: Influence of type of prosthesis on late results after combined mitral-aortic valve replacement. Ann Thorac Surg 1991; 52:84.

11. Brown PJ, Roberts CS, McIntosh CL, et al: Relation between choice of prostheses and late outcome in double-valve replacement. Ann Thorac Surg 1993; 55:631.

12. Cohn LH. Et al., Tricuspid regurgitation secondary to mitral valve disease: when and how to repair. *Journal of Thoracic Cardiovascular Surgery* 1994; 9:237-241

13. De VegaNG, et al., La annuloplastia selective regulable y permanente: una tecnica original para el tratamiento de la insufficienca tricuspide. *Rev Esp Cardiolo* 1972; 25: 555-62.

14. McCarthy PM, Bhudia SK, Rajeswaran J, et al. Tricuspid valve repair: durability and risk factors for failure. *J Thorac Cardiovasc Surg*. 2004; 127: 674-685

15. Matsuyama K, Matsumoto M, Sugita T, et al. Predicotrs of residual tricuspid regurgitation after mitral valve surgery. *Ann Thorac Surg*. 2003; 75: 1826-1828.

16. Duran CM, et al., Is tricuspid valve repair necessary? *J Thorac Cardiovasc Surg*. 1980; 80: 849-860

17. Dreyfus GD, Corbi PJ, Chan KM, Bahrami T. Secondary tricuspid regurgitation or dilatation: which should be the criteria for surgical repair? Ann Thorac Surg 79:127-132.

18. Guidelines on the management of valvular heart disease by the European Society of Cardiology, 2007.

19. McCarthy PM, Bhudia SK, Rajeswaran J, et al. Tricuspid valve repair: durability and risk factors for failure. J Thorac Cardiovasc Surg. 2004; 127: 674-685.

20. Marchand MA *et. al.,* Fifteen year experience with the mitral Carpentier-Edwards PERIMOUNT pericardial bioprostheses. *Ann Thoracic Surgery* 2001; 71: S236-9.

21. David TE *et. al.*, Late results of heart valve replacement with the Hancock II bioprostheses. *J. Thorac Cardiovasc Surg* 2001; 121:268-78. *ARTICLES*

22. Myken PS *et. al*., Seventeen-year experience with the St. Jude Medical Biocor porcine bioprostheses. *The Journal of Heart Valve Disease* 2005; 14: 486-492. *ARTICLES*

23. Carpentier A. From valvular xenograft to valvular bioprostheses (1965-1977). *Med. Instrum.* 1977; 11(2); 98-101.

24. Carpentier A., *et. al.*, Continuing improvements in valvular bioprostheses. *J. Thorac. Cardiovasc. Surg.* 1982; 83(1): 27-42.

25. Bonow RO *et. al.*, ACC/AHA 2006 Guidelines for the management of study subjects with valvular heart disease. *JACC* 2006; Vol. 48, No. 3, e1-e148.

26. Edmunds, LH, Jr. *et al.* Guidelines for reporting morbidity and mortality after cardiac valvular operations. *J Thorac Cardiovasc Surg* 1988; 96: 351-353.

27. Akins, CW *et al.* Guidelines for reporting mortality and morbidity after cardiac valve interventions. *J Thorac Cardiovasc Surg* 2008;135:732-738.

28. Yoganathan, AP *et al.* In vitro hemodynamic characteristics of tissue bioprostheses in the aortic position. *J. Thorac Cardiovasc Surg* 1986; 9212:198-209.

29. Liao K *et. al*., Bovine Pericardium versus porcine aortic valve: comparison of tissue biological properties as prosthetic valves. *Artificial Organs* 1992; 16(4) 261-365.

30. Vesely I *et. al.*, Comparison of the compressive buckling of porcine aortic valve cusps and bovine pericardium. *The Journal of Heart Valve Disease* 1998; 7:34-39.

31. FDA 1994 draft Replacement Heart Valve Guidance

32. Grunkemeier GL, et al., Sample size requirements for evaluating heart valves with constant risk events. *The Journal of Heart Valve Disease* 1994; 3:53-8

33. Thourani VH et al., Outcomes and long-term survival for study subjects undergoing mitral valve repair versus replacement: effect of age and concomitant coronary artery bypass grafting. *Circulation* 2003; 108:298-304

34. Sprent P et al., Applied nonparametric statistical methods. *Chapman & Hall / CRC*. New York, New York 2001

12.0 APPENDIX 1- STS GUIDELINES FOR REPORTING MORBIDITY AND MORTALITY AFTER CARDIAC VALVULAR OPERATIONS

The Journal of
Thoracic and Cardiovascular Surgery

Guidelines for reporting mortality and morbidity after cardiac valve interventions

Cary W. Akins, D. Craig Miller, Marko I. Turina, Nicholas T. Kouchoukos, Eugene H. Blackstone, Gary L. Grunkemeier, Johanna J.M. Takkenberg, Tirone E. David, Eric G. Butchart, David H. Adams, David M. Shahian, Siegfried Hagl, John E. Mayer and Bruce W. Lytle

J Thorac Cardiovasc Surg 2008;135:732-738
DOI: 10.1016/j.jtcvs.2007.12.002

Guidelines

Guidelines for reporting mortality and morbidity after cardiac valve interventions

Cary W. Akins, MD,[a] D. Craig Miller, MD,[a] Marko I. Turina, MD,[c] Nicholas T. Kouchoukos, MD,[b] Eugene H. Blackstone, MD,[a] Gary L. Grunkemeier, PhD,[b] Johanna J. M. Takkenberg, MD, PhD,[c] Tirone E. David, MD,[a] Eric G. Butchart, MD,[c] David H. Adams, MD,[b] David M. Shahian, MD,[b] Siegfried Hagl, MD,[c] John E. Mayer, MD,[b] and Bruce W. Lytle, MD[a]

Since the initial publication of "Guidelines for Reporting Morbidity and Mortality After Cardiac Valvular Operations" in 1988,[1] followed by a revised version in 1996,[2] valvular heart surgery has evolved to include an enhanced understanding of patient- and disease-related factors affecting outcomes, increased numbers of valve repairs, more operations performed for patients with minimal symptoms, new prostheses, novel repair methods, and the emergence of percutaneous interventional (catheter-based) valve repair and replacement. To adapt to this changing environment, the Councils of the American Association for Thoracic Surgery, The Society of Thoracic Surgeons, and The European Association for Cardio-Thoracic Surgery have directed an Ad Hoc Liaison Committee for Standardizing Definitions of Prosthetic Heart Valve Morbidity to review current clinical practice to update and clarify these reporting guidelines. The guidelines are intended to cover treatment of all four cardiac valves in both adult and pediatric patients. Further, these guidelines apply uniformly, irrespective of whether the therapy was carried out as a conventional open operation, as a minimally invasive (video-assisted or robotic) surgical procedure, or with percutaneous interventional catheter techniques.

From The American Association for Thoracic Surgery,[a] The Society of Thoracic Surgeons,[b] and the European Association for Cardio-Thoracic Surgery.[c]

This article is being published concurrently in *The Annals of Thoracic Surgery* and the *European Journal of Cardio-Thoracic Surgery*.

Received for publication Dec 11, 2007; accepted for publication Dec 11, 2007.

Address for reprints: Cary W. Akins, MD, Cardiac Surgery, Cox 648, Massachusetts General Hospital, 55 Fruit St, Boston, MA 02114 (E-mail: cakins@partners.org).

J Thorac Cardiovasc Surg 2008;135:732-8

0022-5223/$34.00

doi:10.1016/j.jtcvs.2007.12.002

Purpose

These reporting guidelines are intended to facilitate analysis and reporting of clinical results of various therapeutic approaches to diseased heart valves such that meaningful comparisons can be made and inferences drawn from investigations of medical, surgical, and percutaneous interventional treatment of patients with valvular heart disease.

Early Mortality

Early mortality is to be reported as all-cause mortality at 30, 60, or 90 days and depicted by actuarial estimates (with number remaining at risk and confidence intervals [CIs]) or as simple percentages, regardless of the patient's location, be it home or in a health care facility.

Definitions of Morbidity

Structural Valve Deterioration

Structural valve deterioration includes dysfunction or deterioration involving the operated valve (exclusive of infection or thrombosis), as determined by reoperation, autopsy, or clinical investigation. Clinical investigation should include periodic echocardiographic surveillance. Substantially increased regurgitation or stenosis of the

Abbreviation and Acronym
CI = confidence interval

operated valve over time should be reported with quantitative or semiquantitative methods. The term *structural valve deterioration* refers to changes intrinsic to the valve, such as wear, fracture, poppet escape, calcification, leaflet tear, stent creep, and suture line disruption of components of a prosthetic valve; it also refers to new chordal rupture, leaflet disruption, or leaflet retraction of a repaired valve.

Nonstructural Dysfunction

Nonstructural dysfunction is any abnormality not intrinsic to the valve itself that results in stenosis or regurgitation of the operated valve or hemolysis. The term *nonstructural dysfunction* refers to problems (exclusive of thrombosis and infection) that do not directly involve valve components yet result in dysfunction of an operated valve, as diagnosed by reoperation, autopsy, or clinical investigation. Examples of *nonstructural dysfunction* include the following: entrapment by pannus, tissue, or suture; paravalvular leak; inappropriate sizing or positioning; residual leak or obstruction after valve implantation or repair; and clinically important intravascular hemolytic anemia. In addition, *nonstructural dysfunction* includes development of aortic or pulmonic regurgitation as a result of technical errors, dilatation of the sinotubular junction, or dilatation of the valve annulus after either valve replacement with stentless prostheses (eg, pulmonary autograft, aortic allograft, and xenograft valves) or aortic valve-sparing operations if the cusps are seen to be normal at reoperation, autopsy, or clinical investigation. For percutaneous and transapical approaches to aortic valve replacement or conventional open aortic valve replacement, new onset of coronary ischemia from coronary ostial obstruction or paravalvular aortic regurgitation is considered *nonstructural dysfunction*. More than mild recurrent or residual mitral or tricuspid regurgitation after surgical or percutaneous interventional valve procedures (coronary sinus interventions, direct reparative methods, or other methods aimed at achieving ventricular remodeling) is *nonstructural dysfunction,* unless there is disruption of the valve components themselves, which would then be *structural deterioration*.

Sudden or progressive dysfunction or deterioration of the operated valve may be structural, nonstructural, or both, as determined by reoperation, autopsy, or clinical investigation.

Valve Thrombosis

Valve thrombosis is any thrombus not caused by infection attached to or near an operated valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Valve thrombus found at autopsy in a patient whose cause of death was not valve related or found at operation for an unrelated indication should also be counted as *valve thrombosis*.

Embolism

Embolism is any embolic event that occurs in the absence of infection after the immediate perioperative period. *Embolism* may be manifested by a *neurologic event* or a *noncerebral embolic event*.

A *neurologic event* includes any central, new neurologic deficit, whether temporary or permanent and whether focal or global, that occurs after the patient emerges from anesthesia.

Stroke is a prolonged (>72 hours) or permanent neurologic deficit that is usually associated with abnormal results of magnetic resonance imaging or computed tomographic scans. Patients with minimal, atypical, or protean symptoms that lead to radiographic imaging demonstrating an acute ischemic event are considered to have sustained a *stroke*.

Transient ischemic attack is characterized by fully reversible symptoms of short duration. If radiographic imaging demonstrates an acute central neurologic lesion (''cerebral infarction with transient symptoms''), however, such patients are reclassified as having sustained a *stroke*.

Multiple or repeated transient events occurring during a short period (a burst or *cluster*) should be recorded as one event for calculation of event rates, but documented as a *cluster*. Rate calculations should be provided not only for all embolic events but also separately for *strokes, transient ischemic attacks,* and *clusters*.

Postoperative neurologic symptoms that mimic those of a preoperatively documented neurologic event and that are confirmed radiographically to be consistent with the former event are not counted as a new neurologic event. Central neurologic events that are clearly related to aortic, internal carotid artery, or vertebral artery disease, such as acute thrombotic occlusion, atheroembolism, or spontaneous arterial dissection, are also not counted. *Psychomotor deficits* found by specialized testing are not considered neurologic events related to operated valves. Patients who do not awaken or who awaken after operation with a new stroke are not considered to have sustained valve-related neurologic events.

A *noncerebral embolic event* is an embolus documented operatively, at autopsy, or clinically that produces signs or symptoms attributable to complete or partial obstruction of a peripheral artery. Intraoperative myocardial infarctions are not counted. Postoperative myocardial infarction is also not counted unless the infarction is caused by a coronary embolus (as detected by operation, autopsy, or clinical imaging). Emboli consisting of nonthrombotic material (eg, atherosclerosis, myxoma) are not counted.

Bleeding Event

A *bleeding event* is any episode of major internal or external bleeding that causes death, hospitalization, or permanent

injury (eg, vision loss) or necessitates transfusion. Major bleeding unexpectedly associated with minor trauma should be reported as a *bleeding event,* but bleeding associated with major trauma or a major operation should not. *Bleeding events* are reported for all patients regardless of whether they are taking anticoagulants or antiplatelet drugs. Although total *bleeding events* must be reported, *bleeding events* can also be reported separately for those who are taking anticoagulants or antiplatelet agents and those who are not.

Antithrombotic Management

The method of initiating antithrombotic treatment during hospitalization should be specified (eg, intravenous unfractionated heparin, subcutaneous low-molecular-weight heparin, antiplatelet agent). If oral anticoagulant therapy is instituted, the following information should be specified: (1) specific drug used (eg, warfarin sodium, acenocoumarol, phenprocoumon), (2) target international normalized ratio for each valve position, (3) average achieved international normalized ratio, (4) method of anticoagulation control (eg, physician or nurse directed, patient home self-management), and (5) duration of treatment for patients with bioprostheses. If antiplatelet drugs are used, they should be specified.

If the patient has a *valve thrombosis, embolism,* or *bleeding event,* the international normalized ratio associated with that event should be reported, together with any antiplatelet therapy.

Composite Thrombosis, Embolism, and Bleeding

The *composite end point of thrombosis, embolism, and bleeding* includes occurrence of all events meeting the previously stated definitions of *valve thrombosis, embolism,* and *bleeding event.* Because thrombogenicity and intensity of anticoagulation may be manifested by several separate complications, this composite end point represents a more accurate overall assessment of the total hazard of thrombogenicity and anticoagulation.[3]

Operated Valve Endocarditis

Operated valve endocarditis is any infection involving a valve on which an operation has been performed. The diagnosis of *operated valvular endocarditis* is based on one of the following criteria: (1) reoperation with evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histologic or bacteriologic studies; (2) autopsy findings of abscess, pus, or vegetation involving a repaired or replaced valve; or (3) in the absence of reoperation or autopsy, meeting of the Duke Criteria for endocarditis.[4] Positive blood cultures are not required for the diagnosis of *operated valve endocarditis. Culture-negative endocarditis* should refer only to negative blood culture results and not just the absence of any proof of infection. Morbidities associated with active infection, such as *valve thrombosis,* thrombotic embolus, *bleeding event,* or paravalvular leak, are included under this category, but not counted in other categories of morbidity.

Reintervention

Reintervention is any surgical or percutaneous interventional catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted prosthesis or repaired valve. In addition to surgical reoperations, enzymatic, balloon dilatation, interventional manipulation, repositioning, or retrieval, and other catheter-based interventions for valve-related complications are also considered *reinterventions.* Indications for *reintervention* must be reported. Open surgical and percutaneous catheter *reinterventions* should be listed separately.

Valve-Related Mortality

Valve-related mortality is any death caused by *structural valve deterioration, nonstructural dysfunction, valve thrombosis, embolism, bleeding event,* or *operated valve endocarditis;* death related to *reintervention* on the operated valve; or *sudden, unexplained death.* Deaths caused by heart failure in patients with advanced myocardial disease and satisfactorily functioning cardiac valves are not counted. Specific causes of valve-related deaths should be reported.

Sudden, Unexplained Death

A *sudden, unexplained death* is one in which the cause of death has not been determined by clinical investigation or autopsy findings and the relationship to the operated valve is undefined. These deaths should be reported as a separate category, but also included in *valve-related mortality.*

Cardiac Death

Cardiac death includes all deaths resulting from cardiac causes. This category includes *valve-related deaths, sudden unexplained deaths,* and deaths from non–valve-related cardiac causes (eg, from heart failure, acute myocardial infarction, or documented arrhythmias).

All-Cause Mortality

All-cause mortality includes all deaths from any cause after a valve intervention. Survival should be referenced to an age- and sex-matched sample from the representative general population being investigated whenever possible.

Permanent Valve-Related Impairment

Permanent valve-related impairment is any permanent neurologic or other functional deficit caused by *structural valve deterioration, nonstructural dysfunction, valve thrombosis, embolism, bleeding event, operated valve endocarditis,* or *reintervention.*

Major Adverse Valve-Related Event

Major adverse valve-related events include the following: (1) *valve-related mortality,* (2) all valve-related morbidity, and (3) need for new permanent pacemaker or defibrillator within 14 days after the valve intervention.

Data Collection

Data collection and reporting for all treated valves should include *location* (aortic, mitral, tricuspid, pulmonary, multiple), *treatment method* (repair, replacement, percutaneous catheter intervention), *repair methods* if valve preserved (including type of annuloplasty ring, suture annuloplasty, or coronary sinus cerclage), and, for valve replacement, *prosthesis type* (mechanical prosthesis, stented bovine pericardial or porcine bioprosthesis, stentless xenograft bioprosthesis, aortic or pulmonary allograft, pulmonary autograft). For prostheses, including annuloplasty rings, *manufacturer* and *model* should be reported. For allografts, method of preservation should be given. Manufacturer *label size* should be stated for each valve location, type, and model; in addition, calibrated annulus size (or maximal dilatation balloon diameter during preliminary balloon valvuloplasty and during valve deployment in cases of percutaneous aortic valve replacement) before valve implantation should also be reported. Not only should the number of treated valves be listed, so too should the number of patients who received them.

Additional Pertinent Material

In addition, the report should specify the following:

1. The patient *population* from which the study cohort was selected, preferably according to CONSORT (Consolidated Standards of Reporting Trials) recommendations (see http://www.consort-statement.org). Inclusive dates of operation and whether the series was consecutive should be stated. Criteria used to select patients should be defined and listed. If a subset of the sample population is reported, the total number of patients who underwent valve intervention during the inclusive dates of the clinical investigation should be reported.
2. The method used for *follow-up*. This includes *type* of follow-up, which may be *active* (direct contact with patients or their families by examination, telephone, letter, or questionnaire) or *passive* (use of administrative or government data not involving direct patient contact). *Mode* of follow-up should be included, whether prospective *anniversary* contact (although periodic follow-up may be at intervals shorter or longer than 1 year) or *cross-sectional,* whereby an entire group of patients is followed up more or less at the same calendar time despite their index procedures having occurred at widely disparate times.
3. Percentages of patient-level *responses* from each method should be given. In case of an anniversary-type follow-up, frequency of follow-up inquiry should be provided.
4. Total *follow-up time* (patient-years), mean (and SD) or median (and quartiles) if the distribution of data is skewed, and maximum years of follow-up should be given. If the study involves multiple valve positions, treatment methods, repair techniques, and prosthesis types, total follow-up time for each should be reported separately.
5. The *time period* (closing interval) required to complete current follow-up should be given if the common closing date method is not used. The closing interval, in which the current status of all patients is determined, should be as short as possible. Alternatively, the status of all patients at their exact anniversary dates, or as of the receipt of the first response to a cross-sectional inquiry, may be used as a *common closing date*.
6. Completeness of follow-up can be calculated as the ratio of total observed person-time to potential person-time of follow-up to the closing date of the study.[5] Although follow-up to death (or explant in a valve-oriented analysis) is 100% complete, because of deaths, observable patient-years will be less than potential patient-years. A modification can be made of Clark and colleagues' C statistic to account for this, which will yield a somewhat higher percentage.[6] To improve statistical validity, every effort should be made to achieve complete current follow-up for more than 90% of patients.
7. Percentage of autopsies and documented modes of death should be reported.

Data Analysis and Reporting

The method of reporting data should facilitate comparison between reports and support the conclusions, inferences, and predictions made. Methods chosen to analyze the collected data depend on the purpose of the report and availability of analytic techniques. Methods used to collect and analyze data should be summarized in the Methods section, with references included or defined in an appendix.

Percentages (Not Time Related)

Some morbid events occurring within a short time frame may be reported as simple percentages, that is, the number of events divided by the number of patients (eg, 30-, 60-, or 90-day mortality), as long as the status of all patients is known. Percentages should be presented with CIs[7] and may be compared by Pearson's χ^2 test or Fisher's exact test.[8] Logistic regression analysis[9] is available for evaluating the simultaneous influence of several risk factors on a dichotomous outcome variable (percentage) and is often used to establish

a risk model, that is, a mathematical formula incorporating such factors.

Time-Related Events

Valve-related events should be reported in a time-related manner, with time of treatment designated as time zero. Kaplan–Meier[10] or other life table techniques[11] provide actuarial estimates of morbid events, and these should be reported with 1 or 2 SEs of the estimate (equivalent to 68% or 95% CIs). Number of patients remaining at risk should be indicated at appropriate intervals, and curves should use dashed lines beyond time frames containing few patients, such as 10% of the initial cohort in a typical-size (hundreds, not thousands, of patients) study. Although comparisons between subsets of patients can be made, actuarial methods are not predictive beyond the time of the last actuarial estimate and cannot be adapted to multivariable analysis. These methods are called *nonparametric* or *distribution free* because they do not assume a particular statistical distribution or model.

Risk Factors

The *Cox proportional hazards* model[12] produces a time-dependent analysis of valve-related events and provides a multivariable regression method to discriminate risk factors associated with specific valve-related morbid events during specific intervals. The Cox method is a semiparametric (model partially specified) approach that makes no assumption about the shape of the underlying hazard function, but identifies risk factors and estimates multipliers of the baseline hazard. These multipliers are the relative risks (called *hazard ratios*) associated with the risk factors. Several methods are available for assessing the assumption of proportional hazards.[13] When such methods reject the hypothesis of proportional hazards, one can be reasonably sure that the method is inappropriate and alternatives to it are needed; if the hypothesis is not rejected, one unfortunately has not learned much, because these methods are sensitive to number of events and tend to be conservative.

Results of a multivariable analysis should be accompanied by a list of the variables considered and a tabular presentation of the numeric results. When modeling event risk (by either logistic or Cox regression), the amount of information available is based on number of events, not number of patients or patient-years. Thus, it is important that a sufficient number of events occur to enable accurate estimates. A "rule of 10" events as the minimum per risk factor considered in the model has been advocated for both logistic regression[14] and Cox regression,[15] although this minimum could be lowered a bit.[16] In cases of few events per risk factor, resampling techniques can be used to test model validity.

Temporal Pattern of Risk

A *fully parametric method* (model completely specified) of calculating a hazard function of valve-related morbid events defines the instantaneous risk of an event at any time after treatment.[17 20] Such methods permit univariable and multivariable analysis (including those specific to various time frames, such as early vs long-term risk), provide predictive information beyond the time of the last event, indicate whether the risk is constant, and provide CIs. For example, the hazard function for structural valve deterioration for bioprostheses is not constant across time, but increases with time since insertion; a Weibull function that accommodates an increasing hazard with time should be considered.[21,22]

Linearized rates

If the risk of an event is constant over time, there is a simple method to calculate that rate. The linearized rate is calculated as total number of observed events divided by total patient-years of follow-up. It is often expressed as events per 100 patient-years (percent per year). These rates should be considered only approximate unless the hazard function for the complication under study is constant during the entire interval considered, which is often not true for complications after a cardiac valve procedure. Linearized rates should be reported with CIs, which can be based on the Poisson distribution[23] or on likelihood ratio methods for comparing the means of exponential distributions.[11,23] Linearized rates can be compared with the likelihood ratio test,[19,20,24] a test that is based on the F statistic,[12,20] or within appropriate multivariable models.

Repeated events

Some valve-related events, such as thromboembolism and bleeding, can occur repeatedly. Although estimating freedom from any such event is meaningful, even more important is enumerating all such events. Some of the previously mentioned methods have been devised or extended to consider repeated events in the same patient.[17,25,26] A simple and widely used approach uses linearized rates, as described previously, to estimate the incidence of multiple events. These rates should be considered only approximate unless the risk of recurrent events is the same as for initial events (which is often not the case). If it is not, a simple approach is to restart time zero at each event occurrence.

Valve Outcome Versus Patient Outcome

Time-related events that estimate valve performance are measured from time of treatment until time of patient death, valve explantation, or censoring; however, patients are interested in learning what events they may encounter during the remainder of their lives. Thus, patient outcome should be measured starting at the time of treatment until death (or censoring). Because patient death competes with event occurrence, it is important to make a clear distinction between valve performance and patient outcome. Because the Kaplan–Meier method assumes patient immortality when estimating cumulative freedom from events, it overestimates

the actual probability of event occurrence for the patient (or a particular patient population). To translate valve outcome (valve performance) to patient outcome (risk of an adverse event), the cumulative incidence method is recommended. For assessment of valve prosthesis performance or durability of repair, which focuses on the valve rather than the patient as the unit of measure, Kaplan–Meier and related actuarial methods are appropriate, rather than cumulative incidence methods.[27] The Kaplan–Meier method is usually used to estimate occurrence of valve-related events. This method is not perfect, because it assumes independence between death and the event of interest, which in most instances is not true. Inverse probability weighting may correct for this to provide a better estimate of true valve performance.[28]

Longitudinal Outcomes

Time-related events after valve replacement are assumed to occur at an instant in time; however, many outcomes of importance are conditions or processes that evolve with time, such as return of regurgitation after valve repair, change in New York Heart Association functional class (graded or ordinal outcomes), regression of ventricular mass (continuous outcome), and use of warfarin sodium (binary outcome).[29] Values for these outcomes are captured at discrete instances in time (''snapshots''), which may be taken repeatedly at prospectively specified follow-up intervals, cross-sectionally, or opportunistically.

Snapshots are subject to many biases. If a condition changes rapidly but snapshots are taken infrequently, aliasing is introduced. If opportunistic follow-up occurs only when symptoms recur, the prevalence of undesirable change may be overestimated. Change is also related to precision of measurements; for example, degree of mitral regurgitation depends on systolic blood pressure and quality of the echocardiogram. Of course, the entire series of assessments is truncated by death or by removal of the valve of interest.

The challenge in analyzing longitudinal data is estimating the average temporal pattern of outcome and its variability in the group of patients. This average must account for sampling challenges, censoring (truncation) by death, unequal number of repeated measurements of the outcome per patient, variability in time among repeated measurements (such as serial echocardiographic assessment at different intervals after treatment), and the fact that sequential measurements obtained for a given patient will be more correlated with themselves than will measurements between individuals. Thus, these kinds of data, methods of longitudinal data analysis have developed rapidly during the last two decades.[30] These methods include mixed models, random and fixed effects models, generalized estimating equation approach, and hierarchic models (such as currently used for The Society of Thoracic Surgeons National Database risk assessment).[31 33] Longitudinal data analysis of a series of assessments is superior to analyzing only condition at last follow-up. This methodology is also superior to dichotomizing outcomes and analyzing them with actuarial methods as if they were events, such as freedom from grade 3+ mitral regurgitation after repair.

We acknowledge the invaluable assistance given by Cindy VerColen of The American Association for Thoracic Surgery for the organization of this review and development of this document.

References

1. Edmunds LH Jr, Cohn LH, Weisel RD. Guidelines for reporting morbidity and mortality after cardiac valvular operations. *J Thorac Cardiovasc Surg*. 1988;96:351-3.
2. Edmunds LH Jr, Clark RE, Cohn LH, Grunkemeier GL, Miller DC, Weisel RD. Guidelines for reporting morbidity and mortality after cardiac valvular operations. Ad Hoc Liaison Committee for Standardizing Definitions of Prosthetic Heart Valve Morbidity of The American Association for Thoracic Surgery and The Society of Thoracic Surgeons. *J Thorac Cardiovasc Surg*. 1996;112:708-11.
3. Akins CW. Results with mechanical cardiac valvular prostheses. *Ann Thorac Surg*. 1995;60:1836-44.
4. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, et al. Proposed modifications to the Duke criteria for the diagnosis of infectious endocarditis. *Clin Infect Dis*. 2000;30:633-8.
5. Clark TG, Altman DG, De Stavola BL. Quantification of the completeness of follow-up. *Lancet*. 2002;359:1309-10.
6. Wu YX, Takkenberg JJ, Grunkemeier GL. Measuring follow-up completeness. *Ann Thorac Surg*. 2008. In press.
7. Vollset SE. Confidence intervals for a binomial proportion. *Stat Med*. 1993;12:809-24.
8. Fleiss JL, Levin B, Paik MC. Statistical methods for rates and proportions. 3rd ed. New York: Wiley Interscience; 2003.
9. Hosmer DW, Lemeshow S. Applied logistic regression. 2nd ed. New York: Wiley Interscience; 2000.
10. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-81.
11. Cutler SJ, Ederer F. Maximum utilization of the life table method in analyzing survival. *J Chron Dis*. 1958;8:699-712.
12. Cox DR, Oakes D. Analysis of survival data. London: Chapman and Hall; 1984.
13. Hess KR. Graphical methods for assessing violations of the proportional hazards assumption in Cox regression. *Stat Med*. 1995;14:1707-23.
14. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol*. 1996;49:1373-9.
15. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis. II. Accuracy and precision of regression estimates. *J Clin Epidemiol*. 1995; 48:1503-10.
16. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol*. 2007;165:710-8.
17. Blackstone EH, Naftel DC, Turner ME Jr. The decomposition of time-varying hazard into phases, each incorporating a separate stream of concomitant information. *J Am Stat Assoc*. 1986;81:615-24.
18. Cohen A, Whitten BJ. Parameter estimation in reliability and life span models. New York: Marcel Dekker; 1988.
19. Lawless JF. Statistical models and methods for lifetime data. 2nd ed. New York: John Wiley; 2003.
20. Gross AJ, Clark VA. Survival distributions: reliability applications in the biomedical sciences. New York: John Wiley; 1975.
21. Banbury MK, Cosgrove DM 3rd, White JA, Blackstone EH, Frater RW, Okies JE. Age and valve size effect on the long-term durability of the Carpentier-Edwards aortic pericardial bioprosthesis. *Ann Thorac Surg*. 2001;72:753-7.
22. Grunkemeier G, Li HH, Naftel DC, Starr A, Rahimtoola SH. Long-term performance of heart valve prostheses. *Curr Probl Cardiol*. 2000;25: 73-154.
23. Sahai H, Khurshid A. Confidence intervals for the mean of a Poisson distribution: a review. *Biom J*. 1993;35:857-67.

24. Lee ET, Wang JW. Statistical methods for survival data analysis. New York: John Wiley; 2003.
25. Nelson W. Graphical analysis of system repair data. *J Qual Technol*. 1988;20:24-35.
26. Nelson W. Hazard plotting for incomplete failure data. *J Qual Technol*. 1969;1:27-52.
27. Bodnar E, Blackstone EH. Editorial: an 'actual' problem: another issue of apples and oranges. *J Heart Valve Dis*. 2005;14:706-8.
28. Grunkemeier GL, Jin R, Eijkemans MJ, Takkenberg JJ. Actual and actuarial probabilities of competing risks: apples and lemons. *Ann Thorac Surg*. 2007;83:1586-92.
29. Banbury MK, Cosgrove DM 3rd, Thomas JD, Blackstone EH, Rajeswaran J, Okies JE, et al. Hemodynamic stability during 17 years of the Carpentier-Edwards aortic pericardial bioprosthesis. *Ann Thorac Surg*. 2002;73:1460-5.
30. Diggle PJ, Heagerty PJ, Liang KY, Zeger SL. Analysis of longitudinal data. 2nd Ed. New York: Oxford University Press; 2002.
31. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics*. 1982;38:963-74.
32. Morris CN. Parametric empirical Bayes inference: theory and applications. *J Am Stat Assoc*. 1983;78:47-55.
33. Goldstein H. Multilevel statistical models, 3rd ed. London: Edward Arnold; 2003.

Guidelines for reporting mortality and morbidity after cardiac valve interventions

Cary W. Akins, D. Craig Miller, Marko I. Turina, Nicholas T. Kouchoukos, Eugene H. Blackstone, Gary L. Grunkemeier, Johanna J.M. Takkenberg, Tirone E. David, Eric G. Butchart, David H. Adams, David M. Shahian, Siegfried Hagl, John E. Mayer and Bruce W. Lytle

J Thorac Cardiovasc Surg 2008;135:732-738
DOI: 10.1016/j.jtcvs.2007.12.002

The Journal of
Thoracic and Cardiovascular Surgery

13.0 APPENDIX 2: SAMPLE SUBJECT INFORMED CONSENT FORM AND HIPAA AUTHORIZATION

Subject Informed Consent form for Participation in Research
Introduction
You are being asked to participate in a research study that will evaluate the Carpentier-Edwards® PERIMOUNT® Magna® Mitral/Magna Mitral Ease™ Bioprostheses, model 7000/7000TFX/7200TFX/7300/7300TFX (also referred to as Magna Mitral valve). The Magna Mitral valve, Model 7000/7000TFX and Model 7200TFX received FDA approval in August 2008 and July 2009, respectively. Model 7300/7300TFX received FDA approval in June 2010.

You are being asked to participate in this research study because your mitral valve is not working properly and your doctor determined that it needs to be replaced. This Magna Mitral valve will be used to replace your diseased mitral valve or a previously implanted prosthesis. Your participation in this research study is voluntary.

Background and Purpose
The purpose of this research study is to learn about the safety and how well the Magna Mitral Valve works for up to eight years in a minimum of 250 subjects at up to 25 hospitals. It is anticipated that the research study will be completed in approximately 10 years.

Procedures
You will undergo routine evaluation including: medical history evaluation, a physical exam, a transthoracic echocardiogram (a probe is placed on your chest and images of your heart are recorded) and laboratory blood work.

The Study Doctor will screen you to decide if you are eligible to participate in this research study. If you are eligible, the Study Doctor will explain the study procedures.

A representative from Edwards Lifesciences may be present in the operating room at the time of your surgery.

After your surgery you will be asked to remain in contact with your cardiologist and/or Study Doctor for a minimum of eight years to monitor your medical progress. Regular visits after the surgery include tests such as laboratory blood work and transthoracic echocardiography. This is the standard procedure for all patients who have an artificial valve. No other procedures will be required for this study.

Risks
The treatment of choice for your disease is heart valve replacement, and that alternative valves are available. The risks of placement of the valve is similar to those associated with any heart valve replacement surgery. As with any prosthetic heart valve, there is a possibility that unforeseeable adverse events could develop that were not anticipated. Your Study Doctor has already discussed any appropriate alternative procedures and these adverse events in detail.

If you have a related complication after the surgery, as described to you by your Study Doctor, you should contact _____(the doctor responsible for your follow-up) at _____.

Benefits
You may or may not receive any direct benefit from this research study of the Magna Mitral Valve, but others may benefit in the future from your participation. Your participation in this study is voluntary and it is your right to refuse to participate or withdraw without penalty or loss of benefits to which you are otherwise entitled.

Financial Obligation and Liability
Edwards Lifesciences is the manufacturer of the Magna Mitral valves and the sponsor of this study. Edwards Lifesciences will charge the hospital a fee for purchase of the prosthesis, and such charges will be incorporated in the hospital's charges to you. This charge is comparable to the cost of other commercially available prostheses. You or your insurance company will be responsible for the cost of this procedure. You will not be paid for your participation in this study. Edwards Lifesciences shall not compensate you for injury or for any additional expenses incurred because of this study.

The hospital cannot assume liability for injury directly attributable to the use of this particular valve or any other valve. In the event physical injury occurs as a result of participating in this study, the necessary facilities, emergency treatment and professional medical services will be available to you, just as they are to the general community.

Confidentiality and Anonymity
After surgery, the doctor who implanted the valve or one of his staff members will give you a card called the Implant Data Card. This card has the name and contact information of the surgeon who implanted the valve as well as the name of the hospital where you had the surgery. This card has information that helps Edwards Lifesciences to indentify the valve that was implanted in your heart. This card allows you to inform healthcare providers what type of implant you have when you seek care.

Upon implantation of the valve, the data collected from your participation may be used for publications on the results of the heart valve you have received. Your participation in this study will remain confidential and any data that may be published will not reveal your identity. Information that is derived from this study will be given to the Edwards Lifesciences and to Federal and other Regulatory agencies, as required in the interest of public safety and regulations. The U.S. Food and Drug Administration, for example, may inspect research records and learn your identity if this study falls within its jurisdiction. By participating in this study, you agree to allow representatives of Edwards Lifesciences, who are involved with this study to have access to your medical records concerning the device. You will also allow them to photocopy information from your medical records for study purposes.

As part of this study, Edwards Lifesciences seeks to gather data in order to assess the costs of the procedure and hospital services prior to, during and following the procedure, and that you are being asked to sign a separate Medical Billing Release Form. Signing the Medical Billing Release Form will only affect whether cost information is collected and will have no impact on your consent to participate in all other aspects of the study.
While participating in this study, you will not participate in any other research project without approval from the Study Doctor. This is to protect you from possible injury arising from such events as extra blood draws, x-rays, interaction of research drugs, or similar hazards.

Any significant new findings that develop during the research study which may relate to your willingness to continue your participation will be provided to you by the Study Doctor. The study investigator may choose to terminate your participation, if you fail to follow the study guidelines, or in view of new information, at any time during the study.

All forms of medical diagnosis and treatment, whether routine or experimental, involve some risk of injury. In spite of all precautions, you might develop medical adverse events from participating in this study. If such adverse events arise, the Study Doctor will assist you in obtaining appropriate medical treatment, but this study does not provide financial assistance for additional medical or other costs. You may withdraw your consent to participate in this study and discontinue participation without penalty at any time. You do not waive any liability rights for personal injury by signing this form.

Voluntary Participation and Termination
You are voluntarily agreeing to participate in this research study and accept the program as outlined above. If the study design or the use of the information is to be changed, you will be informed and your consent will be re-obtained. Please tell your doctor right away if you wish to stop participating in this study. If you decide to stop being a part of the study, your doctor will tell you if there will be any effects or consequences. For your safety, your doctor may ask you to continue to receive care, such as medical tests, even after you quit the study.

You acknowledge that you have read, or have had read to you, the information provided above. You have been given an opportunity to ask questions and all of you questions have been answered to your satisfaction. You also acknowledge that you have been given a copy of this Consent Form.

BY SIGNING THIS FORM, I WILLINGLY AGREE TO PARTICIPATE IN THE RESEARCH IT DESCRIBES.

Subject's Name	Signature of Subject	Date

SIGNATURE OF INVESTIGATOR

I have explained the research to the subject, and answered all of his/her questions. I believe that he/she understands the information described in this document and freely consents to participate.

Name of Investigator	Investigator's Signature	Date	Hospital

SIGNATURE OF WITNESS (optional)

My signature as witnessed certified that the subject signed this consent form in my presence as his/her voluntary act and deed.

Name of Witness	Signature of Witness	Date

Authorization (consent) to permit the use and disclosure of identifiable medical information (protected health information) for research purposes in the United States.

Study Title: Carpentier-Edwards® PERIMOUNT® Magna® Mitral Pericardial Bioprostheses Model 7000/7000TFX and Carpentier-Edwards® PERIMOUNT® Magna Mitral Ease™ Pericardial Bioprostheses Model 7200TFX/7300/7300TFX.

Principal Investigator: (Insert PI name here)

Participant's Name: _____

1. What is the purpose of this form?

The research study in which you are participating may help researchers learn more about the causes, or how to prevent and treat your condition. Researchers would like to use your health information for research. This information may include data that identifies you. Please carefully review the information below. If you agree that researchers can use your personal health information, you must sign and date this form to give them your permission.

2. What personal health information do the researchers want to use?

The researchers want to copy and use the portions of your medical record that they will need for their research. If you enter a research study, information that will be used and/or released may include (but not limited to) the following:

- The history and diagnosis of your disease;
- Specific information about the treatments you received, including previous treatment(s) you may have had;
- Information about other medical conditions that may affect your treatment;
- Medical data, including laboratory test results, measurements, CT scans, MRIs, x-rays, and pathology results;
- Information on side effects (adverse events) you may experience, and how these were treated;
- Long-term information about your general health status and the status of your condition;
- Data that may be related to tissue and/or blood samples that may be collected from you; and
- Numbers or codes that will identify you, such as your medical record number.

3. Why do the researchers want your personal health information?

(Insert reason for use of personal health information here)

4. Who will be able to use your personal health information?

(Insert your institution and department) will have access to the data than includes protected health information.

(Insert your institution and department) will use your health information for research. As part of this research, the below listed groups may have access to your information: (insert all groups that will have access to or receive information)

- The study's sponsor or representative of the sponsor;
- Public Health agencies and other government agencies as authorized or required by law;
- Other people or organizations assisting the company(ies) sponsoring the research with the research efforts;
- Central laboratories, central review centers, and central reviewers. The central laboratories and review agencies may also give your health information to those groups listed in the bullets above;
- The Office of Human Research Protection (OHRP) and/or Food and Drug Administration (FDA)

5. How will information about you be kept private?

Only researchers will have access to your information. We will not release personal health information about you to others except as authorized or required by law and institutional policy. However, once your information is given to other organizations that are not required to follow federal privacy laws, we cannot assure that the information will remain protected.

6. What happens if you do not sign this permission form?

Taking part in a research study is completely voluntary and there is no penalty if you choose not to participate. If you decide not to sign this permission form you will not be able to take part in the research study for which you are being considered. The choice is completely up to you.

7. If you sign this form, will you automatically be entered into the research study?

No, you cannot be entered into any research study without further discussion and a separate consent. After discussion, you may decide to take part in the research study. At that time, you will be asked to sign a specific research consent form.

8. What happens if you want to withdraw your permission?

You can change your mind at any time and withdraw your permission to allow your personal health information to be used in the research. If this happens, you must withdraw your permission in writing. Beginning on the date you withdraw your permission, no new personal

health information will be used for research. However, researchers may continue to use the health information that was provided before you withdrew your permission.

If you sign this form and enter the research study, but later change your mind and withdraw your permission, you will be removed from the research study at that time.

To withdraw your permission, please contact the principal investigator at the number listed below. The study team will make sure your written request to withdraw your permission is processed correctly.

(Insert contact information for the principal investigator or study coordinator)

9. How long will this permission last?

If you agree by signing this form that researchers can use your personal health information, this permission has no expiration date. However, as stated above, you can change your mind and withdraw your permission at any time.

Signatures

You agree that your personal health information may be used for the research purposes described in this form.

_____

Subject's Name	Signature of Subject	Date

Person Obtaining Permission

Name of Investigator	Investigator's Signature	Date

Medical Billing Release Form

1. Study subject's Name: _____
2. Date of Birth: __/__/____ (mm/dd/yyyy)
3. Study subject's Medical Record Number: _____
4. Social Security Number: ___-__-____
5. Is study subject Medicare eligible? ❒ YES ❒ NO
   If yes, Medicare Beneficiary Number _____

The research study you have agreed to participate in to evaluate the Carpentier-Edwards PERIMOUNT Magna Mitral / Magna Mitral Ease Bioprostheses model 7000/7000TFX/7200TFX /7300/7300TFX (the "Magna Mitral valve") includes gathering data in order to assess the costs of the valve replacement procedure and hospital services related to that procedure.

By signing this form, you authorize the Edwards Lifesciences, which is the manufacturer of the Magna Mitral Valve and sponsor of the research study (the "Sponsor") and its representatives to access and use the information set forth in items 1 through 5 above to collect copies of your medical bills for any hospital services potentially related to the valve replacement procedure, whether those services occur prior to, during, or following the procedure.

In doing so, you authorize the Patient Accounting Department at any hospital where you receive care potentially related to the valve replacement procedure to disclose these billing records to the Sponsor. This process may take up to 5 years following your enrollment in the study.

You understand that this information collected by the Sponsor will be kept strictly confidential and be used solely to assess the medical expenses that occur as a result of the valve replacement procedure. The cost information may be added to the pool of cost data collected in the study and included in summary form in publication, but any such data will not reveal the information set forth in items 1 through 5 above.

Additionally, you understand that you have the right to: (1) refuse to sign this authorization; (2) withdraw this authorization at any time by giving written notice to the address listed at the bottom of this form, with the knowledge that this action will not affect any information collected before the notice of withdrawal is received; and (3) receive a copy of this authorization.

6. This billing information may be collected from _____ (study enrollment date) to _____ (5 years from date of enrollment).

7. Signature: _____ ❒ Study Subject
   ❒ Proxy _____
   (relationship)

To withdraw authorization, forward notice of withdrawal to: [add contact information]

14.0 APPENDIX 3: ECHO CORE LAB PROTOCOL

EDWARDS ECHOCARDIOGRAPHY GUIDELINE: CLINICAL STUDIES CONDUCTED FOR MITRAL BIOPROSTHESES

REVISION D: NOVEMBER 18, 2013

Edwards Lifesciences LLC
One Edwards Way
Irvine, CA USA 92614

Table of Contents

1 CONTACT INFORMATION 3

1.1 EDWARDS EUROPE ..... **ERROR! BOOKMARK NOT DEFINED.**
1.2 EDWARDS UNITED STATES / CANADA 3
1.3 CORE LAB EUROPE 3
1.4 CORE LAB UNITED STATES / CANADA 3

2 CLINICAL SITE PROCEDURES 3

2.1 DATA COLLECTION 3
2.2 PERFORMING THE ECHO EXAM 3
2.3 SUBMITTING MEDIA TO THE EUROPEAN CORE LAB 4
2.4 SUBMITTING MEDIA TO THE US / CANADA CORE LAB 4

3 SPONSOR PROCEDURES 5

3.1 MATERIALS 5
3.2 DATA AUDITS 5

4 CORE LAB PROCEDURES 5

4.1 RECEIVING EXAM MEDIA 5
4.2 ECHO TRACKING CASE REPORT FORM (CRF) 5
4.3 ASSESS THE EXAM 6
4.4 DATA COLLECTION / CALCULATION 7
4.4.1 Two-dimensional echo variables 7
4.4.2 Left Ventricle Ejection Fraction 8
4.4.3 Doppler Mitral Valve 8
4.4.4 Doppler LVOT 9
4.4.5 Doppler Aortic Valve 9
4.4.6 Calculated Variables 10
4.4.7 Left Ventricle Assessment 10
4.4.8 Mitral Valve Regurgitation 11
4.4.9 Mitral Valve Stenosis 11
4.4.10 Non-study valve assessment 11
4.5 RECORDS 12

Attachment 1: Core Lab Shipment Log
Attachment 2: Core Lab Receipt Log
Attachment 3: Echo Tracking Form
Attachment 4: Case Report Form

Contact Information

1.1 Edwards United States / Canada/ Europe

[redacted]

1.2 Core Lab Europe

[redacted]

1.3 Core Lab United States / Canada

[redacted]

2 Clinical Site Procedures

2.1 Data Collection

The Clinical site should record the date of the exam, time period, reason for the exam, and a physical assessment of the patient on the Echocardiography Tracking Data Form. Physical assessments are to include heart rate, height, weight, and blood pressure.

2.2 Performing the Echo Exam

Echocardiography exams are to be performed for each time point as specified in the study's Clinical Protocol. The examinations should be conducted as on the example CD provided by the Core lab. The following views should be obtained:

- parasternal long axis view
- parasternal short axis view
- apical four chamber view
- apical two chamber view
- apical three chamber view (apical long axis)
- subcostal four chamber
- subcostal short axis, if necessary
- right parasternal, if necessary
- right suprasternal, if necessary

The sonographer should record 3 beats per view for patients in sinus rhythm and at least 5 beats per view for patients in atrial fibrillation.

2.3 Submitting Media to the European Core Lab

Echo exams should be saved to CD, DVD, or Tape. The preferred format is AVI. Information that can identify the study patient should not be included in the image, or media label. The media should be labeled with the patient's study identification number, initials, time interval and date of assessment. Every echo submission needs to be accompanied by the Echo Tracking Form. Finalized echo media should be sent together with the respective Echo Tracking Form to the respective Core lab listed in section 1.

Alternatively, the echo media can be collected from the site by the respective monitor.

The person (site or sponsor personnel) who sends the echo media to the Core lab should document this on the Core lab Shipment Log (see attachment 1).

2.4 Submitting Media to the US / Canada Core Lab

Echo exams should be saved to CD, DVD, or Tape. The preferred format is DICOM format on CD, with a DICOMDIR (DICOM Directory) file. Information that can identify the study patient should not be included in the image, or media label. The media should be labeled with the patient's study identification number, initials, time interval and date of assessment. Every echo submission needs to be accompanied by a copy of the Echo

Tracking Form. Finalized echo media should be sent together with the respective Echo Tracking Form to the respective Core lab listed in section 1.

Alternatively, the echo media can be collected from the site by the respective monitor.

The person (site or sponsor personnel) who sends the echo media to the Core lab should document this on the Core lab Shipment Log (see attachment 1).

3 Sponsor Procedures

3.1 Materials

Upon request, sponsor will provide the study sites with CDs, DVDs or video tapes.

3.2 Data Audits

The sponsor may conduct an audit of the Core Lab(s) at least once a year. The purpose of the audit is to verify that the conditions of the consulting agreement are being met, ensure proper storage of study media, and ensure study data are complete and accurate An audit of study data may be accomplished by a review of echo reports (print-outs from the echo machine or handwritten) or by observing the Core Lab complete a series of evaluations of study media.

4 Core Lab Procedures

4.1 Receiving Exam Media

The echo core lab should record all incoming echo media on the Core Lab Received log (See Attachment 2). Echos should be assessed within 4 weeks after receipt. The Core lab should inform the sponsor immediately if received echocardiographic images are not evaluable or of poor quality.

4.2 Echo Tracking Form

Verify the label on the media corresponds with the echo tracking form

4.3 Assess the Exam

The quality of the echo will be assessed using the following scale:

Table 1: Echo Quality	
Rating	**Definition**
Excellent	excellent visualization of all structures of the heart
Good	good visualization of LV, LA, LVOT, artificial valve and the endocardial borders
Fair	fair visualization of LV, artificial valve and LVOT; structures and borders can be detected
Unreadable	inadequate visualization of endocardial borders, artificial valve and LVOT; structures and borders cannot be detected

The quality of the Doppler will be assessed using the following scale:

Table 2: Doppler Quality	
Rating	**Definition**
Excellent	Pulsed wave Doppler and continuous wave Doppler envelope are distinct and sharp, peak systolic, diastolic, in color mode atrial reversal velocities can be obtained in excellent pattern
Good	Pulsed wave Doppler and continuous wave Doppler envelope are distinct, peak systolic, diastolic, and atrial reversal velocities in color doppler with precise information
Fair	reduced quality of continuous and pulsed wave doppler curves, but doppler envelopes are readable, peak systolic, diastolic, and atrial reversal velocities can be obtained
Unreadable	fails to yield peak systolic, diastolic, and atrial reversal velocities, color doppler not readable

4.4 Data Collection / Calculation

4.4.1 Two-dimensional echo variables

The variables listed in Table 3 will be measured.

Table 3: 2D Echo Variables

Variable	Unit	Plausible Range	Measured by
Interventricular Septal thickness (IVS)	mm	5 – 30	End-diastolic endocardial border-to-endocardial border of the interventricular septum, assessed in the parasternal long-axis view below the level of the mitral leaflets, perpendicular to the visually assessed long-axis of the left ventricle; excluding RV trabeculae.
Left Ventricular Internal Diameter in diastole (LVEDD)	mm	30 – 90	End-diastolic endocardial border-to-endocardial border of the LV cavity assessed in the parasternal long-axis view below the level of the mitral leaflets, perpendicular to the visually assessed long-axis of the left ventricle.
Posterior Wall thickness (end diastolic) (PW)	mm	5 – 30	End-diastolic endocardial border-to-epiocardial border of the LV posterior wall, assessed in the parasternal long-axis view below the level of the mitral leaflets, perpendicular to the visually assessed long-axis of the left ventricle; excluding the pericardial space.
Left Ventricular Internal Diameter in systole (LVESD)	mm	5 – 90	Systolic endocardial border-to-endocardial border of the LV cavity assessed in the parasternal long-axis view below the level of the mitral leaflets, perpendicular to the visually assessed long-axis of the left ventricle, at the time of minimal LV diameter.
Left Atrium (LA)	mm	19 – 70	Systolic endocardial border-to-endocardial border of the LA cavity assessed in the parasternal long-axis view, perpendicular to the visually assessed long-axis of the left ventricle, at the time of maximal LA size and measured at the location of maximal LA diameter.
Left Ventricular Outflow Tract (LVOT)	mm	14 – 30	Mid-systolic endocardial border-to-endocardial border of LVOT ~ 1 cm below level of aortic valve annulus that correlates with location of LVOT pulsed-wave Doppler sample volume, assessed in the parasternal long-axis view, perpendicular to the visually assessed long axis of the LVOT.

4.4.2 Left Ventricle Ejection Fraction

Ejection Fraction can be measured visually or using Simpson's method. If Simpson's method is used, the left ventricular end diastolic and end systolic volume are to be measured and recorded.

Table 4: Ejection Fraction		
Variable	**Unit**	**Plausible Range**
Left Ventricular Ejection Fraction (LVEF)	%	1 – 100

4.4.3 Doppler Mitral Valve

The variables listed in Table 5 will be measured.

Table 5: Doppler Mitral Valve			
Variable	**Unit**	**Plausible Range**	**Measured / Calculated by**
Mitral Valve Peak Flow Velocity (VmaxMV)	m/s	0.5 – 3.0	Continuous-wave Doppler envelope from apical window: maximal shift from baseline during antegrade flow through the mitral valve in diastole (E-wave or A-wave).
Mean Pressure Gradient: Mitral Valve (MPG MV)	mm Hg	1.0 – 20.0	Continuous-wave Doppler envelope from apical window: computer-assisted planimetry of area under the spectral Doppler envelope of antegrade flow through the mitral valve in diastole, from flow onset (E-wave) until end-diastole as determined by ECG QRS onset. (Note: zero velocity during late diastole should be included in the planimetry to avoid over-estimation of mean transmitral gradient).
Peak Pressure Gradient: Mitral Valve (PPG MV)	mm Hg	1.0 – 36.0	Either: ($4 \times VmaxMV^2$ as determined above, or the computer-generated peak gradient derived from MV MPG continuous-wave Doppler planimetry above.
Mitral Valve Time Velocity Integral (TVI MV)	cm	50 - 999	From MV MPG planimetry as above, the area under the curve of the continuous wave spectral Doppler signal for antegrade transmitral flow during diastole from an apical window.

4.4.4 Doppler LVOT

The variables listed in Table 6 will be measured.

Table 6: Doppler LVOT			
Variable	**Unit**	**Plausible Range**	**Measured by**
LVOT Time Velocity Integral (TVI LVOT)	cm	50 – 300	Pulsed-wave spectral Doppler of the LVOT from an apical window with the sample volume ~ 1 cm below the aortic valve annulus: area under the curve using computer-assisted planimetry of the Doppler envelope, from flow onset through flow cessation.
Heart Rate (HR)	min^{-1}	35 – 199	Determined by QRS R-R interval () at the time of pulsed-wave Doppler assessment of the LVOT. HR may be derived from the echocardiographic ECG sensor if it is accurate, or is calculated as 6×10^4 / R-R interval (ms)

4.4.5 Doppler Aortic Valve

The variables listed in Table 7 will be measured.

Table 7: Doppler Aortic Valve			
Variable	**Unit**	**Plausible Range**	**Measured / Calculated by**
Aortic Valve Peak Flow Velocity (VmaxAV)	m/s	0.5 – 4.0	Continuous-wave spectral Doppler from apical, right parasternal or suprasternal window: maximal shift from baseline during antegrade flow through the aortic valve in systole.
Mean Pressure Gradient: Aortic Valve (MPG AV)	mm Hg	1.0 – 39	Continuous-wave spectral Doppler from apical, right parasternal or suprasternal window: computer-assisted planimetry of area under spectral Doppler envelope of antegrade flow through aortic valve in systole
Aortic Valve Time Velocity Integral (TVI AV)	cm	50 – 999	Continuous-wave spectral Doppler from apical, right parasternal or suprasternal window: area under the curve using computer-assisted planimetry of the Doppler envelope, from flow onset through flow cessation.

4.4.6 Calculated Variables

The variables listed in Table 8 will be measured.

Table 8: Calculated Variables			
Variable	**Unit**	**Plausible Range**	**Calculated by**
Stroke Volume (SV)	mL	30 – 200	Derived as the product of TVI LVOT (cm)and cross-sectional area of the LVOT (= π x ((LVOT diameter/2)^2) (cm^2)
Cardiac Output (CO)	L/min	2.0 – 8.0	Derived as the product of SV (cm^3) and HR (min^{-1}): SV x HR/1000
Cardiac Index (CI)	$L/min/m^2$	1.0 – 4.0	Derived as the ratio of CO (L/min) to body surface area.
Effective Orifice Area: Mitral Valve (EOA MV)	cm^2	1.0 – 8.0	Derived using the continuity equation and the values to TVI MV, TVI LVOT and LVOT cross-sectional area (CSA, described above): EOA MV = (TVI LVOT x CSA LVOT) / TVI MV.

4.4.7 Left Ventricle Assessment

The left ventricle will be assessed for the presence of the conditions listed in Table 9. Other conditions may also be noted.

Table 9: Left Ventricle Assessment	
Finding	**Definition**
Significant wall motion abnormality	Defined as hypokinesis, akinesis or dyskinesis of ≥ 1 anterior circulation myocardial segment or ≥ 2 posterior circulation myocardial segments.
Apical and/or Left Atrial Thrombus	Defined as a soft-tissue density mass clinically consistent with thrombus noted in the left atrium or left ventricle.
Pericardial Effusion	Defined as an echo-lucent space external to and adjacent to the heart, clinically consistent with pericardial effusion. Trace/Minimal: Pericardial effusion evident only in systole but not in diastole. Small: Pericardial effusion larger than trace but no more than 1 cm in maximal diameter, Moderate: Pericardial effusion larger than small but no more than 2 cm in maximal diameter, Large: Pericardial effusion larger than moderate

4.4.8 Mitral Valve Regurgitation

The Mitral valve will be assessed for the presence of the regurgitation. If regurgitation is present the location of the leak will be noted as paravavlular, central, or indeterminate. Regurgitation will also be graded as described in Table 10. The method of calculation for mitral regurgitation will be noted as Color Doppler, Regurgitant Fraction, PISA, or Pulmonary Vein Flow.

Table 10: Mitral Valve Regurgitation	
Finding	**Definition**
+1 Trivial / Trace	Physiological regurgitation, typically penetrating no more than 1 cm into the left atrium and/or a small non-holosystolic regurgitation jet.
+2 Mild	< 20% ratio of regurgitant jet area to left atrial area.
+3 Moderate	20 – 40% ratio of regurgitant jet area to left atrial area.
+4 Severe	> 40% ratio of regurgitant jet area to left atrial area.

4.4.9 Mitral Valve Stenosis

The Mitral valve will be assessed for the presence or absence of the stenosis. Stenosis is present if there is significant antegrade flow acceleration across the mitral valve in diastole, and/or a mean transmitral gradient > 6 mm Hg

4.4.10 Non-study valve assessment

If the echo exam allows, the non study valves (aortic, tricuspid, or pulmonic) should be assessed for the presence of the regurgitation and stenosis. Regurgitation will also be graded as described in Table 11.

Table 11: Non-study Valve Regurgitation	
Finding	**Definition**
None / Trivial	Clinical assessment of no regurgitation or physiological regurgitation.
Mild	Clinical assessment of mild regurgitation.
Moderate	Clinical assessment of moderate regurgitation.
Severe	Clinical assessment of severe regurgitation.

Stenosis will also be graded as described in Table 12.

Table 12: Non-study Valve Stenosis	
Finding	**Definition**
None / Trivial	Clinical assessment of no stenosis or hemodynamically insignificant.
Mild	Clinical assessment of mild stenosis.
Moderate	Clinical assessment of moderate stenosis.
Severe	Clinical assessment of severe stenosis.

4.5 Records

Echo media and copies of echo reports and Case Report Forms will be filed in a secure location for the duration of the study. Only authorized Core Lab personnel should have access to the media and data. Original (white) and yellow Case Report Forms (CRF) will be sent to or collected by the sponsor. The pink copy of the Echocardiography Data CRF remains at the Clinical site. Alternative to 3-part NCR Echocardiography Data CRF is permissible with Sponsor prior approval. Originals or copies of the Echocardiography Tracking Data Form will be provided to the Core Lab.

ATTACHMENT 1

CORELAB SHIPMENT LOG

Edwards Lifesciences

CORE LAB SHIPMENT LOG

CEP Magna Mitral
Study Number 2006-05

Site Name: _____ **Site #:** _____

Investigator: _____

Subject ID	Follow-Up Interval	Date of Echo	Date Shipped	Tracking Number

ATTACHMENT 2

CORELAB RECEIVED LOG

Edwards Lifesciences

CORE LAB RECEIVED LOG

CEP Magna Mitral
Study Number 2006-05

Site Name: _____ **Site #:** _____

Investigator: _____

Subject ID	Follow-Up Interval	Date of Echo	Date Received	Date Echo-CRF sent to EW

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | | Patient Initials (First, Last) | | | Clinic # | | | |

ATTACHMENT 3

ECHO TRACKING FORM

Study Number 2006-05

Edwards

Carpentier-Edwards PERIMOUNT Magna Mitral Valve

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | | Patient Initials (First, Last) | | | Clinic # | | | |

Please Provide The Following Information:

1. ECHO DATE: __ __ __ / __ __ / __ __ __ __
MMM DD YYYY

2. TIME PERIOD: ***(Required preoperatively, at discharge, 6-months, 1, 2, 4, 6 and 8 year follow-up visits)***

- ☐ Preoperatively (≤ 6 months prior to implant)
- ☐ Discharge or 30 days
- ☐ 6 Months (3-6 months)
- ☐ 1 Year (11 – 13 months)
- ☐ 2 Years (23 – 25 months)
- ☐ 4 Years (47 – 49 months)
- ☐ 6 Years (71 – 73 months)
- ☐ 8 Years (95 – 97 months)
- ☐ Other *(Specify):* _____ ☐ Months ☐ Years

3. ECHO RECORDED ON (MEDIA):

☐ Tape ☐ CD
☐ MOD ☐ DVD

4. REASON FOR ECHO:

- ☐ Per protocol
- ☐ Symptomatic, study valve related
- ☐ Symptomatic, non-study valve related
- ☐ Other *(Specify):* _____

5. PHYSICAL ASSESSMENT:

Heart Rate __ __ __ (BPM)
Height __ __ __ (cm)
Weight __ __ __ (kg)
Blood Pressure __ __ __ / __ __ __ (mmHg)

6. DATE MEDIA SENT: __ __ __ / __ __ / __ __ __ __
(**OR COLLECTED**) MMM DD YYYY

ATTACHMENT 4

CASE REPORT FORMS

Edwards

Study Number 2006-05
Carpentier-Edwards PERIMOUNT Magna Mitral Valve

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | | Patient Initials (First, Last) | | | Clinic # | | | |

1. Echo Date: __ __ __/__ __/__ __ __ __
MMM DD YYYY

2. Time Period:
☐ Preoperatively ☐ 1 Year ☐ 6 Year
☐ Discharge ☐ 2 Year ☐ 8 Year
☐ 6 Month ☐ 4 Year ☐ Other *(Specify):* _____ ☐ Months ☐ Years

3. Transducer Position:
☐ Transthoracic
☐ Transesophageal
☐ Other *(Specify):*
_____

4. Echo Quality: *(Select one)*
☐ Excellent
☐ Good
☐ Fair
☐ Poor
☐ Unreadable

5. Doppler Quality: *(Select one)*
☐ Excellent
☐ Good
☐ Fair
☐ Unreadable

6. 2D Echo Variables:
__ __ (mm)IVS
__ __ (mm)LVEDD
__ __ (mm)PW
__ __ (mm)LVESD
__ __ (mm)LA
__ __ (mm)LVOT

7. Left Ventricle Ejection Fraction:
__ __ . __ (%) ☐ Visual
☐ Simpson's
__ __ __ (mL) LV EDV
__ __ __ (mL) LV ESV

8. Doppler Mitral Valve:
__ . __ (m/s) V_{max} MV
__ __ . __ (mmHg) MPG MV
__ __ . __ (mmHg) PPG MV
__ __ . __ (cm) TVI MV

9. Doppler LVOT:
__ __ . __ (cm) TVI LVOT
__ __ __ (min^{-1}) HR (LVOT PW Doppler)

10. Doppler Aortic Valve:
__ . __ (m/s) V_{max} AV
__ __ . __ (mmHg) MPG AV
__ __ . __ (cm) TVI AV

11. Calculated Variables:
__ __ . __ (mL) SV
__ __ . __ (L/min) CO
__ . __ ($L/min/m^2$)CI
__ . __ __ (cm^2) EOA MV

12. Left Ventricle Assessment *(Check all that apply)*
☐ No abnormalities
☐ Significant Wall Motion Abnormality
☐ Apical and/or Left Atrial Thrombi

Pericardial Effusion
☐ Trace / Minimal
☐ Small
☐ Moderate
☐ Large

☐ Other *(Specify)* _____

13. Mitral Valve Regurgitation: ☐ None ☐ Not evaluable

Site	Severity	Method of Calculation
Paravalvular Leak	☐ +1 Trivial/Trace ☐ +2 Mild ☐ +3 Moderate ☐ +4 Severe	☐ Color Doppler ☐ Regurgitant Fraction ☐ PISA ☐ Pulmonary Vein Flow
Central Leak	☐ +1 Trivial/Trace ☐ +2 Mild ☐ +3 Moderate ☐ +4 Severe	☐ Color Doppler ☐ Regurgitant Fraction ☐ PISA ☐ Pulmonary Vein Flow
Indeterminate	☐ +1 Trivial/Trace ☐ +2 Mild ☐ +3 Moderate ☐ +4 Severe	☐ Color Doppler ☐ Regurgitant Fraction ☐ PISA ☐ Pulmonary Vein Flow

14. Mitral Valve Stenosis:
☐ No ☐ Yes ☐ Not evaluable

15. Non-Study Valve Assessment *(If available):*

Valve	Stenosis	Regurgitation
Aortic	☐ None / Trivial ☐ Mild ☐ Moderate ☐ Severe ☐ Not Evaluable	☐ None / Trivial ☐ Mild ☐ Moderate ☐ Severe ☐ Not Evaluable
Tricuspid	☐ None / Trivial ☐ Mild ☐ Moderate ☐ Severe ☐ Not Evaluable	☐ None / Trivial ☐ Mild ☐ Moderate ☐ Severe ☐ Not Evaluable
Pulmonic	☐ None / Trivial ☐ Mild ☐ Moderate ☐ Severe ☐ Not Evaluable	☐ None / Trivial ☐ Mild ☐ Moderate ☐ Severe ☐ Not Evaluable

16. COMMENTS:_____

I have reviewed and approved all information on this form. *(Reviewing Physician's Signature)*

Date
/ /
MMM DD YYYY

White and Yellow: Return to Edwards Lifesciences, Clinical Affairs Pink: Retain for your Records

15.0 APPENDIX 4: INSTRUCTIONS FOR USE

US
Model 7000/7000TFX, Model 7200TFX and Model 7300/7300TFX

Australia
Model 7000TFX

OUS (Outside US and excluding Australia)
Model 7000TFX

Edwards Lifesciences

Carpentier-Edwards PERIMOUNT MAGNA Mitral Pericardial Bioprosthesis Model 7000TFX

Instructions for Use

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

1. Device Description

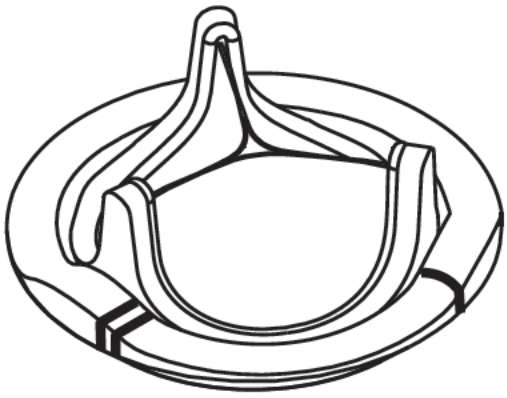
The Carpentier-Edwards PERIMOUNT MAGNA mitral pericardial bioprosthesis (also referred to as the Magna mitral bioprosthesis) is built upon the same proven (Ref. 1) wireform frame and leaflet attachment as the PERIMOUNT mitral pericardial bioprostheses models 6900, 6900P and 6900PTFX. It is available in the sewing ring diameters and sizes shown in Figure 1. The bioprosthesis incorporates a sewing ring specifically designed for the mitral position and is the first bioengineered mitral bioprosthesis design with three selected bovine pericardial leaflets mounted on a flexible metal alloy frame.

Bovine pericardium was selected for its superior intrinsic properties for valve manufacture, notably in terms of collagen content (Ref. 2) and tolerance to high bending curvatures (Ref. 3). 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 bioprosthesis is treated according to the ThermaFix process, which involves heat treatment of the tissue in glutaraldehyde and uses ethanol and Polysorbate-80 (a surfactant). Glutaraldehyde is shown to both reduce the antigenicity of tissue xenograft valves and increase tissue stability (Refs. 4 & 5). Glutaraldehyde alone has not been shown to affect or reduce the calcification rate of the valve.

Tissue thickness is measured for each valve size with the proprietary PeriMap technology, which allows for precisely die-cut leaflets in selected areas of a pericardial sheet. Leaflet deflection testing characterizes each leaflet for elasticity. Three leaflets matched for similar thickness and elasticity are then assembled. Leaflets are mounted underneath the wireform frame to minimize commissural stress points.

The lightweight wireform frame is made of Elgiloy, a corrosion-resistant alloy, chosen because of its superior spring efficiency 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 Magna mitral bioprosthesis is symmetrical and the three commisure supports (struts) are equally spaced.

CP1087-12



Model 7000TFX

An Elgiloy band attached to a polyester film band surrounds the base of the wireform frame providing structural support for the orifice and allows for radiological identification. In addition to maintaining the orifice shape during implantation, the Elgiloy band serves as a point of attachment for the sewing ring.

The sewing ring is made of waffled silicone-rubber and is covered with a porous polytetrafluoroethylene cloth to facilitate tissue in-growth and encapsulation. The sewing ring of the Magna mitral bioprosthesis is uniquely scalloped along its anterior portion and mimics the natural saddle shape of the native mitral valve anatomy. Black suture markers on the anterior portion facilitate the orientation of the bioprosthesis and help avoid obstruction of the left ventricular outflow tract by a strut. The design of the silicone waffle eases needle penetration and provides variable compliance. The waffle has wider cells along the posterior portion, where calcifications or irregularities of the native mitral annulus are more frequent (Ref. 6). 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 Tricentrix holder system is designed to minimize suture or chordae entrapment, ease insertion and increase leaflet visibility. It is secured to the bioprosthesis with sutures. The bioprosthesis and holder attachment are suspended by a clip and a sleeve within a sealed jar that contains a glutaraldehyde packing solution. The bioprosthesis is terminally sterilized in glutaraldehyde.

2. Indications for Use

The Carpentier-Edwards PERIMOUNT MAGNA mitral pericardial bioprosthesis model 7000TFX is indicated for patients who require replacement of their native or prosthetic mitral valve.

3. Contraindications

Do not use if the surgeon believes such would be contrary to the best interests of the patient. The actual decision for or against the use of this bioprosthesis must remain with the surgeon who can evaluate all the various risks involved, including the anatomy and pathology observed at the time of surgery.

4. Warnings

For Single Use Only

DO NOT RESTERILIZE THE BIOPROSTHESIS BY ANY METHOD. Exposure of the bioprosthesis or container to irradiation, steam, ethylene oxide, or other chemical sterilants will render the bioprosthesis unfit for use.

DO NOT FREEZE OR EXPOSE THE BIOPROSTHESIS TO EXTREME HEAT. Each bioprosthesis is contained in a carton with a temperature indicator displayed through a window on the side panel. The temperature indicator is intended to monitor the temperature that the device is exposed to during transit and storage. If the indicator displays any reading other than "OK" do not use the bioprosthesis. Please refer to Packaging section (10.2) for further instructions.

DO NOT USE the bioprosthesis if the tamper evident seal on the jar is broken.

DO NOT USE the bioprosthesis if expiration date has elapsed.

DO NOT USE the bioprosthesis if the container is leaking, damaged, or the glutaraldehyde solution does not completely cover the bioprosthesis.

DO NOT EXPOSE the bioprosthesis to any solutions, chemicals, antibiotics, etc., except for the storage solution or sterile physiological saline solution. Irreparable damage to the leaflet tissue, which may not be apparent under visual inspection, may result.

DO NOT ALLOW the bioprosthesis to dry. It must be kept moist at all times. Maintain tissue moisture with sterile physiological saline irrigation on both sides of the leaflet tissue.

DO NOT PASS CATHETERS, transvenous pacing leads, or any surgical instrument across the bioprosthesis with the exception of a surgical mirror used to examine struts and suture placement. Other surgical devices may cause leaflet tissue damage.

DO NOT USE the bioprosthesis if it has been dropped, damaged, or mishandled in any way. Should a bioprosthesis be damaged during insertion, do not attempt repair.

DO NOT GRASP the leaflet tissue of the bioprosthesis with instruments or cause any damage to the bioprosthesis. Even the most minor leaflet tissue perforation may enlarge in time to produce significant impairment of valve function.

DO NOT OVERSIZE. Oversizing may cause bioprosthesis damage or localized mechanical stresses, which may in turn injure the heart or result in leaflet tissue failure, stent distortion and valve regurgitation.

Clinical data that establish the safety and efficacy of the bioprosthesis for use in patients under the age of 20 are not available; therefore, we recommend careful consideration of its use in younger patients.

The decision to use a bioprosthesis must ultimately be made by the surgeon on an individual basis after a careful evaluation of the short- and long-term risks and benefits to the patient and consideration of alternative methods of treatment.

Long-term durability has not been established for bioprostheses. Serious adverse events, sometimes leading to replacement of the bioprosthesis and/or death, may be associated with the use of prosthetic valves (see **6. Adverse Events**). A full explanation of the benefits and risks should be given to each prospective patient before surgery.

Note: Bioprostheses should be used with caution in the presence of severe systemic hypertension or when the anticipated patient longevity is longer than the known longevity of the prosthesis (see **7. Clinical Studies**).

Careful and continuous medical follow-up (at least by an annual visit to the physician) is advised so that bioprosthesis-related complications, particularly those related to material failure, can be diagnosed and properly managed. Recipients of prosthetic heart valves who are undergoing dental procedures should receive prophylactic antibiotic therapy to minimize the possibility of prosthetic infection. Bioprosthetic heart valve recipients should be maintained on anticoagulant therapy (except where contraindicated) during the initial healing stages after implantation, 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 by the physician on an individual basis (Ref. 7).

Adequate rinsing with physiological saline is mandatory before implantation to reduce the glutaraldehyde concentration (see **11.4 Handling and Preparation Instructions**). No other solutions, drugs, chemicals, antibiotics, etc., should ever be added to the glutaraldehyde or rinse solutions, as irreparable damage to the leaflet tissue, which may not be apparent under visual inspection, may result.

5. Precautions

- Do not sterilize the sizers model 1177HP and handles model 1111 or 1117 in their shipping containers.
- Use only the sterilization tray model TRAY1177HP to sterilize the sizers and the handles.
- The outside of the jar is not sterile and must not be placed in the sterile field.
- To avoid contamination, it is strongly recommended that the jar of a Carpentier-Edwards PERIMOUNT MAGNA mitral pericardial bioprosthesis model 7000TFX not be opened unless implantation is certain.
- Adequate rinsing with physiological saline must be performed before implantation to reduce the glutaraldehyde concentration.
- Avoid contact of the leaflet tissue or the rinse solution with towels, linens, or other sources of lint and particulate matter that may be transferred to the leaflet tissue.

- Do not allow the leaftlet tissue to contact the bottom or sides of the rinse basin.
- Glutaraldehyde may cause irritation of the skin, eyes, nose, and throat. Avoid prolonged or repeated exposure or breathing of the solution. Use only with adequate ventilation. If skin contact occurs, immediately flush the affected area with water; in the event of contact with the eyes, seek immediate medical attention. For more information about glutaraldehyde exposure, please refer to the Material Safety Data Sheet available from Edwards Lifesciences.
- Always deploy the Tricentrix holder system fully to minimize the risk of suture entrapment. It will snap into a secured and locked position.
- A serial number tag is attached to the sewing ring of each bioprosthesis by a suture. This serial number should be checked against the number on the jar and implantation data card; if any difference is noted, the bioprosthesis should be returned unused. Care must be taken to ensure that the serial number tag does not come in contact with the leaflet tissue during rinsing. Inspection of the bioprosthesis and removal of the serial number tag should be performed just prior to implantation. Care should be exercised to avoid cutting or tearing the sewing ring cloth during removal of the serial number tag.
- Careful handling is required for all implantable devices. If the bioprosthesis is dropped, damaged, or mishandled in any way, it must not be used for human implantation.
- To avoid damage to the delicate bioprosthetic leaflet tissue, as a result of contact with calcium deposits, adequate removal of calcium deposits from the patient's annulus must be performed before implantation.
- Handle the bioprosthesis only with Edwards Lifesciences accessories. Only Edwards Lifesciences sizers 1177HP should be used during the selection of the Magna mitral bioprosthesis size; other sizers may result in improper bioprosthesis selection. Edwards Lifesciences sizers are marked for both size and EOA to provide clinically relevant information during surgery and help avoid oversizing (see **11.2 Accessories**).
- Oversizing must be especially avoided as it may cause bioprosthesis damage or localized mechanical stresses, which may in turn injure the heart or result in leaflet tissue failure, stent distortion and regurgitation.
- Special care must be exercised when using chordal preservation techniques to avoid chordae entrapment by a strut.
- Due to the relative flexibility of the frame, care must be exercised to prevent folding or deformation of the stent.
- The surgeon should be familiar with the recommendations for proper sizing and placement of the bioprosthesis according to the suture technique used (see **11.5 Device Implantation**).
- The sewing ring is designed for a specific orientation: the scalloped part of the sewing ring, between the two protrusions, should be placed across the intercommissural anterior portion of the annulus and straddle the left ventricular outflow tract.
- Special care must be exercised to avoid placing a strut in front of the left ventricular outflow tract, as this may impair the long-term hemodynamic performance.
- As with all prostheses that have open cages, free struts, or commissure supports, care must be exercised to avoid looping or catching a suture around a commissure, which would interfere with proper valvular function. To avoid suture looping, it is essential to leave the deployed holder in place until all knots are tied.
- If the deployed holder attachment threads are cut, before at least all the sutures adjacent to the struts are tied down, the holder can no longer prevent suture looping.
- When using interrupted sutures, it is important to cut the sutures close to the knots and to ensure that exposed suture tails will not come into contact with the leaflet tissue.

6. Adverse Events

6.1 Observed Adverse Events

The Carpentier-Edwards PERIMOUNT MAGNA mitral pericardial bioprosthesis model 7000TFX uses the same wireform frame and leaflet attachment as Edwards Lifesciences pericardial mitral bioprostheses models 6900, 6900P and 6900PTFX. Three (3) multi-center, non-randomized, prospective non-US clinical studies were conducted with the mitral pericardial bioprosthesis model 6900. Three hundred one (301) patients had isolated mitral valve replacement (MVR) and 62 patients had double valve replacement (DVR), where the aortic valve was replaced with a Carpentier-Edwards PERIMOUNT pericardial bioprosthesis aortic model. In the first study, bioprostheses were implanted between 1984 and 1986; in the second study, bioprostheses were implanted between 1989 and 1994; and in the third study, bioprostheses were implanted between 1996 and 1997. Patients were evaluated preoperatively, intraoperatively/at discharge, at 1 year, and annually thereafter. Adverse events were captured throughout the postoperative period. Table 1 presents the observed rates for early events ($\leq$ 30 days for valve-related adverse events), the linearized rates for late events ($>$ 30 days postoperatively), and the actuarial adverse event rates at 1, 5, and 8 years postoperatively. The adverse event rates were based on 363 patients at nine centers. The cumulative follow-up was 1100 patient-years with a mean follow-up of 3.0 years (SD = 2.4 years, range = 0 to 8.2 years). Preoperative and operative patient demographics are presented in Tables 2 and 3. Effectiveness results are presented in Tables 4 and 5.

6.2 Potential Adverse Events

Adverse events potentially associated with the use of bioprosthetic heart valves include:

- Angina
- Cardiac arrhythmias
- Endocarditis
- Heart failure
- Hemolysis
- Hemolytic anemia
- Hemorrhage
- Myocardial infarction
- Prosthesis leaflet entrapment
- Prosthesis nonstructural dysfunction
- Prosthesis pannus
- Prosthesis perivalvular leak
- Prosthesis regurgitation

- Prosthesis structural deterioration
- Prosthesis thrombosis
- Stroke
- Thromboembolism

It is possible that these complications could lead to:

- Reoperation
- Explantation
- Permanent disability
- Death

Other adverse events associated with the use of Carpentier-Edwards PERIMOUNT mitral pericardial bioprostheses model 6900 compiled from the literature and from reports received through the Edwards Lifesciences complaint handling system include: stenosis, regurgitation through an incompetent valve, ventricular perforation by stent posts, malfunctions of the valve due to distortion at implant, and fracture of the Elgiloy wireform frame.

7. Clinical Studies

The safety endpoints captured in the prospective studies were complications; blood analyses were used to confirm the absence or presence of certain complications. The safety results are provided in Table 1. Effectiveness endpoints were New York Heart Association (NYHA) functional classification and echocardiographic assessments. Preoperative and operative patient demographics are presented, followed by the effectiveness results. There are no clinical data presently available demonstrating increased resistance of the Carpentier-Edwards PERIMOUNT MAGNA mitral pericardial bioprosthesis model 7000TFX to calcification as compared to other commercially available bioprostheses.

8. Individualization of Treatment

Bioprosthetic heart valve recipients should be maintained on anticoagulant therapy, except where contraindicated, during the initial stages after implantation, as determined by the physician on an individual basis. Long-term anticoagulant and/or antiplatelet therapy should be considered for patients with a dilated left atrium, a history of thrombotic events, an absence of sinus rhythm, calcification of the atrial wall, or with atrial fibrillation or flutter. The decision to use a bioprosthesis must ultimately be made by the physician on an individual basis after a careful evaluation of the short-term and long-term risks and benefits to the patient and consideration of alternative methods of treatment (Ref. 7).

8.1 Specific Patient Populations

The safety and effectiveness of the Carpentier-Edwards PERIMOUNT MAGNA mitral pericardial bioprosthesis model 7000TFX has not been established for the following specific populations because it has not been studied in these populations:

- patients who are pregnant;
- nursing mothers;
- patients with abnormal calcium metabolism (e.g., chronic renal failure, hyperparathyroidism);
- patients with aneurysmal aortic degenerative conditions (e.g., cystic medial necrosis, Marfan's syndrome);
- children, adolescents, or young adults.

9. Patient Counseling Information

Careful and continued medical follow up (at least by an annual visit to the physician) is advised so that valve-related complications, particularly those related to material failure, can be diagnosed and properly managed. Patients with bioprostheses are at risk from bacteremia (e.g., undergoing dental procedures) and should be advised about prophylactic antibiotic therapy. Patients should be encouraged to carry their Implantation Data Card at all times and to inform their healthcare providers that they have a mitral bioprosthetic implant when seeking care.

10. How Supplied

10.1 Available Models and Sizes

The Carpentier-Edwards PERIMOUNT MAGNA mitral pericardial bioprosthesis model 7000TFX is available in labeled sizes 25, 27, 29, 31 and 33 mm (see Figure 1 for nominal specifications).

10.2 Packaging

The Magna mitral bioprosthesis is provided sterile and nonpyrogenic packaged in glutaraldehyde, in a plastic jar to which a seal has been applied. Each bioprosthesis is contained in a carton with a temperature indicator displayed through a window on the side panel. The temperature indicator is intended to monitor the temperature that the device is exposed to during transit and storage. Upon receipt of the bioprosthesis immediately inspect to see if the indicator displays any reading other than "OK", if so do not use the bioprosthesis. Contact the local supplier or Edwards Lifesciences representative to make arrangements for return, authorization and replacement. Any bioprosthesis returned to Edwards Lifesciences must be shipped in its original packaging in which it was received.

Warning: The bioprosthesis must be carefully inspected before implantation for evidence of extreme temperature exposure or other damage.

Due to the biological nature of this bioprosthesis and its sensitivity to physical handling and environmental conditions, it cannot be returned, except as noted above.

Note: Products found to have been subjected to freezing or excessive heat later than 3 days following receipt will be considered to have resulted from environmental conditions within the control of the customer, and subject to replacement at customer's expense.

10.3 Storage

The Magna mitral bioprosthesis should be stored at 10 °C to 25 °C (50-77 °F). Stock inspection and rotation at regular intervals are recommended to ensure that the bioprostheses are used before the expiration date stamped on the package label.

Warning: Do not freeze. Always store bioprostheses in a dry, contamination-free area. Any bioprosthesis that has been frozen, or is suspected of having been frozen, should not be used for human implantation.

11. Directions for Use

11.1 Physician Training

No special training is required to implant the Carpentier-Edwards PERIMOUNT MAGNA mitral bioprosthesis model 7000TFX. The techniques for implanting this bioprosthesis are similar to those for implanting any stented mitral bioprostheses.

11.2 Accessories

Accessories available for use with the Magna mitral bioprosthesis are:

- Tricentrix holder system
- Carpentier-Edwards PERIMOUNT MAGNA mitral sizers 1177HP
- Sterilization tray TRAY1177HP
- Handles 1111 (universal), 1117 (mitral) or 1126 (single use)

All accessories are supplied non-sterile, except for the Tricentrix holder system that is supplied sterile attached to the sterile bioprosthesis and the handle 1126 that is supplied sterile and is for single use only.

Sizers and Tray

Only sizers 1177HP must be used with the Magna mitral bioprosthesis.

Caution: Do not use other manufacturer's valve sizers, or sizers for other Edwards Lifesciences valve prostheses to size the Magna mitral bioprosthesis.

Use only the sizers 1177HP with attached handle (1111, 1117 reusable handles or 1126 single use handle) to determine the appropriate Magna mitral bioprosthesis size. Sizers 1177HP permit direct observation of their fit within the annulus and are provided for each available Magna mitral bioprosthesis size. The barrel of the sizers indicates the external stent diameter at the tip (Figure 1). The lip of the sizers replicates the sewing ring of the bioprosthesis, 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 bioprosthesis sewing ring which should be positioned across the anterior intercommissural portion of the native annulus, in order to saddle the left ventricular outflow tract area.

The sizers 1177HP and tray TRAY1177HP are labeled with both the bioprosthesis size and the mean Effective Orifice Area (EOA). The EOA in cm^2 is taken from the 1 to 2 year post-implant interval as reported in Table 5. The labeled size is not a standardized measurement and may vary from one manufacturer to another (or between different models of a same manufacturer). Surgeons have access to both the labeled size and the EOA at the time of surgery, which may provide clinically relevant information on the expected hemodynamic performance. This may help determine the right size for a particular patient, and prevent improper sizing.

Placing sutures around the native annulus may reduce the size of the bioprosthesis that can be implanted. It is recommended to size or re-size after the sutures have been placed to avoid oversizing. Some techniques such as everting mattress sutures or mitral subvalvular apparatus preservation may further reduce the size of the bioprosthesis that can be implanted. When using these techniques, it is recommended to pass the entire sizer, including the lip, through the native annulus, to ensure enough clearance for the sewing ring or the reefed preserved apparatus (Figure 10). The consistent performance of the PERIMOUNT mitral bioprostheses makes oversizing unnecessary to achieve the desired hemodynamic performance in most patients (Table 5).

Warning: Oversizing may cause bioprosthesis damage or localized mechanical stresses, which may in turn injure the heart or result in leaflet tissue failure, stent distortion and regurgitation.

Tricentrix Holder System and Handles

The holder/handle assembly consists of two (2) components: the Tricentrix holder system that is mounted to the bioprosthesis, and a handle (1111, 1117 or 1126) that is attached to the Tricentrix holder system at the time of surgery (Figure 2).

- The handle 1111 is a universal stainless steel handle that can be used with other Edwards Lifesciences prostheses (Figure 11).
- The handle 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. Its 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 (Figure 11).

Both handles 1111 and 1117 can be resterilized.

- The handle 1126 has a long and thin stainless steel shaft and is intended for single use only (Figure 11).

The Tricentrix holder has short legs and beveled edges to increase suturing space and ease knot tying (Figure 12).

11.3 Accessory Sterilization

The 1126 handle is provided sterile and is intended for single use only. The handles 1111 and 1117 and the sizers 1177HP are supplied non-sterile and must be sterilized before using. The handles 1111 and 1117 and the sizers 1177HP must be disassembled, cleaned, and re-sterilized prior to each use. Sizers and handles should be examined for signs of wear, such as dullness, cracking, or crazing, and should be replaced if any deterioration is observed. **Caution:** Do not sterilize the sizers and handles 1111 or 1117 in their shipping containers.

Use only the sterilization tray TRAY1177HP to sterilize the sizers and the handles.

The accessories can be sterilized using the following recommended autoclave sterilization methods:

I. Gravity Displacement:
   a) Wrapped:
      Temperature: 270-279 °F (132-137 °C)
      Exposure Time: 10-18 minutes
   b) Unwrapped ("flash"):
      Temperature: 270-279 °F (132-137 °C)
      Exposure Time: 3 minutes

II. Prevacuum:
   a) Wrapped:
      Temperature: 270-279 °F (132-137 °C)
      Exposure Time: 3-18 minutes
   b) Unwrapped ("flash"):
      Temperature: 270-279 °F (132-137 °C)
      Exposure Time: 3 minutes

Each institution should use procedures that include biological indicators to determine the effectiveness of the sterilization procedure.

11.4 Handling and Preparation Instructions

The bioprosthesis is packaged sterile in a plastic jar with a screw-cap closure and seal. Before opening, carefully examine the jar for evidence of damage (e.g., a cracked jar or lid), leakage, or broken or missing seals. Remove the seal and turn the lid counter-clockwise to open the container. The bioprosthesis and Tricentrix holder system within the container are sterile.

Caution: The outside of the jar is not sterile and must not be placed in the sterile field. The contents of the jar should be handled in an aseptic manner to prevent contamination.

Caution: Bioprostheses from containers found to be damaged, leaking, without adequate glutaraldehyde, or missing intact seals must not be used for human implantation.

Caution: It is strongly recommended that the jar of a Magna mitral bioprosthesis not be opened unless implantation is certain. This is necessary to reduce the risk of contamination, because it has been established that glutaraldehyde alone is not a 100% effective sterilant against all possible contaminants.

Warning: No attempt should be made to resterilize a Magna mitral bioprosthesis.

Warning: Do not use the bioprosthesis if it has been dropped, damaged, or mishandled in any way. Should a bioprosthesis be damaged during insertion, do not attempt repair.

Warning: Do not grasp the leaflet tissue portion of the bioprosthesis with instruments or cause any damage to the bioprosthesis. Even the most minor leaflet tissue perforation may enlarge in time to produce significant impairment of bioprosthesis function.

Verify that the handle, 1111 or 1117, has been sterilized according to the instructions provided in Section 11.3. If sterile, using handle 1111, 1117 or 1126, attach the handle to the Tricentrix holder system and turn it clockwise until a positive resistance is felt then remove the whole assembly (i.e., plastic sleeve, clip, the Tricentrix holder system and bioprosthesis) from the jar.

A tag with a serial number is attached to the sewing ring of each bioprosthesis by a suture. This serial number should be checked against the number on the jar and implantation card; if any differences are noted, the bioprosthesis should be returned unused. This tag should not be detached from the bioprosthesis until just prior to implantation.

Grasping the plastic sleeve (Figure 3) continue the rotation to overcome the resistance until the holder post reaches the unlock position (Figure 4a and Figure 4b). Apply the required push force on the handle until the post slides across the leaflets and snaps into its fully deployed position (Figure 5).

Caution: If an adequate push force is not applied to the handle when deploying the Tricentrix holder system, the tenting system will not be secured and will not be able to prevent suture entrapment. Always check for proper deployment. There should be no more space between the handle attachment adapter and the clip. The handle/post assembly should not be able to slide any longer.

The holder post should protrude through the leaflets while the three (3) commissures should deflect slightly towards the center of the bioprosthesis. The leaflets will temporarily be wrinkled by the deployed holder post. When the holder is removed following implantation, the leaflets will return to their normal position.

After deployment, remove the sleeve by holding the handle and pulling the sleeve off the clip (Figure 6). Remove the clip by sliding it off the holder in a sideways direction (Figure 7). Both sleeve and clip should be discarded. Once the handle has been attached, it should not be removed from the holder until the bioprosthesis is seated to the annulus.

Rinse Procedure

Within the sterile operative field, prepare two rinse basins, each containing no less than 500 ml of sterile, physiological saline solution. Place the deployed bioprosthesis in the saline solution and make sure that it completely covers the bioprosthesis and holder. Do not rinse with the sleeve and clip attached. With the bioprosthesis and holder submerged, slowly agitate the basin or use the attached handle to gently swirl the bioprosthesis back and forth for a minimum of 1 minute in each of the two previously prepared rinse basins. The bioprosthesis should remain in the second rinse basin until ready for implantation.

Caution: Avoid contact of the leaflet tissue or the rinse solution with towels, linens, or other sources of lint and particulate matter that may be transferred to the leaflet tissue.

Caution: Do not allow the leaflet tissue to contact the bottom or sides of the rinse basin.

Caution: Care must be taken to ensure that the serial number tag does not come in contact with the leaflet tissue during rinsing.

Inspect the bioprosthesis and remove the serial number tag just prior to implantation. Exercise care to avoid cutting or tearing the sewing ring cloth during removal of the serial number tag.

11.5 Device Implantation

Because of the complexity and variation in the surgical procedure of cardiac valve replacement, the choice of surgical technique is left to the discretion of the individual surgeon. In general, the standard implantation technique includes: 1. Proper sizing; 2. Proper seating of the prosthesis; 3. Tying sutures with the holder in place to avoid suture looping or chordal entrapment; 4. Examination of the bioprosthetic leaflets for distortion or leak during tying.

Proper bioprosthesis size selection is an important part of mitral valve replacement.

Verify that the sizers 1177HP have been sterilized according to the recommended instructions in Section 11.3. If sterile, insert the 1111, 1117 or 1126 handle into the sizer and turn it clockwise until positive contact is felt between the handle and sizer.

Caution: Adequate removal of calcium deposits from the patient's annulus must be performed before implantation to avoid damage to the delicate bioprosthesis leaflet tissue as a result of contact with calcium deposits.

Insert the sizer into the mitral annulus. The sizer should always fit comfortably in the annulus.

Warning: Care must always be exercised to avoid the use of too large a prosthesis since oversizing may create damage or localized mechanical stresses, which may in turn injure the heart or result in leaflet tissue failure, stent distortion and regurgitation.

Caution: Only sizers 1177HP should be used during the selection of the Carpentier-Edwards PERIMOUNT MAGNA mitral pericardial bioprosthesis model 7000TFX size; other sizers may result in improper valve selection. Sizers 1177HP are marked for both size and EOA to provide clinically relevant information during surgery and help avoid oversizing (see **11.2 Accessories**).

Like other mitral bioprostheses, the Magna mitral bioprosthesis is usually implanted using pledgeted mattress sutures. It is recommended to size the annulus after the sutures have been placed, as sutures may decrease the size of the bioprosthesis that can be implanted.

Sizing for implantation using non-everting mattress sutures:

When a non-everting mattress suture technique is used, pledgets are typically placed on the ventricular aspect of the annulus. When sizing, the barrel portion of the sizer is passed through the mitral annulus so that the lip of the sizer, which simulates the sewing ring portion of the bioprosthesis, rests on the superior aspect of the annulus. Oversizing of the bioprosthesis should be avoided.

Subvalvular apparatus preservation sizing and implantation:

Chordal preservation techniques may decrease the size of valve that can be implanted. With chordal sparing, the preserved leaflets are reefed within the valve-sutures and compressed between the sewing ring and the native annulus, thereby decreasing the size of the annulus (Ref. 8). When using these techniques, it is recommended that the surgeon sizes the valve after sutures have been placed to ensure that sizing is more accurate and to avoid placing too large a bioprosthesis.

Caution: Special care must be exercised when using chordal preservation techniques to avoid chordae entrapment by a strut.

Due to the elastic nature of a chord, it may be extended by the Tricentrix holder system during implantation but retract back around the post once the holder is removed, entrapping leaflets and impairing function. Sizers 1177HP are made of a transparent material to allow visualization of the subvalvular apparatus during sizing. Make sure no chord will be in the way of the struts.

Caution: Because of the intense temperature and lighting conditions in the operating field, the bioprosthesis should be irrigated frequently (every 1 to 2 minutes is recommended) on both sides with sterile physiological saline to keep the valve moist during the implant procedure.

Proper orientation of the bioprosthesis

Caution: The wireform frame of the Magna mitral bioprosthesis is symmetrical, and the three commissure supports (struts) are equally spaced. However, the sewing ring is designed for a specific orientation of the bioprosthesis. The scalloped part of the sewing ring, between the two silicone protrusions, should be placed across the intercommissural anterior portion of the annulus and straddle the left ventricular outflow tract.

The contrasting suture markers in the sewing ring are intended to aid in proper orientation and denote a typical intercommissural distance. However, this distance may vary for each individual patient. On the left side, two close black sutures indicate where the first stitch should be placed and correspond to the anterior commissure. On the right side, only one black suture indicates the approximate location of the posterior commissure. Using these orientation aids, the third post should naturally fall in place in or around the middle of the posterior leaflet location.

Caution: Special care must be exercised to avoid placing a strut in front of the left ventricular outflow tract, as it may impair the long-term hemodynamic performance.

Firm tension must be maintained on the sutures as the bioprosthesis is lowered into the annulus; this prevents formation of suture loops that might entrap a leaflet. This, when combined with the fully retracted stent posts when the Tricentrix holder system is in place, helps guide the sutures into their correct position behind the struts and onto the sewing ring.

Remove the handle prior to tying the sutures. The handle and adapter must be removed as an assembly. Maintain the bioprosthesis placement in the annulus by gently placing forceps or gloved hands onto the holder and cutting the green thread on the white adapter (Figure 8). Remove the adapter and handle assembly as one unit.

Caution: Avoid looping or catching a suture around the open cages, free struts, or commissure supports of the bioprosthesis, which would interfere with proper valvular function. To avoid suture looping, it is essential to leave the deployed holder in place until all knots are tied.

However, if leaving the holder in place obstructs the surgeon's view, all the sutures adjacent to each of the three frame struts must be tied down before cutting the three holder attachment threads to remove the holder.

Caution: If the deployed holder attachment threads are cut before these adjacent sutures are tied down, the holder can no longer prevent suture looping around the frame struts.

Special attention must be given to avoid tying the sutures on top of the corners of the holder legs. Before tying each suture, examine the leaflets while holding the two strands of the suture under tension. Distortion or movement of the leaflets during this maneuver suggests that the suture is looped around a strut. At no point before or after holder removal should tension on the sutures be released as this may facilitate formation of loops in the sutures and possible entrapment. It is recommended to place a surgical mirror through the leaflets after the holder removal in order to examine each strut and proper suture placement.

Caution: When using interrupted sutures, it is important to cut the sutures close to the knots and to ensure that exposed suture tails will not come into contact with the leaflet tissue (Ref. 8).

The Tricentrix holder system is removed as a unit at the completion of the suturing procedure as follows (Figure 9):

1. Cut each of the three (3) exposed sutures using a scalpel or scissor placed only in the cutting channel. Never attempt to cut a suture below a partially separated holder as a part of the attaching suture may fall in the ventricle. Avoid cutting or damaging the stent or leaflet tissue when cutting the sutures.
2. When all three (3) attaching sutures have been properly cut, remove the Tricentrix holder system from the bioprosthesis as a unit, along with attaching sutures, using sterile gloved hands or protected forceps.
3. Following surgery, remove the holder and discard.

11.6 Return of Explanted Bioprostheses

Edwards Lifesciences is interested in obtaining all recovered clinical specimens of Carpentier-Edwards PERIMOUNT MAGNA mitral pericardial bioprostheses model 7000TFX for analysis. A written report summarizing our findings will be provided to the physician upon completion of our evaluation. Please contact your local representative for return of recovered bioprostheses. The explanted bioprostheses should be placed into a suitable histological fixative such as 10% formalin or 2% glutaraldehyde immediately after excision and returned to the company. Refrigeration is not necessary under these circumstances.

12. Patient Information

12.1 Registration Information

An Implantation Data Card is included in each device package for patient registration. After implantation, please complete all requested information. The bioprosthesis serial number is listed on the bioprosthesis packaging and on the identification tag attached to the bioprosthesis, and is pre-printed on the Implantation Data Card. Return the pre-addressed portion of the card to our Implant Patient Registry. The remaining portions of the card are provided for hospital and surgeon records. Upon receipt by our Implant Patient Registry, a wallet-sized identification card will be produced for the patient. This card allows patients to inform healthcare providers what type of implant they have when they seek care. When a bioprosthesis is discarded or a previous Edwards Lifesciences device is replaced, report this information to our Implant Patient Registry.

12.2 Patient Manual

Patient information materials may be obtained from Edwards or your local representative.

13. Safety in the Magnetic Resonance (MR) Environment

MR Conditional

Non-clinical testing has demonstrated that the Carpentier-Edwards PERIMOUNT MAGNA mitral pericardial bioprosthesis model 7000TFX is MR Conditional. A patient with the Magna mitral bioprosthesis can be scanned safely, immediately after placement of this implant under the following conditions:

- Static magnetic field of 3 tesla or less.
- Spatial gradient field of 720 gauss/cm or less.
- Maximum MR system-reported whole-body-averaged specific absorption rate (SAR) of 3 W/kg for 15 minutes of scanning.

In non-clinical testing, the Magna mitral bioprosthesis produced a temperature rise of less than or equal to 0.5 °C at a maximum MR system-reported whole-body-averaged specific absorption rate (SAR) of 3 W/kg for 15 minutes of MR scanning in a 3 tesla MR system (Excite, Software G3.0-052B, General Electric Healthcare).

MR image quality may be compromised if the area of interest is in the same area or relatively close to the position of the Magna mitral bioprosthesis. Optimization of MR imaging parameters is recommended.

Prices subject to change without notice. This product is manufactured and sold under one or more of the following US patents: US-Patent Nos. 4,885,005; 5,928,281; 5,931,969; 5,961,549; 6,102,944; 6,210,957; 6,214,054; 6,245,105; 6,378,221; 6,409,758; 6,413,275; 6,416,547; 6,547,827; 6,553,681; 6,561,970; 6,585,766; 6,837,902; 6,945,997; and corresponding foreign patents. Additional patents are pending.

References

1. Marchand MA., et al. Fifteen-year Experience with the Mitral Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis. *Ann Thorac Surg.* 2001; 71:S236-9.
2. Liao K., et al. Bovine Pericardium versus Porcine Aortic Valve: Comparison of Tissue Biological Properties As Prosthetic Valves; *Artificial Organs.* 1992; 16(4):361-5.
3. Vesely I., et al. Comparison of the Compressive Buckling of Porcine Aortic Valve Cusps and Bovine Pericardium. *J Heart Valve Dis.* January 1998; 7(1):34-9.
4. Carpentier A. From Valvular Xenograft to Valvular Bioprosthesis (1965-1977). *Med. Instrum.* 1977; 11(2):98-101.
5. Carpentier A., et al. Continuing Improvements in Valvular Bioprostheses. *J. Thorac. Cardiovasc. Surg.* 1982; 83(1):27-42.
6. Arounlangsy P., et al. Histopathogenesis of early stage mitral annular calcification. *J. Med Dent Sci.* 2004; 51(1):35-44.
7. Bonow RO., et al. ACC/AHA Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Valvular Heart Disease). *J Am Coll Cardiol.* 98; 32:1486-588.
8. Aagaard J., et al. Mitral valve replacement with total preservation of native valves and subvalvular apparatus. *J Heart Valve Dis.* May 1997; 6(3):274-8; discussion 279-80.

Table 1: Observed Adverse Event Rates for MVR and DVR

All patients analyzed: N = 363 Cumulative follow-up: 1100 patient-years

	Early Events		Late Events[1]		Freedom from Event (%) [95% CI][2]		
Complication	n[3]	%	n	%/pt-yr	1 year (n = 287)	5 years (n = 141)	8 years (n = 18)
Mortality (all)	34	9.4	50	4.7	85.5 [81.8, 89.2]	75.4 [70.3, 80.6]	65.4 [57.6, 73.2]
Valve-related events							
Mortality (valve-related)	0	0	16	1.5	97.7 [96.0, 99.4]	95.3 [92.8, 97.8]	91.9 [87.5, 96.4]
Explants	0	0	8	0.7	98.7 [98.0, 99.3]	96.7 [95.3, 98.0]	95.6 [93.9, 97.3]
Reoperations	2	0.6	12	1.1	97.1 [96.2, 98.1]	95.1 [93.6, 96.6]	93.0 [90.9, 95.1]
Anticoagulant-related hemorrhage	2	0.6	9	0.8	97.1 [95.2, 99.0]	97.1 [95.2, 99.0]	94.1 [88.2, 100]
Endocarditis	1	0.3	3	0.3	99.0 [97.9, 100]	98.7 [97.4, 98.9]	98.7 [97.4, 98.9]
Hemolysis	0	0.0	1	0.1	99.7 [99.0, 100]	99.7 [99.0, 100]	99.7 [99.0, 100]
Nonstructural dysfunction	0	0.0	3	0.3	100 [100, 100]	99.3 [98.0, 100]	98.3 [95.9, 100]
Perivalvular leak (all)	1	0.3	5	0.5	98.4 [97.0, 99.8]	98.4 [97.0, 99.8]	97.3 [94.9, 99.8]
Structural valve deterioration	0	0.0	5	0.5	100.0 [100, 100]	97.6 [95.2, 100]	92.8 [85.3, 100]
Thromboembolism	5	1.4	8	0.7	97.5 [95.8, 99.2]	96.1 [93.8, 98.5]	96.1 [93.8, 98.5]
Thrombosis	0	0.0	0	0.0	100.0 [100, 100]	100.0 [100, 100]	100.0 [100, 100]

Notes:

1. Late event rates were calculated as linearized rates (%/pt-yr) based on 1072.5 late patient-years (> 30 days postoperatively).
2. Freedom from event rates were calculated using the Kaplan-Meier method. Greenwood's formula was used for calculation of the standard errors of these estimates.
3. n = number of events.

Table 2: Preoperative Patient Demographics

		Study Characteristics (N = 363; 1100 total pt-yrs.)	
Variable	Category	n	% (n/N)[1]
Age at implant	Mean ± SD	363	66.1 ± 10.7
Gender	Female/Male	212/151	58.4%/41.6%
Diagnosis/Etiology	None	30	8.3%
	Stenosis	91	25.1%
	Regurgitation	184	50.7%
	Mixed Disease	58	16.0%

Note:

1. n = number of patients in each category; N = total number of study patients.

Table 3: Operative Patient Demographics

		Study Characteristics (N = 363; 1100 total pt-yrs.)	
Variable	Category	n	% (n/N)[1]
Etiology[2]	Rheumatic heart disease	135	37.2%
	Calcification	82	22.6%
	Degeneration	50	13.8%
	Endocarditis	39	10.7%
	Failed Bioprosthesis	15	4.1%
	Ischemic Heart Disease	14	3.9%
	Congenital Abnormalities	8	2.2%
	Other	44	12.1%
Concomitant Procedures[2]	None	200	55.1%
	CABG[3]	78	21.5%
	Tricuspid Repair	61	16.8%
	Intra-aortic balloon pump	17	4.7%
	Pacemaker[4]	6	1.7%
	Aortic repair/replacement	5	1.4%
	Aneurysm Repair	4	1.1%
	Other	31	8.5%
Pre-existing Conditions[2]	None	122	33.6%
	CAD[5]/CABG	72	19.8%
	Hypertension	61	16.8%
	Atrial Fibrillation	53	14.6%
	Previous MI[6]	45	12.4%
	Cerebrovascular Disease	36	9.9%
	Other	234	64.5%
Valve Size (mm)	25	22	6.1%
	27	110	30.3%
	29	137	37.7%
	31	81	22.3%
	33	13	3.6%

Notes:

1. n = number of patients in each category; N = total number of study patients
2. May be more than one per patient
3. CABG = Coronary Artery Bypass Graft
4. Permanent or temporary
5. CAD = Coronary Artery Disease
6. MI = Myocardial Infarction

Table 4: Effectiveness Outcomes, Functional NYHA

	Preoperative Assessment		Postoperative Assessments			
			1 to 2 Year		5 Year	
NYHA Functional Class	n/N[1]	%	n/N	%	n/N	%
I	11/363	3.0	120/268	44.8	40/129	31.0
II	73/363	20.1	90/268	33.6	25/129	19.4
III	192/363	52.9	15/268	5.6	1/129	0.8
IV	84/363	23.1	0/268	0.0	0/129	0.0
Not Available	3/363	0.8	43/268	16.0	63/129	48.8

Note:

1. n = number of patients in each category; N = total number of study patients.

Table 5: Effective Outcomes, Hemodynamic Results[1]

Hemodynamic Parameter	Results By Valve Size				
	25 mm	27 mm	29 mm	31 mm	33 mm
Discharge/Early Post-Implant (n = 130, 109 MVR[2] and 21 DVR[3])					
Mean gradient[4]	n = 3	n = 23	n = 36	n = 23	n = 3
• mean ± sd	5.7 ± 1.2	4.2 ± 1.7	4.2 ± 1.7	3.6 ± 1.0	7.5 ± 5.8
• min, max	5, 7	2, 9	1, 8	2, 5	3, 14
EOA[5]	n = 1	n = 17	n = 22	n = 25	n = 5
• mean ± sd	1.5	2.9 ± 0.9	3.1 ± 0.9	2.5 ± 0.7	3.0 ± 1.2
• min, max	1.5, 1.5	1.3, 4.1	1.4, 4.2	1.5, 3.8	1.6, 4.9
Regurgitation[6]	n = 3	n = 28	n = 51	n = 40	n = 8
0	3/3 (100%)	22/28 (79%)	36/51 (71%)	30/40 (75%)	4/8 (50%)
1+	0/3 (0%)	5/28 (18%)	13/51 (25%)	7/40 (18%)	4/8 (50%)
2+	0/3 (0%)	0/28 (0%)	1/51 (2%)	3/40 (7%)	0/8 (0%)
3+	0/3 (0%)	0/28 (0%)	1/51 (2%)	0/40 (0%)	0/8 (0%)
4+	0/3 (0%)	0/28 (0%)	0/51 (0%)	0/40 (0%)	0/8 (0%)
Not available	0/3 (0%)	1/28 (3%)	0/51 (0%)	0/40 (0%)	0/8 (0%)
3 to 6 Month Post-Implant Interval (n = 49, 42 MVR[2] and 7 DVR[3])					
Mean gradient[4]	n = 5	n = 19	n = 15	n = 5	n = 2
• mean ± sd	6.4 ± 1.7	5.3 ± 5	3.4 ± 1.2	4 ± 1.9	4 ± 0
• min, max	5, 9	2, 25	2, 6	2, 7	4, 4
EOA[5]	n = 5	n = 18	n = 13	n = 5	n = 2
• mean ± sd	2.9 ± 0.8	2.6 ± 0.7	2.8 ± 0.6	2.9 ± 0.3	2.6 ± 1
• min, max	1.8, 3.6	1.5, 5	2, 3.8	2.4, 3.3	2, 3.3
Regurgitation[6]	n = 5	n = 21	n = 15	n = 6	n = 2
0	3/5 (60%)	17/21 (81%)	6/15 (40%)	4/6 (67%)	1/2 (50%)
1+	0/5 (0%)	4/21 (19%)	8/15 (53%)	2/6 (33%)	0/2 (0%)
2+	1/5 (20%)	0/21 (0%)	1/15 (7%)	0/6 (0%)	1/2 (50%)
3+	0/5 (0%)	0/21 (0%)	0/15 (0%)	0/6 (0%)	0/2 (0%)
4+	1/5 (20%)	0/21 (0%)	0/15 (0%)	0/6 (0%)	0/2 (0%)
Not available	0/5 (0%)	0/21 (0%)	0/15 (0%)	0/6 (0%)	0/2 (0%)
1 to 2 Year Post-Implant Interval (n = 131, 114 MVR[2] and 17 DVR[3])					
Mean gradient[4]	n = 3	n = 40	n = 47	n = 27	n = 4
• mean ± sd	5.2 ± 0.7	4.1 ± 1.6	3.5 ± 1.8	3.1 ± 1.4	2.1 ± 0.5
• min, max	4.7, 6	1, 7	1, 10	1, 7	1.5, 2.7
EOA[5]	n = 2	n = 35	n = 46	n = 29	n = 5
• mean ± sd	1.8 ± 0.4	2.3 ± 0.6	2.6 ± 0.5	2.6 ± 0.7	2.5 ± 0.5
• min, max	1.5, 2.0	1.2, 3.5	1.1, 3.7	1.1, 3.7	2.1, 3.2
Regurgitation[6]	n = 4	n = 42	n = 51	n = 29	n = 5
0	2/4 (50%)	31/42 (74%)	36/51 (71%)	17/29 (59%)	3/5 (60%)
1+	1/4 (25%)	9/42 (21%)	11/51 (21%)	8/29 (27%)	1/5 (20%)
2+	1/4 (25%)	2/42 (5%)	4/51 (8%)	2/29 (7%)	1/5 (20%)
3+	0/4 (0%)	0/42 (0%)	0/51 (0%)	2/29 (7%)	0/5 (0%)
4+	0/4 (0%)	0/42 (0%)	0/51 (0%)	0/29 (0%)	0/5 (0%)
Not available	0/4 (0%)	0/42 (0%)	0/51 (0%)	0/29 (0%)	0/5 (0%)

continued on following page

Table 5: Effective Outcomes, Hemodynamic Results[1], Continued

Hemodynamic Parameter	Results By Valve Size				
	25 mm	27 mm	29 mm	31 mm	33 mm
5 Year Post-Implant Interval (n = 11, 9 MVR[2] and 2 DVR[3])					
Mean gradient[4]	n = 0	n = 6	n = 5	n = 0	n = 0
• mean ± sd	N/A	8.8 ± 8.1	5.1 ± 2.3	N/A	N/A
• min, max	N/A	4, 25	3, 8	N/A	N/A
EOA[5]	n = 0	n = 2	n = 4	n = 0	n = 0
• mean ± sd	N/A	2.0 ± 1.5	2.9 ± 0.6	N/A	N/A
• min, max	N/A	1.0, 3.1	2.1, 3.5	N/A	N/A
Regurgitation[6]	n = 0	n = 6	n = 5	n = 0	n = 0
0	0/0 (0%)	4/6 (66%)	2/5 (40%)	0/0 (0%)	0/0 (0%)
1+	0/0 (0%)	1/6 (17%)	3/5 (60%)	0/0 (0%)	0/0 (0%)
2+	0/0 (0%)	1/6 (17%)	0/5 (0%)	0/0 (0%)	0/0 (0%)
3+	0/0 (0%)	0/6 (0%)	0/5 (0%)	0/0 (0%)	0/0 (0%)
4+	0/0 (0%)	0/6 (0%)	0/5 (0%)	0/0 (0%)	0/0 (0%)
Not available	0/0 (0%)	0/6 (0%)	0/5 (0%)	0/0 (0%)	0/0 (0%)

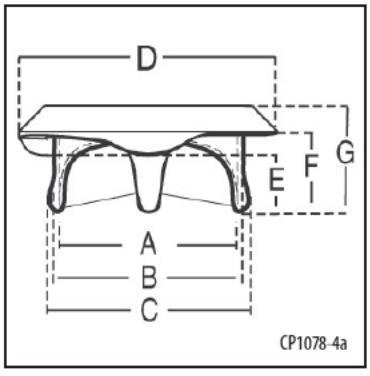
Notes:

1. Hemodynamic evaluations were performed using transthoracic echocardiography (TTE) and in some cases, transesophageal echocardiography (TEE).
2. MVR = mitral valve replacement
3. DVR = double valve replacement
4. Mean gradient in mmHg
5. EOA: Effective Orifice Area, cm^2 - Values at 1-2 year Post-Implant interval are those printed on sizers model 1177HP and sterilization tray model TRAY1177HP
6. Regurgitation = none, 0; mild, 1+; moderate, 2+; moderate/severe, 3+; severe, 4+

Figure 1

Nominal Specifications (mm)

Carpentier-Edwards PERIMOUNT MAGNA Mitral Bioprosthesis, Model 7000TFX



Size	25 mm	27 mm	29 mm	31 mm	33 mm
A. Stent Diameter (Wireform)	25	27	29	31	31
B. External Stent Post Diameter (Base)*	28	29.5	31.5	33.5	33.5
C. External Stent Post Diameter (Tip)	29	31	34	35	35
D. External Sewing Ring Diameter	36	38	40	42	44
E. Effective Profile Anterior	7	7.5	8	8.5	8.5
F. Effective Profile Posterior	10	10.5	11	11.5	11.5
G. Total Profile Height	15	16	17	18	18

*Tissue annulus diameter

CP1083-21a

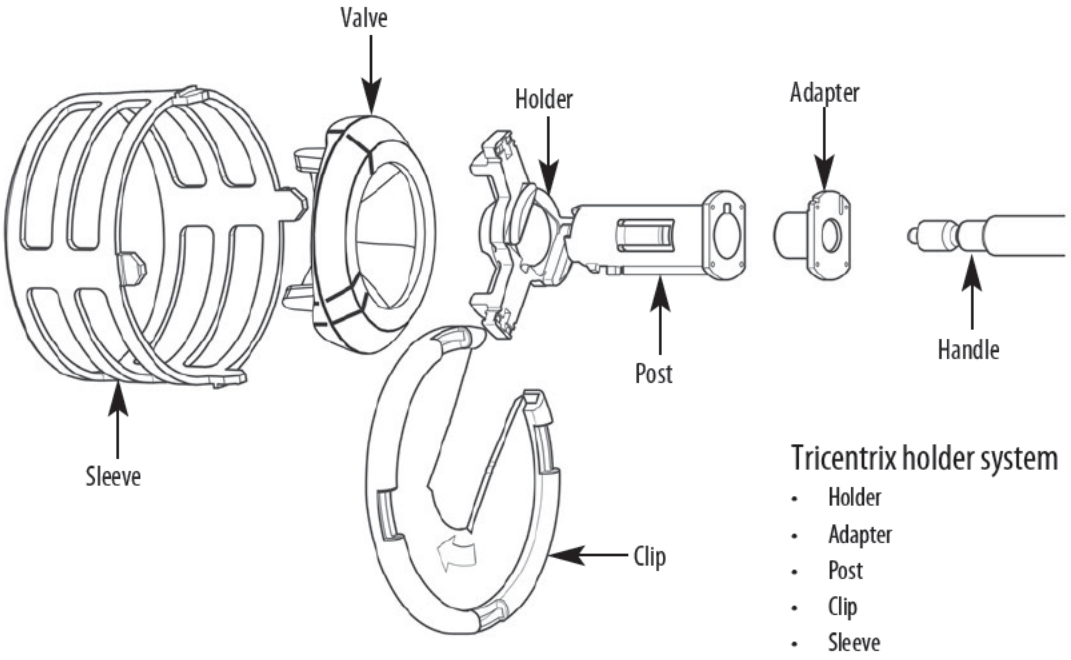


Figure 2

CP1083-15a

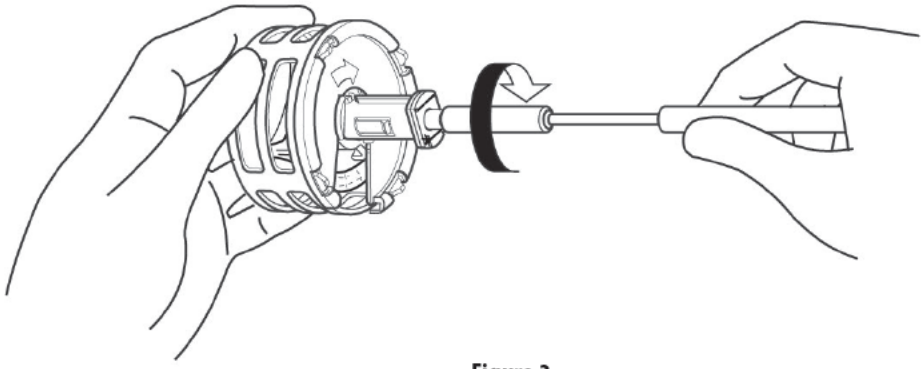


Figure 3

CP1083-16

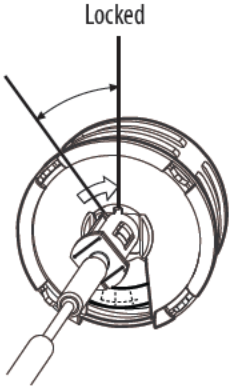


Figure 4a

CP1083-17

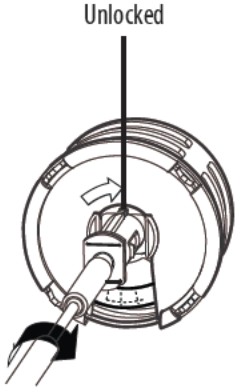


Figure 4b

CP1083-18a

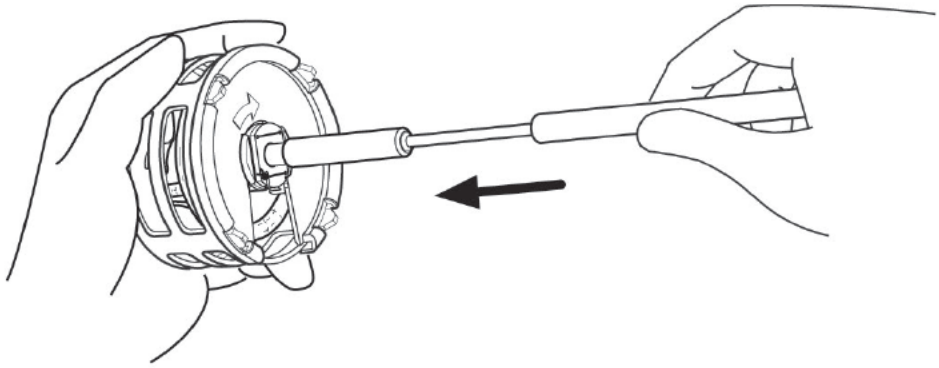


Figure 5

CP1083-19a

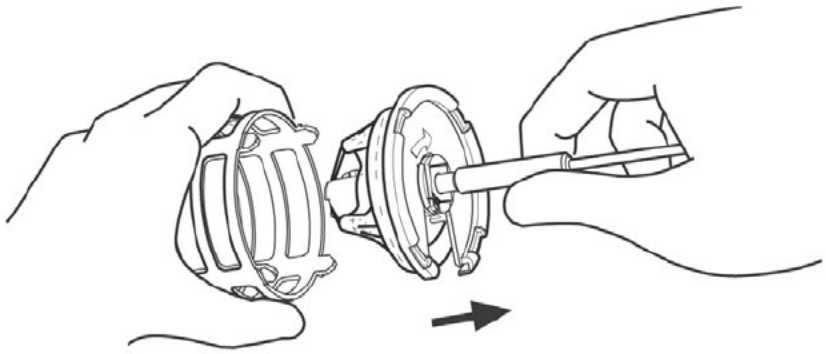


Figure 6

CP1083-20

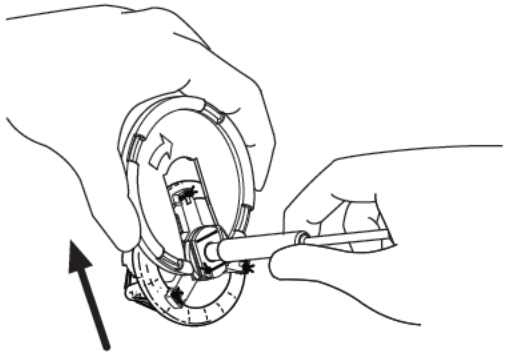


Figure 7

CP1083-11

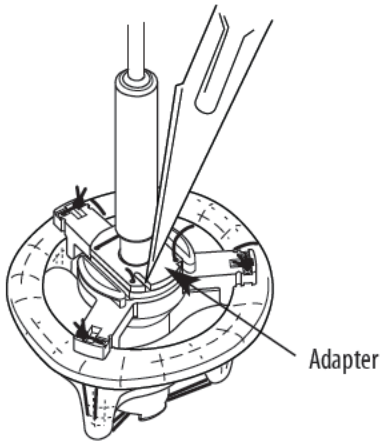


Figure 8

CP1083-12

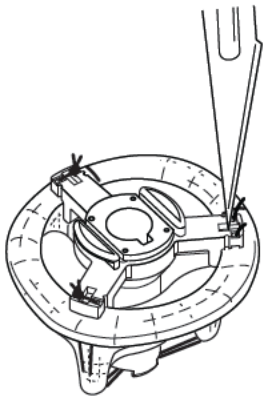


Figure 9

CP1036-49

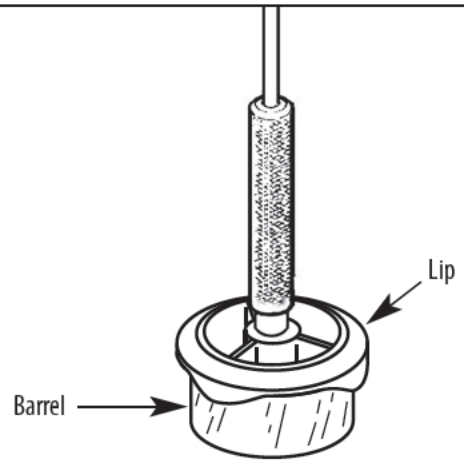
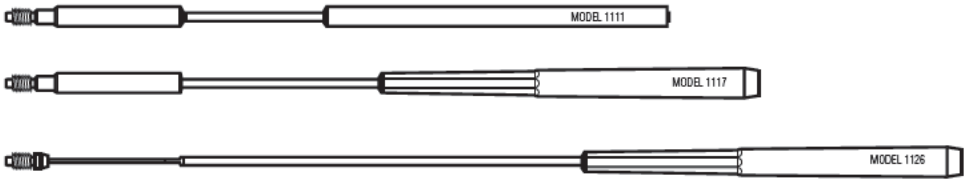


Figure 10

CP1089-1



Model	Length	
	inch	cm
1111	7.0	17.8
1117	9.1	23.2
1126	11.5	29.2

Figure 11

CP1089-2a

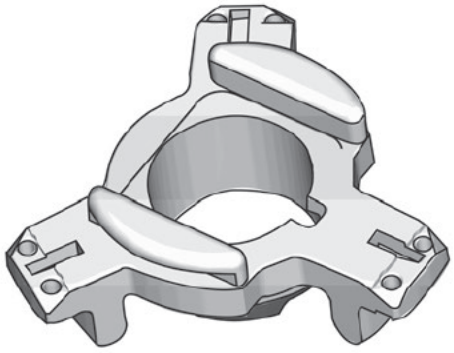


Figure 12

CP1087-14

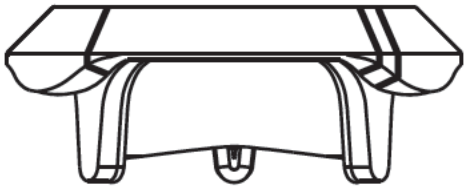


Figure 13

Edwards

4/09
194536007 A

Edwards Lifesciences LLC
One Edwards Way
Irvine, CA 92614-5686 USA
Made in USA

Telephone 949.250.2500
800.424.3278
FAX 949.250.2525

DATA MATRIX
BARCODE FPO

Edwards Lifesciences

Carpentier-Edwards PERIMOUNT Magna Mitral Ease Pericardial Bioprosthesis Model 7200TFX

Instructions for Use

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

1. Device Description

The Carpentier-Edwards PERIMOUNT Magna Mitral Ease pericardial bioprosthesis is built upon the same proven (Ref. 1) wireform frame and leaflet attachment as the PERIMOUNT mitral pericardial bioprostheses models 6900, 6900P, 6900PTFX, and 7000TFX. It is available in the sewing ring diameters and sizes shown in Figure 1. The bioprosthesis incorporates a sewing ring specifically designed for the mitral position and is the first bioengineered mitral bioprosthesis design with three selected bovine pericardial leaflets mounted on a flexible metal alloy frame.

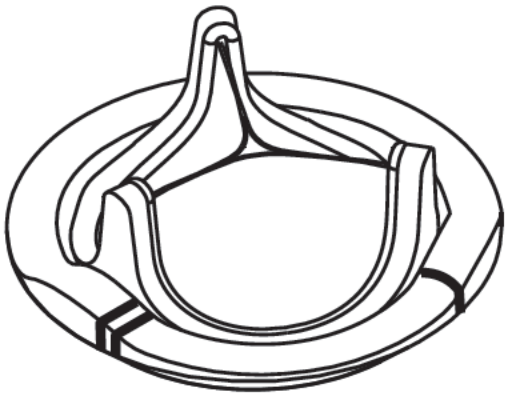
Bovine pericardium was selected for its superior intrinsic properties for valve manufacture, notably in terms of collagen content (Ref. 2) and tolerance to high bending curvatures (Ref. 3). Bovine pericardium tissue is cross-linked using the Neutralogic fixation process in which the tissue is placed in a stress-free bath of buffered glutaraldehyde solution. The bioprosthesis is treated according to the ThermaFix process, which involves heat treatment of the tissue in glutaraldehyde and uses ethanol and Polysorbate-80 (a surfactant). Glutaraldehyde is shown to both reduce the antigenicity of tissue xenograft valves and increase tissue stability (Refs. 4 & 5). Glutaraldehyde alone has not been shown to affect or reduce the calcification rate of the valve.

Tissue thickness is measured for each valve size and leaflets are precisely die-cut in selected areas of a pericardial sheet. Leaflet deflection testing characterizes each leaflet for elasticity. Three leaflets matched for similar thickness and elasticity are then assembled. Leaflets are mounted underneath the wireform frame to minimize commissural stress points.

The lightweight wireform frame is made of a corrosion-resistant cobalt-chromium alloy, chosen because of its superior spring efficiency 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 sewn with polytetrafluoroethylene thread. The wireform frame of the Magna Mitral Ease bioprosthesis is symmetrical and the three commissure supports (struts) are equally spaced.

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

CP1087-12



Model 7200TFX

The sewing ring is made of waffled silicone-rubber and is covered with a porous polytetrafluoroethylene cloth sewn with polytetrafluoroethylene thread. The cloth facilitates tissue in-growth and encapsulation. The sewing ring of the Magna Mitral Ease bioprosthesis is uniquely scalloped along its anterior portion and mimics the natural saddle shape of the native mitral valve anatomy. Black silk suture markers on the anterior portion facilitate the orientation of the bioprosthesis and help avoid obstruction of the left ventricular outflow tract by a strut. The design of the silicone waffle eases needle penetration and provides variable compliance. The waffle has wider cells along the posterior portion, where calcifications or irregularities of the native mitral annulus are more frequent (Ref. 6). 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 Tricentrix holder system is designed to minimize suture or chordae entrapment, ease insertion and increase leaflet visibility. It is secured to the bioprosthesis with sutures. The bioprosthesis and holder attachment are suspended by a clip and a sleeve within a sealed jar that contains a glutaraldehyde packing solution. The bioprosthesis is terminally sterilized in glutaraldehyde.

2. Indications for Use

The Carpentier-Edwards PERIMOUNT Magna Mitral Ease pericardial bioprosthesis model 7200TFX is indicated for patients who require replacement of their native or prosthetic mitral valve.

3. Contraindications

Do not use if the surgeon believes such would be contrary to the best interests of the patient. The actual decision for or against the use of this bioprosthesis must remain with the surgeon who can evaluate all the various risks involved, including the anatomy and pathology observed at the time of surgery.

4. Warnings

For Single Use Only

DO NOT RESTERILIZE THE BIOPROSTHESIS BY ANY METHOD. Exposure of the bioprosthesis or container to irradiation, steam, ethylene oxide, or other chemical sterilants will render the bioprosthesis unfit for use.

DO NOT FREEZE OR EXPOSE THE BIOPROSTHESIS TO EXTREME HEAT. Each bioprosthesis is contained in a carton with a temperature indicator displayed through a window on the side panel. The temperature indicator is intended to monitor the temperature that the device is exposed to during transit and storage. If the indicator displays any reading other than "OK" do not use the bioprosthesis. Please refer to Packaging section (10.2) for further instructions.

DO NOT USE the bioprosthesis if the tamper evident seal on the jar is broken.

DO NOT USE the bioprosthesis if expiration date has elapsed.

DO NOT USE the bioprosthesis if the container is leaking, damaged, or the glutaraldehyde solution does not completely cover the bioprosthesis.

DO NOT EXPOSE the bioprosthesis to any solutions, chemicals, antibiotics, etc., except for the storage solution or sterile physiological saline solution. Irreparable damage to the leaflet tissue, which may not be apparent under visual inspection, may result.

DO NOT ALLOW the bioprosthesis to dry. It must be kept moist at all times. Maintain tissue moisture with sterile physiological saline irrigation on both sides of the leaflet tissue.

DO NOT PASS CATHETERS, transvenous pacing leads, or any surgical instrument across the bioprosthesis with the exception of a surgical mirror used to examine struts and suture placement. Other surgical devices may cause leaflet tissue damage.

DO NOT USE the bioprosthesis if it has been dropped, damaged, or mishandled in any way. Should a bioprosthesis be damaged during insertion, do not attempt repair.

DO NOT GRASP the leaflet tissue of the bioprosthesis with instruments or cause any damage to the bioprosthesis. Even the most minor leaflet tissue perforation may enlarge in time to produce significant impairment of valve function.

DO NOT OVERSIZE. Oversizing may cause bioprosthesis damage or localized mechanical stresses, which may in turn injure the heart or result in leaflet tissue failure, stent distortion and valve regurgitation.

Clinical data that establish the safety and efficacy of the bioprosthesis for use in patients under the age of 20 are not available; therefore, we recommend careful consideration of its use in younger patients.

As with any implanted medical device, there is a potential for patient immunological response (see device description for materials).

The decision to use a bioprosthesis must ultimately be made by the surgeon on an individual basis after a careful evaluation of the short- and long-term risks and benefits to the patient and consideration of alternative methods of treatment.

Long-term durability has not been established for bioprostheses. Serious adverse events, sometimes leading to replacement of the bioprosthesis and/or death, may be associated with the use of prosthetic valves (see **6. Adverse Events**). A full explanation of the benefits and risks should be given to each prospective patient before surgery.

Note: Bioprostheses should be used with caution in the presence of severe systemic hypertension or when the anticipated patient longevity is longer than the known longevity of the prosthesis (see **7. Clinical Studies**).

Careful and continuous medical follow-up (at least by an annual visit to the physician) is advised so that bioprosthesis-related complications, particularly those related to material failure, can be diagnosed and properly managed. Recipients of prosthetic heart valves who are undergoing dental procedures should receive prophylactic antibiotic therapy to minimize the possibility of prosthetic infection. Bioprosthetic heart valve recipients should be maintained on anticoagulant therapy (except where contraindicated) during the initial healing stages after implantation, 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 by the physician on an individual basis (Ref. 7).

Adequate rinsing with physiological saline is mandatory before implantation to reduce the glutaraldehyde concentration (see **11.4 Handling and Preparation Instructions**). No other solutions, drugs, chemicals, antibiotics, etc., should ever be added to the glutaraldehyde or rinse solutions, as irreparable damage to the leaflet tissue, which may not be apparent under visual inspection, may result.

5. Precautions

- Do not sterilize the sizer models 1171B, 1171R, and handle models 1111, 1117, or 1172 in their shipping containers.
- Use only the sterilization tray provided in model SET1171 to sterilize the sizers and the handles.
- The outside of the jar is not sterile and must not be placed in the sterile field.
- To avoid contamination, it is strongly recommended that the jar of a Carpentier-Edwards PERIMOUNT Magna Mitral Ease pericardial bioprosthesis model 7200TFX not be opened unless implantation is certain.
- Adequate rinsing with physiological saline must be performed before implantation to reduce the glutaraldehyde concentration.
- Avoid contact of the leaflet tissue or the rinse solution with towels, linens, or other sources of lint and particulate matter that may be transferred to the leaflet tissue.
- Do not allow the leaflet tissue to contact the bottom or sides of the rinse basin.
- Glutaraldehyde may cause irritation of the skin, eyes, nose, and throat. Avoid prolonged or repeated exposure or breathing of the solution. Use only

with adequate ventilation. If skin contact occurs, immediately flush the affected area with water; in the event of contact with the eyes, seek immediate medical attention. For more information about glutaraldehyde exposure, please refer to the Material Safety Data Sheet available from Edwards Lifesciences.

- Always deploy the Tricentrix holder system fully to minimize the risk of suture entrapment. It will snap into a secured and locked position.
- A serial number tag is attached to the sewing ring of each bioprosthesis by a suture. This serial number should be checked against the number on the jar and implantation data card; if any difference is noted, the bioprosthesis should be returned unused. Care must be taken to ensure that the serial number tag does not come in contact with the leaflet tissue during rinsing. Inspection of the bioprosthesis and removal of the serial number tag should be performed just prior to implantation. Care should be exercised to avoid cutting or tearing the sewing ring cloth during removal of the serial number tag.
- Careful handling is required for all implantable devices. If the bioprosthesis is dropped, damaged, or mishandled in any way, it must not be used for human implantation.
- To avoid damage to the delicate bioprosthetic leaflet tissue, as a result of contact with calcium deposits, adequate removal of calcium deposits from the patient's annulus must be performed before implantation.
- Handle the bioprosthesis only with Edwards Lifesciences accessories. Only Edwards Lifesciences sizers model 1171B or 1171R should be used during the selection of the Magna Mitral Ease bioprosthesis size; other sizers may result in improper bioprosthesis selection.
- Oversizing must be especially avoided as it may cause bioprosthesis damage or localized mechanical stresses, which may in turn injure the heart or result in leaflet tissue failure, stent distortion and regurgitation.
- Special care must be exercised when using chordal preservation techniques to avoid chordae entrapment by a strut.
- Due to the relative flexibility of the frame, care must be exercised to prevent folding or deformation of the stent.
- The surgeon should be familiar with the recommendations for proper sizing and placement of the bioprosthesis according to the suture technique used (see **11.5 Device Implantation**).
- The sewing ring is designed for a specific orientation: the scalloped part of the sewing ring, between the black suture markers, should be placed across the intercommissural anterior portion of the annulus and straddle the left ventricular outflow tract.
- Special care must be exercised to avoid placing a strut in front of the left ventricular outflow tract, as this may impair the long-term hemodynamic performance.
- As with all prostheses that have open cages, free struts, or commissure supports, care must be exercised to avoid looping or catching a suture around a commissure, which would interfere with proper valvular function. To avoid suture looping, it is essential to leave the deployed holder in place until all knots are tied.
- If the deployed holder attachment threads are cut, before at least all the sutures adjacent to the struts are tied down, the holder can no longer prevent suture looping.
- When using interrupted sutures, it is important to cut the sutures close to the knots and to ensure that exposed suture tails will not come into contact with the leaflet tissue.

6. Adverse Events

6.1 Observed Adverse Events

The Carpentier-Edwards PERIMOUNT Magna Mitral Ease pericardial bioprosthesis model 7200TFX uses the same wireform frame and leaflet attachment as Edwards Lifesciences pericardial mitral bioprostheses models 6900, 6900P, 6900PTFX, and 7000TFX. Three (3) multi-center, non-randomized, prospective non-US clinical studies were conducted with the mitral pericardial bioprosthesis model 6900. Three hundred one (301) patients had isolated mitral valve replacement (MVR) and 62 patients had double valve replacement (DVR), where the aortic valve was replaced with a Carpentier-Edwards PERIMOUNT pericardial bioprosthesis aortic model. In the first study, bioprostheses were implanted between 1984 and 1986; in the second study, bioprostheses were implanted between 1989 and 1994; and in the third study, bioprostheses were implanted between 1996 and 1997. Patients were evaluated preoperatively, intraoperatively/at discharge, at 1 year, and annually thereafter. Adverse events were captured throughout the postoperative period. Table 1 presents the observed rates for early events ($\leq$ 30 days for valve-related adverse events), the linearized rates for late events ($>$ 30 days postoperatively), and the actuarial adverse event rates at 1, 5, and 8 years postoperatively. The adverse event rates were based on 363 patients at nine centers. The cumulative follow-up was 1100 patient-years with a mean follow-up of 3.0 years (SD = 2.4 years, range = 0 to 8.2 years). Preoperative and operative patient demographics are presented in Tables 2 and 3. Effectiveness results are presented in Tables 4 and 5.

6.2 Potential Adverse Events

Adverse events potentially associated with the use of bioprosthetic heart valves include:

- Angina
- Cardiac arrhythmias
- Endocarditis
- Heart failure
- Hemolysis
- Hemolytic anemia
- Hemorrhage
- Myocardial infarction
- Prosthesis leaflet entrapment
- Prosthesis nonstructural dysfunction
- Prosthesis pannus
- Prosthesis perivalvular leak
- Prosthesis regurgitation
- Prosthesis structural deterioration
- Prosthesis thrombosis
- Stroke

- Thromboembolism

It is possible that these complications could lead to:

- Reoperation
- Explantation
- Permanent disability
- Death

Other adverse events associated with the use of Carpentier-Edwards PERIMOUNT mitral pericardial bioprostheses model 6900 compiled from the literature and from reports received through the Edwards Lifesciences complaint handling system include: stenosis, regurgitation through an incompetent valve, ventricular perforation by stent posts, malfunctions of the valve due to distortion at implant, and fracture of the wireform frame.

7. Clinical Studies

The safety endpoints captured in the prospective studies were complications; blood analyses were used to confirm the absence or presence of certain complications. The safety results are provided in Table 1. Effectiveness endpoints were New York Heart Association (NYHA) functional classification and echocardiographic assessments. Preoperative and operative patient demographics are presented, followed by the effectiveness results. There are no clinical data presently available demonstrating increased resistance of the Carpentier-Edwards PERIMOUNT Magna Mitral Ease pericardial bioprosthesis model 7200TFX to calcification as compared to other commercially available bioprostheses.

8. Individualization of Treatment

Bioprosthetic heart valve recipients should be maintained on anticoagulant therapy, except where contraindicated, during the initial stages after implantation, as determined by the physician on an individual basis. Long-term anticoagulant and/or antiplatelet therapy should be considered for patients with a dilated left atrium, a history of thrombotic events, an absence of sinus rhythm, calcification of the atrial wall, or with atrial fibrillation or flutter. The decision to use a bioprosthesis must ultimately be made by the physician on an individual basis after a careful evaluation of the short-term and long-term risks and benefits to the patient and consideration of alternative methods of treatment (Ref. 7).

8.1 Specific Patient Populations

The safety and effectiveness of the Carpentier-Edwards PERIMOUNT Magna Mitral Ease pericardial bioprosthesis model 7200TFX has not been established for the following specific populations because it has not been studied in these populations:

- patients who are pregnant;
- nursing mothers;
- patients with abnormal calcium metabolism (e.g., chronic renal failure, hyperparathyroidism);
- patients with aneurysmal aortic degenerative conditions (e.g., cystic medial necrosis, Marfan's syndrome);
- children, adolescents, or young adults.

9. Patient Counseling Information

Careful and continued medical follow-up (at least by an annual visit to the physician) is advised so that valve-related complications, particularly those related to material failure, can be diagnosed and properly managed. Patients with bioprostheses are at risk from bacteremia (e.g., undergoing dental procedures) and should be advised about prophylactic antibiotic therapy. Patients should be encouraged to carry their Implantation Data Card at all times and to inform their healthcare providers that they have a mitral bioprosthetic implant when seeking care.

10. How Supplied

10.1 Available Models and Sizes

The Carpentier-Edwards PERIMOUNT Magna Mitral Ease pericardial bioprosthesis model 7200TFX is available in labeled sizes 27, 29, 31, 33, and 35 (see Figure 1 for nominal specifications).

10.2 Packaging

The Magna Mitral Ease bioprosthesis is provided sterile and nonpyrogenic packaged in glutaraldehyde, in a plastic jar to which a seal has been applied. Each bioprosthesis is contained in a carton with a temperature indicator displayed through a window on the side panel. The temperature indicator is intended to monitor the temperature that the device is exposed to during transit and storage. Upon receipt of the bioprosthesis immediately inspect to see if the indicator displays any reading other than "OK", if so do not use the bioprosthesis. Contact the local supplier or Edwards Lifesciences representative to make arrangements for return, authorization and replacement. Any bioprosthesis returned to Edwards Lifesciences must be shipped in its original packaging in which it was received.

Warning: The bioprosthesis must be carefully inspected before implantation for evidence of extreme temperature exposure or other damage.

Due to the biological nature of this bioprosthesis and its sensitivity to physical handling and environmental conditions, it cannot be returned, except as noted above.

Note: Products found to have been subjected to freezing or excessive heat later than 3 days following receipt will be considered to have resulted from environmental conditions within the control of the customer, and subject to replacement at customer's expense.

10.3 Storage

The Magna Mitral Ease bioprosthesis should be stored at 10 °C to 25 °C (50-77 °F). Stock inspection and rotation at regular intervals are recommended to ensure that the bioprostheses are used before the expiration date stamped on the package label.

Warning: Do not freeze. Always store bioprostheses in a dry, contamination-free area. Any bioprosthesis that has been frozen, or is suspected of having been frozen, should not be used for human implantation.

11. Directions for Use

11.1 Physician Training

No special training is required to implant the Carpentier-Edwards PERIMOUNT Magna Mitral Ease bioprosthesis model 7200TFX. The techniques for implanting this bioprosthesis are similar to those for implanting any stented mitral bioprostheses.

11.2 Accessories

Accessories available for use with the Magna Mitral Ease bioprosthesis are:

- Tricentrix holder system
- Replica Sizer 1171R (Figure 10)
- Barrel Sizer 1171B (Figure 11)
- Sterilization Tray provided in model SET1171
- Flexible Handle models 1111, 1117, 1172, and 1126 (single use) (Figure 13)

All accessories are supplied non-sterile, except for the Tricentrix holder system that is supplied sterile attached to the sterile bioprosthesis and the handle 1126 that is supplied sterile and is for single use only.

Sizers and Tray

Only sizers model 1171B or 1171R may be used with the Magna Mitral Ease bioprosthesis.

Caution: Do not use other manufacturer's valve sizers, or sizers for other Edwards Lifesciences valve prostheses to size the Magna Mitral Ease bioprosthesis.

Use only the sizers model 1171B or 1171R to determine the appropriate Magna Mitral Ease bioprosthesis size. Sizers model 1171B and 1171R permit direct observation of their fit within the annulus and are provided for each available Magna Mitral Ease bioprosthesis size. The barrel of the sizers model 1171B and 1171R indicate the external stent diameter at the base (Figure 1). The lip of the replica sizer 1171R replicates the sewing ring of the bioprosthesis, with its scalloped anterior portion and black markings, to 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 bioprosthesis sewing ring which should be positioned across the anterior intercommissural portion of the native annulus, in order to straddle the left ventricular outflow tract area. The height and location of the stent posts are marked on the replica sizer 1171R to aid in assessing optimal alignment and seating.

The sizers include preattached handles with increased handle length for improved access in the case of a difficult exposure, a deep thoracic cage or minimally invasive access. The posterior handle attachment to the sizer allows an unobstructed view through the barrel into the ventricle for assessment of subvalvular structures. The sizers 1171B and 1171R are labeled with the bioprosthesis size.

Tricentrix Holder System and Handles

The holder/handle assembly consists of two (2) components: the Tricentrix holder system that is mounted to the Magna Mitral Ease bioprosthesis, and a handle (1111, 1117, 1172, or 1126) that is attached to the Tricentrix holder system at the time of surgery (Figure 2).

The following handles (Figure 13) may be used with the Magna Mitral Ease bioprosthesis:

Model	Shaft Material	Overall Length (inches)		Reusable
		inch	cm	
1111	Stainless steel	7.0	17.8	Yes
1117	Nitinol	9.1	23.2	Yes
1126	Stainless steel	11.5	29.2	No
1172	Nitinol	11.3	28.6	Yes

- Handles with a nitinol shaft are more flexible than stainless steel. With each sterilization cycle, they return to their original straight shape for easier attachment to the holder.
- Handle 1172 has been designed to improve access in the case of difficult exposure, a deep thoracic cage, or in minimally invasive procedures.

The Tricentrix holder has short legs and beveled edges to increase suturing space and ease knot tying (Figure 14).

11.3 Accessory Sterilization

The 1126 handle is provided sterile and is intended for single use only. The handles 1111, 1117, and 1172 and the sizers 1171B and 1171R are supplied non-sterile and must be cleaned and sterilized before using. The handles 1111, 1117, and 1172 must be disassembled from any accessories prior to cleaning and sterilization.

Caution: Examine sizers and handles for signs of wear, such as dullness, cracking, or crazing. Replace sizer or handle if any deterioration is observed.

Caution: Do not sterilize the sizers and handles 1111, 1117, or 1172 in their shipping containers.

Use only the sterilization tray provided in model SET1171 to sterilize the sizers and the handles.

The accessories can be sterilized using the following recommended autoclave sterilization methods:

I. Gravity Displacement:
   a) Wrapped:
      Temperature: 270-279 °F (132-137 °C)
      Exposure Time: 10-18 minutes
   b) Unwrapped ("flash"):
      Temperature: 270-279 °F (132-137 °C)
      Exposure Time: 3 minutes

II. Prevacuum:
   a) Wrapped:
      Temperature: 270-279 °F (132-137 °C)
      Exposure Time: 3-18 minutes
   b) Unwrapped ("flash"):
      Temperature: 270-279 °F (132-137 °C)
      Exposure Time: 3 minutes

Each institution should use procedures that include biological indicators to determine the effectiveness of the sterilization procedure.

11.4 Handling and Preparation Instructions

The bioprosthesis is packaged sterile in a plastic jar with a screw-cap closure and seal. Before opening, carefully examine the jar for evidence of damage (e.g., a cracked jar or lid), leakage, or broken or missing seals. Remove the seal and turn the lid counter-clockwise to open the container. The bioprosthesis and Tricentrix holder system within the container are sterile.

Caution: The outside of the jar is not sterile and must not be placed in the sterile field. The contents of the jar should be handled in an aseptic manner to prevent contamination.

Caution: Bioprostheses from containers found to be damaged, leaking, without adequate glutaraldehyde, or missing intact seals must not be used for human implantation.

Caution: It is strongly recommended that the jar of a Magna Mitral Ease bioprosthesis not be opened unless implantation is certain. This is necessary to reduce the risk of contamination, because it has been established that glutaraldehyde alone is not a 100% effective sterilant against all possible contaminants.

Warning: No attempt should be made to resterilize a Magna Mitral Ease bioprosthesis.

Warning: Do not use the bioprosthesis if it has been dropped, damaged, or mishandled in any way. Should a bioprosthesis be damaged during insertion, do not attempt repair.

Warning: Do not grasp the leaflet tissue portion of the bioprosthesis with instruments or cause any damage to the bioprosthesis. Even the most minor leaflet tissue perforation may enlarge in time to produce significant impairment of bioprosthesis function.

Verify that the handle, model 1111,1117, or 1172, has been sterilized according to the instructions provided in Section 11.3. Attach the handle to the Tricentrix holder system and turn it clockwise until a positive resistance is felt then remove the whole assembly (i.e., plastic sleeve, clip, the Tricentrix holder system and bioprosthesis) from the jar.

A tag with a serial number is attached to the sewing ring of each bioprosthesis by a suture. This serial number should be checked against the number on the jar and implantation card; if any differences are noted, the bioprosthesis should be returned unused. This tag should not be detached from the bioprosthesis until just prior to implantation.

Grasping the plastic sleeve (Figure 3) continue the rotation to overcome the resistance until the holder post reaches the unlock position (Figure 4a and Figure 4b). Apply the required push force on the handle until the post slides across the leaflets and snaps into its fully deployed position (Figure 5).

Caution: If an adequate push force is not applied to the handle when deploying the Tricentrix holder system, the tenting system will not be secured and will not be able to prevent suture entrapment. Always check for proper deployment. There should be no more space between the handle attachment adapter and the clip. The handle/post assembly should not be able to slide any longer.

The holder post should protrude through the leaflets while the three (3) commissures should deflect slightly towards the center of the bioprosthesis. The leaflets will temporarily be wrinkled by the deployed holder post. When the holder is removed following implantation, the leaflets will return to their normal position.

After deployment, remove the sleeve by holding the handle and pulling the sleeve off the clip (Figure 6). Remove the clip by sliding it off the holder in a sideways direction (Figure 7). Both sleeve and clip should be discarded. Once the handle has been attached, it should not be removed from the holder until the bioprosthesis is seated to the annulus.

Rinse Procedure

Within the sterile operative field, prepare two rinse basins, each containing no less than 500 ml of sterile, physiological saline solution. Place the deployed bioprosthesis in the saline solution and make sure that it completely covers the bioprosthesis and holder. Do not rinse with the sleeve and clip attached. With the bioprosthesis and holder submerged, slowly agitate the basin or use the attached handle to gently swirl the bioprosthesis back and forth for a minimum of 1 minute in each of the two previously prepared rinse basins. The bioprosthesis should remain in the second rinse basin until ready for implantation.

Caution: Avoid contact of the leaflet tissue or the rinse solution with towels, linens, or other sources of lint and particulate matter that may be transferred to the leaflet tissue.

Caution: Do not allow the leaflet tissue to contact the bottom or sides of the rinse basin.

Caution: Care must be taken to ensure that the serial number tag does not come in contact with the leaflet tissue during rinsing.

Inspect the bioprosthesis and remove the serial number tag just prior to implantation. Exercise care to avoid cutting or tearing the sewing ring cloth during removal of the serial number tag.

11.5 Device Implantation

Because of the complexity and variation in the surgical procedure of cardiac valve replacement, the choice of surgical technique is left to the discretion of the individual surgeon. In general, the standard implantation technique includes: 1. Proper sizing; 2. Proper seating of the prosthesis; 3. Tying sutures with the holder in place to avoid suture looping or chordal entrapment; 4. Examination of the bioprosthetic leaflets for distortion or leak during tying.

Proper bioprosthesis size selection is an important part of mitral valve replacement.

Verify that the sizers 1171B and 1171R have been sterilized according to the recommended instructions in Section 11.3.

Caution: Examine sizers and handles for signs of wear, such as dullness, cracking, or crazing. Do not use sizer or handle if any deterioration is observed.

Caution: Adequate removal of calcium deposits from the patient's annulus must be performed before implantation to avoid damage to the delicate bioprosthesis leaflet tissue as a result of contact with calcium deposits.

Insert the sizer into the mitral annulus. The barrel of the sizer should always fit comfortably in the annulus.

Warning: Care must always be exercised to avoid the use of too large a prosthesis since oversizing may create damage or localized mechanical stresses, which may in turn injure the heart or result in leaflet tissue failure, stent distortion and regurgitation.

Caution: Use only sizers 1171B or 1171R during the selection of the Magna Mitral Ease bioprosthesis size; other sizers may result in improper valve selection (see **11.2 Accessories**).

Like other mitral bioprostheses, the Magna Mitral Ease bioprosthesis is usually implanted using pledgeted mattress sutures. It is recommended to size the

annulus after the sutures have been placed, as sutures may decrease the size of the bioprosthesis that can be implanted.

Sizing for implantation:

Sizing with barrel sizer 1171B: To size with barrel sizer 1171B, pass the barrel portion of the sizer through the mitral annulus.

Sizing with replica sizer 1171R: To size with replica sizer 1171R, pass the barrel portion of the sizer through the mitral annulus so that the lip of the sizer, which simulates the sewing ring portion of the bioprosthesis, rests on the superior aspect of the annulus (Figure 12).

Some techniques such as use of pledgets, leaflet reefing, or mitral subvalvular apparatus preservation may further reduce the size of the mitral annulus which can result in the need for a smaller bioprosthesis to be implanted (Ref. 8). When using these techniques, it is recommended to re-size the annulus to avoid oversizing of the bioprosthesis. The consistent performance of the PERIMOUNT mitral bioprostheses makes oversizing unnecessary to achieve the desired hemodynamic performance in most patients (Table 5).

Due to the elastic nature of a chord, it may be extended by the Tricentrix holder system during implantation but retract back around the post once the holder is removed, entrapping leaflets and impairing function. Sizers 1171B and 1171R are made of a transparent material to allow visualization of the subvalvular apparatus during sizing. Make sure no chord will be in the way of the struts.

Caution: Exercise special care when using subvalvular apparatus preservation techniques to avoid chordae entrapment by a strut.

Warning: Avoid oversizing the bioprosthesis. Oversizing may cause bioprosthesis damage or localized mechanical stresses, which may in turn injure the heart or result in leaflet tissue failure, stent distortion and regurgitation.

Caution: Because of the intense temperature and lighting conditions in the operating field, the bioprosthesis should be irrigated frequently (every 1 to 2 minutes is recommended) on both sides with sterile physiological saline to keep the valve moist during the implant procedure.

Proper orientation of the bioprosthesis

Caution: The wireform frame of the Magna Mitral Ease bioprosthesis is symmetrical, and the three commissure supports (struts) are equally spaced. However, the sewing ring is designed for a specific orientation of the bioprosthesis. The scalloped part of the sewing ring, between the two silicone protrusions, should be placed across the intercommissural anterior portion of the annulus and straddle the left ventricular outflow tract.

The contrasting suture markers in the sewing ring are intended to aid in proper orientation and denote a typical intercommissural distance. However, this distance may vary for each individual patient. On the left side, two close black sutures indicate where the first stitch should be placed and correspond to the anterior commissure. On the right side, only one black suture indicates the approximate location of the posterior commissure. Using these orientation aids, the third post should naturally fall in place in or around the middle of the posterior leaflet location.

Caution: Special care must be exercised to avoid placing a strut in front of the left ventricular outflow tract, as it may impair the long-term hemodynamic performance.

When placing sutures through the sewing ring, sliding drag forces are reduced when sutures are placed straight through the middle to outer portion of the sewing ring. Irrigation with saline can further reduce suture drag forces.

Firm tension must be maintained on the sutures as the bioprosthesis is lowered into the annulus; this prevents formation of suture loops that might entrap a leaflet. This, when combined with the fully retracted stent posts when the Tricentrix holder system is in place, helps guide the sutures into their correct position behind the struts and onto the sewing ring.

Remove the handle prior to tying the sutures. The handle and adapter must be removed as an assembly. Maintain the bioprosthesis placement in the annulus by gently placing forceps or gloved hands onto the holder and cut the green thread on the white adapter (Figure 8). Remove the adapter and handle assembly as one unit.

Caution: Avoid looping or catching a suture around the open cages, free struts, or commissure supports of the bioprosthesis, which would interfere with proper valvular function. To avoid suture looping, it is essential to leave the deployed holder in place until all knots are tied.

However, if leaving the holder in place obstructs the surgeon's view, all the sutures adjacent to each of the three frame struts must be tied down before cutting the three holder attachment threads to remove the holder.

Caution: If the deployed holder attachment threads are cut before these adjacent sutures are tied down, the holder can no longer prevent suture looping around the frame struts.

Special attention must be given to avoid tying the sutures on top of the corners of the holder legs. Before tying each suture, examine the leaflets while holding the two strands of the suture under tension. Distortion or movement of the leaflets during this maneuver suggests that the suture is looped around a strut. At no point before or after holder removal should tension on the sutures be released as this may facilitate formation of loops in the sutures and possible entrapment. It is recommended to place a surgical mirror through the leaflets after the holder removal in order to examine each strut and proper suture placement.

Caution: When using interrupted sutures, it is important to cut the sutures close to the knots and to ensure that exposed suture tails will not come into contact with the leaflet tissue (Ref. 8).

The Tricentrix holder system is removed as a unit at the completion of the suturing procedure as follows (Figure 9):

1. Cut each of the three (3) exposed sutures using a scalpel or scissor placed only in the cutting channel. Never attempt to cut a suture below a partially separated holder as a part of the attaching suture may fall in the ventricle. Avoid cutting or damaging the stent or leaflet tissue when cutting the sutures.
2. When all three (3) attaching sutures have been properly cut, remove the Tricentrix holder system from the bioprosthesis as a unit, along with attaching sutures, using sterile gloved hands or protected forceps.
3. Following surgery, remove the holder and discard.

11.6 Return of Explanted Bioprostheses

Edwards Lifesciences is interested in obtaining all recovered clinical specimens of Carpentier-Edwards PERIMOUNT Magna Mitral Ease pericardial bioprostheses model 7200TFX for analysis. A written report summarizing our findings will be provided to the physician upon completion of our evaluation. Please contact

your local representative for return of recovered bioprostheses. The explanted bioprostheses should be placed into a suitable histological fixative such as 10% formalin or 2% glutaraldehyde immediately after excision and returned to the company. Refrigeration is not necessary under these circumstances.

12. Patient Information

12.1 Registration Information

An Implantation Data Card is included in each device package for patient registration. After implantation, please complete all requested information. The bioprosthesis serial number is listed on the bioprosthesis packaging and on the identification tag attached to the bioprosthesis, and is pre-printed on the Implantation Data Card. Return the pre-addressed portion of the card to our Implant Patient Registry. The remaining portions of the card are provided for hospital and surgeon records. Upon receipt by the Edwards Implant Patient Registry, a wallet-sized identification card will be produced for the patient. This card allows patients to inform healthcare providers what type of implant they have when they seek care. When a bioprosthesis is discarded or a previous Edwards Lifesciences device is replaced, report this information to the Edwards Implant Patient Registry.

12.2 Patient Manual

Patient information materials may be obtained from Edwards or your local representative.

13. Safety in the Magnetic Resonance (MR) Environment

MR Conditional

Non-clinical testing has demonstrated that the Carpentier-Edwards PERIMOUNT Magna Mitral Ease pericardial bioprosthesis model 7200TFX is MR Conditional. A patient with the Magna Mitral Ease bioprosthesis can be scanned safely, immediately after placement of this implant under the following conditions:

- Static magnetic field of 3 tesla or less.
- Spatial gradient field of 720 gauss/cm or less.
- Maximum MR system-reported whole-body-averaged specific absorption rate (SAR) of 3 W/kg for 15 minutes of scanning.

In non-clinical testing, the Magna Mitral Ease bioprosthesis produced a temperature rise of less than or equal to 0.5 °C at a maximum MR system-reported whole-body-averaged specific absorption rate (SAR) of 3 W/kg for 15 minutes of MR scanning in a 3 tesla MR system (Excite, Software G3.0-052B, General Electric Healthcare).

MR image quality may be compromised if the area of interest is in the same area or relatively close to the position of the Magna Mitral Ease bioprosthesis. Optimization of MR imaging parameters is recommended.

Prices subject to change without notice. This product is manufactured and sold under one or more of the following US patents: US-Patent Nos. 5,928,281; 5,931,969; 5,961,549; 6,102,944; 6,210,957; 6,214,054; 6,245,105; 6,378,221; 6,409,758; 6,413,275; 6,416,547; 6,547,827; 6,553,681; 6,561,970; 6,585,766; 6,837,902; 6,945,997; 7,214,344; RE 40570; and corresponding foreign patents. Additional patents are pending.

References

1. Marchand MA., et al. Fifteen-year Experience with the Mitral Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis. *Ann Thorac Surg*. 2001; 71:S236-9.
2. Liao K., et al. Bovine Pericardium versus Porcine Aortic Valve: Comparison of Tissue Biological Properties As Prosthetic Valves; *Artificial Organs*. 1992;16(4):361-5.
3. Vesely I., et al. Comparison of the Compressive Buckling of Porcine Aortic Valve Cusps and Bovine Pericardium. *J Heart Valve Dis*. January 1998; 7(1):34-9.
4. Carpentier A. From Valvular Xenograft to Valvular Bioprosthesis (1965-1977). *Med. Instrum*. 1977; 11(2):98-101.
5. Carpentier A., et al. Continuing Improvements in Valvular Bioprostheses. *J. Thorac. Cardiovasc. Surg*. 1982; 83(1):27-42.
6. Arounlangsy P., et al. Histopathogenesis of early stage mitral annular calcification. *J. Med Dent Sci*. 2004; 51(1):35-44.
7. Bonow RO., et al. ACC/AHA Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Patients With Valvular Heart Disease). *J Am Coll Cardiol*. 98; 32:1486-588.
8. Aagaard J., et al. Mitral valve replacement with total preservation of native valves and subvalvular apparatus. *J Heart Valve Dis*. May 1997; 6(3):274-8; discussion 279-80.

Table 1: Observed Adverse Event Rates for MVR and DVR

All patients analyzed: N = 363 Cumulative follow-up: 1100 patient-years

	Early Events		Late Events[1]		Freedom from Event (%) [95% CI][2]		
Complication	n[3]	%	n	%/pt-yr	1 year (n = 287)	5 years (n = 141)	8 years (n = 18)
Mortality (all)	34	9.4	50	4.7	85.5 [81.8, 89.2]	75.4 [70.3, 80.6]	65.4 [57.6, 73.2]
Valve-related events							
Mortality (valve-related)	0	0	16	1.5	97.7 [96.0, 99.4]	95.3 [92.8, 97.8]	91.9 [87.5, 96.4]
Explants	0	0	8	0.7	98.7 [98.0, 99.3]	96.7 [95.3, 98.0]	95.6 [93.9, 97.3]
Reoperations	2	0.6	12	1.1	97.1 [96.2, 98.1]	95.1 [93.6, 96.6]	93.0 [90.9, 95.1]
Anticoagulant-related hemorrhage	2	0.6	9	0.8	97.1 [95.2, 99.0]	97.1 [95.2, 99.0]	94.1 [88.2, 100]
Endocarditis	1	0.3	3	0.3	99.0 [97.9, 100]	98.7 [97.4, 98.9]	98.7 [97.4, 98.9]
Hemolysis	0	0.0	1	0.1	99.7 [99.0, 100]	99.7 [99.0, 100]	99.7 [99.0, 100]
Nonstructural dysfunction	0	0.0	3	0.3	100 [100, 100]	99.3 [98.0, 100]	98.3 [95.9, 100]
Perivalvular leak (all)	1	0.3	5	0.5	98.4 [97.0, 99.8]	98.4 [97.0, 99.8]	97.3 [94.9, 99.8]
Structural valve deterioration	0	0.0	5	0.5	100.0 [100, 100]	97.6 [95.2, 100]	92.8 [85.3, 100]
Thromboembolism	5	1.4	8	0.7	97.5 [95.8, 99.2]	96.1 [93.8, 98.5]	96.1 [93.8, 98.5]
Thrombosis	0	0.0	0	0.0	100.0 [100, 100]	100.0 [100, 100]	100.0 [100, 100]

Notes:

1. Late event rates were calculated as linearized rates (%/pt-yr) based on 1072.5 late patient-years (> 30 days postoperatively).
2. Freedom from event rates were calculated using the Kaplan-Meier method. Greenwood's formula was used for calculation of the standard errors of these estimates.
3. n = number of events.

Table 2: Preoperative Patient Demographics

		Study Characteristics (N = 363; 1100 total pt-yrs.)	
Variable	Category	n	% (n/N)[1]
Age at implant	Mean ± SD	363	66.1 ± 10.7
Gender	Female/Male	212/151	58.4%/41.6%
Diagnosis/Etiology	None	30	8.3%
	Stenosis	91	25.1%
	Regurgitation	184	50.7%
	Mixed Disease	58	16.0%

Note:

1. n = number of patients in each category; N = total number of study patients.

Table 3: Operative Patient Demographics

		Study Characteristics (N = 363; 1100 total pt-yrs.)	
Variable	Category	n	% (n/N)[1]
Etiology[2]	Rheumatic heart disease	135	37.2%
	Calcification	82	22.6%
	Degeneration	50	13.8%
	Endocarditis	39	10.7%
	Failed Bioprosthesis	15	4.1%
	Ischemic Heart Disease	14	3.9%
	Congenital Abnormalities	8	2.2%
	Other	44	12.1%
Concomitant Procedures[2]	None	200	55.1%
	CABG[3]	78	21.5%
	Tricuspid Repair	61	16.8%
	Intra-aortic balloon pump	17	4.7%
	Pacemaker[4]	6	1.7%
	Aortic repair/replacement	5	1.4%
	Aneurysm Repair	4	1.1%
	Other	31	8.5%
Pre-existing Conditions[2]	None	122	33.6%
	CAD[5]/CABG	72	19.8%
	Hypertension	61	16.8%
	Atrial Fibrillation	53	14.6%
	Previous MI[6]	45	12.4%
	Cerebrovascular Disease	36	9.9%
	Other	234	64.5%
Valve Size (mm)[7]	25	22	6.1%
	27	110	30.3%
	29	137	37.7%
	31	81	22.3%
	33	13	3.6%

Notes:

1. n = number of patients in each category; N = total number of study patients.
2. May be more than one per patient
3. CABG = Coronary Artery Bypass Graft
4. Permanent or temporary
5. CAD = Coronary Artery Disease
6. MI = Myocardial Infarction
7. Refer to Table 6 to correlate the model 7200TFX sizes to these data.

Table 4: Effectiveness Outcomes, Functional NYHA

	Preoperative Assessment		Postoperative Assessments			
			1 to 2 Year		5 Year	
NYHA Functional Class	n/N[1]	%	n/N	%	n/N	%
I	11/363	3.0	120/268	44.8	40/129	31.0
II	73/363	20.1	90/268	33.6	25/129	19.4
III	192/363	52.9	15/268	5.6	1/129	0.8
IV	84/363	23.1	0/268	0.0	0/129	0.0
Not Available	3/363	0.8	43/268	16.0	63/129	48.8

Note:

1. n = number of patients in each category; N = total number of study patients.

Table 5: Effective Outcomes, Hemodynamic Results[1]

Hemodynamic Parameter	Results By Valve Size[7]				
	25 mm	27 mm	29 mm	31 mm	33 mm
Discharge/Early Post-Implant (n = 130, 109 MVR[2] and 21 DVR[3])					
Mean gradient[4]	n = 3	n = 23	n = 36	n = 23	n = 3
• mean ± sd	5.7 ± 1.2	4.2 ± 1.7	4.2 ± 1.7	3.6 ± 1.0	7.5 ± 5.8
• min, max	5, 7	2, 9	1, 8	2, 5	3, 14
EOA[5]	n = 1	n = 17	n = 22	n = 25	n = 5
• mean ± sd	1.5	2.9 ± 0.9	3.1 ± 0.9	2.5 ± 0.7	3.0 ± 1.2
• min, max	1.5, 1.5	1.3, 4.1	1.4, 4.2	1.5, 3.8	1.6, 4.9
Regurgitation[6]	n = 3	n = 28	n = 51	n = 40	n = 8
0	3/3 (100%)	22/28 (79%)	36/51 (71%)	30/40 (75%)	4/8 (50%)
1+	0/3 (0%)	5/28 (18%)	13/51 (25%)	7/40 (18%)	4/8 (50%)
2+	0/3 (0%)	0/28 (0%)	1/51 (2%)	3/40 (7%)	0/8 (0%)
3+	0/3 (0%)	0/28 (0%)	1/51 (2%)	0/40 (0%)	0/8 (0%)
4+	0/3 (0%)	0/28 (0%)	0/51 (0%)	0/40 (0%)	0/8 (0%)
Not available	0/3 (0%)	1/28 (3%)	0/51 (0%)	0/40 (0%)	0/8 (0%)
3 to 6 Month Post-Implant Interval (n = 49, 42 MVR[2] and 7 DVR[3])					
Mean gradient[4]	n = 5	n = 19	n = 15	n = 5	n = 2
• mean ± sd	6.4 ± 1.7	5.3 ± 5	3.4 ± 1.2	4 ± 1.9	4 ± 0
• min, max	5, 9	2, 25	2, 6	2, 7	4, 4
EOA[5]	n = 5	n = 18	n = 13	n = 5	n = 2
• mean ± sd	2.9 ± 0.8	2.6 ± 0.7	2.8 ± 0.6	2.9 ± 0.3	2.6 ± 1
• min, max	1.8, 3.6	1.5, 5	2, 3.8	2.4, 3.3	2, 3.3
Regurgitation[6]	n = 5	n = 21	n = 15	n = 6	n = 2
0	3/5 (60%)	17/21 (81%)	6/15 (40%)	4/6 (67%)	1/2 (50%)
1+	0/5 (0%)	4/21 (19%)	8/15 (53%)	2/6 (33%)	0/2 (0%)
2+	1/5 (20%)	0/21 (0%)	1/15 (7%)	0/6 (0%)	1/2 (50%)
3+	0/5 (0%)	0/21 (0%)	0/15 (0%)	0/6 (0%)	0/2 (0%)
4+	1/5 (20%)	0/21 (0%)	0/15 (0%)	0/6 (0%)	0/2 (0%)
Not available	0/5 (0%)	0/21 (0%)	0/15 (0%)	0/6 (0%)	0/2 (0%)
1 to 2 Year Post-Implant Interval (n = 131, 114 MVR[2] and 17 DVR[3])					
Mean gradient[4]	n = 3	n = 40	n = 47	n = 27	n = 4
• mean ± sd	5.2 ± 0.7	4.1 ± 1.6	3.5 ± 1.8	3.1 ± 1.4	2.1 ± 0.5
• min, max	4.7, 6	1, 7	1, 10	1, 7	1.5, 2.7
EOA[5]	n = 2	n = 35	n = 46	n = 29	n = 5
• mean ± sd	1.8 ± 0.4	2.3 ± 0.6	2.6 ± 0.5	2.6 ± 0.7	2.5 ± 0.5
• min, max	1.5, 2.0	1.2, 3.5	1.1, 3.7	1.1, 3.7	2.1, 3.2
Regurgitation[6]	n = 4	n = 42	n = 51	n = 29	n = 5
0	2/4 (50%)	31/42 (74%)	36/51 (71%)	17/29 (59%)	3/5 (60%)
1+	1/4 (25%)	9/42 (21%)	11/51 (21%)	8/29 (27%)	1/5 (20%)
2+	1/4 (25%)	2/42 (5%)	4/51 (8%)	2/29 (7%)	1/5 (20%)
3+	0/4 (0%)	0/42 (0%)	0/51 (0%)	2/29 (7%)	0/5 (0%)
4+	0/4 (0%)	0/42 (0%)	0/51 (0%)	0/29 (0%)	0/5 (0%)
Not available	0/4 (0%)	0/42 (0%)	0/51 (0%)	0/29 (0%)	0/5 (0%)

continued on following page

Table 5: Effective Outcomes, Hemodynamic Results[1], Continued

Hemodynamic Parameter	Results By Valve Size[7]				
	25 mm	27 mm	29 mm	31 mm	33 mm
5 Year Post-Implant Interval (n = 11, 9 MVR[2] and 2 DVR[3])					
Mean gradient[4]	n = 0	n = 6	n = 5	n = 0	n = 0
• mean ± sd	N/A	8.8 ± 8.1	5.1 ± 2.3	N/A	N/A
• min, max	N/A	4, 25	3, 8	N/A	N/A
EOA[5]	n = 0	n = 2	n = 4	n = 0	n = 0
• mean ± sd	N/A	2.0 ± 1.5	2.9 ± 0.6	N/A	N/A
• min, max	N/A	1.0, 3.1	2.1, 3.5	N/A	N/A
Regurgitation[6]	n = 0	n = 6	n = 5	n = 0	n = 0
0	0/0 (0%)	4/6 (66%)	2/5 (40%)	0/0 (0%)	0/0 (0%)
1+	0/0 (0%)	1/6 (17%)	3/5 (60%)	0/0 (0%)	0/0 (0%)
2+	0/0 (0%)	1/6 (17%)	0/5 (0%)	0/0 (0%)	0/0 (0%)
3+	0/0 (0%)	0/6 (0%)	0/5 (0%)	0/0 (0%)	0/0 (0%)
4+	0/0 (0%)	0/6 (0%)	0/5 (0%)	0/0 (0%)	0/0 (0%)
Not available	0/0 (0%)	0/6 (0%)	0/5 (0%)	0/0 (0%)	0/0 (0%)

Notes:

1. Hemodynamic evaluations were performed using transthoracic echocardiography (TTE) and in some cases, transesophageal echocardiography (TEE).
2. MVR = mitral valve replacement
3. DVR = double valve replacement
4. Mean gradient in mmHg
5. EOA: Effective Orifice Area, cm^2
6. Regurgitation = none, 0; mild, 1+; moderate, 2+; moderate/severe, 3+; severe, 4+
7. Refer to Table 6 to correlate the model 7200TFX sizes to these data.

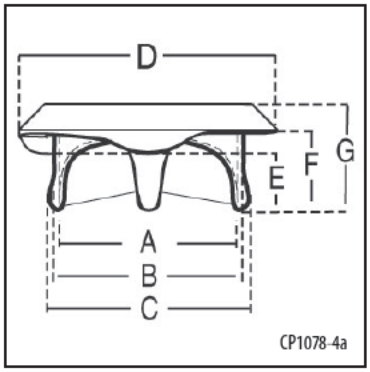
Table 6: Model 6900 and 7200TFX Size Correlation Table

	Size				
Model 6900	25 mm	27 mm	29 mm	31 mm	33 mm
Model 7200TFX	27	29	31	33	35

Figure 1

Nominal Specifications (mm)

Carpentier-Edwards PERIMOUNT Magna Mitral Ease Bioprosthesis, Model 7200TFX



Size	27	29	31	33	35
A. Stent Diameter (Wireform)	25	27	29	31	31
B. External Stent Post Diameter (Base)*	28	29.5	31.5	33.5	33.5
C. External Stent Post Diameter (Tip)	29	31	34	35	35
D. External Sewing Ring Diameter	36	38	40	42	44
E. Effective Profile Anterior	7	7.5	8	8.5	8.5
F. Effective Profile Posterior	10	10.5	11	11.5	11.5
G. Total Profile Height	15	16	17	18	18

*Tissue annulus diameter

CP1083-21a

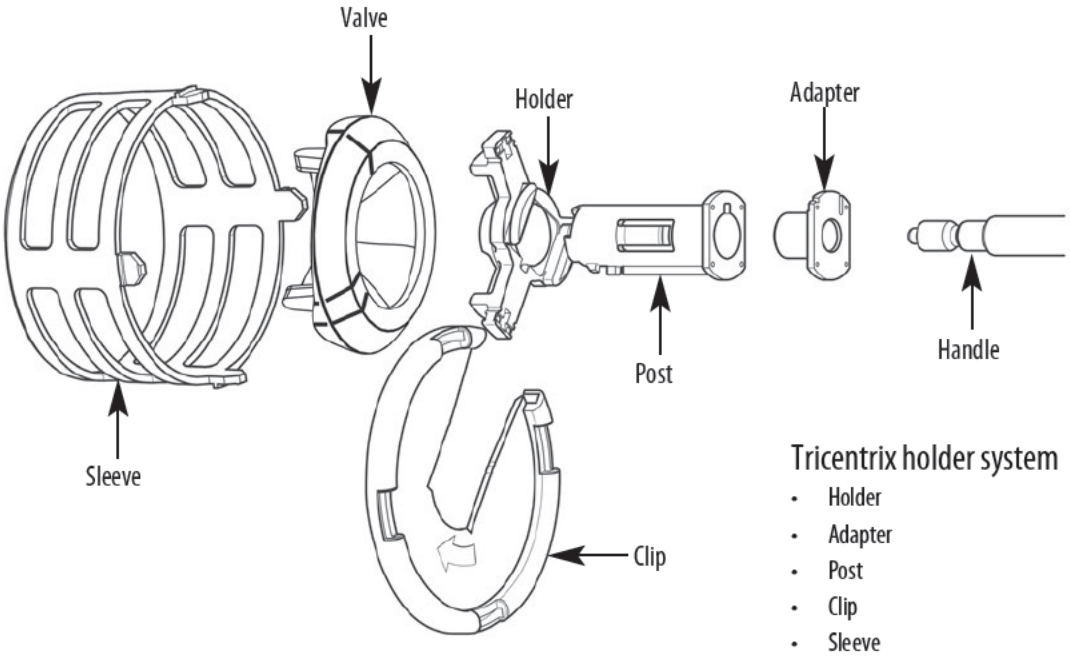


Figure 2

CP1083-15a

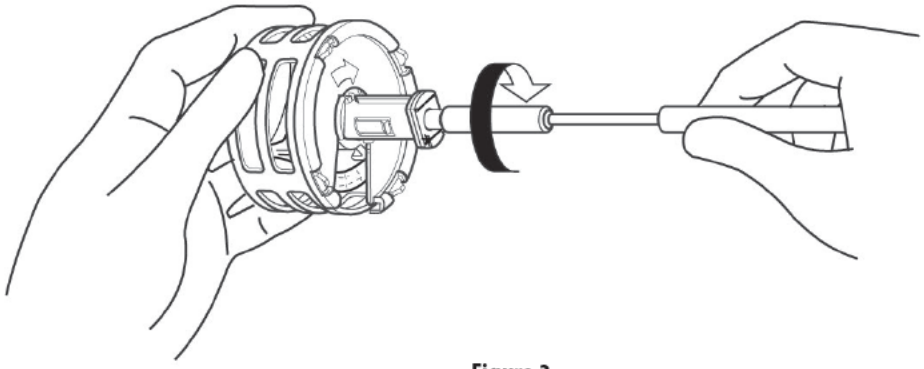


Figure 3

CP1083-16

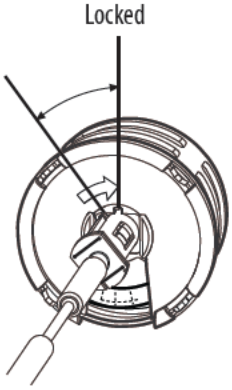


Figure 4a

CP1083-17

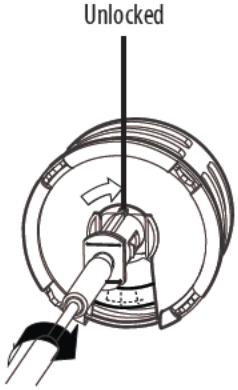


Figure 4b

CP1083-18a

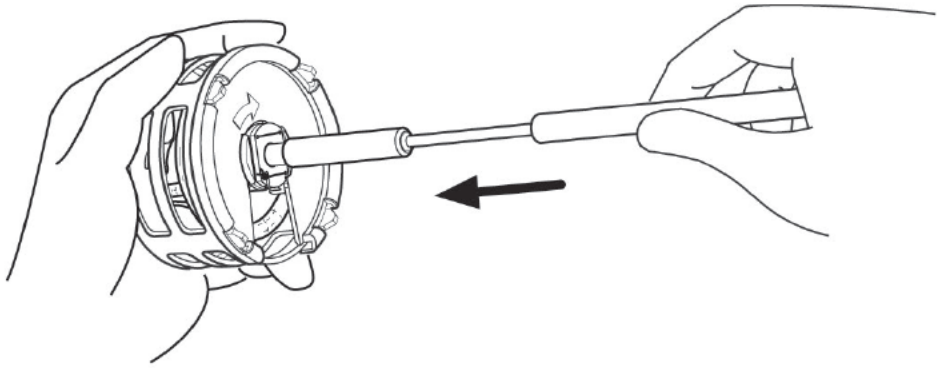


Figure 5

CP1083-19a

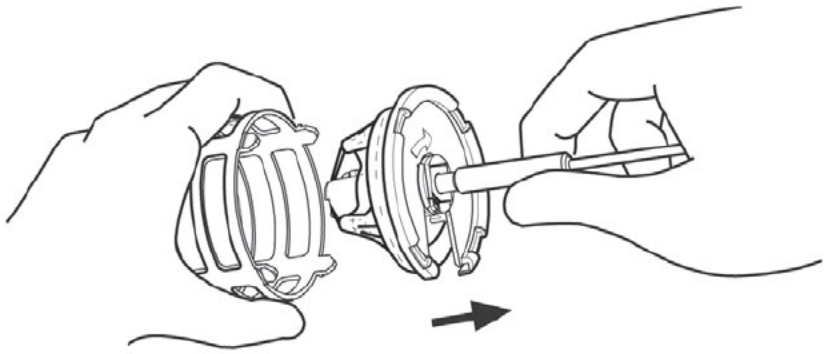


Figure 6

CP1083-20

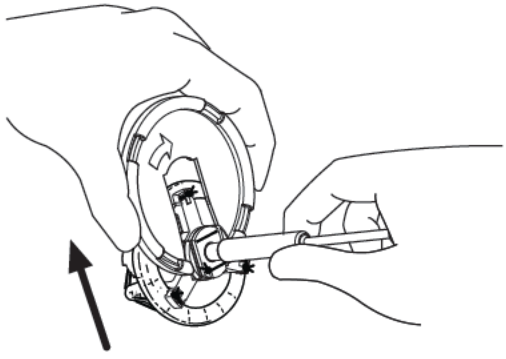


Figure 7

CP1083-11

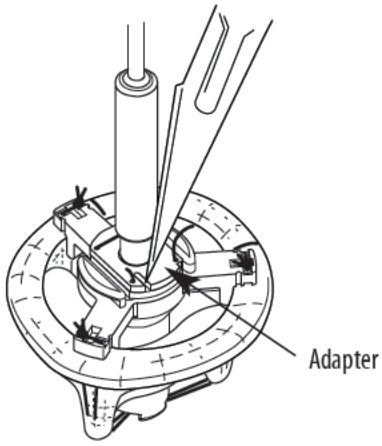


Figure 8

CP1083-12

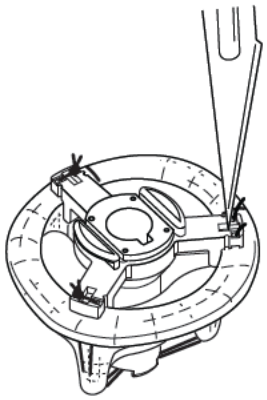


Figure 9

CP1083-40

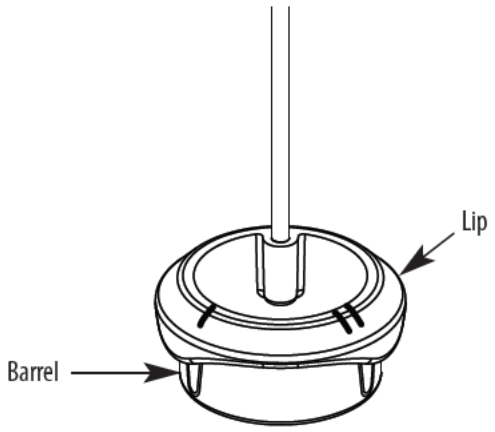


Figure 10. Replica Sizer 1171R

CP1083-42

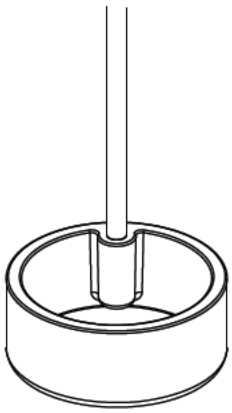
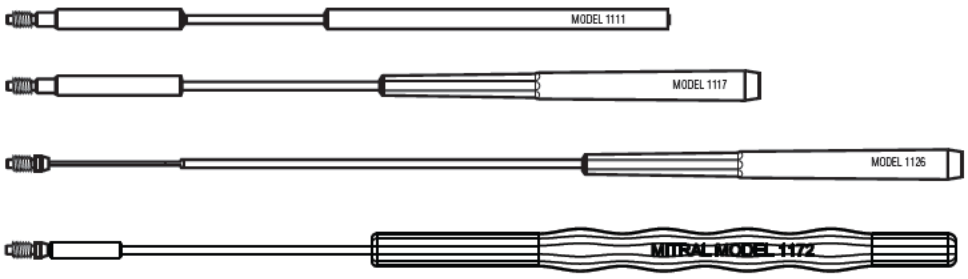


Figure 11. Barrel Sizer 1171B

CP1083-41

Figure 12. Annular Seating with Replica Sizer

CP1089-4a



Model	Length	
	inch	cm
1111	7.0	17.8
1117	9.1	23.2
1126	11.5	29.2
1172	11.3	28.6

Figure 13

CP1089-2a

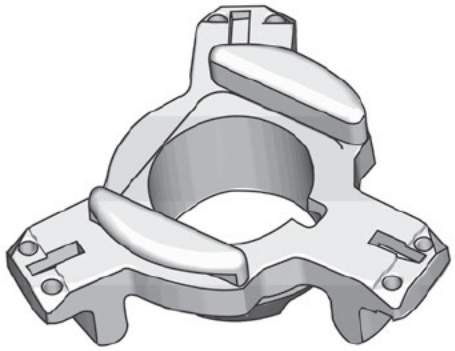


Figure 14

CP1087-14

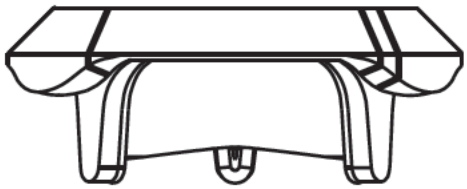


Figure 15

Edwards

7/09
197894001 A

Edwards Lifesciences LLC
One Edwards Way
Irvine, CA 92614-5686 USA
Made in USA

Telephone 949.250.2500
800.424.3278
FAX 949.250.2525

DATA MATRIX
BARCODE FPO

Edwards Lifesciences

Carpentier-Edwards PERIMOUNT Magna Mitral Ease Pericardial Bioprosthesis Model 7300TFX

Instructions for Use

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

1. Device Description

The Carpentier-Edwards PERIMOUNT Magna Mitral Ease pericardial bioprosthesis is built upon the same proven (Ref. 1) wireform frame and leaflet attachment as the PERIMOUNT mitral pericardial bioprostheses models 6900, 6900P, 6900PTFX, and 7000TFX. It is available in the sewing ring diameters and sizes shown in Figure 1. The bioprosthesis incorporates a sewing ring specifically designed for the mitral position and is the first bioengineered mitral bioprosthesis design with three selected bovine pericardial leaflets mounted on a flexible metal alloy frame.

Bovine pericardium was selected for its superior intrinsic properties for valve manufacture, notably in terms of collagen content (Ref. 2) and tolerance to high bending curvatures (Ref. 3). 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 bioprosthesis is treated according to the ThermaFix process, which involves heat treatment of the tissue in glutaraldehyde and uses ethanol and Polysorbate-80 (a surfactant). Glutaraldehyde is shown to both reduce the antigenicity of tissue xenograft valves and increase tissue stability (Refs. 4 & 5). Glutaraldehyde alone has not been shown to affect or reduce the calcification rate of the valve.

Tissue thickness is measured for each valve size and leaflets are precisely die-cut in selected areas of a pericardial sheet. Leaflet deflection testing characterizes each leaflet for elasticity. Three leaflets matched for similar thickness and elasticity are then assembled. Leaflets are mounted underneath the wireform frame to minimize commissural stress points.

The lightweight wireform frame is made of a corrosion-resistant cobalt-chromium alloy, chosen because of its superior spring efficiency 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 sewn with polytetrafluoroethylene thread. The wireform frame of the Magna Mitral Ease bioprosthesis is symmetrical and the three commissure supports (struts) are equally spaced.

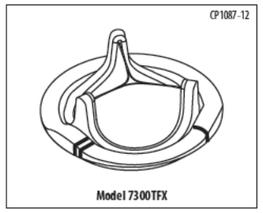
A cobalt-chromium alloy band attached to a polyester film band surrounds the base of the wireform frame providing structural support for the orifice and allows for radiological identification. In addition to maintaining the orifice shape during implantation, the band serves as a point of attachment for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

The sewing ring is made of waffled silicone-rubber and is covered with a porous polytetrafluoroethylene cloth sewn with polytetrafluoroethylene thread. The cloth facilitates tissue in-growth and encapsulation. The sewing ring of the Magna Mitral Ease bioprosthesis is uniquely scalloped along its anterior portion and mimics the natural saddle shape of the native mitral valve anatomy. Black silk suture markers on the anterior portion facilitate the orientation of the bioprosthesis and help avoid obstruction of the left ventricular outflow tract by a strut. A black silk suture guide line circles the sewing ring. Placing sutures through the sewing ring and in the region from the suture guide line to the outer portion of the sewing ring complements the design of the silicone waffle by easing needle penetration and providing variable compliance. The waffle has wider cells along the posterior portion, where calcifications or irregularities of the native mitral annulus are more frequent (Ref. 6). 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 Tricentrix holder system is designed to minimize the potential for suture or chordae entrapment, ease insertion and increase leaflet visibility. The holder consists of three main components: a grey holder, a white holder post, and a blue adapter. It is secured to the bioprosthesis with green sutures. The bioprosthesis and holder attachment are suspended by a clip and a sleeve within a sealed jar that contains a glutaraldehyde packing solution. The bioprosthesis is terminally sterilized in glutaraldehyde.

2. Indications for Use

The Carpentier-Edwards PERIMOUNT Magna Mitral Ease pericardial bioprosthesis model 7300TFX is indicated for patients who require replacement of their native or prosthetic mitral valve.



Model 7300TFX

3. Contraindications

Do not use if the surgeon believes such would be contrary to the best interests of the patient. The actual decision for or against the use of this bioprosthesis must remain with the surgeon who can evaluate all the various risks involved, including the anatomy and pathology observed at the time of surgery.

4. Warnings

FOR SINGLE USE ONLY. This device is designed, intended, and distributed for single use only. Do not re-sterilize or reuse this device. There are no data to support the sterility, nonpyrogenicity, and functionality of the device after reprocessing. Exposure of the bioprosthesis or container to irradiation, steam, ethylene oxide, or other chemical sterilants will render the bioprosthesis unfit for use.

DO NOT FREEZE OR EXPOSE THE BIOPROSTHESIS TO EXTREME HEAT. Exposure of the bioprosthesis to extreme temperatures will render the device unfit for use. Please refer to Packaging section (10.2) for further instructions.

DO NOT USE the bioprosthesis if the tamper evident seal on the jar is broken.

DO NOT USE the bioprosthesis if expiration date has elapsed.

DO NOT USE the bioprosthesis if the container is leaking, damaged, or the glutaraldehyde solution does not completely cover the bioprosthesis.

DO NOT EXPOSE the bioprosthesis to any solutions, chemicals, antibiotics, etc., except for the storage solution or sterile physiological saline solution. Irreparable damage to the leaflet tissue, which may not be apparent under visual inspection, may result.

DO NOT ALLOW the bioprosthesis to dry. It must be kept moist at all times. Maintain tissue moisture with sterile physiological saline irrigation on both sides of the leaflet tissue.

DO NOT PASS CATHETERS, transvenous pacing leads, or any surgical instrument across the bioprosthesis with the exception of a surgical mirror used to examine struts and suture placement. Other surgical devices may cause leaflet tissue damage.

DO NOT USE the bioprosthesis if it has been dropped, damaged, or mishandled in any way. Should a bioprosthesis be damaged during insertion, do not attempt repair.

DO NOT GRASP the leaflet tissue of the bioprosthesis with instruments or cause any damage to the bioprosthesis. Even the most minor leaflet tissue perforation may enlarge in time to produce significant impairment of valve function.

DO NOT OVERSIZE. Oversizing may cause bioprosthesis damage or localized mechanical stresses, which may in turn injure the heart or result in leaflet tissue failure, stent distortion and valve regurgitation.

Clinical data that establish the safety and efficacy of the bioprosthesis for use in patients under the age of 20 are not available; therefore, we recommend careful consideration of its use in younger patients. As with any implanted medical device, there is a potential for patient immunological response (see device description for materials).

The decision to use a bioprosthesis must ultimately be made by the surgeon on an individual basis after a careful evaluation of the short- and long-term risks and benefits to the patient and consideration of alternative methods of treatment.

Long-term durability has not been established for bioprostheses. Serious adverse events, sometimes leading to replacement of the bioprosthesis and/or death, may be associated with the use of prosthetic valves (see **6. Adverse Events**). A full explanation of the benefits and risks should be given to each prospective patient before surgery.

Note: Bioprostheses should be used with caution in the presence of severe systemic hypertension or when the anticipated patient longevity is longer than the known longevity of the prosthesis (see **7. Clinical Studies**). Careful and continuous medical follow-up (at least by an annual visit to the physician) is advised so that bioprosthesis-related complications, particularly those related to material failure, can be diagnosed and properly managed.

Recipients of prosthetic heart valves who are undergoing dental procedures should receive prophylactic antibiotic therapy to minimize the possibility of prosthetic infection. Bioprosthetic heart valve recipients should be maintained on anticoagulant therapy (except where contraindicated) during the initial healing stages after implantation, 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 by the physician on an individual basis (Ref. 7).

Adequate rinsing with physiological saline is mandatory before implantation to reduce the glutaraldehyde concentration (see **11.4 Handling and Preparation Instructions**). No other solutions, drugs, chemicals, antibiotics, etc., should ever be added to the glutaraldehyde or rinse solutions, as irreparable damage to the leaflet tissue, which may not be apparent under visual inspection, may result.

5. Precautions

- Do not sterilize the sizer models 1173B, 1173R and handle models 1111, 1117, or 1173 in their shipping containers.
- Use only the sterilization tray provided in model SET1173 to sterilize the sizers and the handles.
- The outside of the jar is not sterile and must not be placed in the sterile field.
- To avoid contamination, it is strongly recommended that the jar of a Carpentier-Edwards PERIMOUNT Magna Mitral Ease pericardial bioprosthesis model 7300TFX not be opened unless implantation is certain.
- Adequate rinsing with physiological saline must be performed before implantation to reduce the glutaraldehyde concentration.
- Avoid contact of the leaflet tissue or the rinse solution with towels, linens, or other sources of lint and particulate matter that may be transferred to the leaflet tissue.
- Do not allow the leaflet tissue to contact the bottom or sides of the rinse basin.
- Glutaraldehyde may cause irritation of the skin, eyes, nose, and throat. Avoid prolonged or repeated exposure or breathing of the solution. Use only with adequate ventilation. If skin contact occurs, immediately flush the affected area with water; in the event of contact with the eyes, seek immediate medical attention. For more information about glutaraldehyde exposure, please refer to the Material Safety Data Sheet available from Edwards Lifesciences.
- Always deploy the Tricentrix holder system fully to minimize the risk of suture entrapment. It will snap into a secured and locked position.
- A serial number tag is attached to the sewing ring of each bioprosthesis by a suture. This serial number should be checked against the number on the jar and implantation data card; if any difference is noted, the bioprosthesis should be returned unused. Care must be taken to ensure that the serial number tag does not come in contact with the leaflet tissue during rinsing. Inspection of the bioprosthesis and removal of the serial number tag should be performed just prior to implantation. Care should be exercised to avoid cutting or tearing the sewing ring cloth during removal of the serial number tag.
- Careful handling is required for all implantable devices. If the bioprosthesis is dropped, damaged, or mishandled in any way, it must not be used for human implantation.
- To avoid damage to the delicate bioprosthetic leaflet tissue, as a result of contact with calcium deposits, adequate removal of calcium deposits from the patient's annulus must be performed before implantation.
- Handle the bioprosthesis only with Edwards Lifesciences accessories. Only Edwards Lifesciences sizers model 1173B or 1173R should be used during the selection of the Magna Mitral Ease bioprosthesis size; other sizers may result in improper bioprosthesis selection.
- Oversizing must be avoided as it may cause bioprosthesis damage or localized mechanical stresses, which may in turn injure the heart or result in leaflet tissue failure, stent distortion and regurgitation.
- Special care must be exercised when using chordal preservation techniques to avoid chordae entrapment by a strut.
- Due to the relative flexibility of the frame, care must be exercised to prevent folding or deformation of the stent.
- The surgeon should be familiar with the recommendations for proper sizing and placement of the bioprosthesis according to the suture technique used (see **11.5 Device Implantation**).
- The sewing ring is designed for a specific orientation: the scalloped part of the sewing ring, between the black suture markers, should be placed across the intercommissural anterior portion of the annulus and straddle the left ventricular outflow tract.
- Special care must be exercised to avoid placing a strut in front of the left ventricular outflow tract, as this may impair the long-term hemodynamic performance.
- As with all prostheses that have open cages, free struts, or commissure supports, care must be exercised to avoid looping or catching a suture around a commissure, which would interfere with proper valvular function. To minimize the potential for suture looping, it is essential to leave the deployed holder in place until all knots are tied.
- If the deployed holder attachment threads are cut before all the sutures adjacent to the struts are tied down, the holder will no longer minimize the potential for suture looping.
- When using interrupted sutures, it is important to cut the sutures close to the knots and to ensure that exposed suture tails will not come into contact with the leaflet tissue.

6. Adverse Events

6.1 Observed Adverse Events

The Carpentier-Edwards PERIMOUNT Magna Mitral Ease pericardial bioprosthesis model 7300TFX uses the same wireform frame and leaflet attachment as Edwards Lifesciences pericardial mitral bioprostheses models 6900, 6900P, 6900PTFX, and 7000TFX. Three (3) multi-center, non-randomized, prospective non-US clinical studies were conducted with the mitral pericardial bioprosthesis model 6900. Three hundred one (301) patients had isolated mitral valve replacement (MVR) and 62 patients had double valve replacement (DVR), where the aortic valve was replaced with a Carpentier-Edwards PERIMOUNT pericardial bioprosthesis aortic model. In the first study, bioprostheses were implanted between 1984 and 1986; in the second study, bioprostheses were implanted between 1989 and 1994; and in the third study, bioprostheses were implanted between 1996 and 1997. Patients were evaluated preoperatively, intraoperatively/at discharge, at 1 year, and annually thereafter. Adverse events were captured throughout the postoperative period. Table 1 presents the observed rates for early events (≤ 30 days for valve-related adverse events), the linearized rates for late events (> 30 days postoperatively), and the actuarial adverse event rates at 1, 5, and 8 years postoperatively for model 6900. The adverse event rates were based on 363 patients at nine centers. The cumulative follow-up was 1100 patient-years with a mean follow-up of 3.0 years (SD = 2.4 years, range = 0 to 8.2 years). Preoperative and operative patient demographics are presented in Tables 3 and 5. Effectiveness results are presented in Tables 7 and 9.

One (1) multi-center, non-randomized, prospective international clinical study was conducted with patients implanted with the Carpentier-Edwards PERIMOUNT Plus pericardial bioprosthesis model 6900P mitral. One hundred seventy five (175) patients had isolated mitral replacement (MVR) and 34 patients had double valve replacement (DVR), where the aortic valve was replaced with a Carpentier-Edwards PERIMOUNT pericardial bioprosthesis aortic model. In this study, patients were implanted between 1999 and 2007. Patients were evaluated preoperatively, intraoperatively at discharge, at 1 year, and annually thereafter. Adverse events were captured throughout the postoperative period. Table 2 presents the observed rates for early events (≤ 30 days for valve-related adverse events), the linearized rates for late events (> 30 days postoperatively), and the actuarial adverse event rates at 1- and 5-years postoperatively for model 6900P. The adverse event rates were based on two hundred nine (209) patients at seven centers. The cumulative follow-up was 873.18 patient-years with a mean follow-up of 4.2 years (SD = 2.3 years, range = 0 to 8.2 years). Preoperative and operative patient demographics are presented in Tables 4 and 6. Effectiveness results are presented in Tables 8 and 10.

6.2 Potential Adverse Events

Adverse events potentially associated with the use of bioprosthetic heart valves include:

- Angina
- Cardiac arrhythmias
- Endocarditis
- Heart failure
- Hemolysis
- Hemolytic anemia
- Hemorrhage
- Local and/or systemic infection
- Myocardial infarction
- Prosthesis leaflet entrapment
- Prosthesis nonstructural dysfunction
- Prosthesis pannus
- Prosthesis perivalvular leak
- Prosthesis regurgitation
- Prosthesis structural deterioration
- Prosthesis thrombosis
- Stroke
- Thromboembolism

It is possible that these complications could lead to:

- Reoperation
- Explantation
- Permanent disability
- Death

Other adverse events associated with the use of Carpentier-Edwards PERIMOUNT mitral pericardial bioprostheses model 6900 compiled from the literature and from reports received through the Edwards Lifesciences complaint handling system include: stenosis, regurgitation through an incompetent valve, ventricular perforation by stent posts, malfunctions of the valve due to distortion at implant, and fracture of the wireform frame.

7. Clinical Studies

The safety endpoints captured in the prospective studies were adverse events; blood analyses were used to confirm the absence or presence of certain adverse events. The safety results for model 6900 are provided in Table 1 and for model 6900P in Table 2. Preoperative patient demographics for model 6900 are provided in Table 3 and for model 6900P in Table 4. Operative patient demographics for model 6900 are provided in Table 5 and for model 6900P in Table 6. Effectiveness endpoints were New York Heart Association (NYHA) functional classification summarized in Table 7 for model 6900 and Table 8 for model 6900P and echocardiographic assessments summarized in Table 9 for model 6900 and Table 10 for model 6900P.

There are no clinical data presently available demonstrating increased resistance of the Carpentier-Edwards PERIMOUNT Magna Mitral Ease pericardial bioprosthesis model 7300TFX to calcification as compared to other commercially available bioprostheses.

8. Individualization of Treatment

Bioprosthetic heart valve recipients should be maintained on anticoagulant therapy, except where contraindicated, during the initial stages after implantation, as determined by the physician on an individual basis. Long-term anticoagulant and/or antiplatelet therapy should be considered for patients with a dilated left atrium, a history of thrombotic events, an absence of sinus rhythm, calcification of the atrial wall, or with atrial fibrillation or flutter. The decision to use a bioprosthesis must ultimately be made by the physician on an individual basis after a careful evaluation of the short-term and long-term risks and benefits to the patient and consideration of alternative methods of treatment (Ref. 7).

8.1 Specific Patient Populations

The safety and effectiveness of the Carpentier-Edwards PERIMOUNT Magna Mitral Ease pericardial bioprosthesis model 7300TFX has not been established for the following specific populations because it has not been studied in these populations:

- patients who are pregnant;
- nursing mothers;
- patients with abnormal calcium metabolism (e.g., chronic renal failure, hyperparathyroidism);
- patients with aneurysmal aortic degenerative conditions (e.g., cystic medial necrosis, Marfan's syndrome);
- children, adolescents, or young adults.

9. Patient Counseling Information

Careful and continued medical follow-up (at least by an annual visit to the physician) is advised so that valve-related complications, particularly those related to material failure, can be diagnosed and properly managed. Patients with bioprostheses are at risk from bacteremia (e.g., undergoing dental procedures) and should be advised about prophylactic antibiotic therapy. Patients should be encouraged to carry their Implantation Data Card at all times and to inform their healthcare providers that they have a mitral bioprosthetic implant when seeking care.

10. How Supplied

10.1 Available Models and Sizes

The Carpentier-Edwards PERIMOUNT Magna Mitral Ease pericardial bioprosthesis model 7300TFX is available in labeled sizes 25, 27, 29, 31, and 33 mm (see Figure 1 for nominal specifications).

10.2 Packaging

The Magna Mitral Ease bioprosthesis is provided sterile and nonpyrogenic packaged in glutaraldehyde, in a plastic jar to which a seal has been applied. Each bioprosthesis is contained in a carton with a temperature indicator displayed through a window on the side panel. The temperature indicator is intended to identify exposure to temperature extremes during transit. Upon receipt of the bioprosthesis, immediately inspect the indicator and refer to the carton label to confirm a "Use" condition. If the "Use" condition is not apparent, do not use the bioprosthesis and contact the local supplier or Edwards Lifesciences representative to make arrangements for return authorization and replacement. Any bioprosthesis returned to Edwards Lifesciences must be shipped in the original packaging in which it was received.

Warning: The bioprosthesis must be carefully inspected before implantation for evidence of extreme temperature exposure or other damage.

Due to the biological nature of this bioprosthesis and its sensitivity to physical handling and environmental conditions, it cannot be returned, except as noted above.

Note: Products found to have been subjected to freezing or excessive heat later than 3 days following receipt will be considered to have resulted from environmental conditions within the control of the customer, and subject to replacement at customer's expense.

10.3 Storage

The Magna Mitral Ease bioprosthesis should be stored at 10 °C to 25 °C (50-77 °F). Stock inspection and rotation at regular intervals are recommended to ensure that the bioprostheses are used before the expiration date stamped on the package label.

Warning: Do not freeze. Always store bioprostheses in a dry, contamination-free area. Any bioprosthesis that has been frozen, or is suspected of having been frozen, should not be used for human implantation.

11. Directions for Use

11.1 Physician Training

No special training is required to implant the Carpentier-Edwards PERIMOUNT Magna Mitral Ease bioprosthesis model 7300TFX. The techniques for implanting this bioprosthesis are similar to those for implanting any stented mitral bioprostheses.

11.2 Accessories

Accessories available for use with the Magna Mitral Ease bioprosthesis are:

- Tricentrix holder system
- Replica Sizer 1173R (Figure 10)
- Barrel Sizer 1173B (Figure 11)
- Sterilization Tray provided in model SET1173
- Flexible Handle models 1111, 1117, 1173, and 1126 (single use) (Figure 13)

All accessories are supplied non-sterile, except for the Tricentrix holder system that is supplied sterile attached to the sterile bioprosthesis and the handle 1126 that is supplied sterile and is for single use only.

Sizers

Only sizers model 1173B or 1173R may be used with the Magna Mitral Ease bioprosthesis.

Caution: Do not use other manufacturer's valve sizers, or sizers for other Edwards Lifesciences valve prostheses to size the Magna Mitral Ease bioprosthesis.

Use only the sizers model 1173B or 1173R to determine the appropriate Magna Mitral Ease bioprosthesis size. Sizers model 1173B and 1173R permit direct observation of their fit within the annulus and are provided for each available Magna Mitral Ease bioprosthesis size. The barrel of the sizers model 1173B and 1173R indicate the external stent diameter at the base (Figure 1). The lip of the replica sizer 1173R replicates the sewing ring of the bioprosthesis, with its scalloped anterior portion and black markings, to 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 bioprosthesis sewing ring which should be positioned across the anterior intercommissural portion of the native annulus, in order to straddle the left ventricular outflow tract area. The height and location of the stent posts are marked on the replica sizer 1173R to aid in assessing optimal alignment and seating.

The sizers include preattached handles with increased handle length for improved access in the case of a difficult exposure, a deep thoracic cage or minimally invasive access. The posterior handle attachment to the sizer allows an unobstructed view through the barrel into the ventride for assessment of subvalvular structures. The sizers 1173B and 1173R are labeled with the bioprosthesis size.

Tricentrix Holder System and Handles

The holder/handle assembly consists of two (2) components: the Tricentrix holder system that is mounted to the Magna Mitral Ease bioprosthesis, and a handle (1111, 1117, 1173, or 1126) that is attached to the Tricentrix holder system at the time of surgery (Figure 2).

The following handles (Figure 13) may be used with the Magna Mitral Ease bioprosthesis:

Model	Shaft Material	Overall Length		Reusable
		inch	cm	
1111	Stainless steel	7.0	17.8	Yes
1117	Nitinol	9.1	23.2	Yes
1126	Stainless steel	11.5	29.2	No
1173	Nitinol	11.3	28.6	Yes

- Handles with a nitinol shaft are more flexible than stainless steel. With each sterilization cycle, they return to their original straight shape for easier attachment to the holder.
- Handle 1173 has been designed to improve access in the case of difficult exposure, a deep thoracic cage, or in minimally invasive procedures.

The Tricentrix holder has short legs and beveled edges to increase suturing space and ease knot tying (Figure 14).

11.3 Accessory Sterilization

The 1126 handle is provided sterile and is intended for single use only. The handles 1111, 1117, and 1173 and the sizers 1173B and 1173R are supplied non-sterile and must be cleaned and sterilized before use. Refer to the Instructions for Use supplied with the reusable accessories for cleaning and sterilization instructions.

11.4 Handling and Preparation Instructions

The bioprosthesis is packaged sterile in a plastic jar with a screw-cap closure and seal. Before opening, carefully examine the jar for evidence of damage (e.g., a cracked jar or lid), leakage, or broken or missing seals. Remove the seal and turn the lid counter-clockwise to open the container. The bioprosthesis and Tricentrix holder system within the container are sterile.

Caution: The outside of the jar is not sterile and must not be placed in the sterile field. The contents of the jar should be handled in an aseptic manner to prevent contamination.

Caution: Bioprostheses from containers found to be damaged, leaking, without adequate glutaraldehyde, or missing intact seals must not be used for human implantation.

Caution: It is strongly recommended that the jar of a Magna Mitral Ease bioprosthesis not be opened unless implantation is certain. This is necessary to reduce the risk of contamination, because it has been established that glutaraldehyde alone is not a 100% effective sterilant against all possible contaminants.

Warning: No attempt should be made to resterilize a Magna Mitral Ease bioprosthesis.

Warning: Do not use the bioprosthesis if it has been dropped, damaged, or mishandled in any way. Should a bioprosthesis be damaged during insertion, do not attempt repair.

Warning: Do not grasp the leaflet tissue portion of the bioprosthesis with instruments or cause any damage to the bioprosthesis. Even the most minor leaflet tissue perforation may enlarge in time to produce significant impairment of bioprosthesis function.

Verify that the handle, model 1111, 1117, or 1173, has been sterilized according to the instructions provided in the Instructions for Use supplied with the reusable accessories. Attach the handle to the Tricentrix holder system and turn it clockwise until a positive resistance is felt then remove the whole assembly (i.e., plastic sleeve, clip, the Tricentrix holder system and bioprosthesis) from the jar. The plastic sleeve is loosely fitted to the clip and may remain in the jar. This will not affect deployment.

A tag with a serial number is attached to the sewing ring of each bioprosthesis by a suture. This serial number should be checked against the number on the jar and implantation card; if any differences are noted, the bioprosthesis should be returned unused. This tag should not be detached from the bioprosthesis until just prior to implantation.

Grasping the plastic sleeve or clip (Figure 3a or Figure 3b) continue the rotation to overcome the resistance until the white holder post reaches the unlock position (Figure 4a and Figure 4b). Apply the required push force on the handle until the white holder post slides across the leaflets and snaps into its fully deployed position (Figure 5). An audible click may be heard as the deployed position is reached.

Caution: If an adequate push force is not applied to the handle when deploying the Tricentrix holder system, the tenting system will not be secured and will not be able to minimize the potential for suture entrapment. Always check for proper deployment. There should be no more space between the blue adapter and the grey holder. The handle/post assembly should no longer be able to slide.

The white holder post should protrude through the leaflets while the three (3) commissures should deflect slightly towards the center of the bioprosthesis. The leaflets will temporarily be wrinkled by the deployed white holder post. When the holder is removed following implantation, the leaflets will return to their normal position.

After deployment, remove the sleeve (if attached) by holding the handle and pulling the sleeve off the clip (Figure 6). Remove the clip by sliding it off the holder in a sideways direction (Figure 7). Both sleeve and clip should be discarded. Once the handle has been attached, it should not be removed from the holder until the bioprosthesis is seated to the annulus.

Rinse Procedure

Within the sterile operative field, prepare two rinse basins, each containing no less than 500 ml of sterile, physiological saline solution. Place the deployed bioprosthesis in the saline solution and make sure that it completely covers the bioprosthesis and holder. Do not rinse with the sleeve and clip attached. With the bioprosthesis and holder submerged, slowly agitate the basin or use the attached handle to gently swirl the bioprosthesis back and forth for a minimum of 1 minute in each of the two previously prepared rinse basins. The bioprosthesis should remain in the second rinse basin until ready for implantation.

Caution: Avoid contact of the leaflet tissue or the rinse solution with towels, linens, or other sources of lint and particulate matter that may be transferred to the leaflet tissue.

Caution: Do not allow the leaflet tissue to contact the bottom or sides of the rinse basin.

Caution: Care must be taken to ensure that the serial number tag does not come in contact with the leaflet tissue during rinsing. Inspect the bioprosthesis and remove the serial number tag just prior to implantation. Exercise care to avoid cutting or tearing the sewing ring cloth during removal of the serial number tag.

11.5 Device Implantation

Because of the complexity and variation in the surgical procedure of cardiac valve replacement, the choice of surgical technique is left to the discretion of the individual surgeon. In general, the standard implantation technique includes: 1. Proper sizing; 2. Proper seating of the prosthesis; 3. Tying sutures with the holder in place to minimize the potential for suture looping or chordal entrapment; 4. Examination of the bioprosthetic leaflets for distortion or leak during tying.

Proper bioprosthesis size selection is an important part of mitral valve replacement.

Verify that the sizers 1173B and 1173R have been sterilized according to the recommended instructions provided with the reusable accessories.

Caution: Examine sizers and handles for signs of wear, such as dullness, cracking, or crazing. Replace sizer or handle if any deterioration is observed.

Warning: Fragments of the sizers / handles cannot be located by means of an external imaging device.

Caution: Adequate removal of calcium deposits from the patient's annulus must be performed before implantation to avoid damage to the delicate bioprosthesis leaflet tissue as a result of contact with calcium deposits.

Insert the sizer into the mitral annulus. The barrel of the sizer should always fit comfortably in the annulus.

Caution: Use only sizers 1173B or 1173R during the selection of the Magna Mitral Ease bioprosthesis size; other sizers may result in improper valve selection (see **11.2 Accessories**). Like other mitral bioprostheses, the Magna Mitral Ease bioprosthesis is usually implanted using pledgeted mattress sutures. It is recommended to size the annulus after the sutures have been placed, as sutures may decrease the size of the bioprosthesis that can be implanted.

Sizing for implantation:

Sizing with barrel sizer 1173B: To size with barrel sizer 1173B, pass the barrel portion of the sizer through the mitral annulus ensuring the barrel portion is directly in the plane of the mitral annulus (Figure 12b).

Sizing with replica sizer 1173R: To size with replica sizer 1173R, pass the barrel portion of the sizer through the mitral annulus so that the lip of the sizer, which simulates the sewing ring portion of the bioprosthesis, rests on the superior aspect of the annulus (Figure 12a).

Some techniques such as use of pledgets, leaflet reefing, or mitral subvalvular apparatus preservation may further reduce the size of the mitral annulus which can result in the need for a smaller bioprosthesis to be implanted (Ref. 8). When using these techniques, it is recommended to re-size the annulus to avoid oversizing of the bioprosthesis. The consistent performance of the PERIMOUNT mitral bioprostheses makes oversizing unnecessary to achieve the desired hemodynamic performance in most patients (Table 9 and 10).

Due to the elastic nature of a chord, it may be extended by the Tricentrix holder system during implantation but retract back around the post once the holder is removed, entrapping leaflets and impairing function. Sizers 1173B and 1173R are made of a transparent material to allow visualization of the subvalvular apparatus during sizing. Make sure no chord will be in the way of the struts.

Caution: Exercise special care when using subvalvular apparatus preservation techniques to avoid chordae entrapment by a strut.

Warning: Avoid oversizing the bioprosthesis. Oversizing may cause bioprosthesis damage or localized mechanical stresses, which may in turn injure the heart or result in leaflet tissue failure, stent distortion and regurgitation.

Caution: Because of the intense temperature and lighting conditions in the operating field, the bioprosthesis should be irrigated frequently (every 1 to 2 minutes is recommended) on both sides with sterile physiological saline to keep the valve moist during the implant procedure.

Proper orientation of the bioprosthesis

Caution: The wireform frame of the Magna Mitral Ease bioprosthesis is symmetrical, and the three commissure supports (struts) are equally spaced. However, the sewing ring is designed for a specific orientation of the bioprosthesis. The scalloped part of the sewing ring, between the two silicone protrusions, should be placed across the intercommissural anterior portion of the annulus and straddle the left ventricular outflow tract.

The contrasting suture markers in the sewing ring are intended to aid in proper orientation and denote a typical intercommissural distance. However, this distance may vary for each individual patient. On the left side, two close black sutures indicate where the first stitch should be placed and correspond to the anterior commissure. On the right side, only one black suture indicates the approximate location of the posterior commissure. Using these orientation aids, the third post should naturally fall in place in or around the middle of the posterior leaflet location.

Caution: Special care must be exercised to avoid placing a strut in front of the left ventricular outflow tract, as it may impair the long-term hemodynamic performance.

A black suture guide line circles the sewing ring. When placing sutures through the sewing ring, sliding drag forces are reduced when sutures are placed straight through the sewing ring and in the region from the suture guide line to the outer portion of the sewing ring. Irrigation with saline can further reduce suture drag forces.

Firm tension must be maintained on the sutures as the bioprosthesis is lowered into the annulus; this minimizes the potential for formation of suture loops that might entrap a leaflet. This, when combined with the fully retracted stent posts when the Tricentrix holder system is in place, helps guide the sutures into their correct position behind the struts and onto the sewing ring.

Remove the handle prior to tying the sutures. The handle and blue adapter must be removed as an assembly. Maintain the bioprosthesis placement in the annulus by gently placing forceps or gloved hands onto the holder and cutting the green thread on the blue adapter (Figure 8). Remove the blue adapter and handle assembly as one unit.

Caution: Avoid looping or catching a suture around the open cages, free struts, or commissure supports of the bioprosthesis, which would interfere with proper valvular function. To minimize the potential for suture looping, it is essential to leave the deployed holder in place until all knots are tied.

However, if leaving the holder in place obstructs the surgeon's view, all the sutures adjacent to each of the three frame struts must be tied down before cutting the three green holder attachment threads to remove the holder.

Caution: If the deployed holder attachment threads are cut before these adjacent sutures are tied down, the holder will no longer minimize the potential for suture looping around the frame struts.

Special attention must be given to avoid tying the sutures on top of the corners of the holder's grey legs. Before tying each suture, examine the leaflets while holding the two strands of the suture under tension. Distortion or movement of the leaflets during this maneuver suggests that the suture is looped around a strut. At no point before or after holder removal should tension on the sutures be released as this may facilitate formation of loops in the sutures and possible entrapment. It is recommended to place a surgical mirror through the leaflets after the holder removal in order to examine each strut and proper suture placement.

Caution: When using interrupted sutures, it is important to cut the sutures close to the knots and to ensure that exposed suture tails will not come into contact with the leaflet tissue (Ref. 8).

The Tricentrix holder system is removed as a unit at the completion of the suturing procedure as follows (Figure 9):

1. Cut each of the three (3) exposed green sutures using a scalpel or scissor placed only in the cutting channel. Never attempt to cut a suture below a partially separated holder as a part of the attaching suture may fall in the ventricle. Avoid cutting or damaging the stent or leaflet tissue when cutting the sutures.
2. When all three (3) attaching sutures have been properly cut, remove the Tricentrix holder system from the bioprosthesis as a unit, along with attaching sutures, using sterile gloved hands or protected forceps.
3. Following surgery, remove the holder and discard.

11.6 Return of Explanted Bioprostheses

Edwards Lifesciences is interested in obtaining all recovered clinical specimens of Carpentier-Edwards PERIMOUNT Magna Mitral Ease pericardial bioprostheses model 7300TFX for analysis. A written report summarizing our findings will be provided to the physician upon completion of our evaluation. Please contact your local representative for return of recovered bioprostheses. The explanted bioprostheses should be placed into a suitable histological fixative such as 10% formalin or 2% glutaraldehyde immediately after excision and returned to the company. Refrigeration is not necessary under these circumstances.

12. Patient Information

12.1 Registration Information

An Implantation Data Card is included in each device package for patient registration. After implantation, please complete all requested information. The bioprosthesis serial number is listed on the bioprosthesis packaging and on the identification tag attached to the bioprosthesis, and is pre-printed on the Implantation Data Card. Return the pre-addressed portion of the card to our Implant Patient Registry. The remaining portions of the card are provided for hospital and surgeon records. Upon receipt by the Edwards Implant Patient Registry, a wallet-sized identification card will be produced for the patient. This card allows patients to inform health care providers what type of implant they have when they seek care. When a bioprosthesis is discarded or a previous Edwards Lifesciences device is replaced, report this information to the Edwards Implant Patient Registry.

12.2 Patient Manual

Patient information materials may be obtained from Edwards or your local representative.

13. Safety in the Magnetic Resonance (MR) Environment

MR Conditional

Non-clinical testing has demonstrated that the Carpentier-Edwards PERIMOUNT Magna Mitral Ease pericardial bioprosthesis model 7300TFX is MR Conditional. A patient with the Magna Mitral Ease bioprosthesis can be scanned safely, immediately after placement of this implant under the following conditions:

- Static magnetic field of 3 tesla or less.
- Maximum Spatial gradient field of 720 gauss/cm.

- Maximum MR system-reported whole-body-averaged specific absorption rate (SAR) of 3W/kg for 15 minutes of scanning.

In non-clinical testing, the Magna Mitral Ease bioprosthesis produced a temperature rise of less than or equal to 0.5 °C at a maximum MR system reported whole-body-averaged specific absorption rate (SAR) of 3W/kg for 15 minutes of MR scanning in a 3 tesla MR system (Excite, Software G3.0-052B, General Electric Healthcare).

MR image quality may be compromised if the area of interest is in the same area or relatively close to the position of the Magna Mitral Ease bioprosthesis. Optimization of MR imaging parameters is recommended.

Prices subject to change without notice. This product is manufactured and sold under one or more of the following US patents: US-Patent Nos. 5,928,281; 5,931,969; 5,961,549; 6,102,944; 6,210,957; 6,214,054; 6,245,105; 6,378,221; 6,409,758; 6,413,275; 6,416,547; 6,547,827; 6,553,681; 6,561,970; 6,585,766; 6,837,902; 6,878,168; 6,945,997; 6,966,925; 7,214,344; 7,658,763; 7,682,391; RE 40570; and corresponding foreign patents. Additional patents are pending.

References

1. Marchand MA., et al. Fifteen-year Experience with the Mitral Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis. *Ann Thorac Surg.* 2001; 71:S236-9.
2. Liao K., et al. Bovine Pericardium versus Porcine Aortic Valve: Comparison of Tissue Biological Properties As Prosthetic Valves; *Artificial Organs.* 1992;16(4):361-5.
3. Vesely I., et al. Comparison of the Compressive Buckling of Porcine Aortic Valve Cusps and Bovine Pericardium. *J. Heart Valve Dis.* January 1998; 7(1):34-9.
4. Carpentier A. From Valvular Xenograft to Valvular Bioprosthesis (1965-1977). *Med. Instrum.* 1977; 11(2):98-101.
5. Carpentier A., et al. Continuing Improvements in Valvular Bioprostheses. *J. Thorac. Cardiovasc. Surg.* 1982; 83(1):27-42.
6. Arounlangsy P., et al. Histopathogenesis of early stage mitral annular calcification. *J. Med Dent Sci.* 2004; 51(1):35-44.
7. Bonow RO., et al. ACC/AHA Guidelines for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1998 Guidelines for the Management of Patients with Valvular Heart Disease). *J. AmColl Cardiol.* 2006; 48:e1-148.
8. Aagaard J., et al. Mitral valve replacement with total preservation of native valves and subvalvular apparatus. *J. Heart Valve Dis.* May 1997; 6(3):274-8; discussion 279-80.

Table 1: Observed Adverse Event Rates for MVR and DVR (Model 6900)

All patients analyzed: N = 363 Cumulative follow-up: 1100 patient-years

	Early Events		Late Events[1]		Freedom from Event (%) [95% CI][2]		
Complication	n[3]	%	n	%/pt.-yr.	1 year (n = 287)	5 years (n = 141)	8 years (n = 18)
Mortality (all)	34	9.4	50	4.7	85.5 [81.8, 89.2]	75.4 [70.3, 80.6]	65.4 [57.6, 73.2]
Valve-related events							
Mortality (valve-related)	0	0	16	1.5	97.7 [96.0, 99.4]	95.3 [92.8, 97.8]	91.9 [87.5, 96.4]
Explants	0	0	8	0.7	98.7 [98.0, 99.3]	96.7 [95.3, 98.0]	95.6 [93.9, 97.3]
Reoperations	2	0.6	12	1.1	97.1 [96.2, 98.1]	95.1 [93.6, 96.6]	93.0 [90.9, 95.1]
Anticoagulant-related hemorrhage	2	0.6	9	0.8	97.1 [95.2, 99.0]	97.1 [95.2, 99.0]	94.1 [88.2, 100]
Endocarditis	1	0.3	3	0.3	99.0 [97.9, 100]	98.7 [97.4, 98.9]	98.7 [97.4, 98.9]
Hemolysis	0	0.0	1	0.1	99.7 [99.0, 100]	99.7 [99.0, 100]	99.7 [99.0, 100]
Nonstructural dysfunction	0	0.0	3	0.3	100 [100, 100]	99.3 [98.0, 100]	98.3 [95.9, 100]
Perivalvular leak (all)	1	0.3	5	0.5	98.4 [97.0, 99.8]	98.4 [97.0, 99.8]	97.3 [94.9, 99.8]
Structural valve deterioration	0	0.0	5	0.5	100.0 [100, 100]	97.6 [95.2, 100]	92.8 [85.3, 100]
Thromboembolism	5	1.4	8	0.7	97.5 [95.8, 99.2]	96.1 [93.8, 98.5]	96.1 [93.8, 98.5]
Thrombosis	0	0.0	0	0.0	100.0 [100, 100]	100.0 [100, 100]	100.0 [100, 100]

Notes:
1. Late event rates were calculated as linearized rates (%/pt-yr) based on 1072.5 late patient-years (> 30 days postoperatively).
2. Freedom from event rates were calculated using the Kaplan-Meier method. Greenwood's formula was used for calculation of the standard errors of these estimates.
3. n = number of events.

Table 2: Observed Adverse Event Rates (Model 6900P)

All patients analyzed: N = 209 Cumulative follow-up: 873.18 total pt-yrs.

	Early Events		Late Events[1]		Freedom from Event (%) [95% CI][2]	
Complication	n[3]	%	n	%/pt-yr	1 year	5 years
Mortality (all)	3	1.4	45	5.3	93.2 [88.8, 95.9]	74.4 [66.9, 80.5]
Valve-related events						
Mortality (valve-related)	1	0.5	12	1.4	98.5 [95.5, 99.5]	92.0 [86.2, 95.5]
Explants	1	0.5	8	0.9	97.5 [94.0, 98.9]	96.5 [92.2, 98.5]
Reoperations	0	0.0	0	0.0	100.0 [100, 100]	100.0 [100, 100]
Bleeding Events	5	2.4	13	1.5	96.1 [92.3, 98.0]	91.9 [86.5, 95.2]
Endocarditis	1	0.5	3	0.4	99.5 [96.6, 99.9]	97.1 [92.1, 98.9]
Nonstructural dysfunction	0	0.0	1	0.1	99.5 [96.4, 99.9]	99.5 [96.4, 99.9]
Perivalvular leak (all)	1	0.5	2	0.2	99.5 [96.7, 99.9]	98.4 [95.2, 99.5]
Structural valve deterioration	0	0.0	2	0.2	100.0 [100, 100]	99.0 [93.2, 99.9]
Thromboembolism	4	1.9	12	1.4	97.0 [93.5, 98.7]	91.3 [85.8, 94.7]
Thrombosis	0	0.0	0	0.0	100.0 [100, 100]	100.0 [100, 100]

Notes:
1. Late event rates were calculated as linearized rates (%/pt-yr) based on 856.24 late patient-years (> 30 days postoperatively).
2. Freedom from event rates were calculated using the Kaplan-Meier method. Greenwood's formula was used for calculation of the standard errors of these estimates.
3. n = number of events.

Table 3: Preoperative Patient Demographics (Model 6900)

		Study Characteristics (N = 363; 1100 total pt-yrs.)	
Variable	Category	n	% (n/N)[1]
Age at implant (N = 363)	Mean ± SD	66.1 ± 10.7	
Gender	Female/Male	212/151	58.4%/41.6%
Diagnosis/Etiology	None	30	8.3%
	Stenosis	91	25.1%
	Regurgitation	184	50.7%
	Mixed Disease	58	16.0%

Note:
1. n = number of patients in each category; N = total number of study patients.

Table 4: Preoperative Patient Demographics (Model 6900P)

		Study Characteristics (N = 209; 873.18 total pt-yrs.)	
Variable	Category	n	% (n/N)[1]
Age at implant (N = 209)	Mean ± SD	71.4 ± 9.4	
Gender	Female/Male	138/71	66.0%/34.0%
Diagnosis/Etiology	Mixed Disease	48	23.0%
	Regurgitation	121	57.9%
	Stenosis	32	15.3%
	Valve Dysfunction	8	3.8%

Note:
1. n = number of patients in each category; N = total number of study patients.

Table 5: Operative Patient Demographics (Model 6900)

		Study Characteristics (N = 363; 1100 total pt-yrs.)	
Variable	Category	n	% (n/N)[1]
Etiology[2]	Rheumatic heart disease	135	37.2%
	Calcification	82	22.6%
	Degeneration	50	13.8%
	Endocarditis	39	10.7%
	Failed Bioprosthesis	15	4.1%
	Ischemic Heart Disease	14	3.9%
	Congenital Abnormalities	8	2.2%
	Other	44	12.1%
Concomitant Procedures[2]	None	200	55.1%
	CABG[3]	78	21.5%
	Tricuspid Repair	61	16.8%
	Intra-aortic balloon pump	17	4.7%
	Pacemaker[4]	6	1.7%
	Aortic repair/replacement	5	1.4%
	Aneurysm Repair	4	1.1%
	Other	31	8.5%
Pre-existing Conditions[2]	None	122	33.6%
	CAD[5]/CABG	72	19.8%
	Hypertension	61	16.8%
	Atrial Fibrillation	53	14.6%
	Previous MI[6]	45	12.4%
	Cerebrovascular Disease	36	9.9%
	Other	234	64.5%
Valve Size (mm)	25	22	6.1%
	27	110	30.3%
	29	137	37.7%
	31	81	22.3%
	33	13	3.6%

Notes:
1. n = number of patients in each category; N = total number of study patients
2. May be more than one per patient
3. CABG = Coronary Artery Bypass Graft
4. Permanent or temporary
5. CAD = Coronary Artery Disease
6. MI = Myocardial Infarction

Table 6: Operative Patient Demographics (Model 6900P)

		Study Characteristics (N = 209; 873.18 total pt-yrs.)	
Variable	Category	n	% (n/N)[1]
Etiology[2]	Calcified	38	18.2%
	Congenital	1	0.5%
	Degenerative	105	50.2%
	Endocarditis Remote	10	4.8%
	Ischemic	12	5.7%
	Rheumatic	64	30.6%
	Other	36	17.2%
Concomitant Procedures[2]	None	91	43.5%
	Aortic Valve/Annulus Repair	3	1.4%
	CABG[3]	58	27.8%
	Permanent Pacemaker	1	0.5%
	Tricuspid Valve/Annulus Repair	21	10.0%
	Other	78	37.3%
Pre-existing Conditions[2]	None	17	8.1%
	Arrhythmias	95	45.5%
	CAD[4]	85	40.7%
	Cardiomyopathy	13	6.2%
	Congestive Heart Failure	66	31.6%
	Endocarditis	14	6.7%
	Myocardial Infarction	21	10.0%
	Peripheral Vascular Disease	9	4.3%
	Pulmonary Hypertension	66	31.6%
	Rheumatic Fever	16	7.7%
	Systemic Hypertension	49	23.4%
	TIA[5]/CVA[6]	24	11.5%
	Other	35	16.7%
Valve Size (mm)	25	28	13.4%
	27	37	17.7%
	29	84	40.2%
	31	43	20.6%
	33	17	8.1%

Notes:
1. n = number of patients in each category; N = total number of study patients
2. May be more than one per patient
3. CABG = Coronary Artery Bypass Graft
4. CAD = Coronary Artery Disease
5. TIA = Transient Ischemic Attack
6. CVA = Cerebral Vascular Accident

Table 7: Effectiveness Outcomes, Functional NYHA (Model 6900)

	Preoperative Assessment		Postoperative Assessments			
			1 to 2 Year		5 Year	
NYHA Functional Class	n/N[1]	%	n/N	%	n/N	%
I	11/363	3.0	120/268	44.8	40/129	31.0
II	73/363	20.1	90/268	33.6	25/129	19.4
III	192/363	52.9	15/268	5.6	1/129	0.8
IV	84/363	23.1	0/268	0.0	0/129	0.0
Not Available	3/363	0.8	43/268	16.0	63/129	48.8

Note:
1. n = number of patients in each category; N = total number of study patients.

Table 8: Effectiveness Outcomes, Functional NYHA (Model 6900P)

	Preoperative Assessment		Postoperative Assessments			
			1 Year		5 Year	
NYHA Functional Class	n/N[1]	%	n/N	%	n/N	%
I	6/209	2.9	86/187	46.0	30/96	31.3
II	27/209	12.9	68/187	36.4	33/96	34.4
III	121/209	57.9	8/187	4.3	6/96	6.3
IV	55/209	26.3	1/187	0.5	0/96	0.0
Not Available	0/209	0.0	24/187	12.8	27/96	28.1

Note:
1. n = number of patients in each category; N = total number of study patients.

Table 9: Effective Outcomes, Hemodynamic Results[1] (Model 6900)

Hemodynamic Parameter	Results By Valve Size				
	25 mm	27 mm	29 mm	31 mm	33 mm
Discharge/Early Post-Implant (n = 130, 109 MVR[2] and 21 DVR[3])					
Mean gradient[4]	n = 3	n = 23	n = 36	n = 23	n = 3
• mean ± sd	5.7 ± 1.2	4.2 ± 1.7	4.2 ± 1.7	3.6 ± 1.0	7.5 ± 5.8
• min, max	5, 7	2, 9	1, 8	2, 5	3, 14
EOA[5]	n = 1	n = 17	n = 22	n = 25	n = 5
• mean ± sd	1.5	2.9 ± 0.9	3.1 ± 0.9	2.5 ± 0.7	3.0 ± 1.2
• min, max	1.5, 1.5	1.3, 4.1	1.4, 4.2	1.5, 3.8	1.6, 4.9
Regurgitation[6]	n = 3	n = 28	n = 51	n = 40	n = 8
0	3/3 (100%)	22/28 (79%)	36/51 (71%)	30/40 (75%)	4/8 (50%)
1+	0/3 (0%)	5/28 (18%)	13/51 (25%)	7/40 (18%)	4/8 (50%)
2+	0/3 (0%)	0/28 (0%)	1/51 (2%)	3/40 (7%)	0/8 (0%)
3+	0/3 (0%)	0/28 (0%)	1/51 (2%)	0/40 (0%)	0/8 (0%)
4+	0/3 (0%)	0/28 (0%)	0/51 (0%)	0/40 (0%)	0/8 (0%)
Not available	0/3 (0%)	1/28 (3%)	0/51 (0%)	0/40 (0%)	0/8 (0%)
3 to 6 Month Post-Implant Interval (n = 49, 42 MVR[2] and 7 DVR[3])					
Mean gradient[4]	n = 5	n = 19	n = 15	n = 5	n = 2
• mean ± sd	6.4 ± 1.7	5.3 ± 5	3.4 ± 1.2	4 ± 1.9	4 ± 0
• min, max	5, 9	2, 25	2, 6	2, 7	4, 4
EOA[5]	n = 5	n = 18	n = 13	n = 5	n = 2
• mean ± sd	2.9 ± 0.8	2.6 ± 0.7	2.8 ± 0.6	2.9 ± 0.3	2.6 ± 1
• min, max	1.8, 3.6	1.5, 5	2, 3.8	2.4, 3.3	2, 3.3
Regurgitation[6]	n = 5	n = 21	n = 15	n = 6	n = 2
0	3/5 (60%)	17/21 (81%)	6/15 (40%)	4/6 (67%)	1/2 (50%)
1+	0/5 (0%)	4/21 (19%)	8/15 (53%)	2/6 (33%)	0/2 (0%)
2+	1/5 (20%)	0/21 (0%)	1/15 (7%)	0/6 (0%)	1/2 (50%)
3+	0/5 (0%)	0/21 (0%)	0/15 (0%)	0/6 (0%)	0/2 (0%)
4+	1/5 (20%)	0/21 (0%)	0/15 (0%)	0/6 (0%)	0/2 (0%)
Not available	0/5 (0%)	0/21 (0%)	0/15 (0%)	0/6 (0%)	0/2 (0%)
1 to 2 Year Post-Implant Interval (n = 131, 114 MVR[2] and 17 DVR[3])					
Mean gradient[4]	n = 3	n = 40	n = 47	n = 27	n = 4
• mean ± sd	5.2 ± 0.7	4.1 ± 1.6	3.5 ± 1.8	3.1 ± 1.4	2.1 ± 0.5
• min, max	4.7, 6	1, 7	1, 10	1, 7	1.5, 2.7
EOA[5]	n = 2	n = 35	n = 46	n = 29	n = 5
• mean ± sd	1.8 ± 0.4	2.3 ± 0.6	2.6 ± 0.5	2.6 ± 0.7	2.5 ± 0.5
• min, max	1.5, 2.0	1.2, 3.5	1.1, 3.7	1.1, 3.7	2.1, 3.2
Regurgitation[6]	n = 4	n = 42	n = 51	n = 29	n = 5
0	2/4 (50%)	31/42 (74%)	36/51 (71%)	17/29 (59%)	3/5 (60%)
1+	1/4 (25%)	9/42 (21%)	11/51 (21%)	8/29 (27%)	1/5 (20%)
2+	1/4 (25%)	2/42 (5%)	4/51 (8%)	2/29 (7%)	1/5 (20%)
3+	0/4 (0%)	0/42 (0%)	0/51 (0%)	2/29 (7%)	0/5 (0%)
4+	0/4 (0%)	0/42 (0%)	0/51 (0%)	0/29 (0%)	0/5 (0%)
Not available	0/4 (0%)	0/42 (0%)	0/51 (0%)	0/29 (0%)	0/5 (0%)

Continued on next column.

Table 9: Effective Outcomes, Hemodynamic Results[1] (Model 6900), Continued

Hemodynamic Parameter	Results By Valve Size				
	25 mm	27 mm	29 mm	31 mm	33 mm
5 Year Post-Implant Interval (n = 11, 9 MVR[2] and 2 DVR[3])					
Mean gradient[4]	n = 0	n = 6	n = 5	n = 0	n = 0
• mean ± sd	N/A	8.8 ± 8.1	5.1 ± 2.3	N/A	N/A
• min, max	N/A	4, 25	3, 8	N/A	N/A
EOA[5]	n = 0	n = 2	n = 4	n = 0	n = 0
• mean ± sd	N/A	2.0 ± 1.5	2.9 ± 0.6	N/A	N/A
• min, max	N/A	1.0, 3.1	2.1, 3.5	N/A	N/A
Regurgitation[6]	n = 0	n = 6	n = 5	n = 0	n = 0
0	0/0 (0%)	4/6 (66%)	2/5 (40%)	0/0 (0%)	0/0 (0%)
1+	0/0 (0%)	1/6 (17%)	3/5 (60%)	0/0 (0%)	0/0 (0%)
2+	0/0 (0%)	1/6 (17%)	0/5 (0%)	0/0 (0%)	0/0 (0%)
3+	0/0 (0%)	0/6 (0%)	0/5 (0%)	0/0 (0%)	0/0 (0%)
4+	0/0 (0%)	0/6 (0%)	0/5 (0%)	0/0 (0%)	0/0 (0%)
Not available	0/0 (0%)	0/6 (0%)	0/5 (0%)	0/0 (0%)	0/0 (0%)

Notes:
1. Hemodynamic evaluations were performed using transthoracic echocardiography (TTE) and in some cases, transesophageal echocardiography (TEE).
2. MVR = mitral valve replacement
3. DVR = double valve replacement
4. Mean gradient in mmHg
5. EOA: Effective Orifice Area, cm^2
6. Regurgitation = none, 0; mild, 1+; moderate, 2+; moderate/severe, 3+; severe, 4+

Table 10: Effectiveness Outcomes, Hemodynamic Results (Model 6900P)[1]

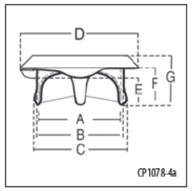
Hemodynamic Parameter	Results By Valve Size				
	25 mm	27 mm	29 mm	31 mm	33 mm
Discharge/Early Post-Implant					
Mean gradient[2]	n = 24	n = 35	n = 83	n = 42	n = 16
• mean ± sd	6.4 ± 1.87	4.4 ± 1.52	3.4 ± 1.47	3.3 ± 1.20	4.0 ± 1.38
• min, max	3, 10	1.96, 8	1.4, 9	1, 7	1.5, 6.91
EOA[3]	n = 8	n = 27	n = 77	n = 41	n = 16
• mean ± sd	2.7 ± 0.87	2.8 ± 0.58	2.9 ± 0.93	2.5 ± 0.67	2.4 ± 0.52
• min, max	1.46, 4.4	1.5, 3.9	1.58, 6	1.32, 4.2	1.55, 3.31
Regurgitation[4]	n = 27	n = 37	n = 83	n = 43	n = 17
Trivial / None	19/27 (70%)	29/37 (78%)	76/83 (92%)	39/43 (91%)	15/17 (88%)
1+ Mild	6/27 (22%)	7/37 (19%)	7/83 (8%)	4/43 (9%)	1/17 (6%)
2+ Moderate	1/27 (4%)	1/37 (3%)	0/83 (0%)	0/43 (0%)	0/17 (0%)
3+ Moderate/Severe	0/27 (0%)	0/37 (0%)	0/83 (0%)	0/43 (0%)	1/17 (6%)
4+ Severe	0/27 (0%)	0/37 (0%)	0/83 (0%)	0/43 (0%)	0/17 (0%)
Not available	1/27 (4%)	0/37 (0%)	0/83 (0%)	0/43 (0%)	0/17 (0%)
3 to 6 Month Post-Implant Interval					
Mean gradient[2]	n = 0	n = 4	n = 3	n = 2	n = 0
• mean ± sd	0 ± 0	4.4 ± 2.25	2.3 ± 0.89	6.6 ± 2.05	0 ± 0
• min, max	0, 0	2.5, 7.5	1.3, 3	5.1, 8	0, 0
EOA[3]	n = 0	n = 3	n = 3	n = 1	n = 1
• mean ± sd	0 ± 0	2.4 ± 0.74	3.2 ± 0.88	2.5 ± 0.00	1.2 ± 0.00
• min, max	0, 0	1.6, 3	2.3, 4.05	2.47, 2.47	1.22, 1.22
Regurgitation[4]	n = 0	n = 5	n = 3	n = 2	n = 2
Trivial / None	0	3/5 (60%)	2/3 (67%)	2/2 (100%)	2/2 (100%)
1+ Mild	0	1/5 (20%)	1/3 (33%)	0/2 (0%)	0/2 (0%)
2+ Moderate	0	1/5 (20%)	0/3 (0%)	0/2 (0%)	0/2 (0%)
3+ Moderate/Severe	0	0/5 (0%)	0/3 (0%)	0/2 (0%)	0/2 (0%)
4+ Severe	0	0/5 (0%)	0/3 (0%)	0/2 (0%)	0/2 (0%)
Not available	0	0/5 (0%)	0/3 (0%)	0/2 (0%)	0/2 (0%)
1 Year Post-Implant Interval					
Mean gradient[2]	n = 16	n = 27	n = 63	n = 34	n = 15
• mean ± sd	5.9 ± 2.36	4.0 ± 1.45	3.0 ± 1.61	3.3 ± 1.26	3.4 ± 1.25
• min, max	3, 12	2, 7	1, 12	1.5, 7	1.9, 6.3
EOA[3]	n = 3	n = 21	n = 59	n = 32	n = 15
• mean ± sd	2.3 ± 0.16	2.4 ± 0.76	2.6 ± 0.74	2.5 ± 0.67	2.3 ± 0.83
• min, max	2.09, 2.4	1.27, 4.76	1.5, 5.7	1.5, 4	1.2, 3.8
Regurgitation[4]	n = 20	n = 28	n = 65	n = 34	n = 16
Trivial / None	17/20 (85%)	24/28 (86%)	53/65 (82%)	29/34 (85%)	13/16 (81%)
1+ Mild	3/20 (15%)	3/28 (11%)	6/65 (9%)	3/34 (9%)	3/16 (19%)
2+ Moderate	0/20 (0%)	0/28 (0%)	3/65 (5%)	2/34 (6%)	0/16 (0%)
3+ Moderate/Severe	0/20 (0%)	0/28 (0%)	1/65 (2%)	0/34 (0%)	0/16 (0%)
4+ Severe	0/20 (0%)	0/28 (0%)	0/65 (0%)	0/34 (0%)	0/16 (0%)
Not available	0/20 (0%)	1/28 (4%)	2/65 (3%)	0/34 (0%)	0/16 (0%)

Notes:
1. Hemodynamic evaluations were performed using transthoracic echocardiography (TTE) and in some cases, transesophageal echocardiography (TEE).
2. Mean gradient in mmHg
3. EOA: Effective Orifice Area, cm^2
4. Regurgitation = Trivial/none, 0; mild, 1+; moderate, 2+; moderate/severe, 3+; severe, 4+

Figure 1

Nominal Specifications (mm)

Carpentier-Edwards PERIMOUNT Magna Mitral Ease Bioprosthesis, Model 7300TFX



Size	25 mm	27 mm	29 mm	31 mm	33 mm
A. Stent Diameter (Wireform)	25	27	29	31	31
B. Tissue Annulus Diameter*	28	29.5	31.5	33.5	33.5
C. External Stent Post Diameter (Tip)	29	31	34	35	35
D. External Sewing Ring Diameter	36	38	40	42	44
E. Effective Profile Anterior	7	7.5	8	8.5	8.5
F. Effective Profile Posterior	10	10.5	11	11.5	11.5
G. Total Profile Height	15	16	17	18	18

*External Stent Post Diameter (Base)

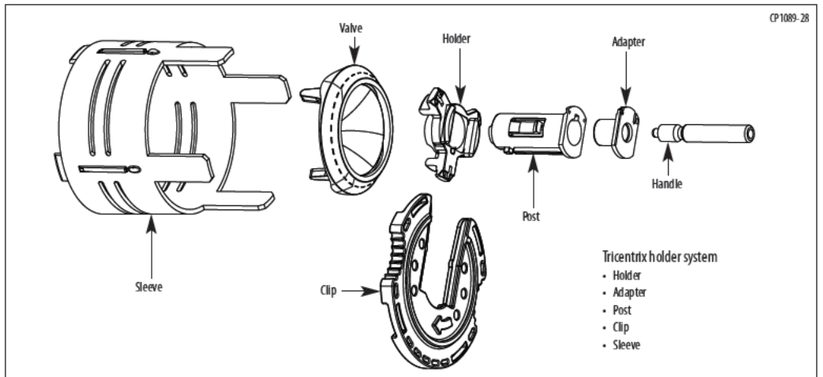


Figure 2

Figure 3a

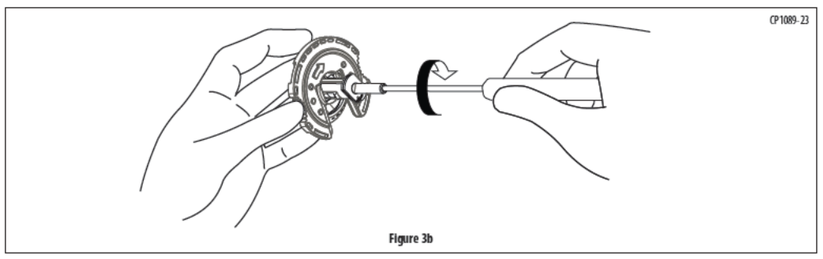


Figure 3b

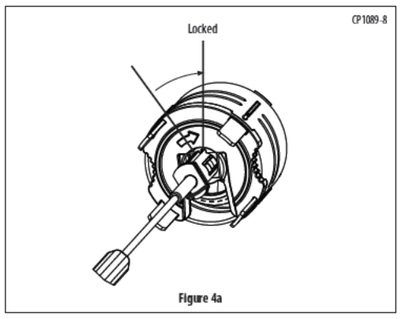


Figure 4a

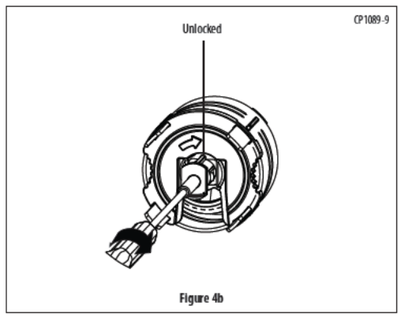


Figure 4b

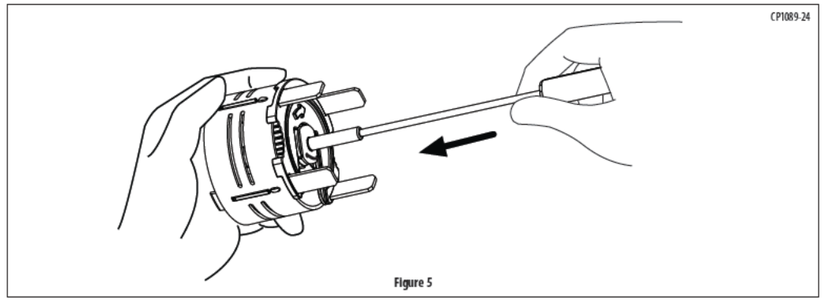


Figure 5

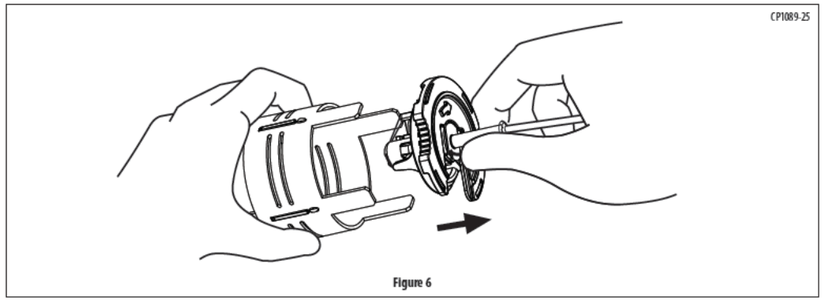


Figure 6

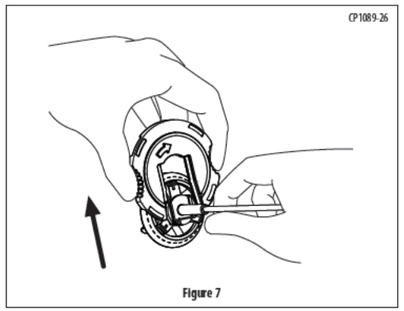


Figure 7

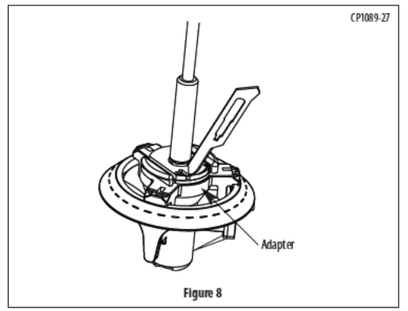


Figure 8

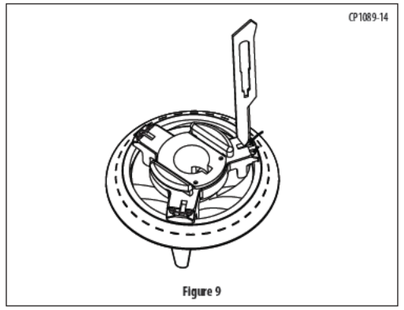


Figure 9

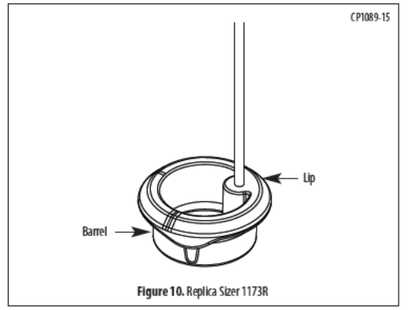


Figure 10. Replica Sizer 1173R

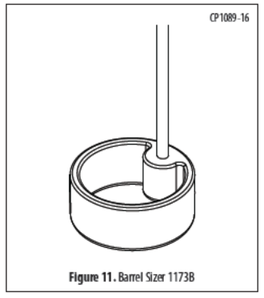


Figure 11. Barrel Sizer 1173B

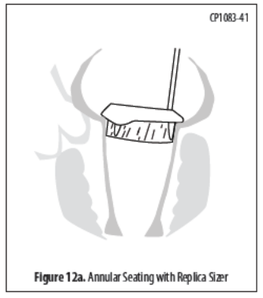


Figure 12a. Annular Seating with Replica Sizer

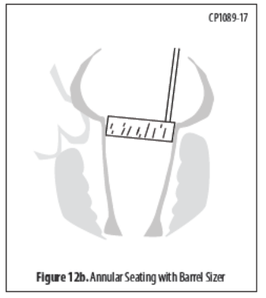
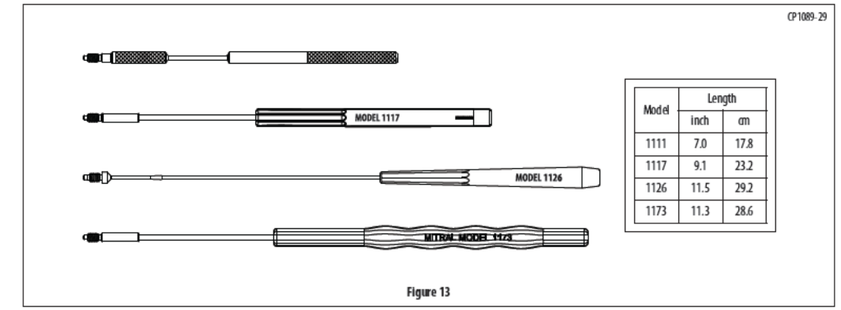


Figure 12b. Annular Seating with Barrel Sizer



Model	Length	
	inch	cm
1111	7.0	17.8
1117	9.1	23.2
1126	11.5	29.2
1173	11.3	28.6

Figure 13

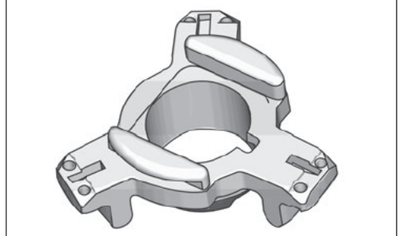


Figure 14

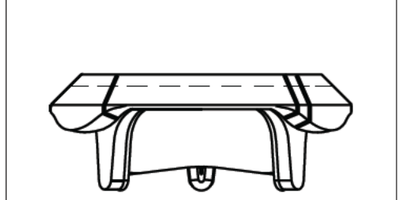


Figure 15

Edwards

9/10
198654002 A

Edwards Lifesciences LLC
One Edwards Way
Irvine, CA 92614-5686 USA
Made in USA

Telephone 949.250.2500
800.424.3278
FAX 949.250.2525

16.0 APPENDIX 5: CASE REPORT FORMS

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | | Clinic # | | | |

I. INCLUSION CRITERIA *A NO answer excludes the subject.*

	YES	NO	
1.	☐	☐	The patient requires, as indicated in the preoperative evaluation, a mitral valve replacement.
2.	☐	☐	The patient has signed and dated the patient informed consent form prior to surgery.
3.	☐	☐	The patient is expected to survive the surgery and be discharged.
4.	☐	☐	The patient is geographically stable and agrees to attend follow-up assessments.
5.	☐	☐	The patient is > or = 18 years of age.

II. EXCLUSION CRITERIA *A YES answer excludes the subject.*

	YES	NO	
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 has active endocarditis within the last 3 months.
3.	☐	☐	The patient is pregnant or lactating.
4.	☐	☐	The patient is an intravenous drug abuser.
5.	☐	☐	The patient is currently a prison inmate.
6.	☐	☐	The patient is currently participating in the study of an investigational drug or device.
7.	☐	☐	The patient requires replacement of a native or prosthetic tricuspid or pulmonic valve.
8.	☐	☐	The patient was previously enrolled in the study.
9.	☐	☐	The patient has had prior aortic, tricuspid and/or pulmonary valve surgery, which included implantation of a bioprosthetic valve, mechanical valve and/or annuloplasty device that will remain *in situ.*
10.	☐	☐	The patient requires replacement of a native or prosthetic aortic valve with a prosthesis other than a commercially available Carpentier-Edwards PERIMOUNT Valve (ie, models 2700, 2700TFX, 2800, 2800TFX, 2900, 3000, 3000TFX, 3300TFX).

III. STUDY INFORMED CONSENT

	Yes	No	
1.	☐	☐	Signed Informed Consent

Date informed consent signed: | | | | | | | | | | (D D M M M Y Y Y Y) | | | : | | | (Time (24 hour format))

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

DATE SIGNED | | | | | | | | | | (D D M M M Y Y Y Y)

INVESTIGATOR SIGNATURE

White and Yellow: Return to Edwards Lifesciences, Clinical Affairs Pink: Retain for your Records

FOR EDWARDS USE ONLY	Clinical Review:		Data Management:		
	First Review:	Second Review: (optional)	First Data Entry:	Second Data Entry:	Subevent # (optional)
	By:	By:	By:	By:	
	Date:__ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | | Clinic # | | | |

1. DATE OF BIRTH: | | | | | | | | | |
D D M M M Y Y Y Y

2. SEX: ☐ Male ☐ Female

3. PHYSICAL ASSESSMENT:

HEART RATE		(bpm)
HEIGHT		(cm)
WEIGHT		(kg)
BLOOD PRESSURE		mmHg

4. PREOPERATIVE NYHA FUNCTIONAL CLASS:

☐ Class I ☐ Class II ☐ Class III ☐ Class IV ☐ NAV

5. NON-CARDIOVASCULAR CONDITIONS: ***(Past or present, check all that apply)***

Yes	No	
☐	☐	Smoking (Current)
☐	☐	Smoking (Past)
☐	☐	Drug Abuse
☐	☐	Alcohol Abuse
☐	☐	Rheumatic Fever
☐	☐	Cancer, specify*:* _____
☐	☐	Liver Disease
☐	☐	Renal Failure *if yes,* ☐ Dialysis ☐ No Dialysis
☐	☐	Pulmonary Disease
☐	☐	Renal Dysfunction
☐	☐	Diabetes *if yes,* ☐ Insulin dependent ☐ Non insulin dependent
☐	☐	Immunosuppressive Therapy
☐	☐	Calcium Metabolic Disorder
☐	☐	Respiratory Dysfunction and/or COPD
☐	☐	Respiratory Failure (Requires ventilator support) (*if yes-exclude)*
☐	☐	Peripheral Vascular Disease
☐	☐	TIA /CVA / RIND /COMA
☐	☐	Other CNS disorder
☐	☐	Other, specify*:* _____

FOR EDWARDS USE ONLY	CLINICAL REVIEW:		DATA MANAGEMENT:		
	FIRST REVIEW:	SECOND REVIEW: (OPTIONAL)	FIRST DATA ENTRY:	SECOND DATA ENTRY:	SUBEVENT # (OPTIONAL)
	BY:	BY:	BY:	BY:	
	DATE: __ __ __/__ __/__ __ __ __	DATE: __ __ __/__ __/__ __ __ __	DATE: __ __ __/__ __/__ __ __ __	DATE: __ __ __/__ __/__ __ __ __	

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | |

Clinic # | | | |

6. CARDIOVASCULAR MEDICAL HISTORY / RISK FACTORS: *(As noted by physician)*

Yes	No		
☐	☐	Dyslipidemia / Hypercholesterolemia	
☐	☐	Marfan's Syndrome *(if yes, exclude)*	
☐	☐	Rheumatic Fever	
☐	☐	Carotid Artery Disease	
☐	☐	Coronary Artery Disease	
☐	☐	Atrial Enlargement	
☐	☐	Cardiomyopathy	
☐	☐	Coagulopathy, specify: _____	
☐	☐	Myocardial Infarction	
☐	☐	Arrhythmias ☐ Not Treated ☐ Medically Treated ☐ Implantation of AICD / Pacemaker	
☐	☐	Congestive Heart Failure	
☐	☐	Endocarditis ☐ Active (within last 3 months) *(exclusion criteria)*	☐ Not Active
☐	☐	Pulmonary Hypertension	
☐	☐	Systemic Hypertension	
☐	☐	Tricuspid Insufficiency, Severity* :_____	
☐	☐	Aortic Insufficiency, Severity* :_____	
☐	☐	Aortic stenosis, Severity* :_____	
		*(*Severity: +1 Trivial/Trace, +2 Mild, +3 Moderate, +4 Severe)*	
☐	☐	Angina ☐ Stable ☐ Unstable	
☐	☐	Aortic Aneurysm	
☐	☐	Cardiomegaly	
☐	☐	Hypotension	
☐	☐	Pulmonary embolism	
☐	☐	Ventricular aneurysm	
☐	☐	Other, specify: _____	

FOR EDWARDS USE ONLY	CLINICAL REVIEW:		DATA MANAGEMENT:		
	FIRST REVIEW:	SECOND REVIEW: (OPTIONAL)	FIRST DATA ENTRY:	SECOND DATA ENTRY:	SUBEVENT # (OPTIONAL)
	BY:	BY:	BY:	BY:	
	DATE: __ __ __/__ __/__ __ __ __	DATE: __ __ __/__ __/__ __ __ __	DATE: __ __ __/__ __/__ __ __ __	DATE: __ __ __/__ __/__ __ __ __	

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | | Clinic # | | | |

7. PREOPERATIVE CARDIAC RHYTHM *(Check all that apply) ECG*

☐ Not Done ***(Complete Protocol Deviation)***

☐ Done Date: | | | | | | | | | | (D D M M M Y Y Y Y)

☐ Normal Sinus ☐ Atrial Fibrillation ☐ Atrial Flutter ☐ Paced

☐ AV Block *(Indicate degree)* ☐ 1st ☐ 2nd ☐ 3rd

☐ Bundle Branch Block *(Indicate branch)* ☐ Left ☐ Right

☐ Other, specify: _____

8. PREVIOUS PROCEDURES / MEDICATIONS

8a. Preoperative Valve Repair(s):

Yes	No	
☐	☐	Aortic
☐	☐	Mitral
☐	☐	Pulmonic
☐	☐	Tricuspid
☐	☐	Unknown

8b. Preoperative Valve Replacement(s):

Yes	No	
☐	☐	Aortic
☐	☐	Mitral
☐	☐	Pulmonic
☐	☐	Tricuspid
☐	☐	Unknown

NOTE: If a bioprosthesis or mechanical valve was previously implanted in the aortic, tricuspid and/or pulmonary position, which remains in situ, patient is ***EXCLUDED*.**

8c. Other Preoperative Cardiovascular Surgery:

Yes	No		
☐	☐	PTCA	
☐	☐	Endarterectomy	
☐	☐	CABG, Number of CABG: _____	Date:										(D D M M M Y Y Y Y)
☐	☐	Tricuspid	
☐	☐	Carotid Surgery	Date:										(D D M M M Y Y Y Y)
☐	☐	AICD Implant	
☐	☐	Pacemaker Implant	

White and Yellow: Return to Edwards Lifesciences, Clinical Affairs Pink: Retain for your Records

FOR EDWARDS USE ONLY	CLINICAL REVIEW:		DATA MANAGEMENT:		
	FIRST REVIEW:	SECOND REVIEW: (OPTIONAL)	FIRST DATA ENTRY:	SECOND DATA ENTRY:	SUBEVENT # (OPTIONAL)
	BY:	BY:	BY:	BY:	
	DATE: __ __ __/__ __/__ __ __ __	DATE: __ __ __/__ __/__ __ __ __	DATE: __ __ __/__ __/__ __ __ __	DATE: __ __ __/__ __/__ __ __ __	

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | | Clinic # | | | |

☐ ☐ Unknown

☐ ☐ Other, specify: _____

8d. Preoperative Antithromboembolic Therapy: (*Check all that apply)*

☐ None

☐ Anticoagulants (Heparin, Coumarine Derivates)

☐ Antiplatelets (Clopidogrel, Dipyridamole, Ticlopidine, Prasugrel)

☐ Aspirin (Acetylsalicylic Acid)

☐ Other, Specify:_____

9. ECHOCARDIOGRAPHY: (Within 6 months prior to implant date)

☐ No, not performed ***(Complete Protocol Deviation)***

☐ Yes, performed ***(Complete Echo Tracking Form and send form to Core Lab with Media)***

10. BLOOD DATA (Drawn within 30 days prior to implant date)

☐ Not Done ***(complete Protocol Deviation)*** ☐ Done Date: | | | | | | | | | | (D D M M M Y Y Y Y)

PREOPERATIVE COAGULATION PROFILE: ☐ NAP (No coumarine derivative treatment)

Int'l Normalized Ratio (INR) | | . | | | **OR** Partial Thromboplastin Time (PTT) | | | | . | | (sec)

ALWAYS COMPLETE A

A. ***BLOOD PARAMETER***	***VALUE***	***UNITS***	***WITHIN NORMAL RANGE?***		***IF NO, CLINICALLY SIGNIFICANT?***	
			YES	***NO***	***YES***	***NO***
WHITE BLOOD CELLS		(x 10^3/µL)	☐	☐	☐	☐
RED BLOOD CELLS		(x 10^6/µL)	☐	☐	☐	☐
HEMOGLOBIN		(gm/dL)	☐	☐	☐	☐
HEMATOCRIT		(%)	☐	☐	☐	☐
RETICULOCYTES		(%)	☐	☐	☐	☐
PLATELET COUNT		(x 10^3/µL)	☐	☐	☐	☐

FOR EDWARDS USE ONLY	CLINICAL REVIEW:		DATA MANAGEMENT:		
	FIRST REVIEW:	SECOND REVIEW: (OPTIONAL)	FIRST DATA ENTRY:	SECOND DATA ENTRY:	SUBEVENT # (OPTIONAL)
	BY:	BY:	BY:	BY:	
	DATE: __ __ __/__ __/__ __ __ __	DATE: __ __ __/__ __/__ __ __ __	DATE: __ __ __/__ __/__ __ __ __	DATE: __ __ __/__ __/__ __ __ __	

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | |

Clinic # | | | |

COMPLETE EITHER B OR C

B. ***BLOOD PARAMETER***	***VALUE***	***UNITS***	***WITHIN NORMAL RANGE?***		***IF NO, CLINICALLY SIGNIFICANT?***	
			YES	***NO***	***YES***	***NO***
PLASMA FREE HEMOGLOBIN		(mg/dL)	☐	☐	☐	☐

OR

C. ***BLOOD PARAMETER***	***VALUE***	***UNITS***	***WITHIN NORMAL RANGE?***		***IF NO, CLINICALLY SIGNIFICANT?***	
			YES	***NO***	***YES***	***NO***
HAPTOGLOBIN		(mg/dL)	☐	☐	☐	☐
SERUM LDH		(U/L)	☐	☐	☐	☐

ELEVATED SERUM LDH – FRACTIONED

LDH 1	LDH 2	LDH 3	LDH 4	LDH 5
(%)	(%)	(%)	(%)	(%)

PREGNANCY TEST

☐ NAP – *(subject is male, or female who is post-menopausal / surgically sterile)*

☐ Not Done (complete Protocol Deviation) ☐ Done Date: | | | | | | | | | |
D D M M M Y Y Y Y

Check one: ☐ Urine Test ☐ Blood Test

Results

☐ Positive (Complete Protocol Deviation Data)

☐ Negative

11. QUALITY OF LIFE SURVEY (EQ-5D): (Within 3 months prior to implant date)

☐ No, patient did not complete (Complete Protocol Deviation Data)

☐ Yes, patient completed (Complete QOL Survey Data)

Comments: _____

_____

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

_____ DATE SIGNED | | | | | | | | | |
INVESTIGATOR SIGNATURE D D M M M Y Y Y Y

FOR EDWARDS USE ONLY	CLINICAL REVIEW:		DATA MANAGEMENT:		
	FIRST REVIEW:	SECOND REVIEW: (OPTIONAL)	FIRST DATA ENTRY:	SECOND DATA ENTRY:	SUBEVENT # (OPTIONAL)
	BY:	BY:	BY:	BY:	
	DATE: __ __ __/__ __/__ __ __ __	DATE: __ __ __/__ __/__ __ __ __	DATE: __ __ __/__ __/__ __ __ __	DATE: __ __ __/__ __/__ __ __ __	

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | | Clinic # | | | |

1. IMPLANT DATE: | | | | | | | | | |
D D M M M Y Y Y Y

2. IMPLANTING SURGEON: _____

3. ETIOLOGY (Answer each Yes or No):

YES	NO	
☐	☐	Rheumatic
☐	☐	Degenerative
☐	☐	Congenital
☐	☐	Remote Endocarditis
☐	☐	Ischemic
☐	☐	Mitral Valve Prolapse
☐	☐	Failed Repair
☐	☐	Calcified

☐ Mild ☐ Moderate ☐ Severe ☐ Other, specify: _____

4. DIAGNOSIS FOR CURRENT REPLACEMENT (check one):

☐ Stenosis
☐ Regurgitation
☐ Mixed Disease (Stenosis and Regurgitation)
☐ Prosthetic Valve Dysfunction
☐ Other, specify: _____

5. PRE-IMPLANT CONDITION Answer each Yes or No:

5a. Anterior of Annulus:

YES	NO	
☐	☐	Normal
☐	☐	Calcified
☐	☐	Dilated

5b. Posterior of Annulus:

YES	NO	
☐	☐	Normal
☐	☐	Calcified
☐	☐	Dilated

FOR EDWARDS USE ONLY	Clinical Review:		Data Management:		
	First Review:	Second Review: (optional)	First Data Entry:	Second Data Entry:	Subevent # (optional)
	By:	By:	By:	By:	
	Date: __ __ __/__ __/__ __ __ __	Date:__ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | | Clinic # | | | |

5c. Chordae:

YES	NO	
☐	☐	Normal
☐	☐	Calcified
☐	☐	Elongation
☐	☐	Tethered
☐	☐	Ruptured

5d. LVOT:

YES	NO	
☐	☐	Normal
☐	☐	Obstructed

5e. LV Wall:

YES	NO	
☐	☐	Normal
☐	☐	Hypertrophic
☐	☐	Friable Tissue
☐	☐	Other, specify: _____

6. PREPARATION PROCEDURE:

6a. Debridement Procedure:

☐ None
☐ Full
☐ Partial

6b. Leaflets and Subvalvular Apparatus

☐ Preserved
☐ Partially Removed *(Specify):* _____
☐ Removed

7. STUDY VALVE IMPLANTATION:

7a Study Valve Implanted: ☐ Yes ☐ No, explain:_____

7b. Valve Size: _____ mm

7c. Tissue Annulus Diameter:

Magna Mitral Sizer *(requested)*:_____mm

Hegar Dilator *(optional)*: _____mm

7d. Valve Model No.

☐ 7000 ☐ 7000TFX ☐ 7200TFX ☐ 7300 ☐ 7300TFX

7e. Valve Serial No. _____

FOR EDWARDS USE ONLY	Clinical Review:		Data Management:		
	First Review:	Second Review: (optional)	First Data Entry:	Second Data Entry:	Subevent # (optional)
	By:	By:	By:	By:	
	Date: __ __ __/__ __/__ __ __ __	Date:__ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | | Clinic # | | | |

7f. Valve Position:

- ☐ Supra-annular
- ☐ Intra-annular

7g. Suture Technique:

- ☐ Everting Mattress
- ☐ Non-Everting Mattress
- ☐ Continuous
- ☐ Other, specify*:* _____

7h. Suture Pattern on Sewing Ring:

Anterior:
- ☐ Uniform Suture Bite Depth
- ☐ Non-Uniform Suture Bite Depth

Posterior:
- ☐ Uniform Suture Bite Depth
- ☐ Non-Uniform Suture Bite Depth

7i. Needle Penetration into Annulus:

- ☐ Easy

Difficult, because tissue is (check all that apply):

- ☐ Calcified
- ☐ Scarred / Fibrous
- ☐ Friable
- ☐ Other, specify*:* _____

7j. Sewing Cuff Compliance to Annulus:

Anterior:
- ☐ Complete
- ☐ Non-Complete but Satisfactory
- ☐ Non-Complete (Explant)

Posterior:
- ☐ Complete
- ☐ Non-Complete but Satisfactory
- ☐ Non-Complete (Explant)

7k. Pledgets:

☐ Yes ☐ No

7l. Difficulty in Seating Valve in Annulus

- ☐ No
- ☐ Yes *(Explain):* _____

FOR EDWARDS USE ONLY	Clinical Review:		Data Management:		
	First Review:	Second Review: (optional)	First Data Entry:	Second Data Entry:	Subevent # (optional)
	By:	By:	By:	By:	
	Date: __ __ __/__ __/__ __ __ __	Date:__ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | | Clinic # | | | |

7m. Anatomic Fit of Valve

- ☐ Restores Native Saddle Shape
- ☐ Reduces / Flattens Saddle Shape
- ☐ Other, specify: _____

7n. Coaptation of Leaflets After Seating in Annulus

- ☐ Complete
- ☐ Incomplete *(Explain):*_____

8. CONDITION OF THE VALVE BEING REPLACED:

YES	NO	
☐	☐	Calcification
☐	☐	Perforation
☐	☐	Myxomatous
☐	☐	Vegetation
☐	☐	Fusion
☐	☐	Other, specify: _____

9. SURGICAL APPROACH:

- ☐ Full Sternotomy
- ☐ Ministernotomy
- ☐ Other *(Specify):* _____

10. Total Cross Clamp Time of the Aorta				(min)
Pump Time				(min)

11. DIFFICULTY WEANING FROM BYPASS:

☐ No ☐ Yes ***(Please complete Adverse Events Form)**:*

FOR EDWARDS USE ONLY	Clinical Review:		Data Management:		
	First Review:	Second Review: (optional)	First Data Entry:	Second Data Entry:	Subevent # (optional)
	By:	By:	By:	By:	
	Date: __ __ __/__ __/__ __ __ __	Date:__ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | | Clinic # | | | |

12. CONCOMITANT PROCEDURES

YES NO

- ☐ ☐ Coronary Artery Bypass Grafting (*Number of Grafts):* _____
- ☐ ☐ Aneurysm Repair
- ☐ ☐ Permanent Pacemaker
- ☐ ☐ Aortic Valve Replacement *(Model Number):* _____ *Valve size:* _____ *mm*
- ☐ ☐ Aortic Valve / Annulus Repair
  - ☐ With Annuloplasty Ring / Band
  - ☐ Without Annuloplasty Ring / Band
- ☐ ☐ Pulmonic Valve / Annulus Repair
  - ☐ With Annuloplasty Ring / Band
  - ☐ Without Annuloplasty Ring / Band
- ☐ ☐ Tricuspid Valve / Annulus Repair
  - ☐ With Annuloplasty Ring / Band
  - ☐ Without Annuloplasty Ring / Band
- ☐ ☐ Ablation
- ☐ ☐ Maze Procedure
- ☐ ☐ Occlusion of Left Atrial Appendage
- ☐ ☐ Occlusion of Right Atrial Appendage
- ☐ ☐ Other, specify: _____

13. WERE THERE ANY INTRA-OPERATIVE ADVERSE EVENTS ☐ No ☐ Yes: ***(Please complete Adverse Events CRF)***

14. COMMENTS: _____

_____

_____

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

DATE SIGNED

D	D	M	M	M	Y	Y	Y	Y

_____
INVESTIGATOR SIGNATURE

White and Yellow: Return to Edwards Lifesciences, Clinical Affairs Pink: Retain for your Records

FOR EDWARDS USE ONLY	Clinical Review:		Data Management:		
	First Review:	Second Review: (optional)	First Data Entry:	Second Data Entry:	Subevent # (optional)
	By:	By:	By:	By:	
	Date: __ __ __/__ __/__ __ __ __	Date:__ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	

STUDY NUMBER 2006-05
CARPENTIER-EDWARDS PERIMOUNT MAGNA MITRAL EASE

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | | Clinic # | | | |

1. PATIENT STATUS: (attach discharge summary)

☐ **ALIVE, DISCHARGED ON**:

DISCHARGE DATE: | | | | | | | | | | (D D M M M Y Y Y Y)

PATIENT WAS NOT DISCHARGED WITH THIS DEVICE DUE TO:

☐ Explant ***(Complete explant, adverse event and study exit form)***
☐ Death ***(Complete adverse event and study exit form)***
☐ Other, specify*:*

2. CARDIAC RHYTHM: ***(Check all that apply) ECG***

☐ Not Done ***(Complete Protocol Deviation)***

☐ Done Date: | | | | | | | | | | (D D M M M Y Y Y Y)

☐ Normal Sinus ☐ Atrial Fibrillation ☐ Atrial Flutter ☐ Paced
☐ AV Block *(Indicate degree)* ☐ 1st ☐ 2nd ☐ 3rd
☐ Bundle Branch Block *(Indicate branch)* ☐ Left ☐ Right
☐ Other, specify: _____

3. PHYSICAL ASSESSMENT:

Heart Rate	| | |	(bpm)
Height	| | |	(cm)
Weight	| | |	(kg)

4. COAGULATION PROFILE

☐ Not Done ***(complete Protocol Deviation)*** ☐ Done Date: | | | | | | | | | | (D D M M M Y Y Y Y)

☐ NAP (No coumarine derivative treatment)

Int'l Normalized Ratio (INR) **OR** Partial Thromboplastin Time (PTT)

		.				.		(sec)

White and Yellow: Return to Edwards Lifesciences, Clinical Affairs Pink: Retain for your Records

FOR EDWARDS USE ONLY	Clinical Review:		Data Management:		
	First Review:	Second Review: (optional)	First Data Entry:	Second Data Entry:	Subevent # (optional)
	By:	By:	By:	By:	
	Date: __ __ __/__ __/__ __ __ __	Date:__ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | | Clinic # | | | |

5. ANTITHROMBOEMBOLIC THERAPY: ***(Check all that apply)***

- ☐ None
- ☐ Anticoagulants (Heparin, Coumarine Derivates)
- ☐ Antiplatelets (Clopidogrel, Dipyridamole, Ticlopidine, Prasugrel)
- ☐ Aspirin (Acetylsalicylic Acid)
- ☐ Other, specify:_____

6. WERE THERE ANY ADVERSE EVENTS? (*Not including Intra-operative complications – Complete AE Form)*

☐ No ☐ Yes

Comments: _____

_____

_____

7. ECHOCARDIOGRAPHY:

☐ No, not performed ***(Complete Protocol Deviation Data)***

☐ Yes, performed (***Complete Echo Tracking Form and send to Core Lab with Media)***

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

DATE SIGNED

D	D	M	M	M	Y	Y	Y	Y

_____
INVESTIGATOR SIGNATURE

White and Yellow: Return to Edwards Lifesciences, Clinical Affairs Pink: Retain for your Records

FOR EDWARDS USE ONLY	Clinical Review:		Data Management:		
	First Review:	Second Review: (optional)	First Data Entry:	Second Data Entry:	Subevent # (optional)
	By:	By:	By:	By:	
	Date: __ __ __/__ __/__ __ __ __	Date:__ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | | Clinic # | | | |

1. ASSESSMENT DATE: | | | | | | | | | | |
D D M M M Y Y Y Y

2. FOLLOW-UP INTERVAL:

- ☐ 6 Month (3 – 6 months)
- ☐ 1 Year (11 – 13 months)
- ☐ 2 Years (23 – 25 months)
- ☐ 3 Years (35 – 37 months)
- ☐ 4 Years (47 – 49 months)
- ☐ 5 Years (59 – 61 months)
- ☐ 6 Years (71 – 73 months)
- ☐ 7 Years (83 – 85 months)
- ☐ 8 Years (95 – 97 months)
- ☐ Other, specify: ___ ☐ Months ☐ Years

3. VISIT STATUS:

Conducted visit: ***(Check one only)***

- ☐ Office Visit / Clinic / Outpatient/ Hospital
- ☐ In-patient Admission
- ☐ Phone (*from whom):*_____
  specify relationship
- ☐ Letter (*from whom):*_____
  specify relationship

OR

Missed visit: ***(Check Only One)***

- ☐ Scheduled, patient missed
- ☐ Unable to contact patient
- ☐ Other (*Explain*): _____

4. PATIENT STATUS:

- ☐ Alive
- ☐ Explant ***(Complete explant, adverse event and study exit form)***
- ☐ Death ***(Complete adverse event and study exit form)***
- ☐ Withdrawn (Reason): _____
- ☐ Other, specify: _____

FOR EDWARDS USE ONLY	Clinical Review:		Data Management:		
	First Review:	Second Review: (optional)	First Data Entry:	Second Data Entry:	Subevent # (optional)
	By:	By:	By:	By:	
	Date: __ __ __/__ __/__ __ __ __	Date:__ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | | Clinic # | | | |

ASSESSMENT DATE: | | | | | | | | | | |
D D M M M Y Y Y Y

5. PHYSICAL ASSESSMENT:

Heart Rate		(bpm)
Weight		(kg)
Blood Pressure	/	mmHg

6. PREOPERATIVE CARDIAC RHYTHM *(Check all that apply) ECG*

☐ Not Done ***(Complete Protocol Deviation)***

☐ Done Date: | | | | | | | | | |
D D M M M Y Y Y Y

☐ Normal Sinus ☐ Atrial Fibrillation ☐ Atrial Flutter ☐ Paced

☐ AV Block *(Indicate degree)* ☐ 1st ☐ 2nd ☐ 3rd

☐ Bundle Branch Block *(Indicate branch)* ☐ Left ☐ Right

☐ Other, specify: _____

7. NYHA FUNCTIONAL CLASS:

☐ Class I ☐ Class II ☐ Class III ☐ Class IV ☐ NAV

8. ANTITHROMBOEMBOLIC THERAPY: *(Check all that apply)*

☐ None

☐ Anticoagulants (Heparin, Coumarine Derivates)

☐ Antiplatelets (Clopidogrel, Dipyridamole, Ticlopidine, Prasugrel)

☐ Aspirin (Acetylsalicylic Acid)

☐ Other, specify:_____

9. WERE THERE ANY ADVERSE EVENTS? (*Since Last Assessment including Death and Explant)*

☐ No ☐ Yes

10. ECHOCARDIOGRAPHY: *(Required at 6-month, 1, 2, 4, 6 and 8 year follow-up visits)*

☐ No, not performed ***(Complete Protocol Deviation Data)***

☐ Yes, performed ***(Complete Echo Tracking Form and send to Core Lab with Media)***

☐ Not required at this visit

FOR EDWARDS USE ONLY	Clinical Review:		Data Management:		
	First Review:	Second Review: (optional)	First Data Entry:	Second Data Entry:	Subevent # (optional)
	By:	By:	By:	By:	
	Date: __ __ __/__ __/__ __ __ __	Date:__ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	

Patient Study ID # 2 0 0 6 0 5 | | | | | Clinic # | | |

ASSESSMENT DATE: | | | | | | | | | | (D D M M M Y Y Y Y)

11. BLOOD DATA

☐ Not Done ***(complete Protocol Deviation)*** ☐ Done Date: | | | | | | | | | | (D D M M M Y Y Y Y)

PREOPERATIVE COAGULATION PROFILE: ☐ NAP (No coumarine derivative treatment)

Int'l Normalized Ratio (INR) | | . | | | **OR** Partial Thromboplastin Time (PTT) | | | . | | (sec)

COMPLETE SECTION A

A. BLOOD PARAMETER	***VALUE***	***UNITS***	***WITHIN NORMAL RANGE?***		***IF NO, CLINICALLY SIGNIFICANT?***	
			YES	***NO***	***YES***	***NO***
WHITE BLOOD CELLS		(x 10^3/µL)	☐	☐	☐	☐
RED BLOOD CELLS		(x 10^6/µL)	☐	☐	☐	☐
HEMOGLOBIN		(gm/dL)	☐	☐	☐	☐
HEMATOCRIT		(%)	☐	☐	☐	☐
RETICULOCYTES		(%)	☐	☐	☐	☐
PLATELET COUNT		(x 10^3/µL)	☐	☐	☐	☐

COMPLETE SECTION B OR C

B. BLOOD PARAMETER	***VALUE***	***UNITS***	***WITHIN NORMAL RANGE?***		***IF NO, CLINICALLY SIGNIFICANT?***	
			YES	***NO***	***YES***	***NO***
PLASMA FREE HEMOGLOBIN		(mg/dL)	☐	☐	☐	☐

FOR EDWARDS USE ONLY	Clinical Review:		Data Management:		
	First Review:	Second Review: (optional)	First Data Entry:	Second Data Entry:	Subevent # (optional)
	By:	By:	By:	By:	
	Date: __ __ __/__ __/__ __ __ __	Date:__ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | |

Clinic # | | | |

ASSESSMENT DATE: | | | | | | | | | |
D D M M M Y Y Y Y

OR

C. BLOOD PARAMETER	***VALUE***	***UNITS***	***WITHIN NORMAL RANGE?***		***IF NO, CLINICALLY SIGNIFICANT?***	
			YES	***NO***	***YES***	***NO***
HAPTOGLOBIN		(mg/dL)	☐	☐	☐	☐
SERUM LDH		(U/L)	☐	☐	☐	☐

12. QUALITY OF LIFE SURVEY: (Required at 6 Month Follow-up Only)

- ☐ Not Appplicable at this follow-up interval
- ☐ No, patient did not complete at 6 Month ***(Complete Protocol Deviation Data)***
- ☐ Yes, patient completed ***(Complete QOL Survey Data)***

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

DATE SIGNED | | | | | | | | | |
D D M M M Y Y Y Y

INVESTIGATOR SIGNATURE

FOR EDWARDS USE ONLY	Clinical Review:		Data Management:		
	First Review:	Second Review: (optional)	First Data Entry:	Second Data Entry:	Subevent # (optional)
	By:	By:	By:	By:	
	Date: __ __ __/__ __/__ __ __ __	Date:__ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	

Patient Study ID# | 2 | 0 | 0 | 6 | 0 | 5 | - | | | | |

Clinic # | | | |

RECORD ONLY ONE ADVERSE EVENT PER FORM

1. **EVENT ONSET DATE** | | | | | | | | | | D D M M M Y Y Y Y ☐ INITIAL REPORT ☐ FINAL REPORT

2. **TIMING OF EVENT ONSET** ☐ PRE-OPERATIVE ☐ INTRA-OPERATIVE ☐ POST-OPERATIVE

3. **EVENT NAME (SEE EVENT LISTING)** _____

4. **EVENT SUMMARY** _____

_____

_____

5. **METHOD OF DETECTION (**CHECK ALL THAT APPLY) ☐ LAB FINDING ☐ IMAGING ☐ ECG ☐ AUTOPSY ☐ OBSERVATION
☐ OTHER (SPECIFY) _____ ☐ EXAM ☐ NONE AVAILABLE

6. **CAUSALITY**

SURGICAL PROCEDURE	☐ YES	☐ NO	☐ UNDETERMINED
STUDY VALVE	☐ YES	☐ NO	☐ UNDETERMINED
STUDY VALVE PROCEDURE	☐ YES	☐ NO	☐ UNDETERMINED
USE ERROR	☐ YES	☐ NO	☐ UNDETERMINED
DEFICIENCY IN INSTRUCTIONS	☐ YES	☐ NO	☐ UNDETERMINED
DEVICE DEPLOYMENT ISSUE	☐ YES	☐ NO	☐ UNDETERMINED
OTHER*	☐ YES	☐ NO	☐ UNDETERMINED

IF "OTHER" IS YES, PROVIDE REASON: _____

_____

7. **MEDICATION CONTRIBUTING TO EVENT?**

CHECK "YES" ONLY IF MED CONTRIBUTED TO EVENT

☐ YES ☐ NO

IF BLEEDING EVENT CHECK CATEGORY BELOW

☐ ANTICOAGULANT MED
☐ ANTIPLATELET MED
☐ ASPIRIN
☐ CO-ENZYME Q10
☐ OTHER (SPECIFY) _____

8. **SERIOUS ADVERSE EVENT** ☐ YES ☐ NO

☐ RESULTED IN DEATH
☐ RESULTED IN LIFE-THREATENING ILLNESS OR INJURY
☐ RESULTED IN PERMANENT IMPAIRMENT
☐ RESULTED IN HOPSITALIZATION OR PROLONGING OF CURRENT HOSPITALIZATION
☐ RESULTED IN SURGICAL INTERVENTION TO PREVENT PERMANENT IMPAIRMENT TO BODY STRUCTURE OR FUNCTION
☐ RESULTED IN FETAL DISTRESS OR DEATH, CONGENITAL ABNORMALITY OR BIRTH DEFECT
☐ RESULTED IN OTHER (SPECIFY) _____

9. **UNANTICIPATED*** ☐ YES ☐ NO ☐ NOT APPLICABLE

QUESTION ONLY APPLIES IF **EVENT IS DEEMED RELATED TO STUDY VALVE OR STUDY VALVE PROCEDURE OR RELATIONSHIP IS UNDETERMINED*

White and Yellow: Return to Edwards Lifesciences, Clinical Affairs Pink: Retain for your Records

FOR EDWARDS USE ONLY	CLINICAL REVIEW:		DATA MANAGEMENT:		
	FIRST REVIEW:	SECOND REVIEW: (OPTIONAL)	FIRST DATA ENTRY:	SECOND DATA ENTRY:	SUBEVENT # (OPTIONAL)
	BY:	BY:	BY:	BY:	
	DATE: __ __ __/__ __/__ __ __ __	DATE:__ __ __/__ __/__ __ __ __	DATE: __ __ __/__ __/__ __ __ __	DATE: __ __ __/__ __/__ __ __ __	

Patient Study ID# | 2 | 0 | 0 | 6 | 0 | 5 | - | | | | |

Clinic # | | | |

EVENT ONSET DATE | | | | | | | | | |
D D M M M Y Y Y Y

10. INTERVENTION (*MULTIPLE RESPONSS POSSIBLE*)

- ☐ NONE
- ☐ PROLONGED HOSPITALIZATION
- ☐ RE-HOSPITALIZATION REQUIRED
- ☐ CARDIOVERSION
- ☐ TRANSFUSION
- ☐ MEDICATION GIVEN, SPECIFY _____
- ☐ PACEMAKER/ICD IMPLANT (NOT PLANNED PRIOR TO AVR - PROVIDE DATE) | | | | | | | | | |
  D D M M M Y Y Y Y
- ☐ SURGICAL INTERVENTION, REOP ON STUDY VALVE OR OTHER INTERVENTION ON STUDY VALVE (SEE EXPLANT REPORT)
- ☐ OTHER INVASIVE INTERVENTION (RE-OP NON VALVE RELATED) | | | | | | | | | |
  D D M M M Y Y Y Y
  (*SPECIFY BELOW – PROVIDE DATE*)

  SPECIFY OTHER INVASIVE INTERVENTION _____

11. OUTCOME

- ☐ ONGOING
- ☐ UNRESOLVED AT STUDY EXIT
- ☐ CHRONIC CONDITION
- ☐ RESOLVED WITH OUT SEQUELAE DATE: | | | | | | | | | |
  D D M M M Y Y Y Y
- ☐ RESOLVED WITH SEQUELAE DATE: | | | | | | | | | |
  D D M M M Y Y Y Y
- ☐ EXPLANT (COMPLETE EXPLANT FORM)
- ☐ DEATH (COMPLETE EXIT FORM) DATE: | | | | | | | | | |
  D D M M M Y Y Y Y

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

DATE SIGNED | | | | | | | | | |
D D M M M Y Y Y Y

INVESTIGATOR SIGNATURE

White and Yellow: Return to Edwards Lifesciences, Clinical Affairs Pink: Retain for your Records

FOR EDWARDS USE ONLY	CLINICAL REVIEW:		DATA MANAGEMENT:		
	FIRST REVIEW:	SECOND REVIEW: (OPTIONAL)	FIRST DATA ENTRY:	SECOND DATA ENTRY:	SUBEVENT # (OPTIONAL)
	BY:	BY:	BY:	BY:	
	DATE: __ __ __/__ __/__ __ __ __	DATE:__ __ __/__ __/__ __ __ __	DATE: __ __ __/__ __/__ __ __ __	DATE: __ __ __/__ __/__ __ __ __	

Edwards

Study Number 2006-05
Carpentier-Edwards PERIMOUNT Magna Mitral Valve

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | |

Clinic # | | | |

1. DATE OF EXPLANT: | | | | | | | | | |
D D M M M Y Y Y Y

2. DEVICE WAS EXPLANTED: ***(Complete adverse event and study exit form)***

☐ At re-operation
☐ At autopsy
☐ Other:_____

3. REASON FOR EXPLANT:

☐ SVD ☐ NSVD ☐ Other, Specify: _____

4. DEVICE WAS RETURNED TO EDWARDS:

☐ YES ☐ NO

5. REPLACEMENT VALVE: ☐ **Not Applicable (Autopsy)** _____ **Manufacturer** _____ **Size**

6. DEVICE EVALUATION:

	No	Yes	Comment
Thrombus	☐	☐	
Vegetation	☐	☐	
Suture Interference	☐	☐	
Instrument Trauma	☐	☐	
Calcification	☐	☐	
Fibrosis	☐	☐	
Dehiscence	☐	☐	
Pannus	☐	☐	
Other	☐	☐	

COMMENTS: _____

_____

_____

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

DATE SIGNED

_____ | | | | | | | | | |
INVESTIGATOR SIGNATURE D D M M M Y Y Y Y

White and Yellow: Return to Edwards Lifesciences, Clinical Affairs Pink: Retain for your Records

FOR EDWARDS USE ONLY	Clinical Review:		Data Management:		
	First Review:	Second Review: (optional)	First Data Entry:	Second Data Entry:	Subevent # (optional)
	By:	By:	By:	By:	
	Date: __ __ __/__ __/__ __ __ __	Date:__ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | | Patient Initials (First, Last) | | | Clinic # | | |

Please Provide The Following Information:

1. ECHO DATE: | | | | | | | | | |
D D M M M Y Y Y Y

2. TIME PERIOD: ***(Required preoperatively, at discharge, 6-months, 1, 2, 4, 6 and 8 year follow-up visits)***

- ☐ Preoperatively (≤ 6 months prior to implant)
- ☐ Discharge or 30 days
- ☐ 1 Year (11 – 13 months)
- ☐ 2 Years (23 – 25 months)
- ☐ 4 Years (47 – 49 months)
- ☐ 4 Years (47 – 49 months)
- ☐ 6 Years (71 – 73 months)
- ☐ 8 Years (95 – 97 months))
- ☐ Other, specify: ____ ☐ Months ☐ Years

3. ECHO RECORDED ON (MEDIA):

☐ Tape ☐ CD
☐ MOD ☐ DVD

4. REASON FOR ECHO:

- ☐ Per protocol
- ☐ Symptomatic, study valve related
- ☐ Symptomatic, non-study valve related
- ☐ Other, specify: _____

5. PHYSICAL ASSESSMENT:

Heart Rate	| | |	(bpm)
Height	| | |	(cm)
Weight	| | |	(kg)
Blood Pressure	| | | / | | |	mmHg

DATE MEDIA SENT: | | | | | | | | | |
D D M M M Y Y Y Y

(**OR COLLECTED BY MONITOR**)

I have reviewed and approved all information on this form. *(Investigator's Signature)* Date

White and Yellow: Return to EDWARDS Edwards CVS Pink: Retain for your Records

FOR BAXTER USE ONLY	Clinical Audit		Tracked: _____	
	First Audit	Second Audit	Data Entered	
	By:	By:	By:	Date: __ __ / __ __ / __ __ __ __
	Date: __ __ / __ __ / __ __ __ __	Date: __ __ / __ __ / __ __ __ __	By:	Date: __ __ / __ __ / __ __ __ __

Edwards

STUDY NUMBER 2006-05

CARPENTIER-EDWARDS PERIMOUNT MAGNA MITRAL VALVE

PROTOCOL DEVIATION

FORM 11.0

Patient Study ID# | 2 | 0 | 0 | 6 | 0 | 5 | - | | | | |

Clinic # | | | |

COMPLETE FORM IN THE EVENT OF DEVIATION FROM STUDY PROTOCOL
PROTOCOL DEVIATION CODES CAN BE FOUND IN CRF COMPLETION INSTRUCTIONS

1. DEVIATION CODE _____ DATE OF DEVIATION | | | | | | | | | | (D D M M M Y Y Y Y)

☐ OTHER, SPECIFY _____

REASON: _____

2. DEVIATION CODE _____ DATE OF DEVIATION | | | | | | | | | | (D D M M M Y Y Y Y)

☐ OTHER, SPECIFY _____

REASON: _____

3. DEVIATION CODE _____ DATE OF DEVIATION | | | | | | | | | | (D D M M M Y Y Y Y)

☐ OTHER, SPECIFY _____

REASON: _____

4. DEVIATION CODE _____ DATE OF DEVIATION | | | | | | | | | | (D D M M M Y Y Y Y)

☐ OTHER, SPECIFY: _____

REASON: _____

5. DEVIATION CODE _____ DATE OF DEVIATION | | | | | | | | | | (D D M M M Y Y Y Y)

☐ OTHER, SPECIFY: _____

REASON: _____

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

DATE | | | | | | | | | | (D D M M M Y Y Y Y)

_____

INVESTIGATOR SIGNATURE

White and Yellow: Return to Edwards Lifesciences, Clinical Affairs Pink: Retain for your Records

FOR EDWARDS USE ONLY	CLINICAL REVIEW:		DATA MANAGEMENT:		
	FIRST REVIEW:	SECOND REVIEW: (OPTIONAL)	FIRST DATA ENTRY:	SECOND DATA ENTRY:	SUBEVENT # (OPTIONAL)
	BY:	BY:	BY:	BY:	
	DATE: __ __ __/__ __/__ __ __ __	DATE:__ __ __/__ __/__ __ __ __	DATE: __ __ __/__ __/__ __ __ __	DATE: __ __ __/__ __/__ __ __ __	

Study Number 2006-05

Carpentier-Edwards PERIMOUNT Magna Mitral Valve

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | |

Clinic # | | | |

Date of Assessment: | | | | | | | | | |
D D M M M Y Y Y Y

Assessment Interval:

☐ Baseline/Pre-operative
☐ 6 month

1. Mobility (Indicate which statement the subject marked on the survey)

☐ I have no problem in walking about
☐ I have some problems in walking about
☐ I am confined to bed

2. Self-Care (Indicate which statement the subject marked on the survey)

☐ I have no problem with self-care
☐ I have some problems washing or dressing myself
☐ I am unable to wash or dress myself

3. Usual Activities (Indicate which statement the subject marked on the survey)

☐ I have no problem with performing my usual activities
☐ I have some problems with performing my usual activities
☐ I am unable to perform my usual activities

4. Pain / Discomfort (Indicate which statement the subject marked on the survey)

☐ I have no pain or discomfort
☐ I have moderate pain or discomfort
☐ I have extreme pain or discomfort

5. Anxiety / Depression (Indicate which statement the subject marked on the survey)

☐ I am not anxious or depressed
☐ I am moderately anxious or depressed
☐ I am extremely anxious or depressed

6. Overall state (Indicate how the subject rated their overall heath today)

Score: _____

Comment: _____

_____

_____

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

DATE SIGNED

| | | | | | | | | |
D D M M M Y Y Y Y

INVESTIGATOR SIGNATURE

White and Yellow: Return to Edwards Lifesciences, Clinical Affairs Pink: Retain for your Records

FOR EDWARDS USE ONLY	Clinical Review:		Data Management:		
	First Review:	Second Review: (optional)	First Data Entry:	Second Data Entry:	Subevent # (optional)
	By:	By:	By:	By:	
	Date: __ __ __/__ __/__ __ __ __	Date:__ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	

Study Number 2006-05

Carpentier-Edwards PERIMOUNT Magna Mitral Valve

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | |

Clinic # | | | |

1. DATE OF LAST PATIENT CONTACT: | | | | | | | | | |
D D M M M Y Y Y Y

2. REASON FOR STUDY EXIT:

- ☐ Screen Failure ***(Complete Form 1: Patient Selection Data) (Signed ICF and did not receive implant)***
- ☐ Completed all study assessments
- ☐ Terminated by Investigator (specify reason in #4)

Voluntary Withdrawal

- ☐ Met enrollment criteria and withdrawn for medical reasons
- ☐ Met enrollment criteria and withdrawn for non medical reasons

- ☐ Lost to Follow-up (unable to contact) ***(Complete Assessment Form)***
- ☐ Death ***(Complete adverse event form)***
- ☐ Device Explanted ***(Complete Explant Data)***
- ☐ Other (specify in #4)

3. STUDY INTERVALS COMPLETED: *(check all that apply)*

- ☐ Preoperative Assessment
- ☐ Device Implant
- ☐ Hospital Discharge
- ☐ 3 – 6 month follow-up assessment
- ☐ 1 year follow-up assessment
- ☐ 2 year follow-up assessment
- ☐ 3 year follow-up assessment
- ☐ 4 year follow-up assessment
- ☐ 5 year follow-up assessment
- ☐ 6 year follow-up assessment
- ☐ 7 year follow-up assessment
- ☐ 8 year follow-up assessment

4. DESCRIBE THE PATIENT'S CONDITION AT LAST VISIT:

_____

_____

_____

_____

_____

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

DATE SIGNED

| | | | | | | | | |
D D M M M Y Y Y Y

_____
INVESTIGATOR SIGNATURE

White and Yellow: Return to Edwards Lifesciences, Clinical Affairs Pink: Retain for your Records

FOR EDWARDS USE ONLY	Clinical Review:		Data Management:		
	First Review:	Second Review: (optional)	First Data Entry:	Second Data Entry:	Subevent # (optional)
	By:	By:	By:	By:	
	Date: __ __ __/__ __/__ __ __ __	Date:__ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	Date: __ __ __/__ __/__ __ __ __	

17.0 APPENDIX 6: QUALITY OF LIFE SURVEY

User Guide

Prepared by:

Mark Oppe
Rosalind Rabin
Frank de Charro

On behalf of the EuroQoL Group

Version 1.0

August 2008

Web: www.euroqol.org
Email: userinformationservice@euroqol.org

Table of contents

1. INTRODUCTION 3

EUROQOL GROUP 3

EQ-5D 4

WHAT IS A HEALTH STATE? 7

VERSIONS OF EQ-5D 8

2. SCORING THE EQ-5D DESCRIPTIVE SYSTEM 9

3. SCORING THE EQ VAS 10

4. CONVERTING EQ-5D STATES TO A SINGLE SUMMARY INDEX 11

5. ORGANISING EQ-5D DATA 12

6. PRESENTING EQ-5D RESULTS 13

HEALTH PROFILES 13

EQ VAS 15

EQ-5D INDEX 16

7. EQ-5D: FREQUENTLY ASKED QUESTIONS 19

8. ADDITIONAL INFORMATION 22

1. Introduction

This guide has been developed in order to give users of EQ-5D basic information on how to use EQ-5D. Topics include administering the instrument, setting up a database for data collected using EQ-5D as well as information about how to present the results. Also included are some frequently asked questions dealing with common issues regarding the use of EQ-5D and a list of currently available EuroQoL products.

EuroQoL Group

- The EuroQoL Group is a network of international multidisciplinary researchers devoted to the measurement of health status. Established in 1987, the EuroQoL Group originally consisted of researchers from Europe, but nowadays includes members from North America, Asia, Africa, Australia, and New Zealand. The Group is responsible for the development of EQ-5D, a preference based measure of health status that is now widely used in clinical trials, observational studies and other health surveys.

- The EuroQoL Group has been holding annual scientific meetings since its inception in 1987.

- The EuroQoL Group can be justifiably proud of its collective scientific achievements over the last 20 years. Research areas include: valuation, EQ-5D use in clinical studies and in population surveys, experimentation with the EQ-5D descriptive system, computerized applications, interpretation of EQ-5D ratings and the role of EQ-5D in measuring social inequalities in self-reported health.

- The EuroQoL Group's website (www.euroqol.org) contains detailed information about EQ-5D, guidance for users, a list of available language versions, EQ-5D references and contact details.

EQ-5D

EQ-5D is a standardised measure of health status developed by the EuroQoL Group in order to provide a simple, generic measure of health for clinical and economic appraisal[1]. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys (Figure 1).

EQ-5D is designed for self-completion by respondents and is ideally suited for use in postal surveys, in clinics, and in face-to-face interviews. It is cognitively undemanding, taking only a few minutes to complete. Instructions to respondents are included in the questionnaire.

EQ-5D essentially consists of 2 pages - the EQ-5D descriptive system (page 2) and the EQ visual analogue scale (EQ VAS) (page 3). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, severe problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. **It should be noted that the numerals 1-3 have no arithmetic properties and should not be used as a cardinal score.** This current 3-level, 5-dimensional format of EQ-5D will remain unchanged for the immediate future. However a EuroQoL task force is developing a 5-level version. This should become available around 2009.

The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

[1] EuroQoL Group. EuroQoL-a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208

Figure 1: EQ-5D (UK English version)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

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

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

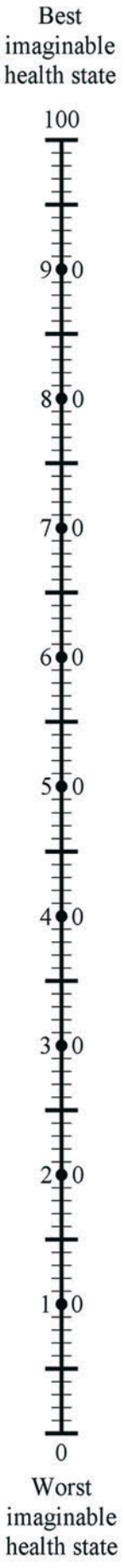
Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



What is a health state?

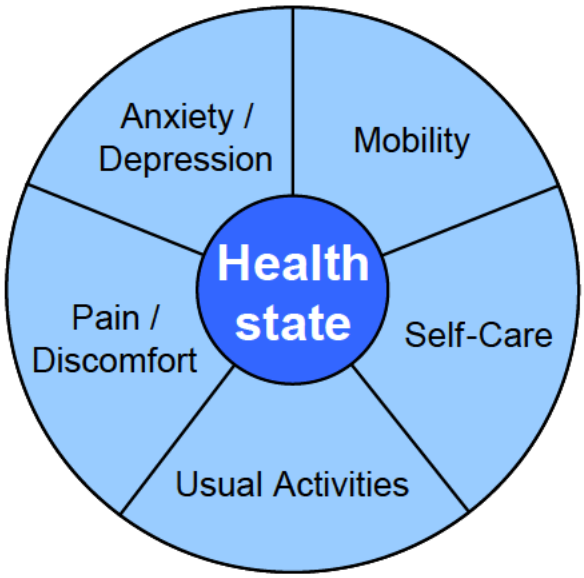
Each of the 5 dimensions comprising the EQ-5D descriptive system is divided into 3 levels of perceived problems:

Level 1: indicating no problem

Level 2: indicating some problems

Level 3: indicating extreme problems

A unique health state is defined by combining 1 level from each of the 5 dimensions.



A total of 243 possible health states is defined in this way. Each state is referred to in terms of a 5 digit code. For example, state 11111 indicates no problems on any of the 5 dimensions, while state 11223 indicates no problems with mobility and self care, some problems with performing usual activities, moderate pain or discomfort and extreme anxiety or depression.

Note: Two further states (unconscious and death) are included in the full set of 245 EQ-5D health states, but information on these states is not collected via self-report.

Versions of EQ-5D

EQ-5D in different languages

Currently there are more than 100 translated versions of EQ-5D. If you want to know if there is an EQ-5D version appropriate for your country, please consult the website.

All translations/adaptations of EQ-5D are produced using a standardised translation protocol that conforms to internationally recognized guidelines. These guidelines aim to ensure semantic and conceptual equivalence and involve a forward/backward translation process and lay panel assessment. Only the EuroQoL Group Executive Office can give permission for a translation to be performed and translations can only be stamped as official if they are performed in cooperation with EuroQoL Group reviewers.

Alternative modes of administration

EQ-5D was primarily designed for self-completion by the patient or respondent. However the Group has brief guidelines for the following alternative modes of administration:

(i) Face-to-face
(ii) Self-completion in the presence of an interviewer
(iii) Telephone interview
(iv) Proxy (asking the proxy to rate how he or she, (i.e. the proxy), would rate the subject's health)

Guidelines for telephone and proxy use are available in a number of different languages.

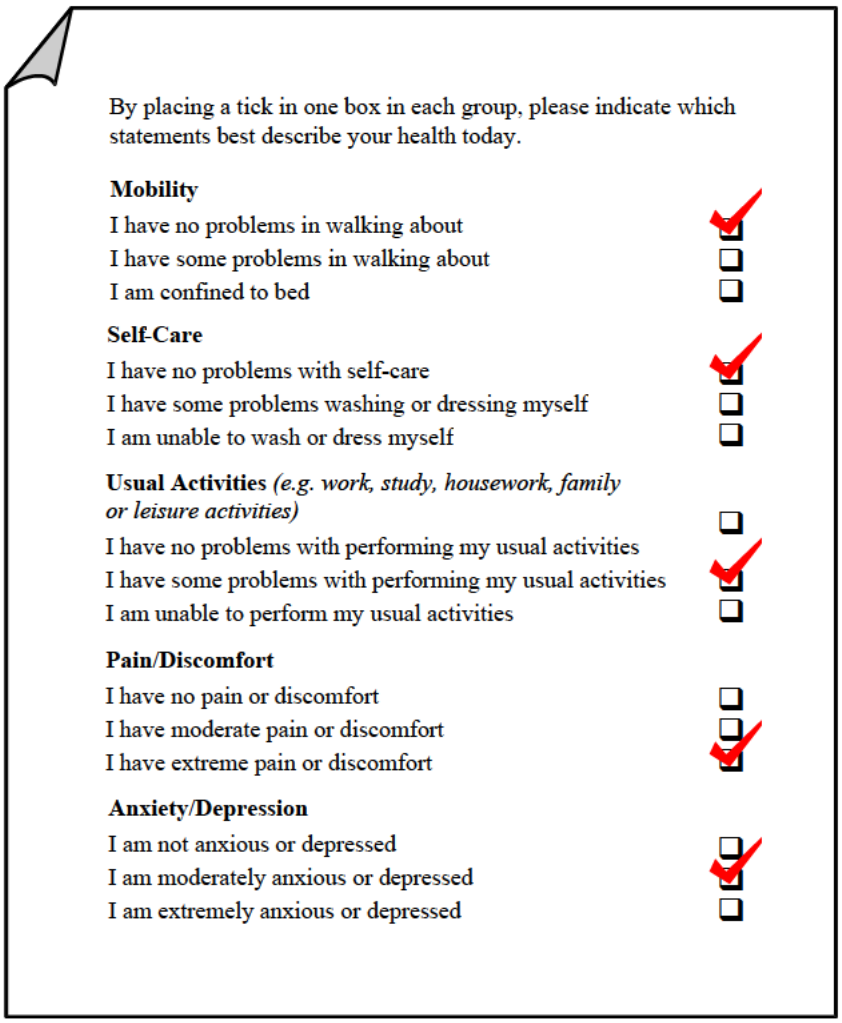
Child versions

EQ-5D is generally considered suitable for children aged 12 years and over (although this may vary in different countries). Currently a EuroQoL Group task force is developing a version for children between 7 and 12 years in international English. This version is being validated in Swedish, Italian, Spanish and German and these versions should become available in 2008.

Please check the EuroQoL website for up-to-date information on the availability of EuroQoL products.

2. Scoring the EQ-5D descriptive system

The EQ-5D descriptive system should be scored as follows:



By placing a tick in one box in each group, please indicate which statements best describe your health today.

Mobility
- I have no problems in walking about ☑
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care
- I have no problems with self-care ☑
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities *(e.g. work, study, housework, family or leisure activities)*
- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☑
- I am unable to perform my usual activities ☐

Pain/Discomfort
- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☑

Anxiety/Depression
- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☑
- I am extremely anxious or depressed ☐

Levels of perceived problems are coded as follows:

☑ ☐ ☐ Level 1 is coded as a '1'

☐ ☑ ☐ Level 2 is coded as a '2'

☐ ☐ ☑ Level 3 is coded as a '3'

NB: There should be only <u>one</u> response for each dimension.

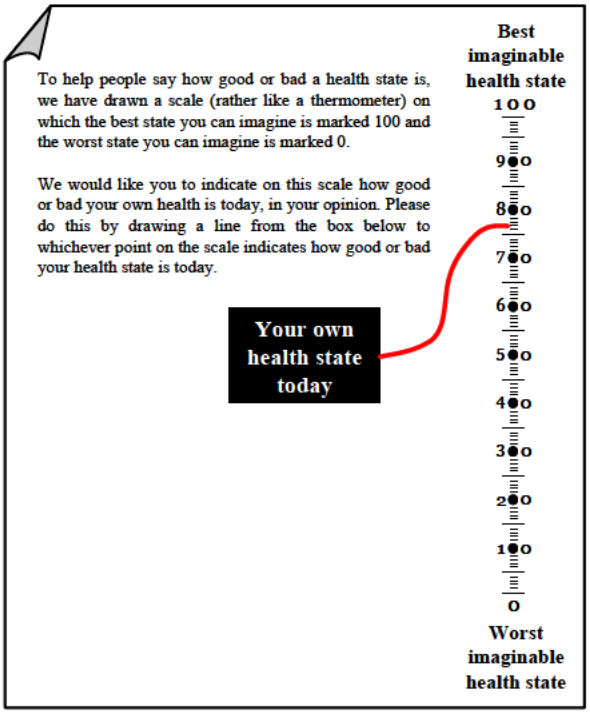
This example identifies the state 11232.

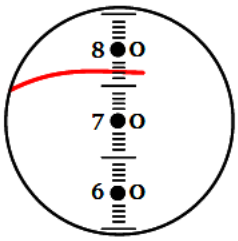
Missing values can be coded as '9'.

Ambiguous values (e.g. 2 boxes are ticked for a single dimension) should be treated as missing values.

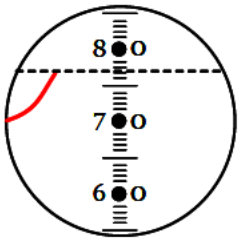
3. Scoring the EQ VAS

The EQ VAS should be scored as follows:





For example this response should be coded as 77



Even though the line does not cross the VAS this response can still be scored by drawing a horizontal line from the end point of the response to the VAS. In this example the response should be coded as 77

Missing values should be coded as '999'.

Ambiguous values (e.g. the line crosses the VAS twice) should be treated as missing values.

4. Converting EQ-5D states to a single summary index

EQ-5D health states, defined by the EQ-5D descriptive system, may be converted into a single summary index by applying a formula that essentially attaches values (also called weights) to each of the levels in each dimension. The index can be calculated by deducting the appropriate weights from 1, the value for full health (i.e. state 11111). Information in this format is useful, for example, in cost utility analysis.

Value sets have been derived for EQ-5D in several countries using the EQ-5D visual analogue scale (EQ-5D VAS) valuation technique or the time trade-off (TTO) valuation technique. The list of currently available value sets with the number of respondents and valuation technique applied is presented in table 1. Most of the EQ-5D value sets have been obtained using a representative sample of the general population, thereby ensuring that they represent the societal perspective. For anyone working with EQ-5D data, an essential guide to the Group's available value sets can be found in: EuroQoL Group Monograph series: Volume 2: EQ-5D value sets: inventory, comparative review and user guide, recently published by Springer (see section 8 for more information).

Table 1: List of available value sets as of May 2007

Country	N	Valuation method
Belgium	548	EQ-5D VAS
Denmark	1179	EQ-5D VAS
Denmark	1332	TTO
Europe	6870	EQ-5D VAS
Finland	928	EQ-5D VAS
Germany	339	EQ-5D VAS
Germany	339	TTO
Japan	543	TTO
New Zealand	919	EQ-5D VAS
Netherlands	298	TTO
Slovenia	370	EQ-5D VAS
Spain	294	EQ-5D VAS
Spain	975	TTO
UK	3395	EQ-5D VAS
UK	3395	TTO
US	3773	TTO
Zimbabwe	2384	TTO

Documents containing the scoring algorithms, information on the valuation studies, tables of values for all 243 health states and SPSS and SAS syntax files can be ordered from the EuroQoL Executive Office (userinformationservice@euroqol.org).

5. Organising EQ-5D data

Data collected using EQ-5D can be entered in a database according to the following schema:

Variable name	ID	COUNTRY	YEAR	MOBILITY	SELFCARE	ACTIVITY	PAIN	ANXIETY
Variable description	patient ID number			1=No Problems, 2=Some problems, 3=Extreme problems, 9=Missing value	1=No Problems, 2=Some problems, 3=Extreme problems, 9=Missing value	1=No Problems, 2=Some problems, 3=Extreme problems, 9=Missing value	1=No Problems, 2=Some problems, 3=Extreme problems, 9=Missing value	1=No Problems, 2=Some problems, 3=Extreme problems, 9=Missing value
Data row 1	1001	UK	2006	2	1	2	2	1
Data row 2	1002	UK	2006	1	1	1	1	1

Variable name	STATE	EQ_VAS	SEX	AGE	EDU	METHOD	SOC_ECON
Variable description		999= Missing value	1=male, 2=female, 9=Missing value	999= Missing value	1=low, 2=medium, 3=high, 9=Missing value	0=postal, 1=interview, 2=telephone, 9=Missing value	1=employed, 2=retired, ….., 9=Missing value
Data row 1	21221	80	1	43	1	0	1
Data row 2	21111	90	2	24	2	0	4

NB: The variable names are just examples. However, the variables for the 5 dimensions of the EQ-5D descriptive system should be named 'mobility', 'selfcare', 'activity', 'pain', and 'anxiety'. If they are given different names the syntax codes containing the value sets that are distributed by the EuroQoL Group will not work properly.

6. Presenting EQ-5D results

Data collected using EQ-5D can be presented in various ways. A basic subdivision can be made according to the structure of the EQ-5D:

1. Presenting results from the descriptive system as a health profile
2. Presenting results of the EQ VAS as a measure of overall self-rated health status
3. Presenting results from the descriptive system as a weighted index

However, the way results are presented is partly determined by what message you, as a researcher, wish to convey to your audience.

Health profiles

One way of presenting data as a health profile is by making a table with the frequency or the proportion of reported problems for each level for each dimension. These tables can be broken down to include the proportions per subgroup, such as age, before vs. after treatment, treatment vs. comparator, etc.

Sometimes it is more convenient to dichotomise the EQ-5D levels into 'no problems' (i.e. level 1) and 'problems' (i.e. levels 2 and 3), thereby changing the profile into frequencies of reported problems. This can be the case, for example, in a general population survey where the numbers of reported level 3 problems are very low. Tables 2 and 3 are examples of how to present EQ-5D data in tabulated form. The data for the tables originates from a general population survey in the UK[2].

[2]Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey Bmj 1998;316 (7133): 736-41.

Table 2: Proportion of levels 1, 2 and 3 by dimension and by age group

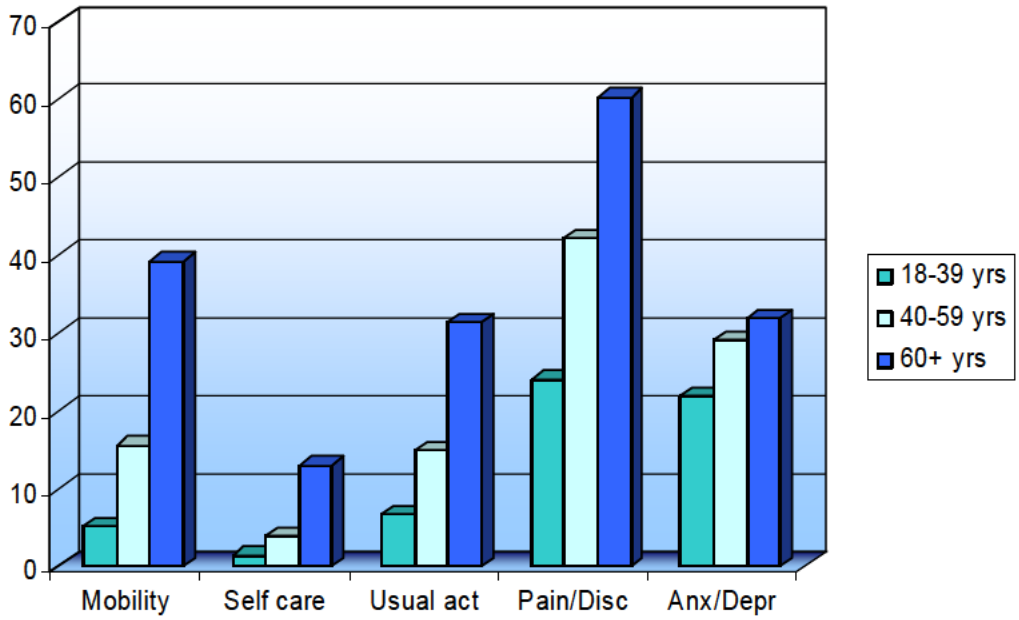
EQ-5D DIMENSION		AGE GROUPS 18-29	30-39	40-49	50-59	60-69	70-79	80+	TOTAL
MOBILITY	Level 1	95.4	92.2	89.7	78.1	70.7	60.2	43.3	81.6
	Level 2	4.6	7.6	9.9	21.9	29.3	39.8	56.7	18.3
	Level 3	0.0	0.1	0.4	0.0	0.0	0.0	0.0	0.1
SELF-CARE	Level 1	99.1	98.4	95.8	94.8	94.3	92.6	83.7	95.7
	Level 2	0.9	1.5	4.0	5.2	5.5	7.1	15.6	4.1
	Level 3	0.0	0.1	0.2	0.0	0.2	0.2	0.7	0.1
USUAL ACTIVITIES	Level 1	93.3	91.4	89.2	78.1	75.3	73.7	56.0	83.7
	Level 2	6.3	7.9	9.4	18.8	21.6	22.1	38.3	14.2
	Level 3	0.4	0.7	1.5	3.0	3.1	4.2	5.7	2.1
PAIN / DISCOMFORT	Level 1	83.9	80.7	74.1	56.3	53.8	44.0	39.7	67.0
	Level 2	15.8	17.7	22.8	38.1	40.6	48.4	49.6	29.2
	Level 3	0.3	1.6	3.1	5.6	5.6	7.6	10.6	3.8
ANXIETY / DEPRESSION	Level 1	86.5	82.6	81.3	72.8	72.0	74.7	75.2	79.1
	Level 2	12.6	16.4	16.9	24.4	25.1	22.6	24.1	19.1
	Level 3	0.9	1.0	1.8	2.8	2.9	2.7	0.7	1.8

Table 3: Frequency of reported problems by dimension and age group

EQ-5D DIMENSION		AGE GROUPS 18-29	30-39	40-49	50-59	60-69	70-79	80+	TOTAL
MOBILITY	No problems	643	631	489	362	339	246	61	2770
	Problems	31	53	56	101	140	162	81	625
SELF-CARE	No problems	668	673	522	439	452	378	119	3251
	Problems	6	11	23	24	27	30	23	144
USUAL ACTIVITIES	No problems	629	625	486	362	361	301	80	2842
	Problems	45	59	59	101	118	107	62	553
PAIN / DISCOMFORT	No problems	566	552	404	261	258	179	56	2275
	Problems	108	132	141	202	221	229	86	1120
ANXIETY / DEPRESSION	No problems	583	565	443	337	345	305	107	2684
	Problems	91	119	102	126	134	103	35	711

In addition to presenting the results in tabulated form, you can also use graphical presentations. Two or 3 dimensional bar charts can be used to summarise the results in 1 graph, (see figure 2). Figure 2 shows the sum of the proportion of reported level 2 and level 3 problems for each of the 5 EQ-5D dimensions for 3 distinct age groups. Older people reported more problems on all dimensions but the effect of age was strongest for mobility and weakest for anxiety/depression.

Figure 2: Profile of the population (% reporting problem)



EQ VAS

In order to present all aspects of the EQ VAS data, you should present both a measure of the central tendency and a measure of dispersion. This could be the mean values and the standard deviation or, if the data is skewed, the median values and the 25th and 75th percentiles. An example is presented in table 4. The data for the table originates from a general population survey in the UK[3].

Table 4: EQ VAS values by age – mean + standard deviation and median + percentiles

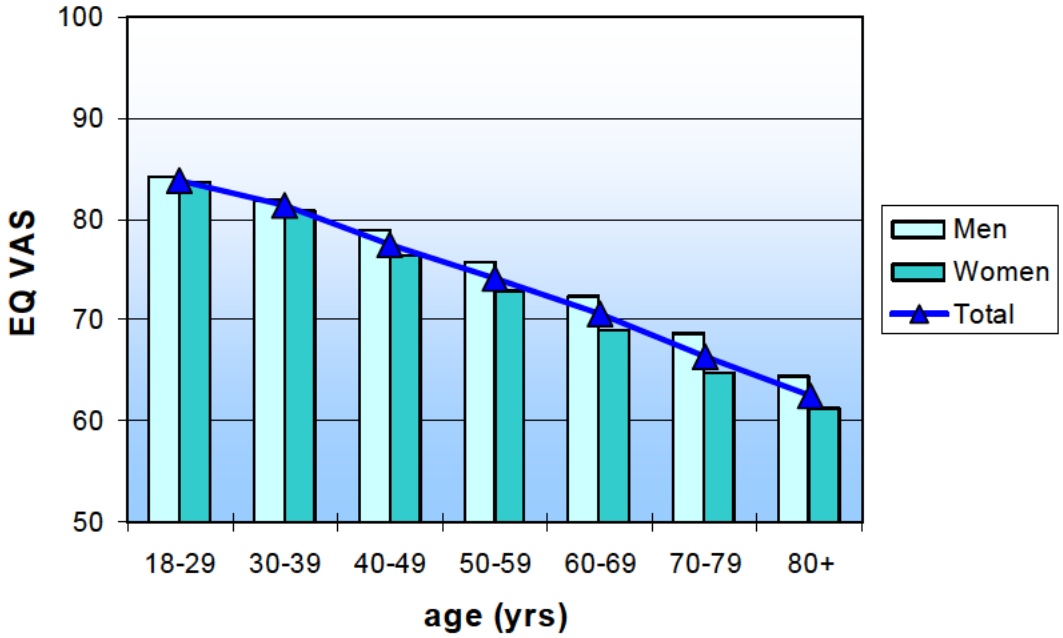
	AGE GROUPS							
EQ VAS	*18-29*	*30-39*	*40-49*	*50-59*	*60-69*	*70-79*	*80+*	*TOTAL*
Mean	87.0	86.2	85.1	81.3	79.8	75.3	72.5	82.8
- Std dev	13.8	14.6	15.5	46.8	17.5	18.5	18.2	23.1
Median	90	90	90	86	85	80	75	90
- 25th	80	80	80	70	70	65	60	75
- 75th	98	95	95	95	93	90	88	95

You can present a graphical representation of the data by using bar charts, line charts, or both (see figure 3). Figure 3 shows the mean EQ VAS ratings reported by

[3] Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey Bmj 1998;316 (7133): 736-41.

men, women and both for 7 distinct age groups. The mean EQ VAS ratings are seen to decrease with increasing age. Also, men of all age groups reported higher EQ VAS ratings than women.

Figure 3: Mean population EQ VAS ratings by age group and sex



EQ-5D index

Information about the EQ-5D index can be presented in much the same way as the EQ VAS data. This means that for the index, you can present both a measure of the central tendency and a measure of dispersion. This could be the mean values and the standard deviation (or standard error). If the data is skewed, the median values and the 25th and 75th percentiles could be presented. Tables 5 and 6 and figures 4 and 5 contain 2 examples of how to present EQ-5D index results. Table 5 and figure 4 present the results from a study where the effect of a treatment on health status is investigated. Table 6 and figure 5 show results for a patient population and 3 subgroups (the tables and figures are based on hypothetical data and for illustration purposes only).

Table 5: EQ-5D index values before and after treatment – mean + standard deviation and median + percentiles

EQ-5D index	before treatment	after treatment
Mean	0.59	0.76
- Std error	0.012	0.015
Median	0.60	0.70
- 25th	0.50	0.65
- 75th	0.70	0.80
N	120	110

Figure 4: EQ-5D index values before and after treatment — mean values and 95% confidence intervals

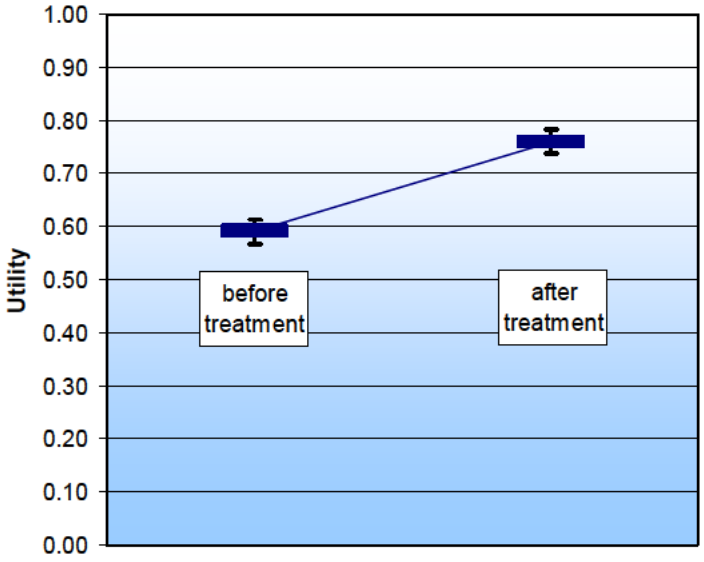
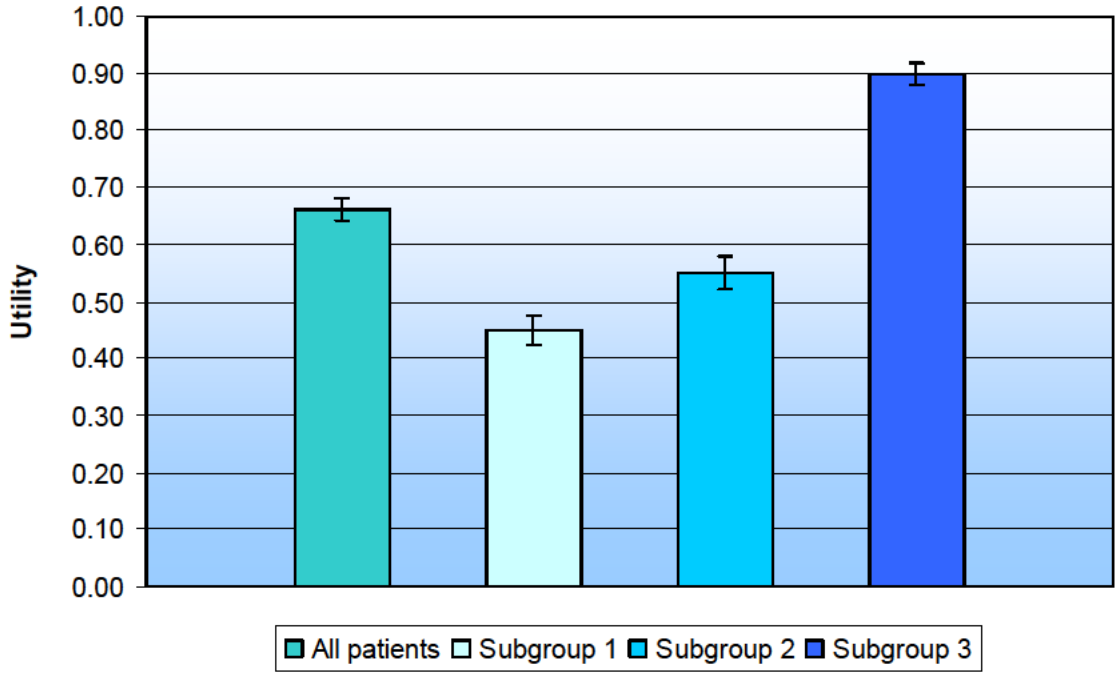


Table 6: EQ-5D index values of the total patient population and the 3 subgroups – mean + standard deviation and median + percentiles

EQ-5D-index	All patients	Subgroup 1	Subgroup 2	Subgroup 3
Mean	0.66	0.45	0.55	0.90
- Std error	0.010	0.013	0.015	0.010
Median	0.55	0.40	0.55	0.95
- 25th	0.50	0.30	0.50	0.80
- 75th	0.70	0.50	0.60	1.00
N	300	100	75	125

Figure 5: EQ-5D index values of the total patient population and the 3 subgroups – mean values and 95% confidence intervals



7. EQ-5D: Frequently asked questions

For what period of time does EQ-5D record health status?

Self-reported health status captured by EQ-5D relates to the respondent's situation at the time of completion. No attempt is made to summarise the recalled health status over the preceding days or weeks, although EQ-5D has been tested in recall mode. An early decision taken by the EuroQoL Group determined that health status measurement ought to apply to the respondent's immediate situation - hence the focus on 'your own health state today'.

General population value sets vs patient population value sets

If you want to undertake a utility analysis you will need to use a value set. Generally speaking utility analysis requires a general population-based value set (as opposed to a patient-based set). The rationale behind this is that the values are supposed to reflect the preferences of local taxpayers and potential receivers of healthcare. Additionally, patients tend to rate their health states higher than the general population because of coping etc, often underestimating their need for healthcare. The EQ-5D value sets are therefore based on the values of the general population.

Difference between the EQ-5D descriptive system and the EQ VAS

The descriptive system can be represented as a health state, e.g. health state 11212 represents a patient who indicates some problems on the usual activities and anxiety/depression dimensions. These health states can be converted to a single index value using (one of) the available EQ-5D value sets. These value sets have been derived using VAS or TTO valuation techniques, and reflect the opinion of the general population. The EQ VAS scores are patient-based and are therefore not representative of the general population. The EQ VAS self-rating records the respondent's own assessment of their health status. The EQ VAS scores however are anchored on 100 = best imaginable health and 0 = worst imaginable health, whereas the value sets are anchored on 11111 = 1 and dead = 0 and can therefore be used in QALY calculations.

Difference between the VAS and TTO techniques

The difference between the value sets based on TTO and those based on VAS is that the techniques used for the elicitation of the values on which the models are based differ. In the TTO task, respondents are asked, for example, to imagine they live in a health state (e.g. 22222) for 10 years and then asked to specify the amount of time they are willing to give up to live in full health instead (i.e. 11111). For example, someone might find 8 years in 11111 equivalent to 10 years in 22222. The VAS technique on the other hand, asks people to indicate where, on a vertical thermometer-like scale ranging from best imaginable health to worst imaginable health, they think a health state should be positioned.

Multinational clinical trials

Information relating to EQ-5D health states gathered in the context of multinational trials may be converted into a single summary index using one of the available EQ-5D value sets. There are different options available to do this using appropriate value sets-however the choice depends on the context in which the information will be used by researchers or decision makers. In cases where data from an international trial are to be used to inform decision makers in a specific country, it seems reasonable to expect decision makers to be interested primarily in value sets that reflect the values for EQ-5D health states in that specific country. So for example, if applications for reimbursement of a drug are rolled out from country to country, country-specific value sets should be applied and reported in each pharmaco-economic report. This is no different from the requirement to use country-specific costs. In the absence of a country-specific value set, the researcher should select another set of values for a population that most closely approximates that country. Sometimes however, information about utilities is required to inform researchers or decision makers in an international context. In these instances, 1 value set applied over all EQ-5D health states data is probably more appropriate.

The decision about which value set to use will also depend on whether the relevant decision making body in each country specifies any requirements or preferences in regard to the methodology used in different contexts (e.g. TTO, standard gamble (SG), VAS or discrete choice modelling (DCM)). These guidelines are the topic of an international ongoing debate but the EuroQoL website is planning to provide a summary of health care decision-making bodies internationally, and their stated requirements regarding the valuation of health states.

Detailed information regarding the valuation protocols, guidelines on which value set to use and tables of all available value sets has recently been published by Springer in: EuroQoL Group Monograph series: Volume 2: EQ-5D value sets: inventory, comparative review and user guide' (see section 8 for more information). Chapter 4 by Nancy Devlin and David Parkin will be of special interest to researchers pondering the issue of which value set to use.

8. Additional information

Key EuroQol references

1. The EuroQol Group (1990). EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 16(3):199-208.

2. Brooks R (1996). EuroQol: the current state of play. Health Policy 37(1):53-72.

3. Dolan P (1997). Modeling valuations for EuroQol health states. Med Care 35(11):1095-108.

4. Roset M, Badia X, Mayo NE (1999). Sample size calculations in studies using the EuroQol 5D. Qual Life Res 8(6):539-49.

5. Greiner W, Weijnen T, Nieuwenhuizen M, et al. (2003). A single European currency for EQ-5D health states. Results from a six country study. Eur J Health Econ; 4(3):222-231.

6. Shaw JW, Johnson JA, Coons SJ (2005). US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care; 43(3): 203-220.

Referring to the EQ-5D instrument in publications

When publishing results obtained with the EQ-5D, the following references can be used:

1. The EuroQol Group (1990). EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 16(3):199-208.

2. Brooks R (1996). EuroQol: the current state of play. Health Policy 37(1):53-72.

If you used a value set in your study you can also include a reference to the publication regarding that value set. The appropriate references for the value sets can be found in the EQ-5D Value Sets Monograph and in the value set summary documents that can be ordered from the EuroQoL Executive Office.

Products available from the EuroQoL Executive Office

EQ-5D language versions/guidelines for different modes of administration

All language versions and guidelines for different modes of administration must be obtained exclusively from the EuroQoL Executive Office. Normally only the language(s) appropriate to the country where the research request originates will be supplied. They are distributed freely provided the research is not being funded by a commercial organization (e.g. a pharmaceutical or medical device company). In these latter instances, sponsorship is requested.

The Measurement and valuation of health status using EQ-5D: A European perspective. Eds Brooks R, Rabin R, de Charro F. Kluwer Acacemic Publishers, 2005

This book reports on the results of the European Union-funded EQ-net project which furthered the development of EQ-5D in the key areas of valuation, application and translation. The book can be obtained from Springer at www.springeronline.com at a cost of €107.95.

Measuring self-reported population health: An international perspective based on EQ-5D. Eds Szende A, Williams A. EuroQoL Group Monographs Volume 1. SpringMed publishing, 2004.

This booklet provides population reference data for a number of different countries and is available on request from the EuroQoL Executive Office.

EQ-5D concepts and methods: a developmental history. Eds Kind P, Brooks R, Rabin R. Springer, 2005.

This book is a collection of papers representing the collective intellectual enterprise of the EuroQoL Group and can be obtained from Springer at www.springeronline.com at a cost of € 85.00.

EQ-5D value sets: Inventory, comparative review and user guide. Eds. Szende A, Oppe M, Devlin N. EuroQoL Group Monographs Volume 2. Springer, 2006.

This book provides an essential guide to the use of the EuroQoL Group's value sets for anyone working with EQ-5D data and can be obtained from Springer at www.springeronline.com at a cost of € 49.95.

Future developments

Since 2002, the EuroQoL Foundation has provided modest funding for EuroQoL members to carry out innovative EQ-5D-related research. Since 2004, the Group has been establishing specific task forces to:

- Investigate the use of EQ-5D in different disease areas
- Develop a 5-level version of EQ-5D
- Explore different valuation methodologies for the 5-level version
- Develop an EQ-5D version for children aged 7-12 years in different languages
- Investigate the use of EQ-5D in population health

- Explore the use of electronic versions of EQ-5D in pc and web-based applications as well as palm pilots and (in the future) cell phones. This task force will also investigate the eliciting of values via the computer

Contact information:

For more information please look at the EuroQoL website at www.euroqol.org or e-mail us at userinformationservice@euroqol.org

Acknowledgements:

Part of this user guide was taken from and is based on the UK user guide that was developed by Professor Paul Kind from York University, UK in 1998.

Patient ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | | Patient Initials (First, Last) | | |

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

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

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

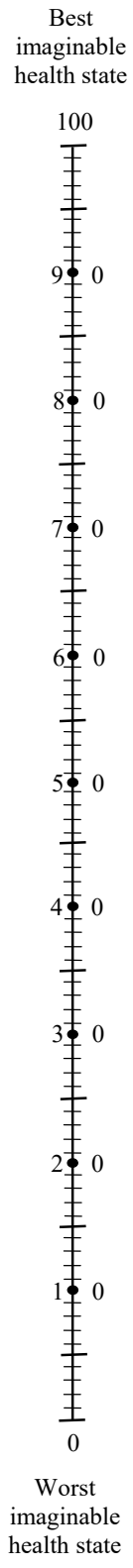
The EuroQol Group (1990). EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 16(3):199-208.

Patient Study ID # | 2 | 0 | 0 | 6 | 0 | 5 | | | | | Patient Initials (First, Last) | | |

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

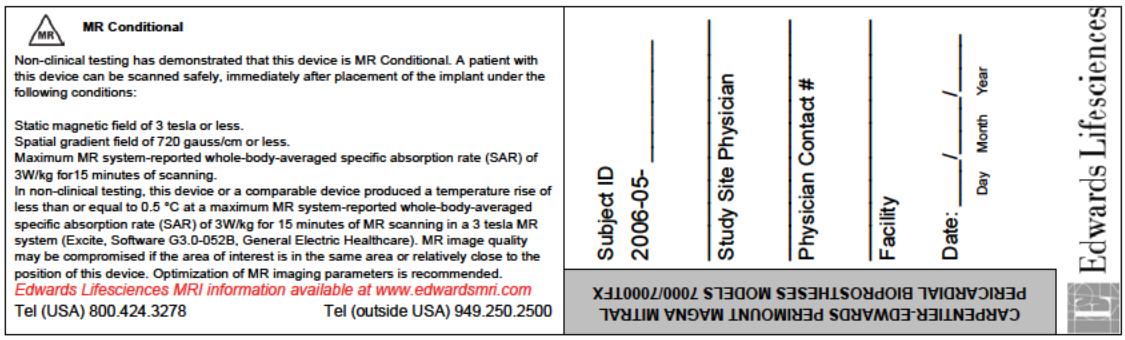
Your own health state today



The EuroQol Group (1990). EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 16(3):199-208.

18.0 APPENDIX 7: IMPLANT DATA CARD

Outside of Card



MR Conditional

Non-clinical testing has demonstrated that this device is MR Conditional. A patient with this device can be scanned safely, immediately after placement of the implant under the following conditions:

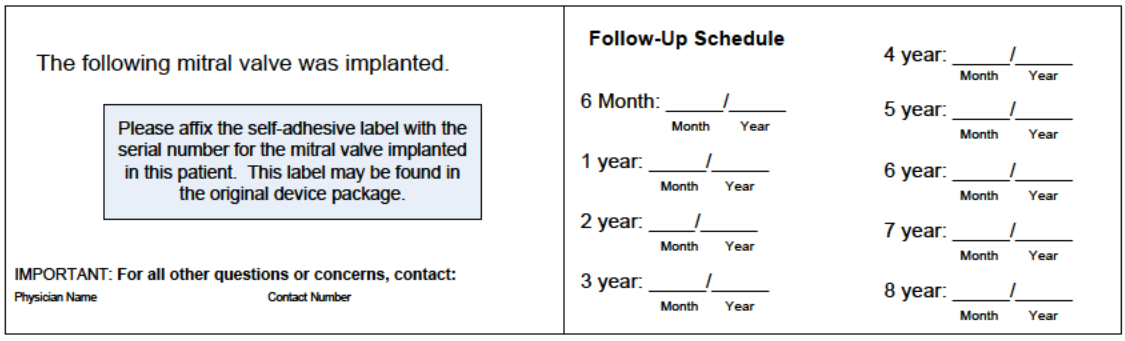
Static magnetic field of 3 tesla or less.
Spatial gradient field of 720 gauss/cm or less.
Maximum MR system-reported whole-body-averaged specific absorption rate (SAR) of 3W/kg for15 minutes of scanning.
In non-clinical testing, this device or a comparable device produced a temperature rise of less than or equal to 0.5 °C at a maximum MR system-reported whole-body-averaged specific absorption rate (SAR) of 3W/kg for 15 minutes of MR scanning in a 3 tesla MR system (Excite, Software G3.0-052B, General Electric Healthcare). MR image quality may be compromised if the area of interest is in the same area or relatively close to the position of this device. Optimization of MR imaging parameters is recommended.

Edwards Lifesciences MRI information available at www.edwardsmri.com

Tel (USA) 800.424.3278 Tel (outside USA) 949.250.2500

Back Front

Inside of Card



The following mitral valve was implanted.

Please affix the self-adhesive label with the serial number for the mitral valve implanted in this patient. This label may be found in the original device package.

IMPORTANT: **For all other questions or concerns, contact:**

Physician Name Contact Number

Follow-Up Schedule

6 Month: _____/_____ Month Year

1 year: _____/_____ Month Year

2 year: _____/_____ Month Year

3 year: _____/_____ Month Year

4 year: _____/_____ Month Year

5 year: _____/_____ Month Year

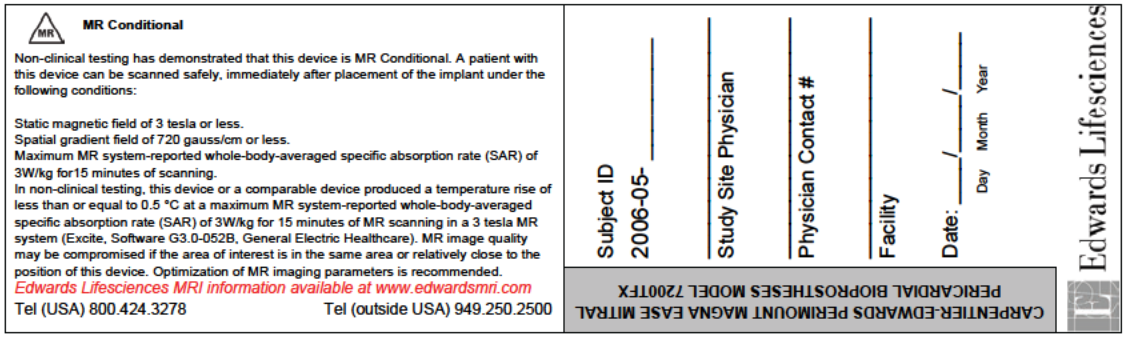
6 year: _____/_____ Month Year

7 year: _____/_____ Month Year

8 year: _____/_____ Month Year

Left Right

Outside of Card



MR Conditional

Non-clinical testing has demonstrated that this device is MR Conditional. A patient with this device can be scanned safely, immediately after placement of the implant under the following conditions:

Static magnetic field of 3 tesla or less.
Spatial gradient field of 720 gauss/cm or less.
Maximum MR system-reported whole-body-averaged specific absorption rate (SAR) of 3W/kg for15 minutes of scanning.
In non-clinical testing, this device or a comparable device produced a temperature rise of less than or equal to 0.5 °C at a maximum MR system-reported whole-body-averaged specific absorption rate (SAR) of 3W/kg for 15 minutes of MR scanning in a 3 tesla MR system (Excite, Software G3.0-052B, General Electric Healthcare). MR image quality may be compromised if the area of interest is in the same area or relatively close to the position of this device. Optimization of MR imaging parameters is recommended.

Edwards Lifesciences MRI information available at www.edwardsmri.com

Tel (USA) 800.424.3278 Tel (outside USA) 949.250.2500

Back

Subject ID 2006-05-_____

Study Site Physician _____

Physician Contact # _____

Facility _____

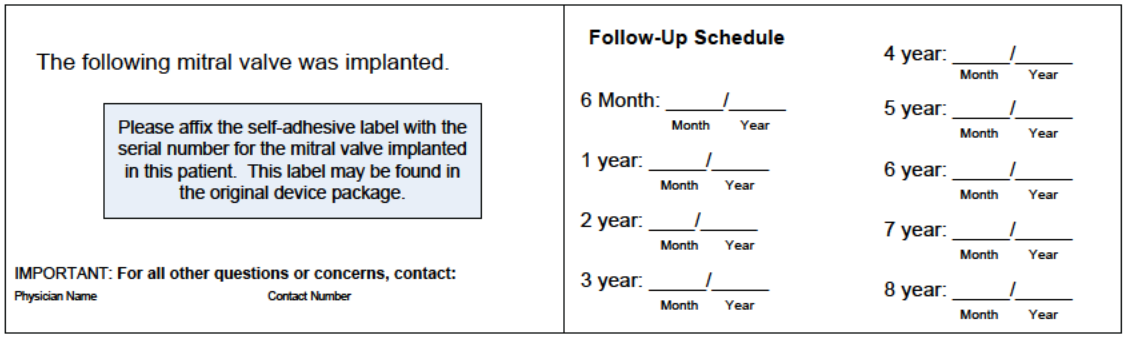
Date: ____/____/____ Day Month Year

CARPENTIER-EDWARDS PERIMOUNT MAGNA EASE MITRAL PERICARDIAL BIOPROSTHESES MODEL 7200TFX

Edwards Lifesciences

Front

Inside of Card



The following mitral valve was implanted.

Please affix the self-adhesive label with the serial number for the mitral valve implanted in this patient. This label may be found in the original device package.

IMPORTANT: **For all other questions or concerns, contact:**

Physician Name Contact Number

Left

Follow-Up Schedule

6 Month: _____/_____ Month Year

1 year: _____/_____ Month Year

2 year: _____/_____ Month Year

3 year: _____/_____ Month Year

4 year: _____/_____ Month Year

5 year: _____/_____ Month Year

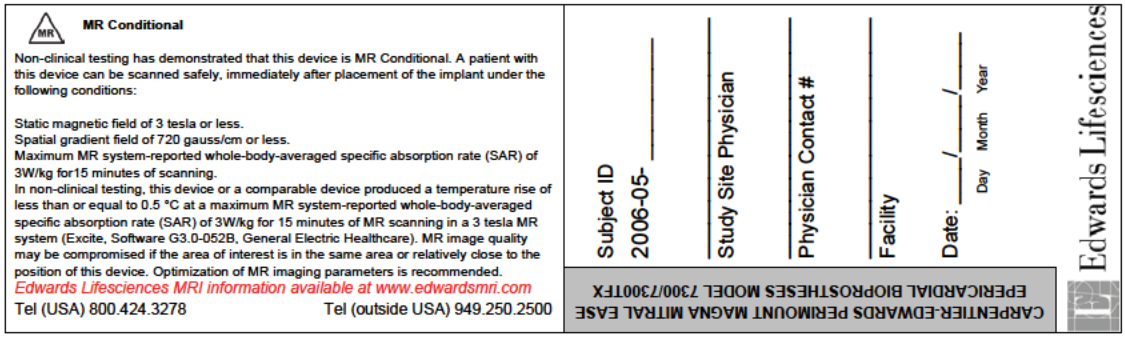
6 year: _____/_____ Month Year

7 year: _____/_____ Month Year

8 year: _____/_____ Month Year

Right

Outside of Card



MR Conditional

Non-clinical testing has demonstrated that this device is MR Conditional. A patient with this device can be scanned safely, immediately after placement of the implant under the following conditions:

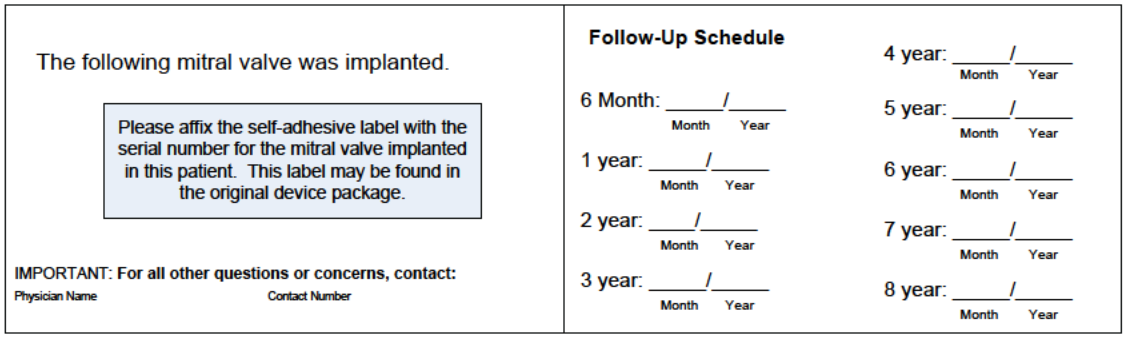
Static magnetic field of 3 tesla or less.
Spatial gradient field of 720 gauss/cm or less.
Maximum MR system-reported whole-body-averaged specific absorption rate (SAR) of 3W/kg for15 minutes of scanning.
In non-clinical testing, this device or a comparable device produced a temperature rise of less than or equal to 0.5 °C at a maximum MR system-reported whole-body-averaged specific absorption rate (SAR) of 3W/kg for 15 minutes of MR scanning in a 3 tesla MR system (Excite, Software G3.0-052B, General Electric Healthcare). MR image quality may be compromised if the area of interest is in the same area or relatively close to the position of this device. Optimization of MR imaging parameters is recommended.

Edwards Lifesciences MRI information available at www.edwardsmri.com

Tel (USA) 800.424.3278 Tel (outside USA) 949.250.2500

Back Front

Inside of Card



The following mitral valve was implanted.

Please affix the self-adhesive label with the serial number for the mitral valve implanted in this patient. This label may be found in the original device package.

IMPORTANT: **For all other questions or concerns, contact:**

Physician Name Contact Number

Follow-Up Schedule

6 Month: _____/_____ Month Year

1 year: _____/_____ Month Year

2 year: _____/_____ Month Year

3 year: _____/_____ Month Year

4 year: _____/_____ Month Year

5 year: _____/_____ Month Year

6 year: _____/_____ Month Year

7 year: _____/_____ Month Year

8 year: _____/_____ Month Year

Left Right

19.0 APPENDIX 8: ADVERSE EVENT DEFINITIONS

	Primary Event Name	Subcategory	General Definition	Device or Procedure Relationship
Bleeding Events	A bleeding event is any episode of major internal or external bleeding that causes death, hospitalization, or permanent injury (eg, vision loss) or necessitates transfusion. Major bleeding unexpectedly associated with minor trauma should be reported as a bleeding event, but bleeding associated with major trauma or a major operation is considered secondary to those events and should not be reported. Bleeding events are reported for all patients regardless of whether they are taking anticoagulants or antiplatelet drugs. Although total bleeding events must be reported, bleeding events can also be reported separately for those who are taking anticoagulants or antiplatelet agents and those who are not. Bleeding Events are further categorized as below.			
	Bleed-Hemorrhage			**ISO 14155-1, Section 3.1 Adverse Device Effect (ADE)** any untoward or unintended response to a medical device. **ISO 14155-1, 3.18: Serious Adverse Device Effect (SADE)** Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.
	Anticoagulant-related Bleed (hemorrhage)		Any episode of major internal or external bleeding related to the use of anticoagulation that causes death, hosptalization, or permanent injury (e.g., vision loss) or necessitates transfusion.	Not defined
		Bleeding Diatheses related to AC	Bleeding diathesis is an unusual susceptibility to bleeding mostly due to a coagulopathy.	
	Coagulopathy		Development of a new bleeding disorder (one that was not diagnosed prior to the index procedure), documented by laboratory studies.	Event is procedure related if it occurs within 30 days of the date of the index procedure.
		DIC	Systemic /widespread formation of thromboses in the microcirculation, mainly within the capillaries. Secondary complication of a wide variety of coagulation disorders which activate the intrinsic coagulation sequence.	Not defined
		Heparin Induced Thrombocytopenia (HITS)	HITS is diagnosed when thrombocytopenia (defined as >50% of the baseline value or a low platelet count between 20–100 × 10^9/liter) is reported caused by administration of various forms of heparin. HITS must be confirmed by a Heparin Assay and or D-Dimer laboratory test.	Not defined

		Other Coagulopathy	Coagulopathy other than DIC or HITS confirmed by laboratory tests.	Not defined
	Hematoma		Collection of blood (or its degradation products) which exceeds 5 cm in diameter, requires treatment or prolongs hospitalization.	Not defined
		Specify site		
	Hemolysis		The destruction of red blood cells, caused by disruption of the cell membrane and resulting in the release of hemoglobin. The clinical diagnosis is made by the measurement of plasma free hemoglobin.	Not defined
	Hemolytic Anemia		Anemia due to hemolysis, either in the blood vessels (Intravascular hemolysis) or elsewhere in the body (extravascular).	Not defined
		Mechanical hemolytic anemia (extravascular)	A form of hemolytic anemia due to mechanically induced damage to red blood cells. Red blood cells, while flexible, may in some circumstances succumb to physical shear and compression. A common form, called *microangiopathic hemolytic anemia*, is a chronic condition due to prosthetic heart valves.	Not defined
	GI Bleed	General Def	Detection or frank blood or hemoglobin in the GI tract documented by diagnostic test or laboratory results that causes death, hospitalization, or permanent injury (eg, vision loss) or necessitates transfusion. Refer to definition of "Bleeding Events" for reportability.	Not defined
		Upper	Detection of frank blood or hemoglobin in the upper gastrointestinal tract confirmed by diagnostic or laboratory test result.	Not defined
		Lower	Detection of frank blood or hemoglobin in the stool documented by hemmocult test or other diagnostic procedure.	Not defined
	Intracranial Bleed		Includes all bleeding within the cranium either subarachnoid, intra-parenchymal, or intracerebral requiring treatment or resulting in neurological deficit. Bleeding related neurological events should be captured as bleeding complications (See Bleeding) while embolic related deficits should be recorded as embolic events.	Not defined
Bleeding Events	**Pericardial Tamponade**		Fluid accumulation between the myocardium and pericardium of the heart creating hemodynamic compromise. Severity of the tamponade may dictate the degree of intervention (invasive or non-invasive, surgical or Pericardiocentesis). This should be documented by either: 1. Echo showing pericardial fluid and signs of tamponade such as right heart compromise. 2. Systemic hypotension due to pericardial fluid compromising cardiac function.	Not defined

	Procedural Bleeding		Any abnormal blood loss that occurs during the index procedure, in the opinion of the investigator. The volume of blood loss during the procedure shall be recorded on the case report form.	Not defined
	Post-Procedural		Abnormal bleeding that is related to the index procedure in the opinion of the investigator, that occurs after the patient leaves the OR.	Not defined
	Other Bleed, specify		Other bleeding event that does NOT fit in one of the above categories.	Not defined
Cardiac Complications				
	Angina		Angina is due to an inadequate supply of oxygen to the heart muscle. Symptoms may include: chest pain, tight or heavy feeling in the chest, or discomfort which spreads from the chest to the arm, back, neck, jaw, or stomach, numbness or tingling in the shoulders, arms or wrists, shortness of breath, and nausea relieved by rest or nitroglycerine. Stable angina has no change in frequency or pattern for 6 weeks. Angina which increases in frequency, intensity, or duration, which occurs at rest, or which is new in onset is considered unstable angina. Event should be documented and confirmed by EKG test results.	
		Angina -stable	No change in frequency or pattern for 6 weeks.	Not defined
		Angina-unstable	Chest pain extending over a 6-hour period that does not respond to treatment.	Not defined
	Annular Dissection		Dissection of the valvular annulus extending into the aorta which may occur due to disease state (friable tissue) or may be due to mechanical trauma such as over sizing of balloon expandable product, insertion of prosthetic valve or other valvular accessory product placement. Annular dissection occurring within 30 days of the index procedure will be considered related.	Event is considered **procedure related** if it occurs within 30 days of the index procedure.
	Aortic Dissection		Disruption of the media layer of the aorta with bleeding within and along the wall of the aorta. Dissection may, and often does, occur without an aneurysm being present. Aortic dissection may occur in the ascending thoracic aorta (Type A dissection) or in thr descending thoracic aorta (Type B dissection). Dissection should be confirmed by imaging.	Not defined
		Type A	Dissection occurs in the ascending aorta.	Not defined
		Type B	Dissection occurs in the descending aorta.	Not defined
	Arrhythmia	General definition	A documented arrhythmia when the specific condition did not exist before, or has been exacerbated since the index procedure . All Arrhythmias should be documented and confirmed with EKG test results.	Not defined
Cardiac Complications		Atrial Fibrillation	Atrial fibrillation is a disorganized, irregular, rapid heart rate. Symptoms may include heart palpitations, shortness of breath, weakness and fatigue and may lead to stroke.	Not defined

		Atrial Flutter	Well organized but overly rapid contractions of the atrium of the heart (usually at a rate of 250-350 contractions per minute).	Not defined
		AV Block	A conduction disorder of the nervous impulse at the level of the atrioventricular junction, i.e. between the atrium and the ventricle.	Not defined
		AV Block I	A conduction disorder of the nervous impulse at the level of the atrioventricular junction, i.e. between the atrium and the ventricle.	Not defined
		AV Block II	A conduction disorder of the nervous impulse at the level of the atrioventricular junction, i.e. between the atrium and the ventricle.	Not defined
		AV Block III	A conduction disorder of the cardiac conduction system with complete absence of AV conduction. With third degree block, no P waves conduct to the ventricle and AV dissociation is complete.	
		Bradycardia	An abnormally slow heart rate (typically defined as <60 bpm in adults) and which may require implantation of a pacemaker to maintain a normal heart rate.	Not defined
		Bundle Branch Block	Bundle branch block is an intraventricular conduction defects (IVCD) that disrupts the normal flow of electrical impulses that result in a normal heart beat. A QRS duration of greater than 110 milliseconds is a diagnostic indication of BBB.	Not defined
		BBB- Left Partial		
		BBB- Left Complete		
		BBB - Right partial		
		BBB- Right complete		
		Superventricular Tachycardia (SVT)	Sustained tachyarrhythmia in which the QRS appears normal and has a duration of < 120 msec.	Not defined
		Ventricular Fibrillation	A rapid irregular ventricular rhythm due to multiple reentrant activity associated with essentially zero cardiac output. VF may be fatal unless treated by defibrillation (electric shock).	Not defined
		Ventricular Tachycardia	Defined as a regular heart rhythm originating from the ventricle with a frequency of 160 to 200 beats per minute.	Not defined
		Other Arrhythmia, specify:	Any other type of arrhythmia not listed above	Not defined

Cardiac Complications	**Arterial Dissection**		Separation of the inner arterial walls due to mechanical dilatation of the artery or ablation of atherosclerotic plaque. Associated with plaque fracture, intimal splitting and localized medial dissection. Tears may extend into the media for varying distances, and may even extend through the adventitia resulting in frank perforation. The National Heart, Lung and Blood Institute (NHLBI) classification system for intimal tears, (dissections) are graded based upon their angiographic appearances as types A through F. In general, type A and B dissections are clinically benign and do not adversely affect procedural outcome. However, types C through F are considered major dissections and carry a significant increase in morbidity and mortality. Note: NHBLI definitions refer to both coronary and peripheral vascular dissections - see Reference.	
		Type A	Minor radiolucent areas within the coronary lumen during contrast injection with little or no persistence of contrast after the dye has cleared.	Not defined
		Type B	Parallel tracts or a double lumen separated by a radiolucent area during contrast injection, with minimal or no persistence after dye clearance.	Not defined
		Type C	Appear as contrast outside the coronary lumen ("extraluminal cap") with persistence of contrast after dye has cleared from the lumen.	Not defined
		Type D	Represent spiral ("barber shop pole") luminal filling defects, frequently with excessive contrast staining of the dissected false lumen.	Not defined
		Type E	Appear as new, persistent filling defects within the coronary lumen.	Not defined
		Type F	Represent those that lead to total occlusion of the coronary lumen without distal antegrade flow.	Not defined
	Cardiac Arrest		Cardiac arrest documented by one of the following: ventricular fibrillation, rapid ventricular tachycardia with hemodynamic instability, asystole.	Not defined
	Cardiogenic Shock		A clinical state of hypoperfusion sustained for greater than 30 minutes, with either systolic blood pressure < 80 mm Hg, and /or Cardiac Index < 1.8 despite maximal treatment (fluids) or 2) requiring intravenous inantropes and/or pressor agent or an intraortic balloon pump (IABP).	Not defined
	Heart Failure (aka Cardiac Failure)		An event is which the heart fails to meet the circulatory requirements of the body under differing physiological circumstances, and/or a state in which cardiac output is reduced relative to the demands of the body, assuming the evidence of adequate venous return. Event is confirmed clinically or by diagnostic testing	Event is considered **Valve Related** if event is new event which is not continued from preoperative heart failure, is caused by one of the following prosthesis related events: AC related hemorrhage, endocarditis, non-structural dysfunction, perivalvular leak, structural deterioration, thromboembolism, thrombosis, re-op or unknown causes.

Cardiac Complications	**Hypotension**		Abnormally low blood pressure. For an adult, hypotension is defined as blood pressure less than 90/50 mmHg. Because arterial pressure is determined by cardiac output, venous pressure and systemic vascular resistance a reduction in either one or all of these variables can lead to hypotension.	Not defined
	Hypertension		Defined as blood pressure > 140 /90 mm Hg for patient without diabetes or kidney disease, >130/80 mmHg for patients on 2 occasions with diabetes or renal disease.	Not defined
	Pericardial Effusion		Excess fluid accumulation in the pericardium that interferes with normal heart function. May be related to inflammation of the pericardium due to disease or injury, but can result from the accumulation of blood after a surgical procedure or injury. Diagnosis of pericardial effusion should be confirmed by echocardiography or CT and reported when it requires medication or medical intervention to resolve.	Not defined
	Perforation of the free myocardial		An abnormal hole or opening in the heart wall caused by a device causing puncture through the wall or by pressure against a weakened portion of the wall.	Not defined
	Myocardial Infarction		Peri-operative Myocardial Infarction (MI) (0-24 hours post-op) as documented by the following criteria: The CK-MB (or CK if MB not available) must be ≥5 times the upper limit of normal, with or without new Q waves present in two or more contiguous ECG leads. No symptoms required. Peri-operative Myocardial Infarction (MI) (> 24 hours post-op) as documented by at least one of the following criteria:1. Evolutionary ST-segment elevations, 2. Development of new Q- waves in two or more contiguous ECG leads, 3. New or presumably new LBBB pattern on the ECG, CK4. The CK-MB (or CK if MB not available) must be greater than or equal to 3 times the upper limit of Normal.	Not defined
Embolic Events				
	Embolism	General Def	An embolism is a free flowing blood clot or lesion material that is located in the systemic or pulmonary circulation that occurs in the absence of infection after immediate perioperative period. May be manifested as neurological event or non-cerebral embolic event. Non-cerebral event is an embolus documented operatively, autopsy or clinically that produces signs and symptoms attributable to partial or complete obstruction of a peripheral artery. Excludes post-operative MI unless detected by operation, clinical imaging or autopsy, emboli caused by non-thrombotic material (atherosclerosis, myxoma).	Not defined
	Thromboembolism		The combination of thrombosis and its main complication, embolism. Thrombosis is the formation of a blood clot inside a blood vessel, obstructing the flow of blood through the circulartory system	Not defined

	Thrombotic obstruction		Obstruction by thrombus formation	Not defined
	Peripheral Embolic Event		A peripheral embolic event is an operative, autopsy, or clinically documented embolus that produces symptoms from complete or partial obstruction of a peripheral (noncerebral) artery. Report under Pulmonary Embolism if event occurs in the lung.	Not defined
		Specify location:		
	Pulmonary Embolism		Clinical evidence of new embolism with confirmation by lung scan or pulmonary angiography.	Event that occurs within 90 days of the index procedure will be considered **procedure related**.
	Stroke		Prolonged (> 72 hrs) or permanent neurological deficit that is usually associated with abnormal results of MRI or CT scans. Patients with minimal, atypical, or protean symptoms that lead to radiographic imaging demonstrating an acute ischemic event are considered to have a stroke.	Not defined
	TIA		Characterized as a fully reversible symptoms of short duration.	Not defined
Hepatic				
	Liver failure	Acute	Acute liver failure (ALF) is a syndrome defined by the occurrence of encephalopathy, coagulopathy and jaundice in an individual with a previously normal liver. These events lead to multiple organ failure and often death. Survival rate is < 20% with medical management alone. Early deaths in ALF are often caused by cerebral oedema or cardio- vascular collapse, whereas late deaths tend to result from sepsis and multiple organ failure. Liver transplantation is the only current definitive treatment in those failing supportive medical management.	Not defined
	Other liver, specify		Other liver problems that do NOT meet the definition of Liver Failure (e.g. liver dysfunction)	Not defined
Infection				
	Bacteremia		Infection of the blood confirmed by two positive blood cultures. Considered an AE when medication or medical intervention is required to treat or resolve the condition.	Not defined
Infection	**Endocarditis**		An inflammation or infection of the endocardium, which is the inner lining of the heart muscle and, most commonly, the heart valves. Typically caused by bacterial infection, but can be caused by fungus. An infection for which no source is identified, and may or may not be associated with classic signs of Endocarditis (red blood cell casts in urine, splinter hemorrhages in finger nails, roof of mouth, lesions on retina, etc) and may or may not be associated with a vegetation inside the atrium or on a valve. Event must be confirmed by 2 consecutive positive blood cultures and /or imaging study, explant or autopsy.	

	Pneumonia		Lung infection documented by blood studies or chest x-ray, requiring treatment with antibiotics, inhalation therapy, intubation or suctioning.	Event will be considered **procedure related** when occurs within 30 days of the index procedure.
	Sepsis/Septicemia		Sepsis (also known as septicemia). Positive blood and clinical evidence of infection (e.g. fever, elevated WBC count, hypotension, end organ dysfunction) Event must be confirmed by 2 consecutive positive blood cultures, explant or autopsy.	Not defined
	Infection local:	Sternal Wound Infection	Deep sternal infection involving muscle, bone, and/or mediastinum. Must include one of the following: 1) wound opened with excision of tissue (I&D); 2) positive culture; 3) treatment with antibiotics. Infection that is contiguous with the sternum on imaging will constitute involvement of the sternum.	Event will be considered **procedure related** when occurs within 30 days of the index procedure.
	Infection local, specify site:		Other localized infection that is NOT related to the sternal access.	
	Infection, systemic: specify		Other systemic infection that is not already identified in another category.	
	Infection, other: specify		Any other infection that cannot be determined to be local or systemic	
Pulmonary				
	Atelectasis		Complete or partial collapse of a previously inflated lung, inability of lung to fully expand.	
	Pleural Effusion		Excess accumulation of blood or other fluids in the pleura, which is common after cardiac surgery. Reportable when it becomes symptomatic and diagnosis is confirmed by appropriate imaging.	
	Pneumothorax		Abnormal presence of air in the pleural cavity. Accumulation of air or gas in the pleural cavity, occurring as a result of disease or injury and requiring medication or medical intervetion to resolve.	
	Pulmonary Edema		An abnormal accumulation of fluid in the lungs requiring medication or medical intervention to resolve.	
	Pulmonary Embolism (PE)		See Embolism-PE.	
Pulmonary	**Pulmonary Hypertension**		Mean pulmonary artery pressure that is greater than 25 mmHg at rest and/or greater than 30 mmHg during exercise confirmed by SG catheter or diagnostic placement in the pulmonary artery bed and condition requires medication or medication intervention to resolve or treat the condition.	

	Respiratory Dysfunction/Insufficiency		Deterioration of patient's respiratory efforts less than 24 hrs after completion of the index procedure.	Respiratory failure reported within 30 days of the index procedure is considered procedure related. Respiratory failure reported later than 30 days arter the index procedure will be recorded as an AE or SAE, but will not be considered procedure related.
	Respiratory Failure		Need for mechanical ventilation required greater than 24 hrs after of completion of the index procedure, or need for reintubation and ventilator support occurring any time within 30 day of the index procedure will be considered related to the index procedure.	Event occurring any time within 30 day of the index procedure will be considered **procedure related.**
	Other Respiratory, specify		Other respiratory event that is NOT respiratory failure.	Event will be considered **procedure related** when occurs within 30 days of the index procedure.
Renal				
	Renal Dysfunction		An acute event or worsening of renal function post-operatively (Increase of serum creatinine to < 2.0, and < 2x most recent preoperative creatinine level) and does NOT require dialysis.	Not defined
	Renal Failure		An acute event or worsening of renal function resulting in one or more of the following: 1) Increase of serum creatinine to >2.0, and 2x most recent preoperative creatinine level. 2) A new requirement for dialysis postoperatively.	Not defined
	Other Renal, specify		Other event that is not renal failure or renal dysfunction	
Vascular				
	Vascular Access Site Complication		Report under Bleeding or Infection.	
	Deep Vein Thrombosis (DVT)		Formation of blood clot (thrombus) in the lower extremities (legs) characterized by swelling, redness, claudication/pain in affected limb. Event should be confirmed by Doppler or Duplex US study, and require medication or medical intervention to resolve.	Not defined
	Other Vascular, specify		Other vascular complications that are not captured in any other AE definition.	Not defined
Valvular				

	Aortic Stenosis		Obstruction of flow at the aortic valve due to restricted leaflet opening, with a mean transvalvular pressure gradient of at least 10 mm Hg. Does not including the subvalvular and supravalvular forms of this disease. The cause of the stenosis can be further defined based on the anatomy and disease process affecting the valve.	
		Mild	Jet velocity (m/s) <3.0; Mean Gradient (mmHg) <25; Valve Area (cm2) < 1.5.	
		Moderate	Jet velocity (m/s) 3.0-4.0; Mean Gradient (mmHg) 25-40; Valve Area (cm2) 1.0- 1.5.	
		Severe	Jet velocity (m/s) >4.0; Mean Gradient (mmHg) >40; Valve Area (cm2) <1.0; Valve Area Index<0.6.	
	Aortic Regurgitation		Incompetence of the aortic valve, in which a portion of the left ventricular forward stroke volume returns to the chamber during diastole. The cause of the regurgitation, is further defined based on the anatomy of the valve and aortic root and the disease process affecting the valve.	
Valvular		Mild	Qualitative: Angiographic grade 1+; Color Doppler jet Width-Central jet, width less than 25% of LVOT. Doppler Vena Contracta Width (cm) <0.3. Quantitative (by Echo or Angio):Regurgitant volume (ml/beat) <30; Regurgitant fraction (%) <30;Regurgitant orifice area (cm2) < 0.10.	
		Moderate	Qualitative: Angiographic grade- 2+; Color Doppler jet Width- Central jet, greater than Mild but no signs of Sever AR. Doppler Vena Contracta Width (cm) 0.3-0.6. Quantitative (by Echo or Angio):Regurgitant volume (ml/beat) 30-59; Regurgitant fraction (%) 30-49;Regurgitant orifice area (cm2) 0.10-0.29.	
		Severe	Qualitative: Angiographic grade- 3-4+; Color Doppler jet Width- Central jet, width > 65% of LVOT. Doppler Vena Contracta Width (cm) >0.6. Quantitative (by Echo or Angio):Regurgitant volume (ml/beat) >60; Regurgitant fraction (%) >50;Regurgitant orifice area (cm2) >0.3.	
	Mitral Stenosis		Mitral stenosis (MS) refers to narrowing of the mitral valve orifice, resulting in impedance of filling of the left ventricle in diastole. It is usually caused by rheumatic heart disease. Less common causes include severe calcification of the mitral annulus, infective endocarditis, systemic lupus erythematosus, rheumatoid arthritis, and carcinoid heart disease. The severity of MS is defined by the mitral valve area (MVA) where normal valve area is 4 to 5 cm2.	
		Mild	Mean gradient (mm Hg) < 5; Pulmonary artery systolic Pressure (mm Hg)< 30; Valve Area (cm2) >1.5.	
		Moderate	Mean gradient (mm Hg) 5-10; Pulmonary artery systolic Pressure (mm Hg) 30-50; Valve Area (cm2) 1.0-1.5.	
		Severe	Mean gradient (mm Hg) > 10; Pulmonary artery systolic Pressure (mm Hg)> 50; Valve Area (cm2)<1.0.	
	Mitral Regurgitation		Also known as mitral incompetence and mitral insufficiency is leakage of blood backward through the mitral valve each time the left ventricle contracts. Diagnosed by auscultation (murmur) or echocardiography.	

		Mild	Qualitative: angiographic grade 1+; Color Doppler jet area- Small, central jet (<4 cm2 or<20% LA area); Doppler vena contracta width (cm) < 0.3. Quantitative (cath or echo):Regurgitant volume (ml/beat) <30;Regurgitant fraction (%) <30; Regurgitant orifice area (cm2) <0.20.	
		Moderate	Qualitative: angiographic grade 2+; Color Doppler jet area- signs of MR greater than Mild present but no criteria for Sever Mr; Doppler vena contracta width (cm) 0.3-69. Quantitative (cath or echo):Regurgitant volume (ml/beat) 30-59;Regurgitant fraction (%) 30-49; Regurgitant orifice area (cm2) 0.20-0.39.	
		Severe	Qualitative: angiographic grade3-4+; Color Doppler jet area- Vena contracta width > 0.7 with large central MR jet (area > 40% of LA area) or with a wall-impinging jetof any size, swirling in LA; Doppler Vena contracta width > 0.7. Quantitative (cath or echo):Regurgitant volume (ml/beat) >/=60;Regurgitant fraction (%) >/=50; Regurgitant orifice area (cm2) >/=0.40.	
	Tricuspid Stenosis		A narrowing of the tricuspid valve opening that increases resistance to blood flow from the right atrium to the right ventricle. Severe tricuspid stenosis is defined as a valve area less than 1.0 cm2.	
	Tricuspid Regurgitation		Insufficiency of the tricuspid valve causing blood flow from the right ventricle to the right atrium during systole. Severe regurgitation characterized by Vena contracta width greater than 0.7 cm and Systolic flow reversal in hepatic veins.	
	Other Valve, specify location:		Other valve (e.g. pulmonic) valve disease or deterioration reported after the AVR procedure.	
	Structural Deterioration		Includes dysfunction or deterioration involving the replacement heart valve (exclusive of infection or thrombosis) determined by reoperation, autopsy or clinical investigation. Refers to changes intrinsic to the valve such as wear, fracture, leaflet escape, calcification, leaflet tear, stent creep, suture line disruption of components of prosthetic valve, new chordal rupture, leaflet disruption, or leaflet retraction of repaired valve.	By definition all are **valve related.**
		Calcification		
		Leaflet tear		
		Stress Fracture		
		Stent creep		
		Suture line disruption		
		Wear damage		
		Loss of structural integrity	Loss of structural integrity of metallic valve component such as wireform, frame, etc.	

		Other Structural Deterioration, specify:		
Valvular	**Non Structural Dysfunction**		Any abnormality not intrinsic to the valve itself that results in stenosis or regurgitation of the replacement heart valve. Refers to problems (exclusive of thrombosis and infection) that do not directly involve valve components yet result in dysfunction as diagnosed by reoperation, autopsy or clinical investigation. E.g. Entrapment by pannus, tissue or suture, PV leak, inappropriate sizing or positioning, residual leak or obstruction after valve implantation or repair, regurgitation due to technical errors, dilatation of the sinotubular junction, dilatation of the valve annulus. In AVR percutaneous approaches: new onset of coronary ischemia from ostial obstruction or PV aortic regurgitation.	
		Annulus dilatation		
		Entrapment-leaflet		
		Specify leaflet		
		Entrapment-pannus		
		Inappropriate Sizing		
		Inappropriate Positioning		
		Ostial obstruction		
		Perivalvular Leak	Clinically or haemodynamically detectable defect between the heart valve substitute and the patient's annulus.	
		Major	1. PAL requiring surgical re intervention, and; 2. PVL requiring medical intervention only (i.e., after load reduction, occasional blood transfusion for mild Hemolysis).	
		Minor	1. Evidence of AI by echo without symptoms and with no Hemolysis that does not require any intervention. 2. Presence of non-laminar flow without symptoms and with no hemolysis that does not require any intervention and requires monitoring.	
		Valve Thrombosis	Blood clot, not associated with infection, causing dysfunction of the heart valve substitute. Diagnosis confirmed by echocardiography, angiocardiography or magnetic resonance imaging, operation, explant, or autopsy.	

		Other Non Structural Dysfunction, specify	Other structural dysfunction not defined above.	
Other Events				
	Allergic Reaction		Hypersensitivity to an allergen such as a medication, contrast agent, food or airborne substance. The reaction can be characterized by rash, nausea, vomiting, upper respiratory congestion, urticaria, shortness-of-breath, vasovagal reaction, or general collapse (anaphylaxis) Specific Allergen should be reported if known.	Not defined
	Esophageal Injury		Any evidence of puncture/dissection/perforation, varices or other damage to the esophagus requiring intervention..	Not defined

20.0 APPENDIX 9: CLINICAL RISK ASSESSMENT

Edwards

CLINICAL RISK ASSESSMENT

Carpentier-Edwards® PERIMOUNT® Plus, Models 6900P / 6900PTFX

Carpentier-Edwards® PERIMOUNT® Magna Mitral Bioprosthesis Model 7000TFX

Carpentier-Edwards® PERIMOUNT® Magna Mitral Ease™ Bioprosthesis Model 7200TFX

Carpentier-Edwards® PERIMOUNT® Magna Mitral Ease™ Bioprosthesis Models 7300 / 7300TFX

Effective Date: April 26, 2010

[redacted]

Edwards Lifesciences LLC
One Edwards Way
Irvine, CA 92614 USA

Table of Contents

1 INTRODUCTION 3

1.1 Device Description 3

1.2 Intended Use 5

1.2.1 Indications *..... 5*

1.2.2 Contraindications *..... 6*

1.3 Proposed Benefit 6

1.4 Risks, Side Effects, and Adverse Effects 6

1.5 Assessment of Clinical Safety and Performance 8

1.5.1 State of the Art *..... 8*

1.5.2 Bench tests *..... 10*

1.5.3 Clinical Data *..... 10*

1.5.4 Literature Review *..... 16*

1.5.5 Marketing History *..... 24*

1.5.6 Post Market Surveillance *..... 25*

2 DISCUSSION AND SUMMARY 30

3 REFERENCES 31

1 Introduction

Manufacturer: Edwards Lifesciences
Irvine, California, USA

Medical Device:
Carpentier-Edwards® PERIMOUNT® Plus, Models 6900P / 6900PTFX
Carpentier-Edwards® PERIMOUNT® Magna Mitral Bioprosthesis Model 7000TFX
Carpentier-Edwards® PERIMOUNT® Magna Mitral Ease™ Bioprosthesis Model 7200TFX
Carpentier-Edwards® PERIMOUNT® Magna Mitral Ease™ Bioprosthesis Models 7300 / 7300TFX

Documents taken into Consideration:

Product Description
Risk Analysis per BS EN ISO14971:2009
Instructions for use
Scientific literature
Complaint Report Period: January 01, 2004 to March 31, 2010

1.1 Device Description

The Carpentier-Edwards PERIMOUNT Magna Mitral Ease pericardial bioprosthesis is built upon the same proven[1] wireform frame and leaflet attachment as the PERIMOUNT mitral pericardial bioprostheses models 6900, 6900P, 6900PTFX, 7000TFX, and 7200TFX. They are available in sizes 25 – 33 mm (model 7200TFX is available in sizes 27 – 35). The bioprosthesis incorporates a sewing ring specifically designed for the mitral position and is the first bioengineered mitral bioprosthesis design with three selected bovine pericardial leaflets mounted on a flexible metal alloy frame.

Bovine pericardium was selected for its superior intrinsic properties for valve manufacture, notably in terms of collagen content [2] and tolerance to high bending curvatures[3]. 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 bioprosthesis is treated according to the ThermaFix process, which involves heat treatment of the tissue in glutaraldehyde and uses ethanol and

[1] Marchand MA., et al. Fifteen-year Experience with the Mitral Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis. *Ann Thorac Surg*. 2001; 71:S236-9.
[2] Liao K., et al. Bovine Pericardium versus Porcine Aortic Valve: Comparison of Tissue Biological Properties As Prosthetic Valves; *Artificial Organs*. 1992;16(4):361-5.
[3] Vesely I., et al. Comparison of the Compressive Buckling of Porcine Aortic Valve Cusps and Bovine Pericardium. *J Heart Valve Dis*. January 1998; 7(1):34-9.

Polysorbate-80 (a surfactant). Glutaraldehyde is shown to both reduce the antigenicity of tissue xenograft valves and increase tissue stability.[4,5] Glutaraldehyde alone has not been shown to affect or reduce the calcification rate of the valve.

Tissue thickness is measured for each valve size and leaflets are precisely die-cut in selected areas of a pericardial sheet. Leaflet deflection testing characterizes each leaflet for elasticity. Three leaflets matched for similar thickness and elasticity are then assembled. Leaflets are mounted underneath the wireform frame to minimize commissural stress points.

The lightweight wireform frame is made of a corrosion-resistant cobalt-chromium alloy, chosen because of its superior spring efficiency 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 sewn with polytetrafluoroethylene thread. The wireform frame of the Magna Mitral Ease bioprosthesis is symmetrical and the three commissure supports (struts) are equally spaced.

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

The sewing ring is made of waffled silicone-rubber and is covered with a porous polytetrafluoroethylene cloth sewn with polytetrafluoroethylene thread. The cloth facilitates tissue in-growth and encapsulation. The sewing ring of the Magna Mitral Ease bioprosthesis is uniquely scalloped along its anterior portion and mimics the natural saddle shape of the native mitral valve anatomy. Black silk suture markers on the anterior portion facilitate the orientation of the bioprosthesis and help avoid obstruction of the left ventricular outflow tract by a strut. A black silk suture guide line circles the sewing ring of models 7300 / 7300TFX . Placing sutures through the sewing ring and in the region from the suture guide line to the outer portion of the sewing ring complements the design of the silicone waffle by easing needle penetration and providing variable compliance. The waffle has wider cells along the posterior portion, where calcifications or irregularities of the native mitral annulus are more frequent.[6] 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 Tricentrix holder system is designed to minimize the potential for suture or chordate entrapment, ease insertion and increase leaflet visibility. The holder consists of

[4] Carpentier A. From Valvular Xenograft to Valvular Bioprosthesis (1965-1977). *Med. Instrum*. 1977; 11(2):98-101.
[5] Carpentier A., et al. Continuing Improvements in Valvular Bioprostheses. *J. Thorac. Cardiovasc. Surg*. 1982; 83(1):27-42.
[6] Arounlangsy P., et al. Histopathogenesis of early stage mitral annular calcification. *J. Med Dent Sci*. 2004; 51(1):35-44.

three main components: a grey holder, a white holder post, and a blue adapter. It is secured to the bioprosthesis with green sutures. The bioprosthesis and holder attachment are suspended by a clip and a sleeve within a sealed jar that contains a glutaraldehyde packing solution. The bioprosthesis is terminally sterilized in glutaraldehyde.

The design of the model 7200TFX valve is identical to the model 7000TFX valve. The differences between the two valves are that the model 7200TFX has a grey Tricentrix holder instead of white, and the sizing conventions of the valves. The model 7000TFX valve is available in sizes 25, 27, 29, 31, and 33 mm. This sizing is based on the wireform diameter. The model 7200TFX sizing is similar to the tissue annulus diameter of the valve and is available in sizes 27, 29, 31, 33, and 35. There are no units associated with these sizes because the sizes do not reflect the actual tissue annulus diameter.

The design of the model 7300TFX valve is identical to the model 7000TFX valve. The differences between the two valves are that the model 7300TFX has a Tricolor Tricentrix holder system to provide additional contrast (blue instead of white adapter, and white instead of grey post) and a black silk suture guide line circles the inflow side of the sewing ring. Modifications were also made to the clip, sleeve, and jar which are packaging components, for user convenience. Modifications were made to the accessories which include two sizer types, the barrel and the replica sizers, and a change to the handle threads to make it compatible with the Tricentrix Holder, make it longer and change in grip color. The only difference between the model 7000 and 7300TFX is that, as with other PERIMOUNT models, the TFX version is manufactured with pericardial leaflets treated with ThermaFix.

1.2 Intended Use

Pericardial valves are intended for use in patients suffering from valvular heart disease. Models 6900P, 6900PTFX, 7000TFX, 7200TFX, 7300 and 7300TFX are intended for use in patients whose mitral valvular disease is sufficiently advanced to warrant replacement of their natural valve with a prosthetic one and when the valve cannot be repaired. It is also intended for use in patients with a previously implanted mitral valve prosthesis that is no longer functioning adequately and requires replacement.

1.2.1 Indications

Mitral valvular heart disease is a condition involving any of the following: obstruction of the mitral heart valve or stenosis; leakage of the mitral valve, known as regurgitation, incompetence, or insufficiency; and combinations of the two, sometimes referred to as mixed disease or combined lesions. Mitral valvular heart disease may be caused by any number of factors, including congenital abnormalities, infection by various

microorganisms, degenerative calcification, and rheumatic heart disease. Pericardial valves are used particularly in those patients for whom long-term anticoagulation is contraindicated or who may be difficult to maintain on anticoagulation therapy.

1.2.2 Contraindications

The contraindications of pericardial valves are determined by the surgeon as those that would be contrary to the best interests of the patient. The decision for or against the use of pericardial valves remain with the surgeon who can evaluate all the various risks involved, including the anatomy and pathology observed at the time of surgery.

In the presence of conditions affecting calcium metabolism or when calcium containing chronic drug therapies are used, the use of a mechanical prosthesis as an alternative should be considered. This is also true in patients under 20 years of age, in patients on a high calcium diet, and in patients who are on maintenance hemodialysis.

1.3 Proposed Benefit

The patients for whom pericardial valves are intended are those seriously or critically ill patients whose prognosis without surgery for replacement of the diseased natural or prosthetic valve is unacceptably poor in terms of survival, quality of life, or both in the opinion of the attending physicians.

1.4 Risks, Side Effects, and Adverse Effects

As with all prosthetic heart valves, serious complications, sometimes leading to death, may be associated with the use of tissue valves. In addition, complications due to individual patient reaction to an implanted device, or to physical or chemical changes in the components, particularly those of biological origin, may occur at varying intervals (hours or days) necessitating reoperation and replacement of the prosthetic device.

Events associated with the use of stented bioprosthetic heart valves include:

- Stenosis
- Regurgitation through an incompetent valve
- Perivavlular leak
- Endocarditis
- Hemolysis
- Thromboembolism
- Thrombotic obstruction
- Bleeding diatheses related to the use of anticoagulant therapy

- Malfunctions of the valve due to distortion at implant, fracture of the Elgiloy wireform, or physical or chemical deterioration of valve components
- Tissue deterioration including infection, calcification, thickening, perforation, degeneration, suture abrasion, instrument trauma, and leaflet detachment from the valve stent posts

Events potentially associated with the use of stented bioprosthetic heart valves include:

- Angina
- Cardiac arrhythmias
- Endocarditis
- Heart failure
- Hemolysis
- Hemolytic anemia
- Hemorrhage
- Local and/or systemic infection
- Myocardial infarction
- Prosthesis leaflet entrapment
- Prosthesis nonstructural dysfunction
- Prosthesis pannus
- Prosthesis perivalvular leak
- Prosthesis regurgitation
- Prosthesis structural deterioration
- Prosthesis thrombosis
- Stroke
- Thromboembolism

It is possible that these complications could lead to:

- Reoperation
- Explantation
- Permanent disability
- Death

These complications may present clinically as abnormal heart murmur, shortness of breath, exercise intolerance, dyspnea, orthopnea, anemia, fever, arrhythmia, hemorrhage, transient ischemic attack, stroke, paralysis, low cardiac output, pulmonary edema, congestive heart failure, cardiac failure, and myocardial infarct.

1.5 Assessment of Clinical Safety and Performance

1.5.1 State of the Art

A. Mechanical Valves

Mechanical valves available for both the aortic and mitral position include the ball-and-cage valves, single tilting disc prostheses, and bileaflet prostheses. The ball-and-cage valve utilizes a metal cage housing a silicone elastomer ball. The tilting disc prosthesis has a single circular occluder controlled by a metal strut. Bileaflet prostheses two semicircular leaflets that rotate about struts attached to the valve housing.

Mechanical valves have the following advantages as described in the ACC/AHA 2006 Guidelines for the Management of Patients with Valvular Heart Disease and the Guidelines on the management of valvular heart disease published by the Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC).

- Standard implantation technique
- Bileaflet valves are relatively quiet
- Bileaflet valves appear to be mechanically stable
- Bileaflet valves are relatively hemodynamically efficient

Mechanical valves have the following disadvantages as described in the ACC/AHA 2006 Guidelines for the Management of Patients with Valvular Heart Disease and the Guidelines on the management of valvular heart disease published by the Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC).

- Need for anticoagulation therapy to prevent thromboembolism
- Risk of bleeding complications
- Risk of thromboembolism despite anticoagulation therapy
- Increased risk of thromboembolism for mitral replacements
- Risk of endocarditis
- Hemodynamic inefficiency in smaller sizes
- ball-and-cage valves are associated with noise
- ball-and-cage valves are associated with hemodynamic inefficiency
- ball-and-cage valves in the mitral position project into the outflow tract causing obstruction
- single-disc valves are prone to severe hemodynamic compromise if disc thrombosis or immobility occurs

B. Homografts or AutoGrafts

Homograft valves donated by other patients and harvested after the patient expires are used as aortic replacements. Pulmonary autografts are also used in the Ross procedure.

Homograft or autograft valves have the following advantages as described in the ACC/AHA 2006 Guidelines for the Management of Patients with Valvular Heart Disease and the Guidelines on the management of valvular heart disease published by the Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC).

- Avoidance of early endocarditis
- Low risk of thromboembolism
- Excellent hemodynamic efficiency
- Pulmonary autografts may grow in children

Homograft or autograft valves have the following disadvantages as described in the ACC/AHA 2006 Guidelines for the Management of Patients with Valvular Heart Disease and the Guidelines on the management of valvular heart disease published by the Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC).

- Reduced availability when compared with xenografts/mechanical valves
- Surgical procedure is more complicated than xenografts/mechanical valves
- Reoperation after homograft AVR is more difficult

Discussion

In the 2008 edition of Cardiac Surgery in the Adult[7], Desai and Christakis discusses the balance of risk and benefits the surgeon and patient must make when selecting between the mechanical and biological valves. Structural deterioration, reoperation, thrombogenicity and bleeding complications are risks that must be taken into consideration, as well as the medical condition and age of the patient.

Results from Edwards' clinical trials and information available in the published literature demonstrate the safety and performance of pericardial valves, justifying their use in surgical treatment of valve disease. Use of the mechanical valve needs to have the cumulative risk of lifelong anticoagulation taken into serious consideration, and pericardial valves present an alternative for patients who wish to avoid long term anticoagulation.

Doenst et. al [2] indicated the Carpentier-Edwards pericardial aortic valve has proved to have durability particularly in older patients, prompting a revival in its mitral counterpart. The design of the mitral valve has enhanced the durability of the pericardium as a valve cusp. Cusps tears are a common cause of failure of previous pericardial valves and are rare with the Carpentier-Edwards pericardial valve. The table

[7] Desai N Di , Christakis G Ti . Bioprosthetic Aortic Valve Replacement: Stented **Pericardial** and Porcine **Valves**. Cohn Lh, ed. Cardiac Surgery in the Adult. New York: McGraw-Hill, 2008:857-894

below (Table 1) demonstrates actuarial freedom from structural valve deterioration (SVD) by age group for patients receiving the Carpentier-Edwards pericardial valve in the mitral position, and confirms patient age is a major determinant of SVD of pericardial valves.

Table 1: Actuarial freedom from structural valve deterioration by age group

Age groups (yr)	Number of patients	5-year (%)	10-year (%)
≤ 40	38	97	80
41-50	109	100	91
51-60	108	99	84
61-70	171	100	95
> 70	85	100	100

Desai and Christakis[8], stated currently available pericardial valves have >90% freedom from structural valve dysfunction and >90% freedom from reoperation at 12-year follow-up, and without any valve failures in patients older than 65 years.

Pericardial valves provide an option for mitral valve replacement in older patients with the need for reoperation as low, and can be used in younger patients with frequent monitoring of valve performance.

1.5.2 Bench tests

Refer to Design Dossier

1.5.3 Clinical Data

Since the designs of the 6900P, 6900PTFX, 7000TFX, 7200TFX, 7300 and 7300TFX valves are based on the model 6900 valve, the following clinical data applies to all models. Error! Reference source not found.**Table 2** correlates the model 7200TFX sizes with the model 6900 data.

Table 2: Models 6900 and 7200TFX Size Correlation Table

	Size				
Model 6900	25 mm	27 mm	29 mm	31 mm	33 mm
Model 7200TFX	27	29	31	33	35

[8] Desai N Di , Christakis G Ti . Bioprosthetic Aortic Valve Replacement: Stented **Pericardial** and Porcine **Valves**. Cohn Lh, ed. Cardiac Surgery in the Adult. New York: McGraw-Hill, 2008:857-894

Model 6900

Three (3) multi-center, non-randomized, prospective clinical studies were conducted with patients implanted with the Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis Model 6900 Mitral. Three hundred one (301) patients had isolated mitral valve replacement (MVR) and 62 patients had double valve replacement (DVR), where the aortic valve was replaced with a Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis aortic model. In the first study, patients were implanted between 1984 and 1986; in the second study, patients were implanted between 1989 and 1994; and in the third study, patients were implanted between 1996 and 1997. Patients were evaluated preoperatively, intraoperatively/at discharge, at 1 year, and annually thereafter.

The adverse event rates were based on 363 patients at nine centers. The cumulative follow-up was 1100 patient-years with a mean follow-up of 3.0 years (SD = 2.4 years, range = 0 to 8.2 years).

In these pooled populations, there were a total of 212 (58.4%) males and 151 (41.6%) females with a mean age at implant (± standard deviation) of 66.1 (± 10.7) years. The indications for valve replacement were regurgitation (50.7%), stenosis (25.1%), mixed disease (16.0%) and none (8.3%).

Model 6900P

One (1) multi-center, non-randomized, prospective international clinical study was conducted with patients implanted with the Carpentier-Edwards PERIMOUNT Pericardial Bioprosthesis Model 6900P mitral. One hundred seventy five (175) patients had isolated mitral replacement (MVR) and 34 patients had double valve replacement (DVR), where the aortic valve was replaced with a Carpentier-Edwards PERIMOUNT pericardial bioprosthesis aortic model. In this study, patients were implanted between 1999 and 2007. Patients were evaluated preoperatively, intraoperatively at discharge, at 1 year, and annually thereafter. Adverse events were captured throughout the postoperative period.

The adverse event rates are based on two hundred and nine (209) patients at seven centers. The cumulative follow-up was 873.18 patient-years with a mean follow-up of 4.2 years (SD = 2.3 years, range = 0 to 8.2 years).

Table 3 (model 6900) below presents the observed rates for early events (≤ 30 days for valve-related adverse events), the linearized rates for late events (> 30 days postoperatively), and the actuarial adverse event rates at 1, 5, and 8 years postoperatively.

Table 3: Observed Adverse Event Rates for MVR and DVR (Model 6900)

All patients analyzed: N = 363 Cumulative follow-up: 1100 patient-years

	Early Events		Late Events[1]		Freedom from Event (%) [95% CI][2]		
Complications	N	%	N	% / pt-year	1 year (n=287)	5 years (n=141)	8 years (n=18)
All Mortality	34	9.4	50	4.7	85.5 [81.8, 89.2]	75.4 [70.3, 80.6]	65.4 [57.6, 73.2]
Valve-related events							
Mortality (valve-related)	0	0	16	1.5	97.7 [96.0, 99.4]	95.3 [92.8, 97.8]	91.9 [87.5, 96.4]
Explants	0	0	8	0.7	98.7 [98.0, 99.3]	96.7 [95.3, 98.0]	95.6 [93.9, 97.3]
Reoperations	2	0.6	12	1.1	97.1 [96.2, 98.1]	95.1 [93.6, 96.6]	93.0 [90.9, 95.1]
Bleeding Event	2	0.6	9	0.8	97.1 [95.2, 99.0]	97.1 [95.2, 99.0]	94.1 [88.2, 100]
Endocarditis	1	0.3	3	0.3	99.0 [97.9, 100]	98.7 [97.4, 98.9]	98.7 [97.4, 98.9]
Hemolysis	0	0.0	1	0.1	99.7 [99.0, 100]	99.7 [99.0, 100]	99.7 [99.0, 100]
Nonstructural dysfunction	0	0.0	3	0.3	100 [100, 100]	99.3 [98.0, 100]	98.3 [95.9, 100]
Perivalvular leak (all)	1	0.3	5	0.5	98.4 [97.0, 99.8]	98.4 [97.0, 99.8]	97.3 [94.9, 99.8]
Structural valve deterioration	0	0.0	5	0.5	100.0 [100, 100]	97.6 [95.2, 100]	92.8 [85.3, 100]
Thromboembolism	5	1.4	8	0.7	97.5 [95.8, 99.2]	96.1 [93.8, 98.5]	96.1 [93.8, 98.5]
Thrombosis	0	0.0	0	0.0	100.0 [100, 100]	100.0 [100, 100]	100.0 [100, 100]

Notes:

1. Late event rates were calculated as linearized rates (%/pt-yr) based on 1072.5 late patient-years (>30 days postoperatively)
2. Freedom from event rates were calculated using the Kaplan-Meier method. Greenwood's formula was used for calculation of the standard errors of these estimates.
3. n = number of events

Table 4 (model 6900P) presents the observed rates for early events (≤ 30 days for valve-related adverse events), the linearized rates for late events (> 30 days postoperatively), and the actuarial adverse event rates at 1- and 5-years postoperatively for model 6900P. The adverse event rates were based on two hundred nine (209) patients at seven centers. The cumulative follow-up was 873.18 patient-years with a mean follow-up of 4.2 years (SD = 2.3 years, range = 0 to 8.2 years).

Table 4: Observed Adverse Event Rates (Model 6900P)

All patients analyzed: N=209. Cumulative follow-up: 873.18 total pt-yrs.

	Early Events		Late Events		Freedom from Event(%)[95% CI]	
Complication	**n**	**%**	**n**	**%/pt-yr**	**1 year**	**5 years**
Mortality (all)	3	1.4	45	5.3	93.2[88.8,95.9]	74.4[66.9,80.5]
Valve-related events						
Mortality (valve-related)	1	0.5	12	1.4	98.5[95.5,99.5]	92.0[86.2,95.5]
Explants	1	0.5	8	0.9	97.5[94.0,98.9]	96.5[92.2,98.5]
Reoperations	0	0.0	0	0.0	100.0[100,100]	100.0[100,100]
Bleeding Events	5	2.4	13	1.5	96.1[92.3,98.0]	91.9[86.5,95.2]
Endocarditis	1	0.5	3	0.4	99.5[96.6,99.9]	97.1[92.1,98.9]
Nonstructural Dysfunction	0	0.0	1	0.1	99.5[96.4,99.9]	99.5[96.4,99.9]
Perivalvular leak(all)	1	0.5	2	0.2	99.5[96.7,99.9]	98.4[95.2,99.5]
Structural Valve Deterioration	0	0.0	2	0.2	100.0[100,100]	99.0[93.2,99.9]
Thromboembolism	4	1.9	12	1.4	97.0[93.5,98.7]	91.3[85.8,94.7]
Thrombosis	0	0.0	0	0.0	100.0[100,100]	100.0[100,100]

Notes:

1. Late event rates were calculated as linearized rates (%/pt-yr) based on 856.24 late patient-years (> 30 days postoperatively).
2. Freedom from event rates was calculated using the Kaplan-Meier method. Greenwood's formula was used for calculation of the standard errors of these estimates.
3. n = number of events.

Table 5 (model 6900) and Table 6 (model 6900P) present, by valve size, the mean gradients and valve areas reported in echocardiograms performed on patients in the pooled study populations.

Table 5: Effective Outcomes, Hemodynamic Results[1] (Model 6900)					
Hemodynamic Parameter	Results By Valve Size				
	25 mm	27 mm	29 mm	31 mm	33 mm
Discharge/Early Post-Implant (n=130, 109 MVR[2] and 21 DVR[3])					
Mean gradient[4]	n = 3	n = 23	n = 36	n = 23	n = 3
• mean ±sd	5.7 ± 1.2	4.2 ± 1.7	4.2 ±1.7	3.6 ±1.0	7.5 ±5.8
• min, max	5, 7	2, 9	1, 8	2, 5	3, 14
EOA[5]	n = 1	n = 17	n = 22	n = 25	n = 5
• mean ± sd	1.5	2.9 ± 0.9	3.1 ± 0.9	2.5 ± 0.7	3.0 ± 1.2
• min, max	1.5, 1.5	1.3, 4.1	1.4, 4.2	1.5, 3.8	1.6, 4.9
Regurgitation[6]	n = 3	n = 28	n = 51	n = 40	n = 8
0	3/3 (100%)	22/28 (79%)	36/51 (71%)	30/40 (75%)	4/8 (50%)
1+	0/3 (0%)	5/28 (18%)	13/51 (25%)	7/40 (18%)	4/8 (50%)
2+	0/3 (0%)	0/28 (0%)	1/51 (2%)	3/40 (7%)	0/8 (0%)
3+	0/3 (0%)	0/28 (0%)	1/51 (2%)	0/40 (0%)	0/8 (0%)
4+	0/3 (0%)	0/28 (0%)	0/51 (0%)	0/40 (0%)	0/8 (0%)
Not available	0/3 (0%)	1/28 (3%)	0/51 (0%)	0/40 (0%)	0/8 (0%)
3 to 6 Month Post-Implant Interval (n=49, 42 MVR[2] and 7 DVR[3])					
Mean gradient[4]	n = 5	n = 19	n = 15	n = 5	n = 2
• mean ±sd	6.4 ±1.7	5.3 ±5	3.4 ±1.2	4 ±1.9	4 ±0
• min, max	5, 9	2, 25	2, 6	2, 7	4, 4
EOA[5]	n = 5	n = 18	n = 13	n = 5	n = 2
• mean ± sd	2.9 ± 0.8	2.6 ± 0.7	2.8 ± 0.6	2.9 ± 0.3	2.6 ± 1
• min, max	1.8, 3.6	1.5, 5	2, 3.8	2.4, 3.3	2, 3.3
Regurgitation[6]	n = 5	n = 21	n = 15	n = 6	n = 2
0	3/5 (60%)	17/21 (81%)	6/15 (40%)	4/6 (67%)	1/2 (50%)
1+	0/5 (0%)	4/21 (19%)	8/15 (53%)	2/6 (33%)	0/2 (0%)
2+	1/5 (20%)	0/21 (0%)	1/15 (7%)	0/6 (0%)	1/2 (50%)
3+	0/5 (0%)	0/21 (0%)	0/15 (0%)	0/6 (0%)	0/2 (0%)
4+	1/5 (20%)	0/21 (0%)	0/15 (0%)	0/6 (0%)	0/2 (0%)
Not available	0/5 (0%)	0/21 (0%)	0/15 (0%)	0/6 (0%)	0/2 (0%)
1 to 2 Year Post-Implant Interval (n=131, 114 MVR[2] and 17 DVR[3])					
Mean gradient[4]	n = 3	n = 40	n = 47	n = 27	n = 4
• mean ±sd	5.2 ±0.7	4.1 ± 1.6	3.5 ±1.8	3.1 ± 1.4	2.1 ±0.5
• min, max	4.7, 6	1, 7	1, 10	1,7	1.5, 2.7
EOA[5]	n = 2	n = 35	n = 46	n = 29	n = 5
• mean ±sd	1.8 ±0.4	2.3 ±0.6	2.6 ±0.5	2.6 ±0.7	2.5 ±0.5
• min, max	1.5, 2.0	1.2, 3.5	1.1, 3.7	1.1, 3.7	2.1, 3.2
Regurgitation[6]	n = 4	n = 42	n = 51	n = 29	n = 5
0	2/4 (50%)	31/42 (74%)	36/51 (71%)	17/29 (59%)	3/5 (60%)
1+	1/4 (25%)	9/42 (21%)	11/51 (21%)	8/29 (27%)	1/5 (20%)
2+	1/4 (25%)	2/42 (5%)	4/51 (8%)	2/29 (7%)	1/5 (20%)
3+	0/4 (0%)	0/42 (0%)	0/51 (0%)	2/29 (7%)	0/5 (0%)
4+	0/4 (0%)	0/42 (0%)	0/51 (0%)	0/29 (0%)	0/5 (0%)
Not available	0/4 (0%)	0/42 (0%)	0/51 (0%)	0/29 (0%)	0/5 (0%)
5 Year Post-Implant Interval (n=11, 9 MVR[2] and 2 DVR[3])					
Mean gradient[4]	n = 0	n = 6	n = 5	n = 0	n = 0
• mean ±sd	N/A	8.8 ±8.1	5.1 ±2.3	N/A	N/A
• min, max	N/A	4, 25	3, 8	N/A	N/A
EOA[5]	n = 0	n = 2	n = 4	n = 0	n = 0
• mean ±sd	N/A	2.0 ±1.5	2.9 ±0.6	N/A	N/A
• min, max	N/A	1.0, 3.1	2.1, 3.5	N/A	N/A
Regurgitation[6]	n = 0	n = 6	n = 5	n = 0	n = 0
0	0/0 (0%)	4/6 (66%)	2/5 (40%)	0/0 (0%)	0/0 (0%)
1+	0/0 (0%)	1/6 (17%)	3/5 (60%)	0/0 (0%)	0/0 (0%)
2+	0/0 (0%)	1/6 (17%)	0/5 (0%)	0/0 (0%)	0/0 (0%)
3+	0/0 (0%)	0/6 (0%)	0/5 (0%)	0/0 (0%)	0/0 (0%)
4+	0/0 (0%)	0/6 (0%)	0/5 (0%)	0/0 (0%)	0/0 (0%)
Not available	0/0 (0%)	0/6 (0%)	0/5 (0%)	0/0 (0%)	0/0 (0%)

Notes:

1. Hemodynamic evaluations were performed using transthoracic echocardiography (TTE) and in some cases, transesophageal echocardiography (TEE)
2. MVR = mitral valve replacement
3. DVR = double valve replacement
4. Mean gradient in mmHg
5. EOA: Effective Orifice Area, cm2
6. Regurgitation = none, 0; mild, 1+; moderate, 2+; moderate/severe, 3+; severe, 4+

Table 6: Effectiveness Outcomes, Hemodynamic Results (Model 6900P)[1]					
	Results By Valve Size				
Hemodynamic Parameter	25mm	27mm	29mm	31mm	33mm
Discharge/Early Post-Implant					
Mean gradient[2]	n=24	n=35	n=83	n=42	n=16
Mean+/-SD	6.4+/-1.87	4.4+/-1.52	3.4+/-1.47	3.3+/-1.20	4.0+/-1.38
Min,Max	3, 10	1.96, 8	1.4, 9	1, 7	1.5, 6.91
EOA[3]	n=8	n=27	n=77	n=41	n=16
Mean+/-SD	2.7+/-0.87	2.8+/-0.58	2.9+/-0.93	2.5+/-0.67	2.4+/-0.52
Min,Max	1.46, 4.4	1.5, 3.9	1.58, 6	1.32, 4.2	1.55, 3.31
Regurgitation[4]	n=27	n=37	n=83	n=43	n=17
Trivial / None	19/27(70%)	29/37(78%)	76/83(92%)	39/43(91%)	15/17(88%)
1+ Mild	6/27(22%)	7/37(19%)	7/83(8%)	4/43(9%)	1/17(6%)
2+ Moderate	1/27(4%)	1/37(3%)	0/83(0%)	0/43(0%)	0/17(0%)
3+ Moderate/Severe	0/27(0%)	0/37(0%)	0/83(0%)	0/43(0%)	1/17(6%)
4+ Severe	0/27(0%)	0/37(0%)	0/83(0%)	0/43(0%)	0/17(0%)
Not Available	1/27(4%)	0/37(0%)	0/83(0%)	0/43(0%)	0/17(0%)
3 to 6 Month Post-Implant Interval					
Mean gradient	n=0	n=4	n=3	n=2	n=0
Mean+/-SD	0+/-0	4.4+/-2.25	2.3+/-0.89	6.6+/-2.05	0+/-0
Min,Max	0, 0	2.5, 7.5	1.3, 3	5.1, 8	0, 0
EOA	n=0	n=3	n=3	n=1	n=1
Mean+/-SD	0+/-0	2.4+/-0.74	3.2+/-0.88	2.5+/-0.00	1.2+/-0.00
Min,Max	0, 0	1.6, 3	2.3, 4.05	2.47, 2.47	1.22, 1.22
Regurgitation	n=0	n=5	n=3	n=2	n=2
Trivial / None	0	3/5(60%)	2/3(67%)	2/2(100%)	2/2(100%)
1+ Mild	0	1/5(20%)	1/3(33%)	0/2(0%)	0/2(0%)
2+ Moderate	0	1/5(20%)	0/3(0%)	0/2(0%)	0/2(0%)
3+ Moderate/Severe	0	0/5(0%)	0/3(0%)	0/2(0%)	0/2(0%)
4+ Severe	0	0/5(0%)	0/3(0%)	0/2(0%)	0/2(0%)
Not Available	0	0/5(0%)	0/3(0%)	0/2(0%)	0/2(0%)
1 Year Post-Implant Interval					
Mean gradient	n=16	n=27	n=63	n=34	n=15
Mean+/-SD	5.9+/-2.36	4.0+/-1.45	3.0+/-1.61	3.3+/-1.26	3.4+/-1.25
Min,Max	3, 12	2, 7	1, 12	1.5, 7	1.9, 6.3
EOA	n=3	n=21	n=59	n=32	n=15
Mean+/-SD	2.3+/-0.16	2.4+/-0.76	2.6+/-0.74	2.5+/-0.67	2.3+/-0.83
Min,Max	2.09, 2.4	1.27, 4.76	1.5, 5.7	1.5, 4	1.2, 3.8
Regurgitation	n=20	n=28	n=65	n=34	n=16
Trivial / None	17/20(85%)	24/28(86%)	53/65(82%)	29/34(85%)	13/16(81%)
1+ Mild	3/20(15%)	3/28(11%)	6/65(9%)	3/34(9%)	3/16(19%)
2+ Moderate	0/20(0%)	0/28(0%)	3/65(5%)	2/34(6%)	0/16(0%)
3+ Moderate/Severe	0/20(0%)	0/28(0%)	1/65(2%)	0/34(0%)	0/16(0%)
4+ Severe	0/20(0%)	0/28(0%)	0/65(0%)	0/34(0%)	0/16(0%)
Not Available	0/20(0%)	1/28(4%)	2/65(3%)	0/34(0%)	0/16(0%)

Notes:

1. Hemodynamic evaluations were performed using transthoracic echocardiography (TTE) and in some cases, transesophageal echocardiography (TEE).
2. Mean gradient in mmHg
3. EOA: Effective Orifice Area, cm^2
4. Regurgitation = Trivial/none, 0; mild, 1+; moderate, 2+; moderate/severe, 3+; severe, 4+

Table 7 (model 6900) and Table 8 (model 6900P) presents data comparing preoperative NYHA Functional Class to postoperative NYHA Functional Class.

Table 7: Effectiveness Outcomes, Functional NYHA (Model 6900)

	Preoperative Assessment		Postoperative Assessments			
			1 to 2 Year		5 Year	
NYHA Functional Class	n/N[1]	%	n/N	%	n/N	%
I	11/363	3.0	120/268	44.8	40/129	31.0
II	73/363	20.1	90/268	33.6	25/129	19.4
III	192/363	52.9	15/268	5.6	1/129	0.8
IV	84/363	23.1	0/268	0.0	0/129	0.0
Not Available	3/363	0.8	43/268	16.0	63/129	48.8

Note:
1. n = number of patients in each category; N = total number of study patients.

Table 8: Effectiveness Outcomes, Functional NYHA (Model 6900P)

	Preoperative Assessment		Postoperative Assessments			
			1 Year		5 Year	
NYHA Functional Class	n/N[1]	%	n/N	%	n/N	%
I	6/209	2.9	86/187	46.0	30/96	31.3
II	27/209	12.9	68/187	36.4	33/96	34.4
III	121/209	57.9	8/187	4.3	6/96	6.3
IV	55/209	26.3	1/187	0.5	0/96	0.0
Not Available	0/209	0.0	24/187	12.8	27/96	28.1

Note:
1. n = number of patients in each category; N = total number of study patients.

1.5.4 Literature Review

The literature review has been conducted according to MEDDEV 2.7.1. April 2003 "Guidelines on Medical Devices, Evaluation of Clinical Data." The objective of this literature search was to demonstrate that the Carpentier-Edwards PERIMOUNT pericardial bioprostheses are safe and perform as intended by the manufacturer. The types of studies that are relevant to this objective are specified. The relevance of data and the extent to which the scientific articles relate to the device in question and to similar devices are shown below.

The scientific literature was searched for articles related to all of the Edwards pericardial bioprostheses using PubMed (www.pubmed.gov). The following key words search terms were entered in the online search engine with publication dates from January 01, 2003 to March 31, 2010:

- Carpentier-Edwards pericardial

- Edwards pericardial
- Carpentier Edwards bovine
- Edwards bovine
- Bovine pericardial valve
- Stented bovine valve
- Stented pericardial valve
- Carpentier-Edwards valve
- Pericardial valve
- Carpentier-Edwards PERIMOUNT Plus
- Edwards PERIMOUNT Plus
- PERIMOUNT Plus
- Carpentier-Edwards PERIMOUNT Mitral
- Edwards PERIMOUNT Mitral
- PERIMOUNT Mitral
- 6900P
- Carpentier-Edwards PERIMOUNT Magna Mitral
- Carpentier-Edwards PERIMOUNT Magna Mitral Ease
- Edwards PERIMOUNT Magna Mitral
- Edwards PERIMOUNT Magna Mitral Ease
- PERIMOUNT Magna Mitral
- PERIMOUNT Magna Mitral Ease
- Magna Mitral Ease
- Magna Mitral
- 7000
- 7200

The search yielded 14 journal articles published from 2003-2010 which described various techniques of valve replacement with the Carpentier-Edwards PERIMOUNT pericardial bioprostheses, echo studies, case studies and in-vitro studies. The abstracts were reviewed and pertinent articles are presented below.

[1] Daebritz et al reported results on a study of mitral valve replacements including the stented Perimount mitral valve. BACKGROUND: Current heart valve prostheses are constructed mimicking the native aortic valve. Special hemodynamic characteristics of the mitral valve such as a nonaxial central inflow with creation of a left ventricular vortex have so far not been taken into account. A new polycarbonaturethane (PCU) bileaflet heart valve prosthesis with special design for the mitral position is introduced, and results of animal testing are presented. METHODS AND RESULTS: After in vitro testing, 7 PCU-prostheses and 7 commercial bioprostheses (Perimount, n=4; Mosaic, n=3) were implanted in mitral position into growing Jersey calves (age 3-5 months, weight 60-97 kg) for 20 weeks. 2-Dimensional echocardiography was performed after implantation and before sacrification. Autopsy included histologic, radiographic, and electron microscopic examination of the valves. In vitro durability was proven for >15

years. After implantation 2-dimensional-echocardiography showed no relevant gradient or regurgitation of any prosthesis. Clinical course of the animals with PCU valves was excellent. In contrast, 5 of 7 calves with bioprostheses were sacrificed after 1-9 weeks because of congestive heart failure. 2-Dimensional echocardiography of the PCU valves after 20 weeks showed mild leaflet thickening with trivial regurgitation; mean gradient was 8.1+/-5.0 mm Hg (weight: 160-170 kg). The explanted PCU prostheses revealed mild calcification and no structural degeneration. All of the Perimount bioprostheses were severely calcified and degenerated after 11+/-7 weeks. One Mosaic bioprosthesis was thrombosed after 1 week, and 2 showed severe and mild-to-moderate degeneration after 4 and 22 weeks, respectively. CONCLUSIONS: Polycarbonaturethane valve prostheses with special design for mitral position show excellent hemodynamic performance and durability in vivo. Calcification and structural changes are mild compared with bioprostheses. Controlled clinical studies are planned.

[2] Doenst et al reported results on a study of mitral valve replacements including the stented Perimount mitral valve. Pericardial valve bioprostheses were introduced in early 1970s and were widely used in the 1980s. The long-term results with the Ionescu-Shiley valve, the first commercially available pericardial valve, were disappointing because of high rate cusp tears during the first decade after implantation. The enthusiasm for this type of bioprosthetic valve was further hampered by the premature failure of the Hancock pericardial valve. The long-term results of aortic valve replacement with the Carpentier-Edwards pericardial valve, which was introduced in 1981, indicated that that valve was durable and the issue of cusp tears had been resolved by an appropriate design. This knowledge prompted surgeons to revisit the merits of pericardial valves for mitral valve replacement and several other pericardial valves are now commercially available. The largest data on long-term results are with the Carpentier-Edwards pericardial mitral valve. The reported freedom from structure valve failure ranged from 69% to 85% at 10 years in patient population with mean age of 60 to 70 years. Young age is a major determinant of valve failure, which is largely due to calcification. There are also long-term data, albeit more limited on the Sorin Pericarbon and Mitroflow valves used for mitral valve replacement. This paper reviews the published experience with various pericardial bioprosthetic valves used for mitral valve replacement during the past 3 decades.

[3] Goetze et al reported results on a study of mitral valve replacements including the stented Perimount mitral valve. We sought to determine the hemodynamic performance of the Carpentier-Edwards Perimount pericardial valve in the mitral position. We reviewed the Doppler echocardiographic data on 189 patients (110 women; 68 +/- 12 years of age) who were implanted with this valve (7.6 days +/- 13 postoperatively) at our institution between September 2000 and May 2002. The average ejection fraction was 47%. For all valves, the peak velocity was 1.9 +/- 0.3 m/s, peak gradient was 15 +/- 4.8 mm Hg, and mean gradient was 5.8 +/- 2 mm Hg. The pressure half-time was 93 +/- 24 milliseconds, with a calculated effective orifice area of 2.5 +/-

0.6 cm2. The average effective orifice area by continuity equation (83 valves) was 1.5 +/- 0.5 cm2. The mitral regurgitation was graded mild or less in 97.5% of all valves. This is the largest series establishing the favorable hemodynamic behavior of the different sizes of a new Perimount mitral valve, and the reported data could serve as a reference.

[4] Kheradvar et al reported results on a study of mitral valve replacements including the stented Perimount mitral valve. In vitro assessment of different profiles for prosthetic mitral valves can result in better understanding of the physics of transmitral flow for each design. It has been postulated that decreasing the profile height of the mitral bioprosthetic valve has potential clinical benefit. In the present study, we compared the atrial and ventricular flow characteristics in different conditions using Carpentier-Edwards Perimount mitral valves with various profile heights. Each valve was placed at the intersection of the left ventricle, made of transparent silicone rubber, and the left atrium in Caltech's left heart pulsed flow simulator system. Digital particle image velocimetry has been used as the quantitative flow visualization technique. With the intention of studying the blood wash out around each valve, circulation and particle residence time were computed based on the vorticity and velocity fields around each valve, respectively. Results show that by increasing the profile's height at the atrial side of the valve, the magnitude of circulation near the atrial side of the valve decreases while particle residence time increases. However, extreme reduction of profile height in the ventricular side may increase the magnitude of circulation around the valve and decrease the particle residence time.

[5] Murayama et al reported results on a case of mitral valve replacements including the stented Perimount mitral valve. We report the case of a mitral Carpentier-Edwards pericardial bioprosthesis that was explanted from a 43-year-old female patient because of structural valve deterioration 16 years following implantation. Upon removal, the prosthesis was found to be discolored and all leaflets were stiff and hard, showing extensive calcification, pannus overgrowth, leaflet hematoma, and multiple disruptions. One leaflet presented a wavy free margin due to commissural disruptions, leading to incomplete cusp coaptation. The accumulated physical symptoms of the patient were consistent with these findings.

[6] Tateishi et al reported results on a case of mitral valve replacements of a stented Perimount mitral valve. A 73-year-old woman who underwent mitral valve replacement with a 31 mm Carpentier Edwards Pericardial Xenograft 19 years ago. She revealed sudden onset of a grade IV/VI a seagull like diastolic murmur at the apex, and severe hematuria. Echocardiography demonstrated severe mitral regurgitation. These findings were consistent with acute primary tissue valve failure. Therefore we performed emergency reoperation. At operation, valve leaflet was torn at the commissural stitch, and bioprosthesis strut was buried in the left posterior ventricular wall. The mitral prosthetic valve replaced with a 25 mm CarboMedics OptiForm using a technique of

valve-in-valve replacement. This procedure would be one option for replacement of bioprosthetic mitral valve

[7] Chambers et al reported that stented bovine pericardial valve might be less obstructive than a stented porcine valve. This study compared early hemodynamic function in a prospective series of 99 patients randomized to receive either a Mosaic or Perimount replacement aortic valve. Echocardiography was performed early after surgery and at 1 year after surgery. Patients also filled in psychologic questionnaires and underwent a 6-minute walk. The groups were matched demographically. The Perimount valve was significantly less obstructive in terms of mean pressure difference (11 +/- 5 vs. 17 +/- 7 mm Hg; P < .0001), with a trend in favor of a larger effective orifice area (1.47 +/- 0.45 vs. 1.28 +/- 0.46 cm (2); P = .05) postoperatively. There were no differences in left ventricular mass regression, aortic regurgitation, 6-minute walk, psychologic questionnaires, or mortality and clinical events. The stented bovine pericardial valve was less obstructive than the stented porcine valve. Both valves were associated with similar and significant improvements in quality of life, exercise ability, and regression of left ventricular mass.

[8] Risteski et al reported on randomized trials comparing stentless to stented bioprostheses for aortic valve replacement in elderly are scarce. The aim of this study was early and mid-term evaluation of these bioprostheses, with regards to clinical outcome and hemodynamic performance. Between September 1999 and January 2001, 40 patients with aortic stenosis, over the age of 75 years, were randomly assigned to receive either the stented Perimount (n=20) or the stentless Prima Plus (n=20) bioprosthesis. Clinical outcomes, left ventricular mass regression, effective orifice area, ejection fraction and mean gradients were evaluated at discharge, six months, one year and five years after surgery. At five years, there were 5/20 (25%) deaths in the stentless group and 6/20 (30%) deaths in the stented group (all non-valve-related). There was one case of endocarditis in each group, early postoperatively. Overall, a significant decrease in left ventricular mass was found five years postoperatively. However, there was no significant difference in the rate and completeness of LV-mass regression between the groups (LV mass index 114+/-34.1 vs. 120+/-27.2). Furthermore, hemodynamic performance of the valves (mean gradient of 9.9+/-4.8 mmHg vs. 10.2+/-4.2 mmHg) did not differ significantly between the groups. At five years, stentless valves were not superior to the stented valves, with regards to hemodynamic performance, regression of left ventricular mass and clinical outcome.

[9] Accola et al reported that aortic valve dysfunction is the most common form of valvular heart disease. As the population continues to age, a greater number of patients will become candidates for aortic valve replacement (AVR); hence, prosthetic valve choice becomes of paramount importance. A retrospective analysis was conducted on 801 patients aged > or =65 years who underwent isolated AVR or AVR + coronary artery

bypass grafting (CABG) between January 1989 and June 2003 with a Carpentier Edwards Perimount (CEP) pericardial bioprosthesis (n = 398) or a St. Jude Medical (SJM) mechanical valve (n = 403). The mean age of CEP patients was 74.5 years (range: 65-89 years), and of SJM patients 73.9 years (range: 65-90 years). The follow up was 96.2% and 96.5% complete for CEP and SJM patients, respectively. Propensity scoring was used to establish homogeneity of the groups and reduce bias. The operative mortality was 4.0% (n = 16) among CEP patients and 6.5% (n = 26) among SJM patients. Predictors of hospital mortality included: peripheral vascular disease (p = 0.018), surgical urgency (p = 0.010), preoperative intra-aortic balloon pump (IABP) (p = 0.010), intraoperative perfusion time (p = 0.046) and intraoperative IABP (p = 0.001). Postoperative morbidities were similar for the two groups. The mean follow up was 72.4 and 59.2 months for CEP and SJM patients, respectively. The five-year actuarial survival was 70.9 +/- 2.3% for CEP and 71.8 +/- 2.4% for SJM patients; at 10 years the actuarial survival was 32.6 +/- 3.3% and 38.2 +/- 3.8%, respectively. Freedom from reoperation for AVR, stroke and non-fatal myocardial infarction was 98.8% (159/161), 99.4% (160/161) and 99.4% (160/161), respectively, in CEP patients, and 100.0% (220/220), 97.7% (215/220) and 97.7% (215/220), respectively, in SJM patients (p = NS). Predictors of late death (>30 days) included chronic obstructive pulmonary disease (p = 0.001) and mechanical valve replacement (p = 0.001). In comparable elderly patients, the outcomes of CEP and SJM valves after AVR showed no significant differences in hospital morbidity, mortality, mid-term survival or late cardiac events. However, the cumulative risk of lifelong anticoagulation with a mechanical valve is a serious consideration that must be factored into the selection algorithm.

[10] Kume et al reported on a study to evaluate the impact of Doppler-derived energy loss coefficient (ELCo) on the regression of left ventricular (LV) hypertrophy after aortic valve replacement (AVR) in patients with severe aortic stenosis. Twenty-four patients with severe aortic stenosis who underwent AVR with Carpentier-Edwards pericardial bioprosthetic valves (valve size 19 mm, n = 16; valve size 21 mm, n = 8) were examined. Within 12 months after AVR, follow-up echocardiography and Doppler measurements were performed. The effect of AVR was quantified on the basis of absolute and relative LV mass regression. There were significant correlations between indexed ELCo and absolute (r = 0.50, P = .013) and relative (r = 0.48, P = .018) LV mass regression. The mean value of relative LV mass regression was 25%, and a cutoff value of 0.9 cm(2)/m(2) for indexed ELCo could detect patients with relative LV mass regression > 25% after AVR with sensitivity of 71% and specificity of 100%. ELCo, which can be calculated noninvasively from echocardiography, might be an important value to relate to LV mass regression in patients after AVR.

[11] Hilker et al reported observations among Karlsburg patients in 2006 revealed that the majority of very low platelet levels inducing postoperative heparin-induced-thrombocytopenia (HIT)-diagnostics with at the end negative results appeared related to aortic valve replacement (AVR) with stentless bioprostheses. We compared the postoperative courses of platelet counts in patients having had AVR with stentless

prostheses (Sorin Biomedica Freedom Solo [SOLO]) or stented prostheses (Carpentier Edwards Perimount [PM]). Between February 2005 and April 2007, 209 patients received AVR with SOLO, in 137 patients a PM-prosthesis was implanted. The mean platelet levels were compared from the first up to the fifth postoperative day. A higher occurrence of platelet levels below 100 Gpt/l between the second and the fifth postoperative day was found in the SOLO-group (71.9%) compared with the other biological substitute PM (36.6%). Differences in platelet counts between SOLO- and PM-subgroups were measured for day 2 (P=0.03), day 3 (P=0.0004) day 4 (P=0.0007), day 5 (P=0.0002) and at discharge (P<0.0001). Following intervention with conventional biological AVR, differences in the postoperative recovery of platelet counts can be detected, depending on the prosthesis used. The causes for and the clinical implications of this phenomenon are not yet assessed.

[12] Kubota et al reported a case of Carpentier-Edwards PERIMOUNT (CEP) mitral pericardial bioprosthesis explanted 22 years after the valve replacement. This patient underwent the previous replacement at the age of 50. The extracted bioprosthesis showed three rigid leaflets, one of which had a tear causing severe mitral regurgitation. The X-ray demonstrated calcification of varied extent among these leaflets, ranging from none to severe. When leaflet calcification is suppressed, perhaps the lifespan of a CEP valve can be prolonged more than previously expected. When a literature search was conducted, this case was found to represent the longest reported interval from the implantation of a CEP valve in the mitral position to the explantation as a result of severe mitral regurgitation caused by structural valve deterioration (SVD).

[13] M Thalmann et al in a letter to Editor, regarding the world's first implant of a 23 mm Carpentier-Edwards Perimount Magna mitral bioprosthesis, pointed out the need for appropriate sizing to avoid patient-prosthesis mismatch and infrequent but potentially lethal LV rupture.

[14] Alsoufi B, et al reported the ideal valve substitute in children does not exist. Biologic and bioprosthetic valves do not require anticoagulation however their use is complicated by accelerated degeneration and requirement for reoperation. We examine results following mitral (MVR) or aortic (AVR) replacement with biologic and bioprosthetic valves at our institution. METHODS: Medical records of children who underwent AVR or MVR from 1986 to 2006 were reviewed. Median follow-up duration was 10.5 years. Competing-risks methodology determined time-related prevalence and associated factors for three mutually exclusive end states: death, valve reoperation, and survival without subsequent reoperation. RESULTS: One hundred and ten children (age 15.6+/-2.6 years, 80% females) underwent 123 valve replacements with biologic and bioprosthetic substitutes including 87 MVR and 36 AVR (13 had both). Underlying pathology was mainly rheumatic fever (91%). Thirty-nine patients (35%) had undergone a previous cardiac surgery. Most common mitral substitute was Hancock (73%) and

homograft (8%); most common aortic substitute was homograft (41%) and Carpentier-Edwards (39%). Competing-risks analysis showed 15 years after valve replacement, 16% of patients had died without subsequent reoperation, 66% underwent valve reoperations, and only 18% remained alive without further reoperation. Factors associated with increased reoperation risk included younger age at surgery (p=0.005), AVR (p=0.005), male gender (p=0.02) and homograft use (p=0.007) especially in the mitral position (p=0.002). Fifteen-year freedom from endocarditis was 97% while freedom from bleeding and thromboembolic complications was 100%. Majority of patients (95%) were in NYHA functional classes I/II at last follow-up. CONCLUSION: While valve reoperation is inevitable following AVR and MVR with biologic and bioprosthetic substitutes, favorable results such as low valve-related morbidity rate, good long-term survival and functional status encourage their consideration as valid replacement alternatives in selected children, especially females. Valve durability is higher in the mitral position and longevity of bioprosthetic valves is greater than that of homografts especially in the mitral position.

1.5.5 Marketing History

The approval dates for each PERIMOUNT valve are shown below in Table 9.

Table 9: Global product approvals					
Model	**Europe**	**Australia**	**Canada**	**Japan**	**US**
6900P	May 2000	Oct 1991	Sept 1998	Apr 2007	Nov 2001
6900PTFX	Apr 2004	Sep 2005	Dec 2007	NA	Jan 2004
7000	NA	Nov 2008	Nov 2005	NA	Aug 2008
7000TFX	Aug 2005	Nov 2008	Nov 2005	NA	Aug 2008
7200TFX	Mar 2010	NA	NA	NA	Jul 2009

[redacted]

[redacted]

1.5.6 Post Market Surveillance

[redacted]

All expiration, reoperations, explants and complications are evaluated for their relationship to the valve, with special attention being paid to incidences of angina, anticoagulant related hemorrhage, arrhythmia, cardiac arrest, endocarditis, heart failure, hemolysis, myocardial infarction, nonstructural dysfunction, perivalvular leak, structural deterioration, thromboembolism, thrombosis and unacceptable hemodynamics.

All cardiovascular related symptoms, such as abnormal heart murmur, shortness of breath, exercise intolerance, dyspnea, orthopnea, anemia, fever, transient ischemic attack, stroke, paralysis, low cardiac output and pulmonary edema are assessed as to their relation to the valve.

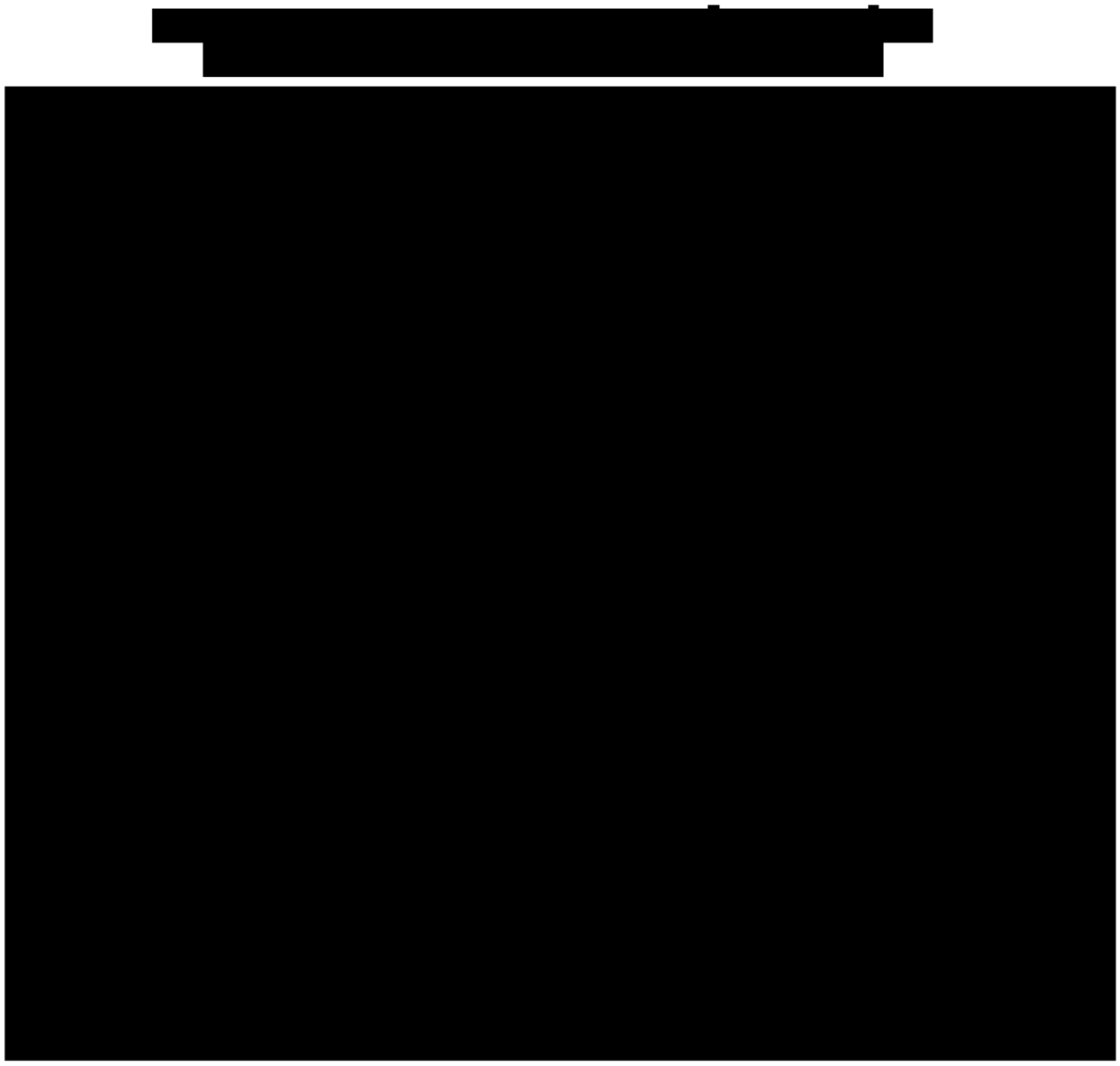
The information used to perform this evaluation is taken from the complications handled through the Edwards complaint-handling system, and from supporting documentation, i.e., autopsy reports and expiration summaries. When the review is inconclusive as to valve relatedness, a conservative choice is made and the complication is classified as “valve-related.”

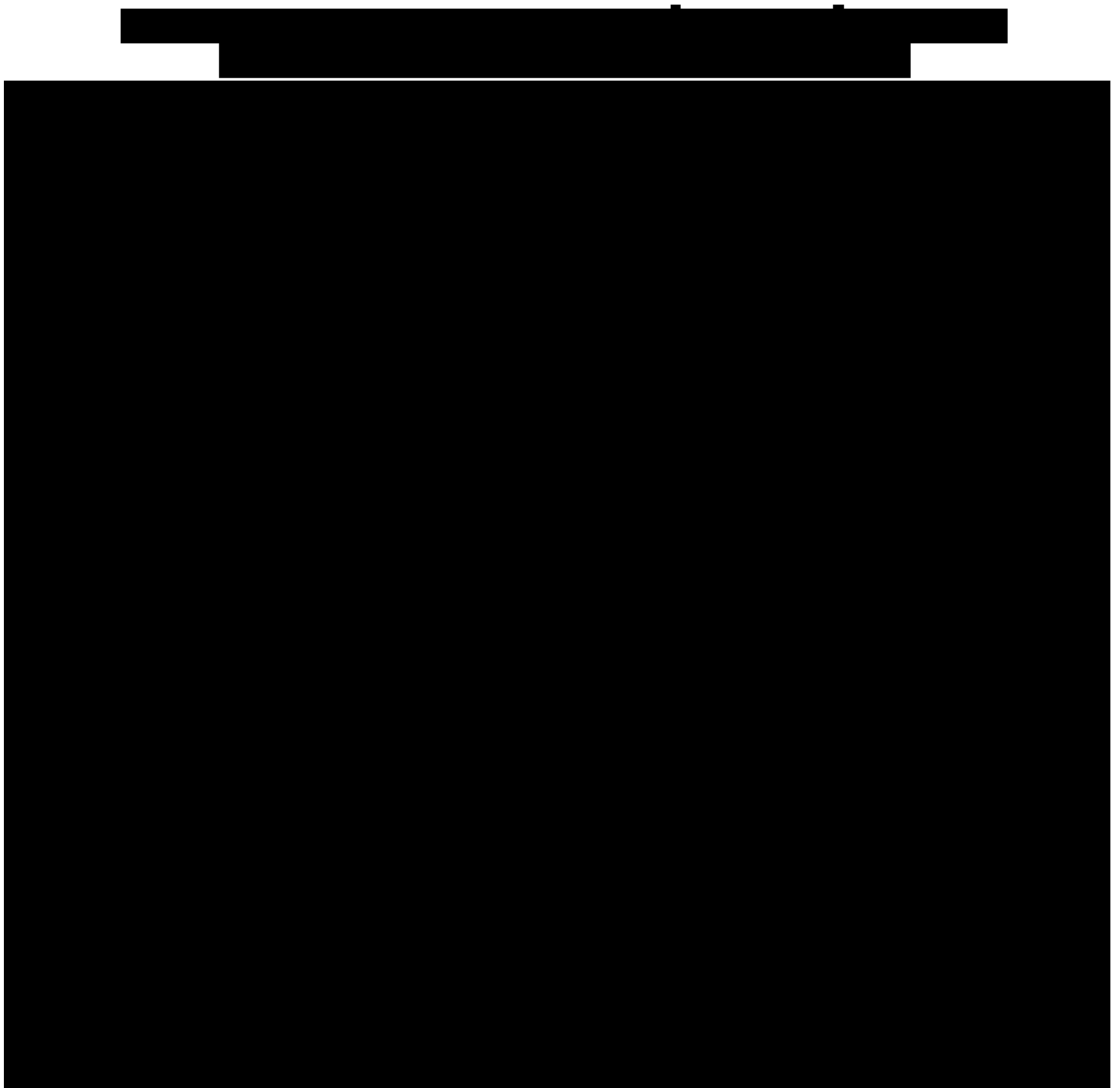
[redacted]

[redacted]

[redacted]

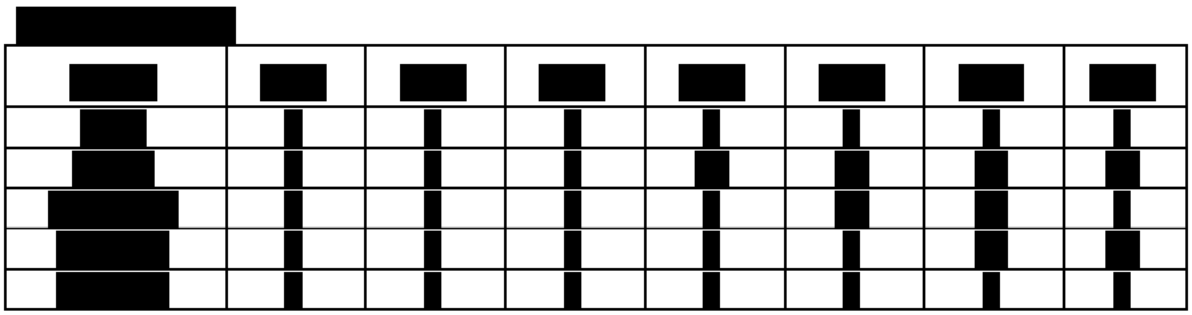
[redacted]





[redacted]

[redacted]



2 Discussion and Summary

The pericardial valves have been on the market in Europe for over 17 years beginning with the model 6900. Throughout the years, design modifications have been made and new models received the CE marking. Evidence of safety and efficacy of these devices is established and well documented in clinical studies, the scientific literature, in addition to complaint reports. The scientific literature, as presented in this document, has not raised any safety signals and has continued to confirm the safety and efficacy as previously known. In addition, the low post market surveillance complaint rates support the safety/benefit profile of these devices. The risks associated with the use of bioprosthetic valves and the risks of open-heart cardiac surgery are well known in the surgical community and generally accepted.

3 References

1. Daebritz SH, Sachweh JS, Hermanns B, Fausten B, Franke A, Groetzner J, Klosterhalfen B, Messmer BJ. Introduction of a flexible polymeric heart valve prosthesis with special design for mitral position. Circulation. 2003 Sep 9;108 Suppl 1:II134-9.

2. Doenst T, Borger MA, David TE. Long-term results of bioprosthetic mitral valve replacement: the pericardial perspective. J Cardiovasc Surg (Torino). 2004 Oct;45(5):449-54.

3. Goetze S, Brechtken J, Agler DA, Thomas JD, Sabik JF 3rd, Jaber WA. In vivo short-term Doppler hemodynamic profiles of 189 Carpentier-Edwards Perimount pericardial bioprosthetic valves in the mitral position. J Am Soc Echocardiogr. 2004 Sep;17(9):981-7.

4. Kheradvar A, Kasalko J, Johnson D, Gharib M. An in vitro study of changing profile heights in mitral bioprostheses and their influence on flow. ASAIO J. 2006 Jan-Feb;52(1):34-8.

5. Murayama H, Watanabe T, Yano T, Kida N, Hatano Y, Ohara K, Kobayashi A. The case of an explanted 16-year-old mitral Carpentier-Edwards pericardial bioprosthesis. J Artif Organs. 2006;9(4):259-62. Epub 2006 Dec 21.

6. Tateishi M, Koide M, Kunii Y, Watanabe K, Ohsawa M. [Valve-in-valve replacement of primary tissue valve failure of bovine pericardial valve minor] Kyobu Geka. 2006 Jan;59(1):61-4.

7. Chambers JB, Rajani R, Parkin D, Rimington HM, Blauth CI, Venn GE, Young CP, Roxburgh JC. Bovine pericardial versus porcine stented replacement aortic valves: early results of a randomized comparison of the Perimount and the Mosaic valves. J Thorac Cardiovasc Surg. 2008 Nov;136(5):1142-8. Epub 2008 Aug 15

8. Risteski PS, Martens S, Rouhollahpour A, Wimmer-Greinecker G, Moritz A, Doss M. Prospective randomized evaluation of stentless vs. stented aortic biologic prosthetic valves in the elderly at five years. Interact Cardiovasc Thorac Surg. 2009 Apr;8(4):449-53. Epub 2009 Jan 6

9. Accola KD, Scott ML, Palmer GJ, Thompson PA, Sand ME, Suarez-Cavalier JE, Bott JN, Ebra G. Surgical management of aortic valve disease in the elderly: A retrospective comparative study of valve choice using propensity score analysis. J Heart Valve Dis. 2008 Jul;17(4):355-64; discussion 365

10. Kume T, Okura H, Kawamoto T, Watanabe N, Neishi Y, Hayashida A, Tanemoto K, Yoshida K. Impact of Energy Loss Coefficient on Left Ventricular Mass Regression in Patients Undergoing Aortic Valve Replacement: Preliminary Findings. : J Am Soc Echocardiogr. 2009 Mar 21

11. Hilker L, Wodny M, Ginesta M, Wollert HG, Eckel L. Differences in the recovery of platelet counts after biological aortic valve replacement. Interact Cardiovasc Thorac Surg. 2009 Jan;8(1):70-3. Epub 2008 Oct 8

12. Kubota S, Wakasa S, Ooka T, Tachibana T, Shiiya N, Matsui Y. A case of Carpentier-Edwards pericardial bioprosthesis in mitral position explanted 22 years after implantation. J Artif Organs. 2010 Apr;13(1):48-50. Epub 2010 Feb 17.

13. Thalmann M, Gorlitzer M, Grabenwöger M, Moidl R. Commented on: World's first implant of a 23-mm Carpentier-Edwards Perimount Magna mitral bioprosthesis. J Heart Valve Dis. 2009 May;18(3):352-3.

14. Alsoufi B, Manlhiot C, McCrindle BW, Canver CC, Sallehuddin A, Al-Oufi S, Joufan M, Al-Halees Z. Aortic and mitral valve replacement in children: is there any role for biologic and bioprosthetic substitutes? Eur J Cardiothorac Surg. 2009 Jul;36(1):84-90; discussion 90. Epub 2009 Apr 14.