Multi-CenTer Experience with the Rapid Deployment EDWARDS INTUITY Valve System FOR Aortic Valve ReplaceMent (TRANSFORM™ Post Approval Phase)

NCT01700439

Study Document Date: 03 November 2017

Multi-CenTer Experience with the Rapid Deployment EDWARDS INTUITY Valve System FOR Aortic Valve ReplaceMent (TRANSFORM™ Post Approval Phase)

Protocol Number: 2011-02

Version: 3 November 2017, Rev. P

Edwards Lifesciences
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Prepared By:

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Director, Clinical Affairs Date

Reviewed and Approved By:

_____ _____
Vice President, Clinical and Regulatory Affairs Date

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Staff Biostatistician – Biostatistics Date

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PERSONNEL AND FACILITIES

Sponsor: Edwards Lifesciences
One Edwards Way
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Principal Investigators:

Trial Director:

Echocardiography Core Lab:

Data Monitoring Committee: **Chairman:**

Members:

Clinical Event Committee:

SIGNATURE PAGE

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Investigator's Signature

I have read this protocol and agree to participate in the clinical trialof the EDWARDS INTUITY Valve System sponsored by Edwards Lifesciences, LLC. I agree to conduct this trial according to the requirements of the trial protocol and in accordance with Good Clinical Practice, applicable State and U.S. Federal regulations and conditions imposed by the reviewing Investigational Review Board. I agree to supervise all sub-investigators at my site.

Investigator's Signature	*Date*
Printed Name	

This protocol contains confidential proprietary information with respect to Edwards Lifesciences' products and clinical trials. I agree to hold this information in confidence and not to disclose it to any third parties for a period of five years from the date of this agreement, or until this information becomes a matter of public knowledge or until a formal agreement for that purpose is entered into by the parties.

Investigator's Signature	*Date*

TABLE OF CONTENTS

SYNOPSIS

Protocol Number	2011-02
Title	Multi-CenTer Experience with the Rapid Deployment EDWARDS INTUITY Valve System FOR Aortic Valve ReplaceMent (TRANSFORM™ Post Approval Phase)
Sponsor	Edwards Lifesciences
Objectives	To assess the safety and effectiveness of the EDWARDS INTUITY Valve System in subjects with aortic stenosis or stenosis-insufficiency requiring primary replacement of the native aortic valve in the premarket and post market phases. Safety was determined by comparing safety endpoints to the objective performance criteria (OPC) defined by ANNEX R, Section R2, Table R.1 of BS EN ISO 5840:2009 (Cardiovascular implants – Cardiac valve prostheses) and effectiveness was evaluated based on improvement in NYHA Class and hemodynamic parameters compared to baseline.
Trial Design	Prospective, non-randomized, multi-center trial. Pre market analysis was performed when the total late-patient years reached 800 and the number of subjects completing the one year (or greater) follow-up reached or exceeded 300. Post-market, all active subjects will be followed until the last enrolled subject completes their 5-year follow up.
Trial Population	The trial population consists of subjects enrolled in the TRANSFORM™ Trial.
Number of Subjects	There were 934 subjects enrolled at 29 clinical sites. All active subjects will continue follow up until the last enrolled subject completes their 5-year follow up
Gender/Age	Males and females, 18 years of age or older During the enrollment phase of the trial, the following Inclusion, Exclusion and Intra-operative Exclusion Criteria was required:

Inclusion Criteria

1. Male or female, age 18 years or older
2. Has aortic stenosis or stenosis-insufficiency of an aortic valve requiring a planned replacement as indicated in the preoperative evaluation
3. Is scheduled to undergo planned aortic valve replacement with or without concomitant coronary bypass surgery
4. Provide written informed consent
5. Geographically stable and agrees to attend follow-up assessments until all subjects have completed 5 years of follow up

Pre-operative Exclusion Criteria

1. Pure aortic insufficiency
2. Requires emergency surgery
3. Previous aortic valve replacement
4. Had prior mitral, tricuspid or pulmonic valve surgery, which included implant of a bioprosthetic valve, mechanical valve, or annuloplasty ring that will remain *in situ*
5. Requires multiple valve replacement/repair
6. Requires a surgical procedure outside of the cardiac area (e.g., vascular endarterectomy, vascular bypass, tumor removal)
7. Aneurysm of the aortic root and/or ascending aorta requiring surgical intervention
8. Active endocarditis/myocarditis or endocarditis/ myocarditis within 3 months prior to the scheduled AVR surgery
9. Myocardial infarction (MI) within thirty (30) days prior to valve replacement surgery
10. Renal insufficiency as determined by creatinine ≥ 2.5 mg/dL at screening or end-stage renal disease requiring chronic dialysis
11. Hyperparathyroidism
12. MRI or CT-scan confirmed cerebrovascular accident (CVA), or transient ischemic attack (TIA) within 6 months (180 days) of the procedure
13. Presence of non-cardiac disease limiting life expectancy to less than 12 months
14. Hypertrophic obstructive cardiomyopathy (HOCM)
15. Left ventricular ejection fraction ≤ 25%

16. Documented history of substance (drug or alcohol) abuse within the last 5 years
17. Echocardiographic evidence of an intra-cardiac mass, thrombus, or vegetation
18. Hemodynamic or respiratory instability requiring inotropic support, mechanical circulatory support, or mechanical ventilation within 30 days prior to the procedure
19. Pregnancy, lactation, or planning to become pregnant;
20. Currently incarcerated or unable to give voluntary informed consent
21. Leucopenia (WBC < 3.5x 10^3/µL), or acute anemia (Hgb < 10.0 gm/dL or 6 mmol/L), or thrombocytopenia (platelet count < 50x 10^3/µL), or history of bleeding diathesis or coagulopathy
22. History of myxomatous disease/connective tissue disorders (e.g., Marfan's Syndrome)
23. Current or recent participation (within 6 weeks prior to surgery) in an investigational drug or device trial

Intra-operative Exclusion Criteria

24. Anatomic variances which contraindicate implant of the trial valve, such as:
    a. anomalous coronary arteries
    b. annular deformation or extensive calcification of the annulus or aortic root which cannot be removed
    c. significant calcium on the anterior mitral leaflet
    d. pronounced septal calcification
    e. position of coronary ostia relative to Model 8300ACA/ACD valve that would result in obstruction of blood flow
25. Available devices are not suitably sized for the subject's annulus

Trial Device

EDWARDS INTUITY Valve System, Model 8300 which includes: EDWARDS INTUITY Aortic Valve, Model 8300ACA and EDWARDS INTUITY Delivery System, Model 8300DCA or EDWARDS INTUITY Aortic Valve, Model 8300ACD and EDWARDS INTUITY Delivery System, Model 8300DCD

Indication for Use

During the pre-market phase of the TRANSFORM™ Trial, the EDWARDS INTUITY Valve System (EDWARDS INTUITY Aortic Valve, Model 8300ACA/8300ACD and EDWARDS INTUITY Delivery System, Model

8300DCA/8300DCD) was indicated for use in subjects with aortic stenosis or stenosis plus insufficiency of an aortic valve requiring a planned replacement of their native aortic valve. Post market, the trial device is indicated for the replacement of diseased, damaged, or malfunctioning native or prosthetic aortic valves.

Schedule of Visits

- Screening (Day -90 to Day -1)
- Operative procedure (Day 0)
- Discharge (Post-op – Day of Discharge)
- Postoperative day POD 36 (-5/+10 days; by phone)
- POD 105 (-15/+30 days);
- POD 195 (-15/+45 days); only for subjects with paravalvular leak >mild or an implant related new or worsened cardiac conduction disturbance[1] on 3-month electrocardiogram;
- POD 390 (-25/+45 days)
- PO Year 2 (-60/+60 days)
- PO Year 3 (-60/+60 days)
- PO Year 4 (-60/+60 days)
- PO Year 5 (-60/+60 days)
- Annually thereafter until the last subject completes 5-year follow-up visit

  - At the time of this protocol revision, all patients had completed these visits

Safety Endpoints

The primary safety endpoints consist of:

- All cause mortality
  - Trial valve-related mortality
- Valve thrombosis (trial valve)
- Thromboembolism
- All hemorrhage
  - Major hemorrhage
- All paravalvular leak (trial valve)
  - Major paravalvular leak (trial valve)
- Endocarditis (trial valve)
- Structural valve deterioration (trial valve)
- Non-Structural valve deterioration (trial valve)

[1] Defined as new or worsened first degree atrioventricular (AV) block, second degree AV block (Mobitz I or Mobitz II), third degree AV block, incomplete right bundle branch block, right bundle branch block, intraventricular conduction delay, left bundle branch block, left anterior fascicular block, or left posterior fascicular block, including block requiring permanent pacemaker implant.

  - Valve Malposition
  - Valve Migration/ embolization
  - Valve Instability
  - Valve Dislodgment
- Hemolysis
- Reoperation
  - Trial valve-related reoperation
- Explant
  - Trial valve explant
- Implant-related new or worsened cardiac conduction disturbance
  - requiring permanent pacemaker implant
  - not requiring permanent pacemaker implant

The Data Monitoring Committee (DMC) will conduct a final meeting after the last subject has completed their 5-year follow up

Effectiveness Endpoints

The following effectiveness endpoints will be assessed:

- Device technical success is defined as the successful delivery and deployment of the trial valve with maximum of two attempts and subject leaving the OR with valve in place
- Procedural success is defined as device technical success followed by the absence of adverse events resulting in device reoperation implant of permanent pacemaker (with baseline sinus rhythm and no other pre-existing conduction issues), or valve-related death within discharge or 10 days post index procedure, whichever comes first.
- Cross-clamp time (for labeling claim)
- Cardiopulmonary bypass time (for labeling claim)
- Length of time in the intensive care unit
- NYHA functional class compared to baseline
- Hemodynamic performance (mean gradient, peak gradient, effective orifice area [EOA], EOA index, performance index, cardiac output [CO], cardiac index [CI], valvular regurgitation [including

paravalvular leak] confirmed by echocardiography and Core lab evaluation)

Other Outcomes

The following data also will be collected:

- Change in Quality of Life questionnaire Short Form 12 version 2 (SF-12v2) from Screening to 1 year
- Laboratory testing (White Blood Cell Count, Red Blood Cell Count, Hemoglobin, Hematocrit, Plasma-free Hemoglobin or haptoglobin or serum LDH, Platelet Count) at screening, discharge and at 3, 6, and 12 months and annually thereafter at each follow-up visit

ABBREVIATIONS

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

1.0 INTRODUCTION

1.1 BACKGROUND

Regulatory History

Edwards Lifesciences began discussions of the EDWARDS INTUITY Elite Valve System with FDA in September 2007. The TRANSFORM™ Study Investigational Device Exemptions (IDE) application was submitted in October 2011 and IDE G110189 was approved in June 2012. Enrollment in the study began September 26, 2012 and closed August 25, 2016.

Annual follow up will continue on all subjects enrolled in the TRANSFORM™ Study until the last subject completes 5-year follow up visit.

Premarket Approval P150036 (PMA) was granted August 12, 2016. The conditions of the PMA approval include the following:

> The sale and distribution of this device are restricted to prescription use in accordance with 21CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device.
>
> Submission of Annual Report

1.2 EDWARDS INTUITY VALVE SYSTEM

The EDWARDS INTUITY Elite valve system consists of the EDWARDS INTUITY Elite valve, model 8300AB and the EDWARDS INTUITY Elite delivery system, model 8300DB. The pericardial stented aortic valve is based on the design and the proven performance of the PERIMOUNT valve family. A balloon expandable stainless steel cloth-covered frame is incorporated into the inflow aspect of the valve. The valve is implanted with the aid of a delivery system, which incorporates a balloon catheter to expand the frame within the left ventricular outflow tract (LVOT). The expandable frame works in conjunction with the sewing ring to position and stabilize the valve at implant. The system reduces the number

of sutures required to secure the valve, while the frame establishes a seal within the LVOT. The system may be used in both traditional and less invasive surgical procedures for heart valve replacement.

Two generations of the EDWARDS INTUITY Valve System were investigated in the TRANSFORM Trial:

- **GEN-I**: Valve Model 8300ACA and Delivery System Model 8300DCA
- **GEN-II**: Valve Model 8300ACD and Delivery System Model 8300DCD

The GEN-I device was used early on in the IDE trial and was replaced by the GEN-II device.

The trial valve system consists of the trial valve, model 8300ACA, (Figure 1-A) and the trial delivery system, model 8300DCA (Figure 1-C) or trial valve, model 8300ACD (Figure 1-B) and the trial delivery system, model 8300DCD, (Figure 1-D). The trial valve is a modified Carpentier-Edwards PERIMOUNT Magna Ease Aortic bioprosthesis (model 3300TFX[2]). The trial valve enables the surgeon to position and secure the valve with three sutures and then further secure the valve in the annulus with a balloon expandable frame to control paravalvular leak. An expandable stainless steel cloth-covered frame is incorporated into the inflow aspect of the valve and is implanted with the aid of a delivery system, which is used to expand the frame within the left ventricular outflow tract (LVOT) and works in conjunction with the sewing ring to position and stabilize the trial valve at implant. The system reduces the number of sutures required to secure the trial valve, while establishing the seal between the aortic annulus and the frame. The system may be used in both traditional and less invasive surgical procedures (mini sternotomy or right thoracotomy) for aortic heart valve replacement in patients with aortic stenosis or aortic stenosis/insufficiency. It is not intended for patients with pure insufficiency and it cannot be implanted using a transcatheter or transapical approach.

[2] PMA P860057/S042 approved on May 7, 2009

Figure 1-A: Trial Valve System, model 8300ACA

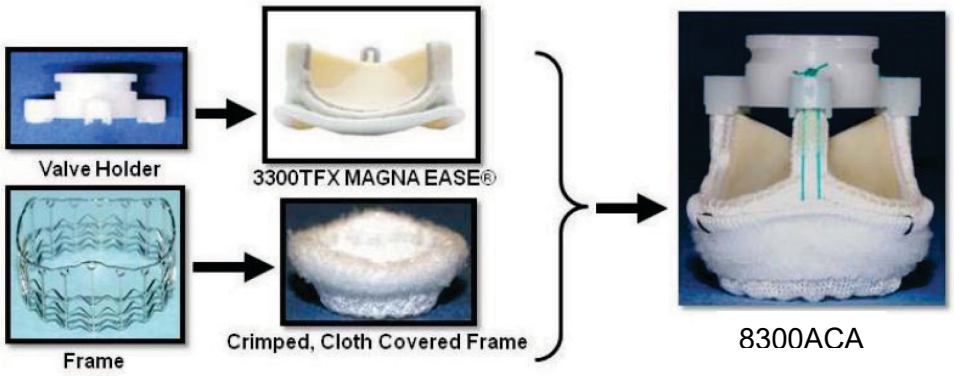
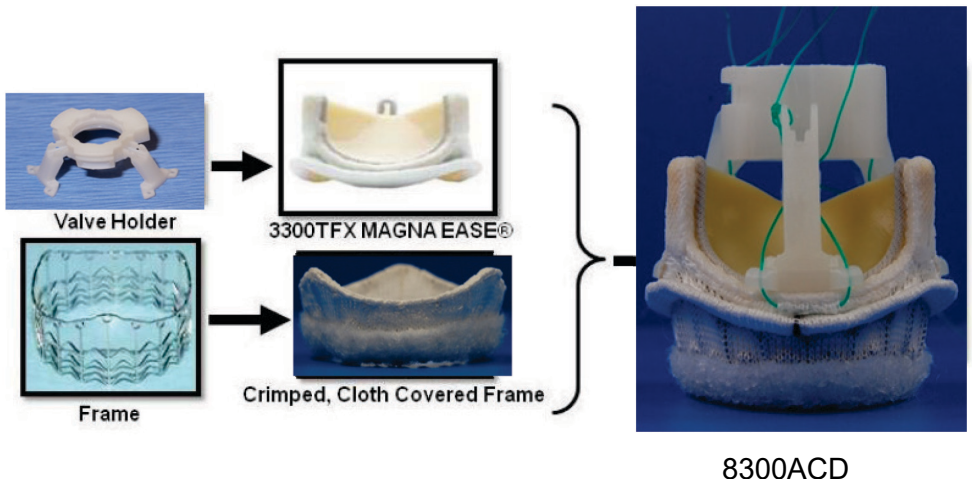


Figure 1-B: Trial Valve System, model 8300ACD



The trial valve is a stented trileaflet valve comprised of bovine pericardium that has been preserved in a buffered glutaraldehyde solution.

The leaflets are mounted on a flexible cobalt-chromium alloy wireform. The inflow of the bioprosthesis incorporates the cloth-covered balloon expandable stainless steel frame that is attached to the inflow side of the valve. The valve leaflets are treated with the Carpentier-Edwards ThermaFix process, which involves heat treatment of the tissue in glutaraldehyde and uses ethanol and polysorbate-80 (a surfactant). The valve is packaged and terminally sterilized in glutaraldehyde. Glutaraldehyde is shown to both reduce the antigenicity of

tissue xenograft bioprostheses and increase tissue stability. The trial valve is available in sizes 19, 21, 23, 25, and 27 mm.

The wireform is made of a corrosion resistant, cobalt-chromium alloy chosen due to its spring efficiency and fatigue-resistant characteristics. The wireform is covered with a knitted polyester fabric. A thin, cobalt-chromium alloy/polyester film laminate band surrounds the base of the wireform. A silicone sewing ring which is covered with a porous, seamless polytetrafluoroethylene (PTFE) cloth is attached to the wireform. The scalloped sewing ring is designed to conform to the natural aortic annulus. The annulus frame which is made from stainless steel (SST) is sewn to the inflow side of the valve in order to control paravalvular leak. The annulus frame has a scallop-shaped continuous ring on the outflow side which matches the contour of the inflow side of the model 3300TFX valve. The scallop-shaped ring is sewn and not welded to the valve wireform and hence does not affect the outward cusp movement of the trial valve wireform during valve operation. The annulus frame sits in the intra-annular position. The inner and outer surfaces of the frame are covered with a knitted PTFE cloth and the annulus frame is covered with polyethyleneterephthalate (PET) cloth. The annulus frame is crimped as part of the manufacturing process and remains in this state until used. Please note that the base valve in the trial valve system is never crimped. The compliant nature of the sewing ring facilitates coaptation between the bioprosthesis and an often irregular or calcific tissue bed. The sewing ring has three suture markers to aid in valve orientation and suture placement. A holder is attached to the valve by means of sutures to facilitate handling, deployment, and suturing the valve during implantation. The holder is easily detached by the surgeon.

1.2.1 MODEL 8300ACA/ACD VALVE DIFFERENCES

Three minor modifications were made to achieve the valve model 8300ACD. 1) In order to enhance seating of the valve during implant the cloth on the frame was shifted down closer to the inflow edge of the annulus frame. Since the cloth on the annulus frame was moved down, the resulting tissue annulus diameter (TAD) was reduced by one mm, which is identical to the model 3300TFX. 2) The single crimped cloth-covered expandable stainless steel frame is now double crimped to further reduce the implant profile. 3) The valve holder is cusp-mounted instead of commissural-mounted to increase the visibility for the nadir suture markers. Also, there was a modification in the method of sewing the holder

onto the valve. Additionally, the holder material was changed to Delrin 500 which is the same material used with all Edwards' valve holders and can now be molded as opposed to machined. Finally, the new holder has a key-lock fitting which is size-dependent to match the modified delivery system, Model 8300DCD.

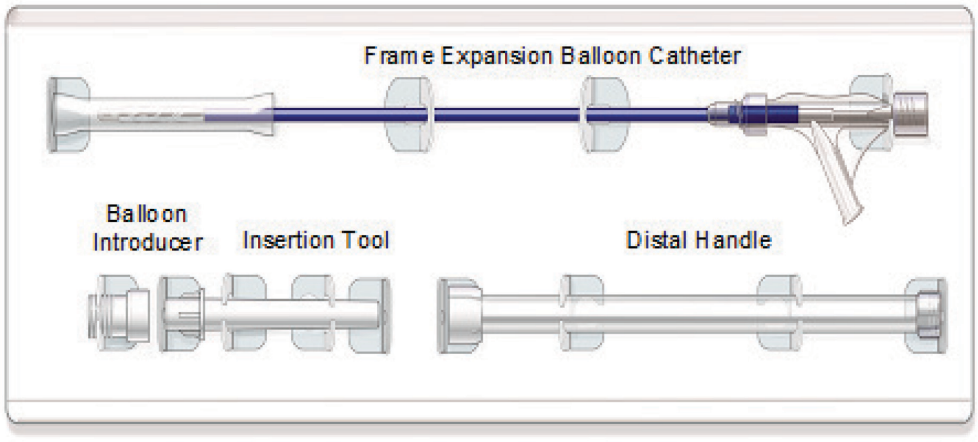
There are no changes to the implant procedure, materials, or packaging. The valve is still attached to the native annulus with only three sutures and uses a pressure-based delivery system to expand the annulus frame. The product name remains the same.

The trial delivery system is designed to introduce the trial valve to the surgical site after removal of the diseased native leaflets. A delivery system is available for each size of the trial valve and consists of the following components:

Model 8300DCA Delivery System

- Balloon Introducer
- Insertion Tool
- Distal Handle
- Frame Expansion Balloon Catheter

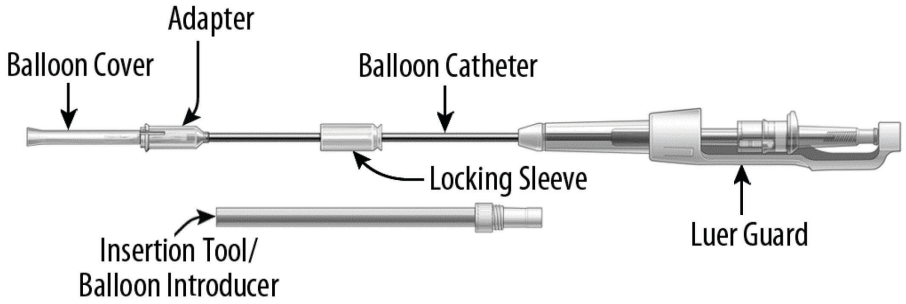
Figure 1-C: Model 8300DCA Delivery System



Model 8300DCD Delivery System

- Insertion Tool/Balloon Introducer
- Integrated Balloon Catheter

Figure 1-D: Model 8300DCD Delivery System



1.2.2 MODEL 8300DCA/DCD DELIVERY SYSTEM DIFFERENCES

All modifications to Model 8300DCD delivery system were to enhance device safety, ease of use and manufacturability. The delivery system includes an integrated balloon catheter and tubular handle shaft through which the catheter extends. The major change was the distal handle is now incorporated into the balloon catheter as a one-piece design in the modified delivery system and this modification provides one less component for the end user to assemble. The distal end of the handle shaft includes an adapter, which mates with the holder of the valve, and a locking sleeve for rapidly connecting the delivery system to the valve holder. The balloon portion of the delivery system resides within the adapter, and advances distally into position for expanding the frame. A tubular balloon introducer sleeve, attached when removing the valve from a storage jar, facilitates passage of the balloon through the valve. The malleable handle is made of aluminum and has chromate conversion coating applied over the entire surface of the part.

1.3 MODEL SECTION

Model 8300ACA/DCA and 8300ACD/DCD were included in the trial. Investigational sites utilizing Model 8300ACA/DCA were transitioned to Model 8300ACD/DCD upon completion of the following; IRB approval, device training and scheduling of investigational product exchange. Each site only had access to either model 8300ACA/DCA or 8300ACD/DCD at any given time. No site had concurrent access to both models.

1.4 INDICATION FOR USE

The EDWARDS INTUITY Elite valve is indicated for the replacement of diseased, damaged, or malfunctioning native or prosthetic aortic valves.

2.0 TRIAL OBJECTIVES

The purpose of this clinical investigation is to assess the safety and effectiveness of the EDWARDS INTUITY Valve System in subjects with aortic stenosis or stenosis-insufficiency requiring replacement of the native aortic valve in premarket and post market phases.

Safety was determined by comparing safety endpoints to the objective performance criteria (OPC) defined by ANNEX R, Section R2, Table R.1 of BS EN ISO 5840:2009 (Cardiovascular implants – Cardiac valve prostheses) and effectiveness was evaluated based on improvement in NYHA Class and hemodynamic parameters compared to baseline.

2.1 PRIMARY SAFETY ENDPOINTS

The primary safety endpoints consist of:

- All cause mortality
    - Trial valve-related mortality
- Thromboembolism
- Valve thrombosis (trial valve)
- All hemorrhage
    - Major hemorrhage
- All paravalvular leak (trial valve)
    - Major paravalvular leak (trial valve)
- Endocarditis (trial valve)
- Structural valve deterioration (trial valve)
- Non-Structural valve deterioration (trial valve)
- Valve Malposition
- Valve Migration/ embolization
- Valve Instability
- Valve Dislodgment
- Hemolysis
- Reoperation
    - Trial valve-related reoperation
- Explant
    - Trial valve explant
- Implant-related new or worsened cardiac conduction disturbance*
    - requiring permanent pacemaker implant
    - not requiring permanent pacemaker implant

*Defined as new or worsened first degree atrioventricular (AV) block, second degree AV block (Mobitz I or Mobitz II), third degree AV block, incomplete right bundle branch block, right bundle branch block, intraventricular conduction delay, left bundle branch block, left anterior fascicular block, or left posterior fascicular block.

2.2 EFFECTIVENESS ENDPOINTS

The following effectiveness endpoints for assessment are:

- Device technical success is defined as the successful delivery and deployment of the trial valve with maximum of two attempts and subject leaving the OR with valve in place
- Procedural success is defined as device technical success followed by the absence of adverse events resulting in device reoperation implant of permanent pacemaker (with baseline sinus rhythm and no other pre-existing conduction issues), or valve-related death within discharge or 10 days post index procedure, whichever comes first.
- Cross-clamp time
- Cardiopulmonary bypass time
- The length of time in the intensive care unit (ICU)
- New York Heart Association (NYHA) functional class compared to baseline
- Hemodynamic performance (mean gradient, peak gradient, effective orifice area [EOA], EOA index, performance index, cardiac output [CO], cardiac index, valvular regurgitation (including paravalvular leak) by echocardiography)

A comparison of all effectiveness data for the EDWARDS INTUITY valve were made to current state of the art prosthetic heart valve literature published in peer reviewed journals at the time of PMA submission.

2.3 OTHER OUTCOMES

The following outcomes for additional evaluation are:

- Change in Short Form 12 version 1 (SF-12v2) Quality of Life questionnaire from Baseline to 1 year
- Laboratory testing (White Blood Cell Count, Red Blood Cell Count, Hemoglobin, Hematocrit, Plasma-free Hemoglobin or haptoglobin or serum LDH, Platelet Count) at screening and at 3, 6, 12 months and annually thereafter from post implant

2.4 GOOD CLINICAL PRACTICES STATEMENT

This trial was conducted in compliance with all applicable U.S. Federal regulations pertaining to trial devices including but not limited to: 21 CFR Part 50, Part 54, Part 56, Part 812, Good Clinical Practice (GCP) standards, and Health and Insurance Portability and Accountability Act (HIPAA).

3.0 RISK/BENEFITS ANALYSIS

3.1 RISK

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.

For a complete listing of anticipated adverse events in this trial, see section 7.4 of this document. All safety events will be reported throughout the entire trial. Investigators will be notified of any additional risks identified that could affect the health, safety or welfare of the trial subjects.

3.2 MINIMIZING SUBJECT RISK

All adverse event rates will be collected, reviewed and evaluated. Clinical outcomes for all trial subjects will be routinely monitored by the Sponsor during the course of the trial. An independent Clinical Events Committee (CEC) will review and adjudicate safety endpoint related events as outlined in the CEC charter.

3.3 BENEFITS

Information gained from the continued follow up of these subjects may be of benefit to other patients with the same medical condition in the future.

4.0 FOLLOW UP PLAN

4.1 TRIAL DESIGN

This is a multi-center, prospective, non-randomized, single-arm, clinical trial to assess the safety and effectiveness of the trial valve system in subjects with aortic stenosis or stenosis-insufficiency requiring primary replacement of the native aortic valve. Premarket analysis was performed when the total late-patient years reached 800 and the number of subjects completing the one year (or greater) follow-up reached and/or exceeds 300. Post-market, all active subjects will be followed until the last enrolled subject completes their 5-year follow up.

4.2 TRIAL DESCRIPTION

Continued follow-up evaluations will be conducted on all active enrolled TRANSFORM™ Trial subject until the last enrolled subject complete the 5-year follow up.

5.0 TRIAL POPULATION

The trial population consists of subjects enrolled in the TRANSFORM™ Trial.

5.1 INCLUSION CRITERA

During the enrollment phase of the trial, the following Inclusion, Exclusion and Intra-operative Exclusion Criteria was required:

1. Male or female, age 18 years or older
2. Subject has aortic stenosis or stenosis-insufficiency of an aortic valve requiring a planned replacement as indicated in the preoperative evaluation
3. Subject is scheduled to undergo planned aortic valve replacement with or without concomitant coronary bypass surgery
4. Provide written informed consent
5. Geographically stable and agrees to attend follow-up assessments until all subjects have completed 5 years of follow up

5.2 EXCLUSION CRITERIA

Pre-operative Exclusion Criteria:

1. Subjects with pure aortic insufficiency
2. Subjects requiring emergency surgery
3. Previous aortic valve replacement
4. Had prior mitral, tricuspid or pulmonic valve surgery, which included implant of a bioprosthetic valve, mechanical valve, or annuloplasty ring that will remain *in situ*;
5. Subjects requiring multiple valve replacement/repair
6. Requires a surgical procedure outside of the cardiac area (e.g., vascular endarterectomy, vascular bypass, tumor removal)
7. Aneurysm of the aortic root and/or ascending aorta requiring surgical intervention
8. Active endocarditis/myocarditis or endocarditis/myocarditis within 3 months prior to the scheduled AVR surgery
9. Myocardial infarction (MI) within thirty (30) days prior to valve replacement surgery;
10. Renal insufficiency as determined by creatinine ≥ 2.5 mg/dL at Screening or end-stage renal disease requiring chronic dialysis
11. Hyperparathyroidism
12. MRI or CT-scan confirmed cerebrovascular accident (CVA), or transient ischemic attack (TIA) within 6 months (180 days) of the procedure
13. Presence of non-cardiac disease limiting life expectancy to less than 12 months;
14. Hypertrophic obstructive cardiomyopathy (HOCM)
15. Left ventricular ejection fraction ≤ 25%
16. Documented history of substance (drug or alcohol) abuse within the last 5 years
17. Echocardiographic evidence of an intracardiac mass, thrombus, or vegetation
18. Hemodynamic or respiratory instability requiring inotropic support, mechanical circulatory support, or mechanical ventilation within 30 days prior to the procedure
19. Pregnancy, lactation, or planning to become pregnant
20. Currently incarcerated or unable to give voluntary informed consent
21. Leukopenia (WBC < 3.5x 10^3/μL), or acute anemia (Hgb < 10.0 gm/dL or 6 mmol/L), or thrombocytopenia (platelet count < 50x 10^3/μL), or history of bleeding diathesis or coagulopathy

22. History of myxomatous disease/connective tissue disorders (e.g., Marfan's Syndrome)
23. Current or recent participation (within 6 weeks prior to surgery) in an investigational drug or device trial

Intra-operative Exclusion Criteria

24. Subjects with anatomic variances which contraindicate implant of the trial valve, such as:
    a. anomalous coronary arteries
    b. annular deformation or extensive calcification of the annulus or aortic root which cannot be removed
    c. significant calcium on the anterior mitral leaflet
    d. pronounced septal calcification
    e. position of coronary ostia relative to Model 8300ACA/ACD valve that would result in obstruction of blood flow
25. Available devices are not suitably sized for the subject's annulus

6.0 TRIAL PROCEDURES

A trial scheme in tabular format is provided in xxxxxx.

6.1 INFORMED CONSENT

All trial subjects were consented appropriately prior to enrollment in the TRANSFORM™ Trial. If re-consenting is required, an Institutional Review Board's (IRB's) approved informed consent will be utilized.

Each subject shall be given ample time to read the ICF in its entirety and ask questions in order to make an informed decision. The subject must sign and date the trial site's IRB approved ICF. In addition, the Investigator, or designee, and any witnesses will sign and date the ICF, as indicated.

6.2 SUBJECT SCREENING

At the time of this protocol revision, all subjects were enrolled in the trial and followed through 1-year follow up. For a complete description of the Subject Screening, Surgical Procedure, Subject Enrollment, Implant Procedure, Post Procedure Follow-Up, Discharge, POD 36, and POD 105 visits, please refer to a previous version (Revision N) of the TRANSFORM™ Protocol.

6.2.1 POD 195 VISIT (-15/+45 DAYS)

This visit is only required if echocardiography at three months showed a PVL >mild as determined by the Echo Core Lab or an implant-related new or worsened cardiac conduction disturbance.

These subjects will return for follow-up between POD 180 to 240 and the following assessments will be performed:

Subject status	
Date of Follow-Up	
NYHA Classification	
Echocardiography (TTE)	Peak and mean pressure gradients, EOA, EOA index, performance index, cardiac output, cardiac index, valvular regurgitation (including paravalvular leak)
Electrocardiogram	12-Lead ECG (Cardiac Rhythm)
Anticoagulant therapy/Concomitant cardiovascular medications	Anticoagulants/anti-platelets and other Concomitant cardiovascular medications
Coagulation profile	May include PTT or PT or INR if subject is on anticoagulant therapy only
Laboratory Testing	WBC, RBC, hemoglobin, hematocrit, platelets, plasma-free hemoglobin (a 2nd lab draw for plasma free hemoglobin is required within 48 hours if the first draw is >40mg/dl) or haptoglobin or serum LDH
Vital signs	Blood pressure, heart rate, weight
Adverse events/Complications	If applicable

6.2.2 POD 390 VISIT (- 25/+45 DAYS)

Subjects will return for follow-up between POD 365 to 435 and the following assessments will be performed:

Subject status	
Date of Follow-Up	
NYHA Classification	
Echocardiography (TTE)	Peak and mean pressure gradients, EOA, EOA index, performance index, cardiac output, cardiac index, valvular regurgitation (including paravalvular leak**)**
Electrocardiogram	12-Lead ECG (Cardiac Rhythm)
Anticoagulant therapy/Concomitant cardiovascular medications	Anticoagulants/anti-platelets and other Concomitant cardiovascular medications
Coagulation profile	May include PTT or PT or INR if subject is on anticoagulant therapy only
Laboratory Testing	WBC, RBC, hemoglobin, hematocrit, platelets, plasma-free hemoglobin (a 2nd lab draw for plasma free hemoglobin is required within 48 hours if the first draw is >40mg/dl) or haptoglobin or serum LDH
QOL Survey	SF-12v2
Vital signs	Blood pressure, heart rate, weight
Adverse events/Complications	If applicable

6.2.3 PO YEAR 2 THROUGH SUBSEQUENT ANNUAL VISITS

After the POD 390 visit, the subject will return for follow-up site annually -60/+60 days until the trial ends. The following assessments will be performed:

Subject status	
Date of Follow-Up	
NYHA Classification	
Echocardiography (TTE)	Peak and mean pressure gradients, EOA, EOA index, performance index, cardiac output, cardiac index, valvular regurgitation (including paravalvular leak)
Electrocardiogram	12-Lead ECG (Cardiac Rhythm)
Anticoagulant therapy/Concomitant cardiovascular medications	Anticoagulants/anti-platelets and other Concomitant cardiovascular medications
Coagulation profile	May include PTT or PT or INR if subject is on anticoagulant therapy only
Laboratory Testing	WBC, RBC, hemoglobin, hematocrit, platelets, plasma-free hemoglobin (a 2nd lab draw for plasma free hemoglobin is required within 48 hours if the first draw is >40mg/dl) or haptoglobin or serum LDH
Vital signs	Blood pressure, heart rate, weight
Adverse events/Complications	If applicable

At each postoperative assessment, the Investigator will determine the subject's availability for future follow-up visits. If any subject is seen at a time in addition to regularly scheduled follow-up visits, the visit will be recorded as an interim visit. The procedures performed at an unscheduled visit will be at the Investigator's discretion. Available data obtained at an unscheduled visit will be transcribed onto an Unscheduled Visit CRF.

6.2.4 VISIT WINDOWS

Visits must be scheduled for specific times before and after the date of the index procedure. It is important that this schedule is maintained for all subjects. To facilitate compliance, each visit has a visit window as described in Table 1 below. Visits not completed within these windows will be considered "done out of window." Additional visits completed will be considered unscheduled visits. Trial visits should be scheduled as close to the early part of the visit window as possible so that if it is necessary to cancel and reschedule the visit, the visit may still be conducted within the required visit window.

Table 1: Follow-up Visit Days & Visit Windows

Visit	Visit Window (Days)	Timing from Implant (Day 0)
POD 195*	- 15/+45	Day 180 to Day 240
POD 390	- 25/+45	Day 365 to Day 435
PO Year 2	- 60/+60	Day 670 - 790
PO Year 3	- 60/+60	Day 1035 - 1155
PO Year 4	- 60/+60	Day 1400 - 1520
PO Year 5	- 60/+60	Day 1765 - 1885

* Required for subjects with PVL >mild on POD 105 echocardiography as determined by the Echo Core Lab or an implant-related new or worsened cardiac conduction disturbance.

6.3 SUBJECT WITHDRAWAL

Subjects may voluntarily withdraw consent at any time during the clinical trial without jeopardizing their medical care. In addition, the Investigator, the IRB and or Edwards Lifesciences has the right to withdraw subjects from the trial for the following reasons: when continuation may jeopardize the health of the subject, protocol violations, adverse events or concurrent conditions, administrative or other reasons.

Subjects who withdraw from the trial for any reason will not be replaced

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6.4 SUBJECT REMOVAL FROM CLINICAL TRIAL

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

All subjects are expected to continue in the trial until the Sponsor 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 trial. A copy of such requests will be kept with the source documentation.

A subject will be considered "*lost to follow-up*" and terminated from the trial when all of the following criteria are met:

- Failure to complete two consecutive visits without due cause
- Documentation of three unsuccessful attempts on three different dates over a period of at least 1 month by the Investigator or designee to contact the subject or next of kin.

All subjects who receive a commercial (a non-trial) heart valve and any subjects who have the EDWARDS INTUITY heart valve explanted will be followed through the end of the trial. Subjects previously exited from the trial due to receiving a commercial valve (at any time point) will be contacted and a request will be made to have them re-consented and reenrolled in the trial and followed through the end of the trial.

6.5 TRIAL TERMINATION

If the Sponsor and/or the Principal Investigator should discover conditions arising during the trial that indicate that the trial should be terminated prematurely, an appropriate schedule for termination will be instituted. All trial subjects enrolled at the time the trial is terminated, will be followed by the Clinical Investigator for a period of five (5) years from the date of enrollment.

The trial plan includes continued annual follow-up until 5 years of follow up are completed on all subjects enrolled in the clinical trial.

6.6 INVESTIGATIONAL DEVICE MANAGEMENT

At the time of this protocol revision, all subjects were enrolled in the trial. Unused devices were returned to the Sponsor and investigational device reconciliation was complete. For a description of investigational device management, please refer to a previous version (Revision N) of the TRANSFORM™ Protocol

7.0 SAFETY ASSESSMENTS

Safety assessments will include examination and reporting of adverse events, ECGs, laboratory parameters, vital signs and any changes from baseline.

Adverse events, whether observed by the Investigator or reported by the subject, will be recorded on the Adverse Event CRF. At each visit, the Investigator or designee will determine whether any adverse events occurred by evaluating the subject. Adverse events may be observed directly, reported spontaneously, or identified by questioning the subject at each trial visit. Questioning subjects should be in a general way, without asking about the occurrence of any specific symptoms. The Investigator must appraise all trial related laboratory values. The Investigator should follow subjects with adverse events until the event has resolved or the condition has stabilized.

Pre-existing medical conditions or symptoms reported prior to device implant will not be recorded as an AE. In the event there is worsening of a pre-existing medical condition or symptoms following the index procedure, then an AE must be recorded. The adverse event report should note the existence of pre-index procedure history when appropriate.

7.1 SAFETY PROCESS

The Safety Process in the TRANSFORM™ Trial has been established with three (3) levels of independent review of reported clinical outcomes (Adverse Events; AE) conducted by Data Monitoring Committee (DMC), Sponsor's Safety Department (HVT Safety), and an independent Clinical Endpoints Committee (CEC).

Data Monitoring Committee (DMC): The DMC provided a consistent, independent review of clinical outcomes reported in TRANSFORM™ trial during the enrollment period, The Committee will also review the data at the end of the study follow-up. The DMC reviews data reported from the sites, along with CEC-adjudicated data and Echo Core Lab data, and identifies any potential safety issues such as higher than expected SAE and/or death rates, Unanticipated Adverse Device Effects (UADE), or hemodynamic performance that is substantially worse than expected, to determine if the trial should be stopped, suspended, or modified at any time, as specified in the DMC Charter.

Sponsor's Safety Department (HVT Safety): HVT Safety provides an initial review of new adverse events directly following notification that an event has occurred. The review includes a Serious Adverse Event (SAE) and UADE assessment and reporting to the relevant regulatory or trial groups, within the appropriate time frame, in accordance with the applicable regulatory requirements which include, 21 CFR Part 812 (Investigational Device Exemptions), 21 CFR Part 814 (Premarket Approval of Medical Devices), MEDDEV 2.7/3 (Clinical Investigations: Serious Adverse Event Reporting, 2010), and ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects), as well as with the Sponsor's internal standard operating procedures.

Clinical Endpoints Committee (CEC): The primary role of the CEC is to review (adjudicate) and decide on safety endpoints which will be included in the final analysis. The adjudication process and the events selection is based on the approved study endpoints definitions and the CEC Charter. HVT Safety may also include events determined to be possibly related to a safety endpoint during their initial review of the event. Events designated as requiring CEC review are forwarded with relevant source documentation to the CEC by HVT Safety. The CEC can also identify additional events, not previously reported, during their review. These events will also be adjudicated.

7.2 ADVERSE EVENTS

An adverse event (AE) is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical event in a subject, whether or not related to the investigational medical device. Note: A procedure is not an AE, but the reason for the procedure may be an AE.

7.3 SERIOUS ADVERSE EVENTS

A serious adverse event (SAE), defined as an event that leads to one of the following:

- death;
- a serious deterioration in the health of the trial subject that:
  - Results in life-threatening illness or injury;
  - Results in a permanent impairment of a body structure or a body function;
  - Requires in-subject hospitalization or prolongation of existing hospitalization;
  - Results in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment;
- Congenital defect or anomaly

Note: Elective hospitalizations for pre-treatment conditions (e.g., elective cosmetic procedures, cataract removal) are not serious adverse events (SAE).

Each AE/SAE is considered to be either anticipated or unanticipated as described below.

7.4 ANTICIPATED ADVERSE EVENTS

As with all prosthetic heart valves, serious complications, sometimes leading to death, are associated with the use of tissue valves as well as the replacement procedure. In addition, complications due to individual subject reaction to an implanted device, or to physical or chemical components, particularly those of biological origin, may occur at varying intervals (hours or days) necessitating reoperation and replacement of the prosthetic device.

Known risks associated with the use of stented bioprosthetic heart valves include:

- Allergic reaction to valve materials
- Angina
- Annulus (damage, dissection, tear)
- Aortic Insufficiency –Regurgitation/Stenosis
- Aorta (damage, dissection, tear)
- Blood - Coagulopathy
- Blood - Hemolysis
- Blood - Hemorrhage/anemia
- Blood Pressure alteration (hypotension, hypertension)
- Cardiac Arrest
- Cardiac Arrhythmias/conduction disturbances
- Cardiac Failure (heart failure)
- Chordae Tendineae damage (Mitral valve)
- Coronary artery Ostia blockage
- Death
- Endocarditis
- Explant
- Infection – local
- Neurologic Events
  - Stroke (CVA)
  - Transient Ischemic Attack (TIA)
- Reduced exercise tolerance
- Thromboembolism
- Transvalvular or Valvular Leaking
- Valve instability/ migration/ embolization
- Valve dislodgement
- Valve - Non structural dysfunction
  - Paravalvular Leak
  - Leaflet impingement (Aortic or Mitral valve)
  - Leaflet tissue damage (instruments /sutures or pannus)
  - Subject Prosthesis Mismatch (PPM) (due to inappropriate sizing)
  - Distortion at implant
- Valve - Structural dysfunction/deterioration (*e.g.,* wear, leaflet tear, calcification, leaflet detachment from stent posts, component deterioration – physical or chemical)
- Valve - Thrombosis
- Valve Wireform and or Frame Fracture or Distortion (from chest compression or trauma)
- Valve stent fracture
- Valve stent separation
- Annulus frame fracture
- Annulus frame separation

Potential risks associated with aortic valve replacement surgery include:
• Allergic reaction • Annular dissection • Aortic or arterial dissection • Asystole and/or cardiac arrest • Bleeding – Peri- or post-procedural – Anticoagulant related – Pericardial tamponade – Hematoma – Cerebral vascular • Cardiogenic shock • Disseminated intravascular coagulation (DIC) • Embolism, pulmonary • Esophageal tear/rupture • Heart failure • Hypo- or hypertension • Hypoxemia • Infection, local or wound or systemic • Infection, Septicemia – bacterial, viral, fungal • Myocardial infarction • Myocardial perforation, free wall • Multi-system organ failure (MOF) • Pericardial effusion • Pleural effusion • Pulmonary edema • Pneumonia • Renal failure, acute • Respiratory failure • Thrombocytopenia, (Non-HIT) • Thrombocytopenia, heparin induced (HIT) • Thromboembolism ○ Venous, peripheral or central ○ Arterial, peripheral or central ○ Pulmonary, thrombus or other

Based on a review of the scientific literature, preliminary animal studies, risk analysis and a Failure Modes and Effects Analysis (FMEA), other potential risks associated with the use of the trial valve include:

- Loss of frame structural integrity resulting in damage to LVOT
- Delivery system impingement resulting in mitral leaflet chordae trauma or damage
- Annular frame damage or under-flaring resulting in a reduction of EOA
- Annular frame overexpansion resulting in conduction interruptions or disturbances (i.e., arrhythmia)
- Separation of the annular frame from the sewing ring
- Mitral valve impingement or abrasion with or without mitral regurgitation
- Insufficient frame expansion/suturing resulting in PVL requiring intervention or reoperation
- Device malpositioning resulting in coronary ostial blockage
- Device embolization into the aorta or ventricle

7.5 UNANTICIPATED ADVERSE DEVICE EFFECT

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

The Investigator must submit to the Sponsor or its designee and to the reviewing IRB, a report of any UADE occurring during this clinical investigation as soon as possible, but under no circumstance, later than 10 working days after the Investigator first learns of the event. Full and complete written documentation must follow this report. The Investigator must document all UADE, including the time and date of onset, complete description of the event, severity, duration, actions taken and outcome. Record all UADE on the appropriate CRF.

The Sponsor will immediately conduct an evaluation of any unanticipated device-related event. In addition, the Sponsor will notify the DMC of an UADE within five (5) business days after Edwards or its designee first receives notice of the event.

7.6 ADVERSE EVENT DEFINITIONS/ REPORTABLE EVENTS

Since assessment of safety requires comparison of the occurrence of adverse events to the OPC, it is extremely important to provide definitions of adverse events and to adhere to these definitions. The method of reporting shall conform to the most recently published "*Guidelines for reporting mortality and morbidity after cardiac valve interventions"* by Akins et al [14].

In addition, it is of utmost importance to determine the primary event since secondary morbid events will not be included in the calculation of any complication rates. However, secondary events will be reported for informational purposes. For example, if a subject has endocarditis and develops a PVL secondary to the infection, the PVL will not be counted in the PVL rate. The endocarditis will be included in the calculation of the endocarditis rate.

Multiple events of the same complication in the same subject will be counted as a single event if the complication does not resolve. For example, if a subject experiences multiple TIAs in a two-week period, only one event will be included in the linearized rate, although all events will be reported as a cluster. Similarly, if a subject exhibits a PVL at six months, and that leak remains at the POD 365-415 visit, only one event will be included in the linearized rate calculation. If, however, a subject has a stroke and then 6 months later experiences another stroke, both events will be included in the calculation of the linearized stroke rate.

MORTALITY REPORTING:

In the event of subject death, every effort should be made to obtain a copy of the autopsy report and/or death summary. The Investigator will provide information about the cause of death and will determine relationship to the clinical investigational device. The Clinical Events Committee (CEC) will adjudicate each death for device relatedness and procedure relatedness. The site will send the Sponsor copies of an autopsy report, if available, and/or a death summary.

If explant of a device occurs during autopsy, return the device to the Sponsor for analysis. Return kits for explanted devices will be provided upon request by the clinical site manager.

EXPLANT REPORTING:

In the event a trial valve is explanted in the late post-operative period, the Investigator will provide information on the explant and determine the relationship to the trial valve. Every effort should be made to supply copies of available explant reports, to the Sponsor. As soon as possible, explanted trial valves should be returned to the Sponsor for analysis. Sponsor will provide "return kits" for explanted devices upon request by the clinical site manager.

A complete list of Adverse Event Definitions/ Reportable Events is located in XXX.

7.7 ASSESSMENT OF ADVERSE EVENTS

The Investigator at each participating site is ultimately responsible for reporting AEs and complications. Medical and scientific judgment should be exercised in determination of the AE description while adhering to the provided definitions. The Investigator is required to complete the adverse event case report form (Adverse Event CRF see xxxxx) at each trial visit. The Adverse Event CRF for a given visit must report all adverse events that occurred since the last documented visit.

Description of each AE must be as follows: AE description, the date of onset, date of resolution, serious (yes/no; see Section 7.2), frequency of the event (single episode, intermittent, continuous), action taken (none, medical and/or surgical), relationship to device, relationship to the procedure, and seriousness criteria.

CAUSALITY:

The causal relationship of the AE to the device and the procedure should be rated as follows:

- Not Related: Evidence exists that the adverse event definitely has a cause other than the trial procedure or device (e.g., pre-existing condition or underlying disease, intermittent illness, or concomitant medication) and does not meet any other criteria listed. There is no relationship between the event and the device or procedure.

- Related: Evidence exists that the trial device or procedure caused the adverse event. There is a temporal relationship between the event onset and trial device or procedure. The subject's clinical state and concomitant therapies are ruled out as a cause.
- Unknown: There is no evidence or relevant data available to assess the relationship between the event and the device or procedure.

Adverse event outcome defined as follows:

- Recovered/Resolved (the subject fully recovered from the adverse event with no residual effect observed).
- Recovered/Resolved with Sequelae (the residual effects of the adverse event are still present and observable).
- Ongoing (The adverse event itself is still present and observable).
- Death.
- Explant.
- Ongoing at the time of trial exit
- Chronic Condition (*e.g.,* Cancer, Shingles, Herpes)

Action Taken for Event (identify all that apply):

- None (no treatment was required).
- Medication required (prescription and/or over the counter medication was required to treat the adverse event.
- Hospitalization or Prolongation of Hospitalization Required (hospitalization was required or prolonged due to the adverse event)
- Surgical intervention (not involving the trial valve)
- Reoperation or explant of the trial valve
- Other (specify).

7.8 ELECTROCARDIOGRAMS

An ECG will be performed with the subject in supine position at, POD 180-240 (optional), and annually thereafter until the trial ends. An expert cardiologist knowledgeable in cardiac conduction disturbances will determine the cardiac rhythm, and assess the ECG as normal or abnormal, and will specify any clinically significant abnormal findings.

Any new or worsened cardiac conduction disturbance defined as new or worsened first degree atrioventricular (AV) block, second degree AV block (Mobitz I or Mobitz II), third degree AV block, incomplete right bundle branch block, right bundle branch block, intraventricular conduction delay, left bundle branch block, left anterior fascicular block, or left posterior fascicular block will be reported.

7.9 LABORATORY TESTING

Blood data (red blood count, white blood count, hematocrit, hemoglobin, platelet count, and plasma-free hemoglobin or haptoglobin or serum LDH) will be collected POD 180-240 (optional), POD 365-435, and annually thereafter until the trial ends.

For all measured blood parameters, individual results will be compared to documented normal ranges. The Investigator will determine for each parameter that is out-of-range whether the value is abnormal not clinically significant, or abnormal clinically significant. Since summary statistics involving laboratory parameters will be provided, an out-of-range value does not necessarily constitute an AE; other signs and symptoms must be taken into an account in order to report the occurrence of an AE.

Coagulation profile (which may include prothrombin time [PT], or partial thromboplastin time [PTT], or international normalized ratio [INR]) will be collected at the POD 180-240 (optional visit) and annually thereafter, coagulation profile will only be determined for subjects on anticoagulant therapy.

8.0 EFFECTIVENESS ASSESSMENTS

8.1 PERI-PROCEDURAL PARAMETERS

Device technical success was defined as the successful delivery and deployment of the trial valve with maximum of two attempts and subject leaving the OR with valve in place. In addition, cross-clamp and cardiopulmonary bypass times, and length of stay in the ICU will be documented.

Procedural success was defined as device technical success followed by the absence of adverse events resulting in device reoperation implant of permanent pacemaker (with baseline sinus rhythm and no other pre-existing conduction issues), or valve-related death within discharge or 10 days post index procedure, whichever comes first.

8.2 NYHA CLASSIFICATION

The percentage of subjects in each specific NYHA functional class and the change in NYHA classifications from screening will be analyzed at each time point where NYHA is obtained to evaluate if implanting the trial valve results in an improvement in NYHA classification.

8.3 HEMODYNAMIC PERFORMANCE

Echocardiography will be conducted at POD 180-240 (optional), POD 365-435 and annually thereafter until the trial ends. The Echocardiography Core Lab Manual is provided in XXX for specific information regarding the conduct of these procedures.

The echo core lab will determine: peak systolic and mean aortic valve gradient, EOA, EOA index, performance index, cardiac output, cardiac index, valvular regurgitation (including paravalvular leak), left and right atrial size, left and right ventricular size, left and right ventricular function, ventricular septal and left ventricular posterior wall thickness, cavitary thrombi or other masses, pericardial abnormalities (e.g., effusion) and aortic root diameter.

9.0 STATISTICAL METHODS

The following section describes only those activities that will be conducted after the approval of the study product. All detailed analyses conducted for the PMA submission are XXXX and a xxxx all post approval analyses.

9.1 STATISTICAL ANALYSIS

9.1.1 ANALYSIS POPULATION

There will be two analysis populations for the trial: the enrolled or intent-to-treat population and the valve implant or as-treated population. The valve implant population will include all subjects who receive the trial valve and leave the operating room with the trial valve in place.

The valve implant population will be used for all analyses of NYHA and echocardiographic data.

9.1.2 SAFETY ANALYSIS

The analyses of the safety data will be performed for enrolled (ITT) patientsand all valve implant (as-treated) patients. However, the primary analysis population for all safety analyses will be the valve implant (as-treated) population.

9.1.2.1 Primary Safety Endpoints

For the safety endpoints listed in Section 2.1, the early adverse events within 30 days of implant will be reported as the number of events divided by the number of patients for the events. Linearized rates will be used to summarize adverse events for the late (>30 days) post-operative period. The linearized rates will be calculated as the number of late events divided by the total late-patient years.

Actuarial analysis using the Kaplan-Meier method will be used to estimate the probability of freedom from each primary safety endpoint. Primary analyses of the primary safety endpoints (post 30 days) will be based on linearized rates, which account for multiple

events from a single patient. Actuarial (Kaplan-Meier) analysis of the time to first event per patient will be provided as an additional analysis.

9.1.2.2 Other Safety Data

Percentages for the early events and linearized rates for the late events will be calculated for all complications. If valve malposition, valve instability, valve dislodgement or valve migration/embolization occurs, any consequent adverse events or procedures (e.g. coronary ostia blockage, mitral valve impingement, or abrasion, intraoperative intervention, or reoperation) will be noted and rates presented.

9.1.3 EFFECTIVENESS ANALYSIS

Subjects will be analyzed according to the NYHA classification preoperatively, at POD 31-46, POD 90-135, and annually post implant for 5 years. The distribution (numbers of subjects and percentages) in the various NYHA classes and the change from baseline (improved, same and worse) will be tabulated and stratified by baseline NYHA at each follow-up interval. Echocardiography data will be obtained preoperatively, intraoperatively, at discharge, POD 90-135, POD 180-240 (optional) and annually post implant until the trial ends. Descriptive statistics for the continuous echo variables (e.g. mean, standard deviation, and range) will be categorized by time interval and valve size. Regurgitation data will be summarized by counts and percentages at each severity level.

A comparison of all effectiveness data for the EDWARDS INTUITY valve will be made to current state of the art prosthetic heart valve literature published in peer reviewed journals at the time of PMA submission.

9.1.4 OTHER OUTCOMES ANALYSIS

The change in Short Form 12 version 1 (SF-12v2) Quality of Life questionnaire from screening to 1 year will be summarized by N, mean, and standard deviation.

Blood data will be analyzed to determine if significant subclinical and unreported hemolysis is occurring due to the implant of the trial valve. A trend analysis of two postoperative data points will be conducted to determine if hemolysis is increasing over time. The following parameters will be included in the trend analysis: plasma-free hemoglobin, haptoglobin, serum LDH, hemoglobin and hematocrit.

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

9.1.5 MISSING DATA

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

9.2 ADDITIONAL INFORMATION

The following additional information will be provided:

- the follow-up duration information, including the mean follow-up, standard deviation and range of follow-up and cumulative follow-up in late-patient years will be determined and reported;
- subject compliance data for follow-up visits, NYHA functional classification data, echocardiographic data and clinical laboratory results will be determined and reported;
- listing of AEs/complications by subject ID number;
- case summaries of each death with a determination whether the death represents an early or late death;
- available autopsy reports;
- case summaries of explants and reoperations;
- analyses of valves when a valve was explanted or an autopsy performed;

- summary of subjects not completing the trial due to lost to follow-up, explant or death; and
- confounding factors such as gender, age at implant, preoperative NYHA Class, concomitant procedures, co-existing (cardiac) conditions, valve size, etc., will be considered in a hazard regression analysis to determine which factors may affect the incidence of reoperation, explant and death;
- summary of subject complaints received.

10.0 TRIAL COMMITTEES AND CORE LABORATORY

10.1 CLINICAL EVENTS COMMITTEE

A CEC consisting of independent physicians familiar with the treatment of valvular heart disease and cardiac surgery will evaluate the adverse events including adverse events resulting in death as outlined in their charter and adjudicate these events for their relatedness to the trial device, and the trial device procedure.

Members of the CEC will not have scientific, financial, or other conflict of interest related to the Sponsor or the Investigators. CEC members must sign a non-conflict-of-interest statement in this regard.

10.2 DATA MONITORING COMMITTEE

A DMC composed of two or more independent physicians including a cardiothoracic surgeon and cardiologist, and a statistician evaluated the rates of OPC's, study endpoints and serious adverse events including deaths and explants for all subjects in the clinical investigation as well as the hemodynamic performance of the EDWARDS INTUITY aortic valve during the enrollment phase. Members of the DMC did not have scientific, financial, or other conflict of interest related to the Sponsor or the Investigators. DMC members signed a non-conflict-of-interest statement in this regard.

The DMC activities and meeting schedule was regulated by the DMC Charter.

10.3 ECHOCARDIOGRAPHY CORE LAB

The purpose of the Echocardiographic Core Laboratory is to ensure unbiased, timely and consistent analysis of these diagnostic data. The Core Lab is responsible for evaluating changes in subject status over the course of the trial based on serial echocardiographic studies conducted in the same subject. Personnel at the Core Lab will have training and experience appropriate for analyzing Doppler Echocardiography data. The Sponsor will ensure that Core Lab personnel are familiar with the valve. The Sponsor or its designee will periodically perform audits of the Core Lab. The Sponsor will review the data provided by the Core Lab as appropriate.

Doppler echocardiograms must be conducted as described in xxx; original videotapes or CDs of Doppler echocardiograms will be sent directly from the trial sites to the Core Lab. The Core Lab will review the Doppler echocardiograms upon receipt and notify the site promptly if the quality of the echocardiogram is insufficient for analysis.

11.0 DATA INTEGRITY, COLLECTION AND QUALITY ASSURANCE

To protect subject confidentiality, the subject's name must not appear anywhere on the imaging media sent for evaluation by the Core Lab, or on copies of supporting documentation removed from the investigational center. Each page should be identified with the subject's ID number only. All other subject identifiers (e.g., subject name, address, medical record number etc.) are to be obscured. Electronic records will be compliant with 21 CFR Part 11.

11.1 DATA COLLECTION

All required data for this investigation are to be collected on standardized eCRFs for individual enrolled subjects; sample eCRFs are provided in xxxxx. The eCRF must be electronically signed by the Principal Investigator or co-Investigator listed in the Clinical Studies Agreement and/or Delegation of Authority Log. If for any reason the eCRFs are unavailable and/or inaccessible, paper CRFs will be provided by the Sponsor to be completed, signed by the Principal Investigator or designee and submitted to the Sponsor. Case Report Form Instructions will be provided to assist the Investigator(s) and appropriate investigational staff in the completion of the required eCRFs.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include, but are not limited to, hospital records, clinical and office charts, laboratory records, and correspondence.

Electronic CRFs must be kept current to reflect enrolled subject status during the course of the investigation.

11.2 DATA QUALITY ASSURANCE

Edwards Lifesciences clinical affairs and data management departments have quality assurance procedures to ensure that complete, accurate and timely data are collected, that the Investigational Plan requirements are followed and that all complications and adverse events are reported in a timely manner.

Electronic CRFs are used for collecting and recording of data for enrolled subjects at all trial sites. Investigators or their designees are responsible for the timely completion of these forms.

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

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

Follow-up Doppler echocardiograms will be evaluated by the designated Echo Core Lab. A standardized written report generated by the Core Lab for each Doppler echocardiogram will be entered into an electronic database maintained by the Sponsor. The Clinical Site Manager or Sponsor designee shall notify the Investigator should there be any indication of a complication or discrepancy that the Investigator may not have noted. This will allow the Investigator an opportunity to further review the test results and clarify the findings if necessary.

The electronic database is subject to predefined electronic data checks to identify potential discrepancies and inconsistencies. Furthermore, trial content data reviews are conducted to ensure that data collected are scientifically and medically valid. Regular feedback and reports will be provided to the site manager, so that all queries can be resolved in a timely fashion.

12.0 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for ensuring that this clinical trial is conducted according to the Investigator Agreement, Protocol, all conditions of FDA and IRB approval and applicable FDA regulations. Written IRB approval of the protocol and ICF must be provided to the Sponsor.

Subjects were informed that their medical records will be subject to review by the Sponsor, its authorized designee or representatives of FDA. Subjects were informed that they may withdraw at any time without prejudice to future care. The informed consent provided by each trial site's IRB was signed prior to trial participation. The original signed informed consent for each subject must be retained by the Investigator and is subject to review by the Sponsor and the FDA. A copy of the informed consent will be provided to the subject.

Other specific responsibilities of the Investigator include:

Financial Disclosure:

The Investigator provided sufficient and accurate financial disclosure information prior to trial, and will promptly update the Sponsor of relevant changes during the course of the trial and for 1 year following completion of the trial.

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Inspection:

The Investigator shall permit authorized FDA employees at reasonable times and in as reasonable manner to enter and inspect any establishment where devices are held, inspect and copy all records relating the investigation, to inspect and copy records that identify subjects when the FDA has reason to suspect that records are incomplete, inaccurate, false or misleading.

12.1 INVESTIGATOR RECORDS

Investigators will maintain complete, accurate and current trial records for whichever of the following periods is shortest:

a. A period of two years after the date on which the FDA approves the marketing of the device for the purpose that was the subject of the trial.
b. A period of five years after the date on which the results of the trial are submitted to the FDA in support of the marketing of the device for the purpose that was the subject of the trial.

If the Investigator withdraws from the responsibility to maintain records, the custody of records may be transferred. Notice of transfer shall be given to the FDA no later than 10 working days after transfer occurs.

Investigator records shall include the following materials:

Correspondence:

Documentation of all verbal and written correspondence with FDA, the Sponsor or its designee including the Clinical Monitor, the Medical Monitor, the DMC and other Investigators regarding this clinical trial or any subject enrolled therein.

Device Accountability:

Accountability records of receipt, use and disposition of all investigational devices and other trial materials, including:

- The type and quantity of the devices, dates of receipt and serial or lot numbers
- The names of all persons who received, used or disposed of each device and
- Why and how many units of the device are returned to Edwards Lifesciences, or otherwise disposed of.

Subject records:

Available subject records will include: signed informed consent, supporting documents (admission summary, operative reports, discharge letters, pertinent consultation reports diagnostic tests, laboratory tests, medical records, etc.) and records of exposure of each subject to the device.

Investigational Plan (Trial Protocol):

A Trial Site Regulatory binder will be maintained by the Investigator and site coordinator and will include a current copy of the Investigational plan including the IFU of the trial valve and other specified documents as listed in the binder table of contents.

Unanticipated Adverse Device Effects:

The Investigator will maintain records of all reports and information pertaining to unanticipated device effects.

IRB Information:

All information pertaining to IRB review and approval of this clinical trial including a copy of the IRB letter and that the IRB approved the Investigational Plan, a blank ICF approved by the IRB, and certification from the IRB Chairman that the IRB complies with FDA regulations (21CFR, Part 56).

Investigator Agreements:

The Investigator will maintain copies of signed Investigator Agreements and current CVs of all participating clinical trial staff members.

Other:

The Investigator will maintain any other records that may be required by applicable state or U.S. federal laws.

Investigator Reports:

The Investigator will prepare and submit the following reports:

Withdrawal of IRB Approval:

If applicable, withdrawal of approval shall be reported to the Sponsor within five working days. The Investigator will provide a written report of the reason(s) approval was withdrawn.

Progress Reports:

The Investigator will submit progress reports to the Sponsor in the form of completed CRFs. The same forms will be used at all trial sites for the recording of data on the findings of follow-up evaluations and complications. In addition, the Investigator may be asked to submit progress reports to the Sponsor and the reviewing IRB that include the number of trial subjects, a summary of follow-up data and AEs/complications and a general description of trial progress.

Final Report:

The Investigator shall submit a final report within three months of termination, completion of the trial or completion of the Investigator's participation in the trial, to the Sponsor and the IRB.

Deviations from the Trial Protocol:

The Investigator will not deviate from the protocol without the prior written approval of the Sponsor except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the subject's risk or affect the validity of the trial. Any subsequent revisions to the protocol, including the Informed Consent Form and the Case Report Forms, other than very minor revisions, must be approved by the Sponsor, the FDA, and the IRB. In medical emergencies, prior approval for protocol deviations will not be required, but the Sponsor or its designee and IRB must be notified within 5 working days of the incident. Periodic monitoring of protocol compliance will be performed for each site. Deviations will be documented on the appropriate case report form.

Other Reports:

Upon the request of FDA, the reviewing IRB, or the Sponsor, the Investigator will provide accurate and timely information about any aspect of the clinical trial.

13.0 SPONSOR RESPONSIBILITIES

The Sponsor is responsible for ensuring that this trial will be conducted in compliance with all applicable U.S. Federal regulations pertaining to investigational devices including but not limited to: 21 CFR Part 50, Part 54, Part 56, Part 812, Good Clinical Practice (GCP) standards, and Health and Insurance Portability and Accountability Act (HIPAA).

The Sponsor will prepare and submit the following complete, accurate and timely reports:

Unanticipated Adverse Device Effects (UADE)

UADEs shall be reported to FDA and to all reviewing IRBs and participating investigators within 10 working days after the Sponsor receives notice of the effect.

Withdrawal of IRB Approval

Any withdrawal of approval of an investigation or a part of an investigational by a reviewing IRB shall be reported to FDA and all reviewing IRBs and participating investigators within 5 working days after receipt of the withdrawal of approval.

Withdrawal of FDA Approval

Any withdrawal of approval of an investigation or a part of an investigational by FDA shall be reported to all reviewing IRBs and participating investigators within 5 working days after receipt of the withdrawal of approval.

Progress Report

A progress report shall be submitted to FDA and reviewing IRBs annually.

Final Report

A final report shall be submitted to FDA and all reviewing IRBs within 6 months of trial completion or termination.

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The Sponsor will provide Investigators with the information and training required to conduct the clinical trial properly and in accordance with the clinical protocol. The Sponsor must ensure proper monitoring of the Clinical Trial, that IRB approval is

obtained and remains current, and that FDA and the IRB are informed of significant new information about the clinical trial. The Sponsor of this trial is Edwards Lifesciences, LLC.

Trial Director:

The clinical trial manager is responsible for the conduct and administration of this clinical trial. These responsibilities include maintaining regular contact with each trial site and ensuring the conduct of all on-site monitoring visits at each trial site to ensure compliance with this clinical, to verify that accurate and complete data are being submitted in a timely manner and to verify that the investigational site facilities continue to be adequate. The Clinical Manager of this trial is:

Trial Manager:

13.1 SELECTION OF INVESTIGATORS

Edwards Lifesciences will select qualified Investigators by education, training and experience and verify the adequacy of the trial site.

13.2 TRAINING

The Sponsor or designee will train the Principal Investigator(s) and support staff on the use of the trial Valve and the trial delivery system, the Protocol, eCRFs and Electronic Data Capture (EDC) system, GCP Guidelines and other investigation documents as applicable. A “Delegation of Authority Form” will be maintained at each investigational center designating which individuals are allowed to perform specific clinical investigation related tasks. The delegated tasks will determine what the training requirements are for each member of the investigation support staff. Training will be documented for each site.

13.2.1 ECHOCARDIOGRAPHIC EXAMINATIONS

Clinical sites may be trained by the core lab staff or may self–train. See xxxx for a copy of the Echo Core Lab Manual.

13.2.2 DOCUMENTATION

Training will be documented on a training record provided by the Sponsor, which the trainee must sign and date. The training of investigation support staff must be completed and documented before the staff member may perform the specific clinical investigation related tasks delegated to them by the Principal Investigator.

13.3 MONITORING METHODS

The Sponsor has established procedures for monitoring clinical investigations to assure the quality of the trial and to assure that each person involved in the monitoring process carries out his or her duties. Standardized written procedures, sufficiently detailed to cover the general aspects of clinical investigations, will be used as a basic monitoring plan and will be supplemented by more specific or additional procedures, as required by the clinical investigation. A pre-investigation “Qualification Visit” was conducted to ensure that the Investigator clearly understood and accepted the obligations incurred in undertaking the clinical investigation as set forth in 21 CFR 56 and 21 CFR 812, and that the facilities are acceptable throughout the clinical investigation. Only qualified investigational sites participated in the trial. Periodic monitoring visits will be conducted with adequate frequency to ensure that the Investigator’s obligations as set forth in 21 CFR 56 and 21 CFR 812 are being fulfilled and that the facilities continue to be acceptable. The Sponsor assigns a monitor to oversee the progress of the clinical investigation at each investigational center. The monitor will remain in close contact with each investigational center throughout the duration of the investigation to provide any needed materials, (i.e., investigation forms) and answer any questions. The monitor will be responsible for verifying that the subject signed the consent, reviewing all data recorded on the eCRFs (100% source data verification), and visiting each investigational center periodically to observe trial progress and compliance with clinical protocol and regulations applicable to this clinical investigation.

Monitoring visits will be scheduled throughout the duration of the clinical investigation between the monitor and the Principal Investigator at a mutually convenient and available time. These visits will assure that the facilities are still acceptable, the protocol and investigational plan are being followed, the IRB is notified of approved protocol changes as required, complete records are being maintained, appropriate timely reports (incl. AEs, SAEs and UADEs) are made to the Sponsor and IRB, and device inventory is controlled and the Investigator is carrying out all agreed upon activities. Any personnel changes must be reported to the monitor immediately and a training program must be scheduled and documented. Additionally, the monitor will perform 100% source data

verification of events contributing to the primary safety endpoints and unanticipated device effects (UADEs) to assure CRF data accuracy and completeness.

13.3.1 MONITORING VISITS

Periodic monitoring visits will be made at all trial centers in accordance with center enrollment rates. Trial centers should be visited a minimum of once each year by the monitor.

Upon termination or conclusion of the clinical investigation, the monitor will perform a close-out visit to ensure that all clinical trial materials and patient data are properly documented and returned to the Sponsor.

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