COMMENCE-P Trial

COMMENCE Pulmonary: Clinical Evaluation of Edwards Pericardial Aortic Bioprosthesis (Model 11000A) for Pulmonary Valve Replacement (COMMENCE-P)

NCT02656290

August 4, 2017

Edwards Lifesciences LLC
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Protocol Number 2015-03

CLINICAL INVESTIGATIONAL PLAN

Version B

04-Aug-17

Prospective, Non-randomized, Single Arm, Multicenter Clinical Evaluation of the **INSPIRIS RESILIA Pulmonary Valve** *(Model 11500P) for Pulmonary Valve Replacement (2015-03 TRIAL)*

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

1. INVESTIGATOR SIGNATURE PAGE

Trial Title:	*Prospective, Non-randomized, Single Arm, Multicenter Clinical Evaluation of the* INSPIRIS RESILIA *Pulmonary Valve (Model 11500P) for Pulmonary Valve Replacement (2015-03 TRIAL)*
Protocol Number:	**2015-03**
Version Number:	**Rev. B**
Date:	**04 August 2017**

I have read this protocol [redacted]s and agree to participate in the clinical investigation sponsored by Edwards Lifesciences LLC. I agree to conduct this investigation in accordance with the study agreement, the investigational plan, the instructions for use, applicable FDA regulations and conditions of approval imposed by the reviewing Institutional Review Board. I agree to supervise the use of all of the investigational devices at my institution and to ensure appropriate informed consent is obtained from all subjects prior to inclusion in this trial. I further agree to maintain accurate, complete, and current records relating to my participation in this investigational trial as required by 21CFR812.140.

INVESTIGATOR NAME

DATE

INVESTIGATOR SIGNATURE

2. TRIAL CONTACT PERSONNEL

2.1 SPONSOR CONTACTS

TRIAL MANAGER	TRIAL SITE PROJECT MANAGER
[redacted]	[redacted]

MEDICAL MONITOR	SAFETY OFFICER
[redacted]	[redacted]

2.2 TRIAL CONTACTS

NATIONAL PRINCIPAL INVESTIGATOR	NATIONAL PRINCIPAL INVESTIGATOR
[redacted]	[redacted]

NATIONAL COORDINATOR

[redacted]

CLINICAL EVENTS COMMITTEE

[redacted]

ECHOCARDIOGRAPHY CORE LAB

[redacted]

DATA SAFETY MONITORING BOARD

[redacted]

3. PROTOCOL SYNOPSIS

Title:	*Prospective, Non-randomized, Single Arm, Multicenter Clinical Evaluation of the INSPIRIS RESILIA Pulmonary Valve (Model 11500P) for Pulmonary Valve Replacement (2015-03 TRIAL)*
Protocol Number	2015-03
Trial Sponsor:	Edwards Lifesciences One Edwards Way Irvine, CA 92614 [redacted]
Trial Device:	INSPIRIS RESILIA Pulmonary Valve, Model 11500P
Study Indication:	The INSPIRIS RESILIA Pulmonary Valve, Model 11500P, is indicated for pediatric and adult patients five years or older requiring replacement of their native or prosthetic pulmonary valve.
Trial Objective:	The objective of this trial is to assess the safety and effectiveness of the INSPIRIS RESILIA Pulmonary Valve, Model 11500P, in the pulmonary position in pediatric and adult subjects five years or older requiring replacement of their native or prosthetic pulmonary valve.
Trial Design:	Prospective, Non-Randomized, Single Arm, Multicenter study. Up to one hundred (100) pulmonary valve replacement (PVR) subjects at up to ten (10) clinical sites will be enrolled. Clinical data will be collected from at least 3 centers with data available on patients who have completed the 1 year follow-up visit. Sites will not be allowed to implant more than 50% of total sample size.
Trial Sites:	Participating sites are chosen based on their experience in conducting clinical trials, their surgical experience implanting bioprosthetic valves, as well as their ability to maintain robust subject enrollment and follow-up. The investigational sites will be selected throughout the United States.
Trial Duration:	Total enrollment period for this trial is estimated to be 3 years.

Subject participation begins with the enrollment of the first subject and ends after the last subject enrolled has completed the five (5) year follow up visit or has exited the trial.

Overall trial duration is estimated to be 9 years. This includes subjects being monitored, all outstanding data queries resolved and all trial sites closed to follow-up.

Trial Assessment Visits:

Visit	Visit Window (Days)
Screening/Baseline	_____
Procedure	_____
Discharge[1]	_____
30 Days[2]	+/- 7 days
6 Months	+/- 21 days
Year 1	+/- 30 days
Year 2	+/- 45 days
Year 3	+/- 45 days
Year 4	+/- 45 days
Year 5	+/- 45 days

[1] Subjects who are not discharged within 10 days post procedure must have an echocardiogram to assess performance of the trial valve. Those subjects will not require an additional echocardiogram at discharge.
[2]May be Clinic or Telephone Visit

Trial Endpoints:

Safety Endpoints

Primary Endpoint:

- The primary safety endpoint for the trial is freedom from device or procedure-related death and/or reoperation at 1 year.

Secondary Endpoint:

The following safety endpoints will also be assessed:

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

Effectiveness Endpoints:

- Clinically acceptable hemodynamic performance confirmed by core lab evaluation of echocardiography

- Functional improvement from baseline (NYHA/Modified Ross Heart Failure Classification)

Subject Enrollment:

Inclusion Criteria:

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

1. Has pulmonary valve disease requiring pulmonary valve replacement of their native or prosthetic valve
2. Is greater than or equal to 5 years of age
3. Subject and/or subject's legal representative has provided written informed consent as approved and required by the respective institutional review board and agrees to its provisions. NOTE: Written consent must be obtained prior to any research related test being performed.

Exclusion criteria:

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

1. Valve-in-conduit procedure
2. Requires emergency surgery
3. Has acute myocardial infarction (MI) within 30 days prior to screening date
4. Has MRI or CT scan confirmed stroke, cerebrovascular accident (CVA) or transient ischemic attack (TIA) within 6 months (180 days) prior to screening date
5. Has hemodynamic or respiratory instability requiring inotropic support, mechanical circulatory support, or mechanical ventilation within 30 days prior to screening date
6. Has active endocarditis/myocarditis or endocarditis/myocarditis within 3 months prior to screening date
7. Has renal insufficiency as determined by creatinine (S-Cr) level ≥ 2.5 mg/dL within 60 days prior to screening visit or end-stage renal disease
8. Has documented leukopenia (WBC < 3.5x 10^3/µL), acute anemia (Hgb < 10.0 g/dL or 6 mmol/L), or thrombocytopenia (platelet count < 50x10^3/µL) accompanied by history of bleeding diathesis or coagulopathy within 60 days prior to screening date
9. Diagnosed with abnormal calcium metabolism and hyperparathyroidism

10. Echocardiographic evidence of an intra-cardiac mass, thrombus, or vegetation
11. RVOT aneurysm *unless* treated during pulmonary valve replacement surgery
12. Has prior organ transplant or is currently an organ transplant candidate
13. Was previously implanted with INSPIRIS RESILIA Pulmonary valve
14. Previously implanted with an aortic, mitral, or tricuspid bioprosthetic valve, mechanical valve, or annuloplasty ring
15. Need for concomitant replacement of the aortic, mitral or tricuspid valves
16. Has presence of non-cardiac disease limiting life expectancy to less than 12 months
17. Is currently or has recently participated (within 6 weeks) in another investigational drug or device trial
18. Positive urine or serum pregnancy test in female subjects of child-bearing potential and/or nursing mothers, or planning to become pregnant within 1 year of study valve implant
19. Has left ventricular ejection fraction ≤ 20% as validated by diagnostic procedure prior to screening date
20. Currently incarcerated or unable to give voluntary informed consent
21. Documented history of substance (drug or alcohol) abuse within the last 5 years prior to screening date
22. Patients with hypersensitivity to metal alloys that contain cobalt, chromium, nickel, molybdenum, manganese, carbon, beryllium and iron
23. Patients with hypersensitivity to latex

Intra-Op Exclusion Criterion:

24. Significant injury to the heart upon entry defined as emergent cardiopulmonary bypass requiring femoral cannulation

4. ABBREVIATIONS

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

Table of Contents

5. TRIAL OVERVIEW

5.1 INTRODUCTION AND BACKGROUND

Congenital heart disease (CHD) is the most common congenital disorder in newborns. The reported prevalence of congenital heart disease (CHD) at birth ranges from 6 to 13 per 1000 live births. Survival of children with CHD has improved significantly and as a result increasing numbers of patients undergo pulmonary valve replacement (PVR). Surgical management of congenital heart disease (CHD) such as Tetralogy of Fallot (TOF) and pulmonary stenosis includes relief of right ventricular outflow tract (RVOT) obstruction using techniques that may result in pulmonary valve dysfunction and varying degrees of right ventricular (RV) volume and pressure overload. Pulmonary regurgitation, a common sequelae, may initially be well tolerated but eventually leads to exercise intolerance, progressive RV dilation and dysfunction, ventricular and atrial tachycardia, congestive heart failure, and sudden cardiac death [1]. Implantation of a competent pulmonary valve is commonly undertaken to avoid these adverse clinical outcomes and preserve RV function. The detrimental effects of pulmonary regurgitation are now widely accepted, which in turn, has led to earlier PVR in most instances before overt symptoms and cardiovascular decompensation develop. Delayed pulmonary valve replacement may contribute to higher perioperative mortality due to advanced right ventricular dysfunction. Therefore, timing and indications for replacement of an incompetent pulmonary valve are key issues.

5.1.1 PULMONARY HEART DISEASE

Congenital defects involving the right ventricular outflow tract require iterative surgical interventions and/or corrections throughout a patient's growing years and young adulthood. Some of the defects include pulmonary atresia and pulmonary stenosis. Other defects that are more complex and require complex surgeries include transposition of the great arteries, Tetralogy of Fallot with or without pulmonary atresia, truncus arteriosus, or double outlet right ventricle.

The occurrence of pulmonary insufficiency and/or pulmonary stenosis is not uncommon after surgery for congenital heart defects [1] [2] [3] [4]. Surgical repair of congenital heart disease such as Tetralogy of Fallot and pulmonary stenosis includes relief of right ventricular outflow tract obstruction using techniques that may result in significant pulmonary insufficiency [1]. Late morbidity and mortality following repair is predominantly secondary to the effects of progressive right heart failure and arrhythmias, to which pulmonary insufficiency (PI) contributes [5]. Patients require long-term follow-up, as they are at risk for

the chronic postoperative complications including arrhythmias including atrial tachycardia and ventricular tachycardia (VT), and sudden cardiac death. Surgical pulmonary valve replacement may be necessary to restore pulmonary valve competence, improve right ventricular function and improve the symptoms.

5.1.2 SURGICAL OPTIONS FOR PULMONARY VALVE REPLACEMENT (PVR)

There are no approved surgical options for pulmonary valve replacement. As of January 27, 2015, the Medtronic Melody® Transcatheter Pulmonary Valve has been approved in the US as a catheter-delivered stent valve for use in a limited population. The transcatheter pulmonary valve replacement (TPVR) is approved as an adjunct to surgery in the management of pediatric and adult patients with 1) the existence of a full RVOT conduit equal to or greater than 16 mm in diameter when originally implanted and 2) dysfunctional RVOT conduit with a clinical indication for intervention: regurgitation ≥ moderate and/or mean RVOT gradient≥ 35 mmHg. It is available in two sizes: 16mm and 18mm (Source: FDA PMA Database).

Not yet approved surgical options for pulmonary valve replacement include bioprostheses, homografts, and mechanical valves. Controversy regarding the optimal valve in the pulmonary position remains. Bioprosthetic valves perform well hemodynamically but are prone to structural degeneration. The homograft has a drawback of limited availability. Mechanical valves lead to a persistent need for anticoagulation; and despite positive reports in the literature have generally been associated with pulmonary thromboembolic complications [6]. Long-term data are available for bioprosthetic valve durability in the aortic position and these data are typically extrapolated to decision making and counseling for pulmonary valve replacement.

The ideal pulmonary valve substitute has not yet been clearly defined but compared with mechanical, homograft and polytetrafluoroethylene valves, stented bioprosthetic valves in the pulmonary valve position have been shown to be a better option [4].

5.1.3 SURGICAL PULMONARY VALVE REPLACEMENT (PVR)

Retrospective studies documented in literature have shown statistically significant improvements in performance following surgical pulmonary valve replacement (PVR). Significant improvements are seen in right ventricular end-diastolic volume or pressure [3] [6] [7] [8] [9], right ventricular end-systolic volume [8], right ventricular end-diastolic volume index [3], pulmonary regurgitation [4] [6] [10], pulmonary valve Doppler velocities [10], tricuspid regurgitation [3] [6], peak pulmonary valve gradient [3] [11], estimated

right ventricular pressure [3], cardiothoracic ratio on chest x-ray [8, 12], maximal oxygen uptake [10], QRS width [10] [12], left ventricular ejection fraction [9] [12], right ventricular enlargement [9], and right ventricular dysfunction [9] [13]. One study found statistically significantly fewer subjects with moderate or greater pulmonary stenosis and pulmonary insufficiency that were treated with porcine versus bovine valves [4]. However, the authors also noted that the follow-up duration was significantly shorter for the porcine group versus the bovine group (31.7 versus 55.7 months, $P < 0.001$). This study also found that subjects who received a PVR at an age greater than 15 years had significantly lower percentages of moderate or greater pulmonary stenosis and insufficiency.

Retrospective review of New York Heart Association functional class of subjects that underwent PVR showed an improvement in function class postoperatively, with five studies reaching statistical significance [1] [6] [7] [9] [10] [11] [12] [13] [5].

Freedom from re-intervention/reoperation specific to patients who received the Carpentier-Edwards PERIMOUNT valve were 100% at 2.5 years [5], 50% and 97.7% at 5 years [14] [1], 74.7% at 7 years [8], and 79% [15] and 94% at 10 years [11]. Risk factors found to be associated with increased risk for reintervention/reoperation in a multivariate analysis included younger age at PVR [4] [2] [9], underlying diagnosis of pulmonary atresia with ventricular septal defect [2], and use of stentless porcine valve [2].

Six studies provided results on the freedom from structural valve deterioration/ failure/dysfunction/explant or freedom from moderate-severe or severe pulmonary insufficiency [3] [6] [2] [11] [1] [9]. The overall 5 year rates ranged from 74% to 92.2% and overall 10 year rates ranged from 20.2% to 98%. Rates specific to patients who received the Carpentier-Edwards PERIMOUNT valve were 89.1% [1] and 92% [6] at 5 years and 79% [15] and 98% [11] at 10 years. Lee et al (2011) also found that stented bovine valves had a statistically significantly higher freedom from valve failure and dysfunction rate than stentless porcine valves ($p = 0.015$), but valve-specific rates were not provided. Risk factors found to be associated with increased risk for structural valve deterioration or failure in a multivariate analysis included younger age at PVR [3], higher indexed valve internal diameter [3], and use of a homograft in the early phase (within 3 years of surgery) [15]. However, higher indexed valve ID at implantation, which is indicative of valve oversizing, was an independent predictor of SVD within younger patients.

Babu-Narayan et al conducted a retrospective study investigating the survival rate after repair of Tetralogy of Fallot at a single tertiary center. Mortality was the primary outcome measure. In total, 221 surgical pulmonary valve replacements were performed in 220 patients (130 male patients; median age, 32 years; range, 16–64 years). The article concluded that surgical pulmonary valve replacement (PVR) has a low and improving mortality, with low 10 year re-intervention rates. The more recently operated on patients (2005-2010) were less symptomatic and had better exercise capacity at the time of referral for surgical PVR compared with those in the earlier era (1993-2004). The trend of earlier PVR was associated with lower mortality [16].

Jang et al retrospectively reviewed surgical outcomes of 131 PVRs performed at a single center from 2001 to 2010. The mean age was 14.8 yrs $\pm$ 6.7 years. There were no early or late mortality; the rate of freedom from reoperation at 10 years was 66.4$\pm$ 4.4%; implanted valve type; young age; and large sized valve implantation were risk factors for repeat PVR in the univariate analysis [8].

Retrospective studies have shown use of stented bioprosthetic valves to treat pulmonary valvular disease has become a standard treatment in clinical practice with optimal rates of survival and freedom from re-operation. Tweddell's retrospective comparative study of 122 subjects (median age 14.6; range 0.6-49 yrs) concluded heterograft valves should be the first choice among patients with TOF requiring pulmonary valve replacement as there was no difference in survival or freedom from re-intervention and they have the potential advantages of lower cost and availability [17] . Additionally, clinical data supporting the safety of the Carpentier-Edwards PERIMOUNT valve showed a good safety profile [5]. Neukamm's case series assessed the largest published series of 90 patients who received the Carpentier-Edwards PERIMOUNT valve in the pulmonary position with excellent midterm results in small children as young as 2 years old. Results showed the Carpentier-Edwards PERIMOUNT valve had the least stenosis and insufficiency compared to Bicuspid, Contegra, Homograft, and Monocusp valves [18]. The availability, handling characteristics, and excellent early outcomes make the Edwards Pericardial Aortic Bioprosthesis a promising option for surgeons seeking to provide pulmonary valve competence to the previously repaired RVOT [5], but further follow up is needed to define long-term function and durability.

A number of studies were identified in the literature that presented data on pulmonary valve replacements. Although none of the studies were randomized controlled trials (RCT), these data are of acceptable quality and the studies represent an acceptable level of scientific rigor and objectivity. The

use of bioprosthetic valves to treat pulmonary valvular disease, including Tetralogy of Fallot, has become a standard treatment in clinical practice and has been the subject of multiple publications. Data found in publications evaluating bioprosthetic valves to treat pulmonary valvular disease also supported the performance of the Carpentier-Edwards PERIMOUNT Aortic Bioprosthesis.

Based on the results of the aortic pre-clinical data, the OUS clinical trial, the interim results of the COMMENCE trial and literature review, the use of the investigational valve is justified.

The goal of this trial is to provide prospective, controlled data with limiting confounding factors on the use of the INSPIRIS RESILIA Pulmonary Valve, Model 11500P in children and adults requiring pulmonary valve replacement.

5.1.4 **CLINICAL TRIAL PURPOSE**

The objective of this trial is to assess the safety and effectiveness of the INSPIRIS RESILIA Pulmonary Valve, Model 11500P in the pulmonary position in pediatric and adult subjects five years or older requiring replacement of their native or prosthetic pulmonary valve.

5.2 REGULATORY HISTORY

The INSPIRIS RESILIA Pulmonary Valve (model 11500P) is the same valve as the INSPIRIS RESILIA Aortic Valve (model 11500A). The Model 11500A is a surgical bioprosthetic heart valve that is a design modification to the Edwards Pericardial Aortic Bioprosthesis, Model 11000A.

The Edwards Pericardial Aortic Bioprosthesis (model 11000A) received CE mark on April 24, 2012 for the replacement of native or prosthetic aortic heart valves.

The model 11000A has not been commercially released in the EU, or in any other country or geographic region as of the date of this document.

INSPIRIS RESILIA Aortic Valve (model 11500A) received CE mark on September 29, 2016 for the replacement of native or prosthetic aortic heart valves.

INSPIRIS RESILIA Aortic Valve (model 11500A) is currently under PMA review (PMA # P150048) for the replacement of native or prosthetic aortic heart valves. The PMA has been found to be approvable pending results of final inspections; Ref. FDA letter dated February 21, 2017.

5.3 PREVIOUS DEVICE ITERATION DESCRIPTION

Edwards Pericardial Aortic Bioprosthesis, Model 11000A

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

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

The wireform is made of a cobalt-chromium alloy and is covered with a woven polyester fabric. A cobalt-chromium alloy/polyester film laminate band surrounds the base of the wireform frame. A silicone sewing ring that is covered with a porous polytetrafluoroethylene (PTFE) cloth is attached to the wireform frame. The sewing ring has three, equally spaced black silk suture markers at the cusp centers to aid in bioprosthesis orientation and suture placement.

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

The Model 11000A, is being evaluated as part of the COMMENCE trial (ClinicalTrials.gov # NCT01757665, Protocol Number 2012-02) to confirm safety and effectiveness in subjects who require replacement of their native or prosthetic aortic. Safety and performance for the Edwards Pericardial Aortic Bioprosthesis, Model 11000A and Edwards Pericardial Mitral Bioprosthesis, Model 11000M is supported by the interim clinical data from the COMMENCE trial, see section 5.4.2.

5.4 CURRENT DEVICE ITERATION DESCRIPTION

INSPIRIS RESILIA Pulmonary Valve, Model 11500P

[redacted]

The INSPIRIS RESILIA Pulmonary Valve, Model 11500P, incorporates two novel features (available on sizes 19 – 25 mm only) designed for potential future valve-in-valve (ViV) procedures: fluoroscopically visible size markers and an expandable cobalt chromium alloy band.

As in the Edwards Pericardial Aortic Bioprosthesis, Model 11000A, a thin cobalt-chromium alloy band and polyester support band surround the base of the valve beneath the wireform frame providing structural support for the orifice.

In the INSPIRIS RESILIA Pulmonary Valve, model 11500P which is the same valve as model 11500A, the ends of the cobalt-chromium alloy band are secured by a polyester shrink sleeve on the sizes 19 – 25 mm (Figure 1a) to allow the internal orifice of the valve to expand. The polyester support band allows expansion at each commissure when subjected to radial forces. The expandable cobalt-chromium alloy band does not impact suture placement or implant technique. Valves with expandable bands (sizes 19 – 25 mm) will maintain a stable diameter at implant and under intracardiac conditions, which was demonstrated during compression resistance testing and accelerated wear testing.

In the sizes 27 and 29 mm (Figure 1b), the free ends of the cobalt-chromium alloy band are permanently secured using a weld joint.

Similar to other Edwards' bioprosthetic valves, the cobalt-chromium alloy wireform in the model 11500P can be identified on fluoroscopy. The fluoroscopically visible size marker is designed to aid the clinician in surgical valve size identification after implantation. A representation of the commissure size markers for the sizes 19 – 25 mm is shown in Figure 1c.

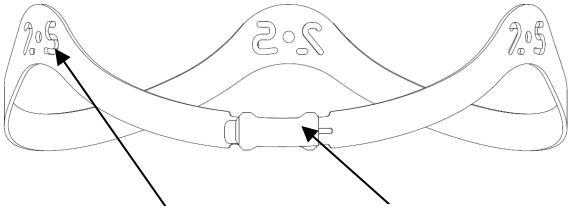
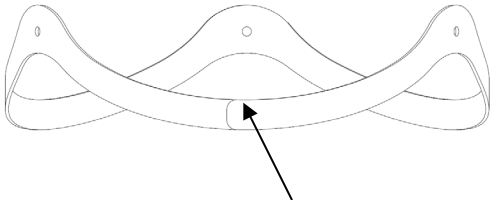
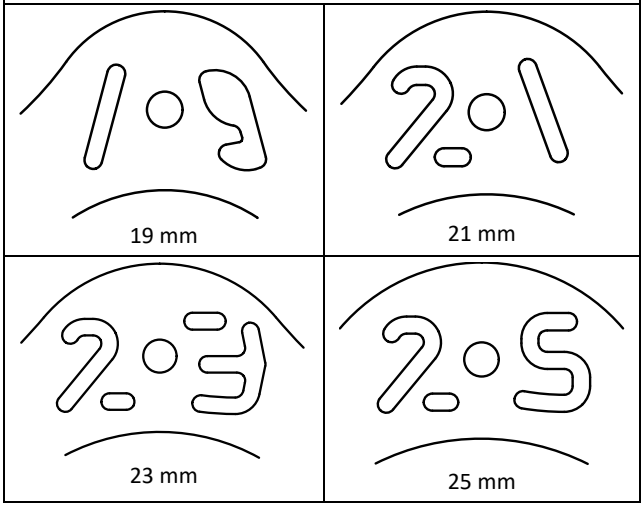
Figure 1a (Sizes 19 – 25 mm Cobalt Chromium Alloy Band)	**Figure 1b (Sizes 27 and 29 mm Cobalt Chromium Alloy Band)**
	

Figure 1c (Sizes 19 – 25 mm Size Markers)



5.4.1 DEVICE INDICATION FOR USE

The INSPIRIS RESILIA Pulmonary Valve, Model 11500P, is indicated for pediatric and adult patients five years or older requiring replacement of their native or prosthetic pulmonary valve.

5.4.2 CONTRAINDICATION

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

5.4.3 DEVICE TRAINING

Sponsor will present formal device training to applicable study personnel prior to performing first implant. Formal device training will further enhance training per the Instructions for Use (IFUs) provided in the protocol.

5.5 REPORT OF PRIOR INVESTIGATIONS

5.5.1 EUROPEAN STUDY INFORMATION- CLINICAL TRIAL OF THE EDWARDS AORTIC BIOPROSTHESIS, MODEL 11000

A prior confirmatory clinical trial (ClinicalTrials.gov #NCT01651052, Protocol #2010-03) initiated in Europe in July 2011 is also underway to gather data on the Model 11000A. This is a prospective, non-randomized clinical trial of the trial valve for subjects undergoing aortic valve replacement (AVR). The trial enrolled

and successfully implanted one hundred thirty-three (133) subjects at two sites in Poland. Enrollment for this trial was closed as of 19 February 2013. Follow-up compliance of 100% (131/131) at discharge, 99.2% (129/130) at 3-months, 97.6% (122/125) at 1-year, 92.5% (111/120) at 2-years, 93.8% (105/112) at 3-years, 92.7% (101/109) at 4-years, and 100% (17/17) at 5-years has been achieved for all eligible subjects as of 07 April 2017. Follow-up is ongoing until all subjects complete the 5 year follow-up.

To date, three (3) early (≤30 POD) and sixteen (16) late deaths have occurred in the enrolled cohort. One (1) early and three (3) late deaths were adjudicated by the CEC as study valve related including one death attributed to late study valve thrombosis. One (1) study valve explant has occurred on POD 234 due to endocarditis. One (1) incident of late non-structural valve dysfunction has been reported: the 2-year follow-up echocardiogram demonstrated high gradients which had worsened from the 1-year follow-up due to patient prosthesis mismatch, as adjudicated by the CEC. There have been no reports involving unanticipated adverse device effects or structural valve deterioration.

5.5.2 U.S. STUDY INFORMATION- PROSPECTIVE, NON-RANDOMIZED, MULTICENTER CLINICAL EVALUATION OF THE EDWARDS PERICARDIAL AORTIC AND MITRAL BIOPROSTHESES (MODELS 11000A AND 11000M) WITH A NEW TISSUE TREATMENT PLATFORM

The objective of the COMMENCE trial (protocol 2012-02, NCT#01757665) is to confirm that tissue processing, valve sterilization and packaging used in the Model 11000A and Model 11000M do not raise any new questions of safety and effectiveness in subjects who require replacement of their native or prosthetic aortic or mitral valve. IRB or EC approval of the investigational plan has been obtained at thirty-five (35) investigational sites in the US, Canada, and Europe. Enrollment was completed in the aortic arm in March 2016, and completed in the mitral arm in July 2016. Six hundred ninety-four (694) subjects were enrolled in the aortic cohort across twenty-seven (27) investigational sites and eighty three (83) subjects were enrolled in the mitral cohort across seventeen (17) investigational sites. Of the enrolled population, six hundred eighty nine (689) subjects were treated and successfully implanted with Model 11000A and eighty two (82) subjects with the Model 11000M.

For the aortic cohort, follow-up compliance of 100% at discharge, 97.2% at 3-months, 97.0% at 1-year, 92.8% at 2-years, and 88.5% at 3-years has been achieved for all eligible implanted subjects. To date, nine (9) early (≤ 30 POD) deaths and twenty eight (28) late deaths have occurred. Ten (10) deaths, three (3) early and seven (7) late, were considered related to the study valve per CEC adjudication. Three (3) study valve explants have occurred, due to endocarditis. There have been no reported incidences of valve

thrombosis, structural valve deterioration, and all other complications fall within accepted performance criteria.

For the mitral cohort, follow-up compliance of 100% at discharge, 95% at 3-months, 100% at 1-year, and 100% at 2-years has been achieved for all eligible implanted subjects. To date, one (1) early death and seven (7) late deaths have occurred, of which one (1) early and one (1) late death were considered to be related to the study valve per CEC adjudication. No explants have occurred to date. Two (2) late events of structural valve deterioration have been site reported due to worsening central regurgitation.

Safety and performance for the Edwards Pericardial Aortic Bioprosthesis, Model 11000A and Edwards Pericardial Mitral Bioprosthesis, Model 11000M is supported by the early clinical data. Continued subject follow-up will confirm that the new tissue process modifications do not raise new safety and effectiveness questions.

6. BENEFITS AND RISKS

6.1 BENEFITS

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

The anticipated additional benefits are to eliminate the need for rinsing the bioprosthesis prior to implantation, less exposure to the risks of glutaraldehyde, and elimination of hazardous waste requiring special disposal. Additionally, the V-fit technology (available on sizes 19 – 25 mm) incorporates two novel features designed for potential future valve-in-valve (ViV) procedures: fluoroscopically visible size markers and an expandable cobalt chromium alloy band [redacted].

6.2 RISKS

As with all prosthetic heart valves, serious complications, including death may be associated with the use of tissue valves. Complications due to individual subject reaction to an implanted device, or to physical or chemical changes in the components, particularly those of biological origin, may occur at varying intervals (hours or days) necessitating reoperation and replacement of the prosthetic device. Some or all of the risks listed below could require a reoperation or explant, and/or they may lead to permanent disability or death.

Known/potential risks associated with stented bioprosthetic heart valves include but not limited to:

- Angina
- Bleeding diatheses (coagulopathy) related to anticoagulant therapy
- Cardiac arrhythmias
- Cardiac failure
- Coronary ostial blockage
- Endocarditis
- Hemolysis/Hemolytic anemia
- Hemorrhage
- Immunological response
- Leaflet entrapment (impingement)
- Myocardial infarction
- Nonstructural valve dysfunction
- Paravalvular/Perivalvular/Transvalvular or Valvular Leaking
- Malfunctions of valve due to distortion at implant, fracture of wireform, physical and or chemical deterioration of valve components
- Patient prosthetic mismatch (PPM)
- Regurgitation/insufficiency
- Stenosis
- Thromboembolism/stroke
- Tissue deterioration including infection, calcification, thickening, perforation, degeneration, suture abrasion, instrument trauma, and or leaflet detachment
- Transient ischemic attack (TIA)
- Valve pannus
- Valve thrombosis
- Valve dislodgement/instability

Potential risks associated with pulmonary valve replacement surgery include but not limited to:

- Allergic reaction
- Annular dissection
- Atelectasis
- Pulmonary artery (damage, dissection, tear)
- Bleeding, anticoagulant related
- Bleeding, procedural
- Bleeding, post-procedural
- Cardiac arrest
- Cardiogenic shock
- Disseminated intravascular coagulation (DIC)
- Esophageal rupture
- Ventricular dysfunction/Heart failure
- Hematoma
- Heparin induced thrombocytopenia (HITs)
- Hypotension
- Hypertension
- Coronary artery compression
- Hypoxemia
- Infection, local or wound
- Infection, systemic (septicemia)
- Myocardial infarction
- Multi-system organ failure (MOF)
- Pericardial effusion
- Pericardial tamponade
- Pleural effusion
- Pneumothorax
- Pulmonary edema
- Pneumonia
- Renal dysfunction
- Respiratory failure
- Thromboembolism
  - Venous, peripheral or central
  - Arterial, peripheral or central
  - Pulmonary, thrombus or other
- Tricuspid valve insufficiency

Risks associated with trial valve are anticipated to be the same as those listed above for other pulmonary, aortic or mitral bioprosthetic valves and valve replacement surgery. Based on the results of the aortic pre-clinical data, the OUS clinical trial, and the interim results of the COMMENCE trial it is not anticipated that any new risks associated with the trial valve tissue process, sterilization method, or packaging will be observed.

Risks associated with stand-alone balloon pulmonary valvuloplasty procedures are pulmonary valve incompetence, and with valve-in-valve procedures, are instability / migration / embolization for the transcatheter device anchored within. Specific risk information related to the band expansion is provided in the device Instructions for Use.

6.3 MINIMIZING SUBJECT RISK

Several safeguards are incorporated into the trial to minimize subject risk. All pre-clinical device testing for the implantable valve is performed in accordance with FDA regulations, ISO 5840 and recognized standards. All test results have passed the required specifications supporting reasonable safety for this clinical product.

This clinical trial is conducted under the direction of qualified physicians experienced with cardiac surgery including pulmonary valve replacement and the use of investigational devices. All participating investigators and sites are screened and qualified. They must be experienced in conducting clinical research and have adequate personnel to assure compliance to the trial protocol. All clinical investigators performing the implant procedure will receive training specific to the trial valve procedure. The Instructions for Use [redacted] provides detailed instructions on the proper handling and implantation of these investigational valves.

Clinical outcomes for all trial subjects will be routinely monitored by the Sponsor during the course of the trial.

7. TRIAL DESIGN

The trial design methodology is based on the primary safety endpoint of freedom from device or procedure-related death and/or reoperation at 1 year as discussed in Sections 7.3 and 9.

A number of studies were identified in the literature that presented data on pulmonary valve replacements. Although none of the studies were randomized controlled trials (RCT), these data are of acceptable quality and the studies represent an acceptable level of scientific rigor and objectivity. The

use of bioprosthetic valves to treat pulmonary valvular disease, including Tetralogy of Fallot, has become a standard treatment in clinical practice and has been the subject of multiple publications. Data found in publications evaluating bioprosthetic valves to treat pulmonary valvular disease also supported the performance of the Carpentier-Edwards PERIMOUNT Aortic Bioprosthesis.

Based on the results of the aortic pre-clinical data, the OUS clinical trial, the interim results of the COMMENCE trial and literature review, the use of the investigational valve is justified.

7.1 OBJECTIVE

The objective of this trial is to assess the safety and effectiveness of the INSPIRIS RESILIA Pulmonary Valve, Model 11500P, in the pulmonary position in pediatric and adult subjects five years or older requiring replacement of their native or prosthetic pulmonary valve.

7.2 DESIGN

Prospective, Non-Randomized, Single Arm, Multicenter study. Up to one hundred (100) pulmonary valve replacement (PVR) subjects at up to ten (10) clinical sites will be enrolled. Clinical data will be collected from at least 3 centers with data available on patients who have completed the 1 year follow-up visit. Sites will not be allowed to implant more than 50% of total sample size.

The trial design includes methods to minimize bias. Efficacy endpoints will be independently evaluated by an independent Echo Core Lab. Members will be independent from the Sponsor, the Investigators, or trial staff involved in the medical care of the study subjects.

Study oversight includes a Data Monitoring Committee (DMC) and a Clinical Events Committee (CEC). The DMC and CEC are independent from the Sponsor, the Investigators, or anyone involved in the medical care of the study subjects. Member will not have conflict of interest related to the Sponsor. Committee Members must sign a non-conflict of interest statement in this regard.

The Data Monitoring Committee (DMC) will review aggregate safety data during the enrollment period to determine if the trial is being conducted safely and will decide if the clinical investigation should be modified, suspended and/or stopped. The Clinical Events Committee (CEC) evaluates the adverse events that are endpoint related as well as those resulting in death. The CEC adjudicates early and late events for their relatedness to the investigational device and/or the valve implant procedure.

7.3 ENDPOINTS

Safety and effectiveness data will be compared to available, control data published in articles in the prosthetic heart valve literature.

7.3.1 SAFETY

The primary safety endpoint for the trial is freedom from device or procedure-related death and/or reoperation at 1 year. The null hypothesis is that the rate of device or procedure-related death and/or reoperation at 1 year is greater than 25%. The alternative hypothesis is that this rate is less than 25%.

The following safety endpoints will also be assessed:

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

7.3.2 EFFECTIVENESS

Effectiveness endpoints include the following:

- Clinically acceptable hemodynamic performance confirmed by echocardiography and core lab evaluation which will include the following parameters:
    - Mean gradient
    - Peak gradient
    - Valvular regurgitation
    - TR gradient
    - Peak Velocity
    - Doppler Velocity Index (DVI)
    - Transvalvular VTI
- Functional improvement from baseline:
    - NYHA for subjects older than 12 years
    - Modified Ross Heart Failure Classification for subjects 12 years and under

7.4 ADDITIONAL CLINICAL MEASURES

- White Blood Cell Count
- Red Blood Cell Count
- Hemoglobin
- Hematocrit
- Platelet Count
- Plasma free hemoglobin or haptoglobin or serum LDH
- INR/PTT
- Urine urobilinogen (if necessary for subjects 12 years and under)

7.5 NUMBER OF SUBJECTS

Clinical data will be collected from at least 3 centers with data available on patients who have completed the 1 year follow-up visit. Sites will not be allowed to implant more than 50% of total sample size. Up to one hundred (100) pulmonary valve replacement (PVR) subjects at up to ten (10) clinical sites will be enrolled.

7.6 METHODS OF FOLLOW-UP

All subjects undergo a pre-operative echocardiogram to document the function of their current valve prior to surgery. Evaluation of the echocardiogram (echo) is performed by a qualified cardiologist at the site and over-read by an independent core lab. Other baseline exams include physical assessment, recording of pertinent medical history, electrocardiogram (ECG), NYHA or Modified Ross Heart Failure Classification, and selected hematological variables.

Sponsor allows standard of care tests to be used for screening/baseline data collection provided they are performed within 60 days before implant date and there are no significant changes in subject's condition that would invalidate the results. Standard of care tests are performed for all valve patients scheduled for valve replacement surgery whether or not being considered for the trial. If the patient agrees to participate in the trial, they are then consented and any ***trial related*** tests are performed post consent.

During the procedure, a transesophageal echo (TEE) will be completed. In addition, follow-up will occur at or prior to hospital discharge where physical assessment, ECG, echo and evaluation of selected hematological variables will occur. A post-op echocardiogram must be completed on or prior to post-operative Day 10. A telephone follow-up visit is conducted at POD 30 to document anti-thromboembolic therapy (medications), adverse events and determine NYHA or Modified Ross Heart Failure Classification. At 6 month follow-up visit, a physical assessment, NYHA or Modified Ross Heart Failure Classification, ECG,

echocardiogram, and selected hematological variables will be evaluated. The subsequent follow-up visits will be made annually thereafter up to 5 years. **Table 1** lists the follow-up visit time points and visit windows.

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

Table 1. Visit Follow-Up Schedule

Visit	Visit Window (Days)	Timing from Implant (Day 0)
Screening/Baseline	_____	Day -60 to Day 0
Index Procedure	_____	Day 0
Discharge[1]	_____	Prior to Discharge to Day 10
POD 30[2]	+/- 7 days	Day 23 to 37
6 Months	+/- 21 days	Day 162 to Day 204
Year 1	+/- 30 days	Day 335 to Day 395
Year 2	+/- 45 days	Day 685 to Day 775
Year 3	+/- 45 days	Day 1050 to Day 1140
Year 4	+/- 45 days	Day 1415 to Day 1505
Year 5	+/- 45 days	Day 1780 to Day 1870

[1] Subjects who are not discharged within 10 days post procedure must have an echocardiogram to assess performance of the trial valve. Those subjects will not require an additional echocardiogram at discharge.
[2] May be Clinic or Telephone Visit

All subjects will be followed until five (5) year follow-up visit is completed and the last subject enrolled exits the trial.

8. TRIAL POPULATION

8.1 INCLUSION CRITERIA:

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

1. Has pulmonary valve disease requiring pulmonary valve replacement of their native or prosthetic valve
2. Is greater than or equal to 5 years of age
3. Subject and/or subject's legal representative has provided written informed consent as approved and required by the respective institutional review board and agrees to its provisions. NOTE: Written consent must be obtained prior to any research related test being performed.

8.2 EXCLUSION CRITERIA:

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

1. Requires valve-in-conduit procedure
2. Requires emergency surgery
3. Has acute myocardial infarction (MI) within 30 days prior to screening date
4. Has MRI or CT scan confirmed stroke, cerebrovascular accident (CVA) or transient ischemic attack (TIA) within 6 months (180 days) prior to screening date
5. Has hemodynamic or respiratory instability requiring inotropic support, mechanical circulatory support, or mechanical ventilation within 30 days prior to screening date
6. Has active endocarditis/myocarditis or endocarditis/myocarditis within 3 months prior to screening date
7. Has renal insufficiency as determined by creatinine (S-Cr) level ≥ 2.5 mg/dL within 60 days prior to screening visit or end-stage renal disease
8. Has documented leukopenia (WBC < 3.5x 10^3/µL), acute anemia (Hgb < 10.0 g/dL or 6 mmol/L), or thrombocytopenia (platelet count < 50x10^3/µL) accompanied by history of bleeding diathesis or coagulopathy within 60 days prior to screening date
9. Diagnosed with abnormal calcium metabolism and hyperparathyroidism
10. Echocardiographic evidence of an intra-cardiac mass, thrombus, or vegetation
11. RVOT aneurysm *unless* treated during pulmonary valve replacement surgery
12. Has prior organ transplant or is currently an organ transplant candidate
13. Was previously implanted with INSPIRIS RESILIA Pulmonary valve

14. Previously implanted with an aortic, mitral, or tricuspid bioprosthetic valve, mechanical valve or annuloplasty ring
15. Need for concomitant replacement of the aortic, mitral or tricuspid valves
16. Has presence of non-cardiac disease limiting life expectancy to less than 12 months
17. Is currently or has recently participated (within 6 weeks) in another investigational drug or device trial
18. Positive urine or serum pregnancy test in female subjects of child-bearing potential and/or nursing mothers, or planning to become pregnant within 1 year of study valve implant
19. Has left ventricular ejection fraction ≤ 20% as validated by diagnostic procedure prior to screening date
20. Currently incarcerated or unable to give voluntary informed consent
21. Documented history of substance (drug or alcohol) abuse within the last 5 years prior to screening date
22. Patients with hypersensitivity to metal alloys that contain cobalt, chromium, nickel, molybdenum, manganese, carbon, beryllium and iron
23. Patients with hypersensitivity to latex

Intra-Op Exclusion Criterion:

24. Significant injury to the heart upon entry defined as emergent cardiopulmonary bypass requiring femoral cannulation

8.3 ENROLLED POPULATION

Subjects will be included in the enrolled population after signing the informed consent, meeting all the enrollment criteria, and after the surgeon assesses the subject's anatomy, sizes the annulus, and determines that the trial valve can be implanted. If the surgeon is unable to complete the implant procedure, the subject is considered "intent to treat" and will be followed for 30 days or until any device related adverse events experienced by subject are resolved.

Each investigator or qualified designee screens subjects for potential inclusion into the trial. Screening results are used to make a final determination as to subject suitability for enrollment. Subjects must meet **all** applicable inclusion criteria and **no** pre-operative exclusion criteria at the time of enrollment evaluation in order to participate.

8.4 INDEX VALVE POPULATION

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

8.5 SUBJECT AND TRIAL DURATION

Total enrollment period for this trial is estimated to be 3 years.

Subject participation begins with the enrollment of the first subject and ends after the last subject enrolled has completed the five (5) year follow up visit or has exited the trial.

Overall trial duration is estimated to be 9 years. This includes subjects being monitored, all outstanding data queries resolved and all trial sites closed to follow-up.

8.6 SUBJECT TERMINATION OR WITHDRAWAL

Once enrolled, subjects may discontinue participation at any time by withdrawing informed consent or meeting the requirement for termination. Participation in the trial is entirely voluntary. Subject participation for any explanted patient will be terminated at either 30 days post-explant or when all post-explant adverse events are resolved (whichever comes last). If the surgeon is unable to complete the implant procedure and/or subject meets intra-op exclusion criteria (see section 8.2), those subjects are considered enrolled as "intent to treat" and will be followed for 30 days or until any adverse events experienced by this cohort are resolved and then will be exited from the trial.

9. STATISTICAL METHODS

9.1 ANALYSIS POPULATION

The analysis populations will include the enrolled population and the investigational valve population. The index valve population will include all subjects who meet enrollment criteria, provide written informed consent, meet intraoperative eligibility criteria and who receive the index valve. The enrolled population will include the index valve population and the "intent to treat" population[1]. For the enrolled population, the number of patients enrolled per site will be reported. Summaries of baseline and procedural data will

[1] If the surgeon is unable to complete the implant procedure, those subjects are considered enrolled as "intent to treat" and will be followed for 30 days or until any adverse events experienced by this cohort are resolved and then will be exited from the trial.

be based on the enrolled population. The analysis of mortality and all safety data shall in general be based on the investigational valve population. For the investigational valve population, the number of subjects implanted per site will be reported, stratified by valve size.

9.2 SAMPLE SIZE

Up to 100 implanted subjects at up to 10 US sites will compromise the subject group. See below for a power analysis.

9.3 STATISTICAL ANALYSIS

9.3.1 SAFETY ANALYSIS

9.3.1.1 Primary Safety Endpoint

The primary safety endpoint for the trial is freedom from device or procedure-related death and/or reoperation at 1 year. Survival probabilities and standard errors will be estimated using the Kaplan Meier method. Time to event will be calculated in days and freedom from death and reoperation at 1 year will be estimated at 365 days from the Kaplan Meier survival curve. Standard errors will use the Greenwood algorithm. If we let p denote the probability that an implanted subject will experience device or procedure-related death and/or reoperation at 1 year, then the null and alternative hypotheses for the primary safety endpoint are:

$$H_0: p > 25\%$$

$$H_a: p \leq 25\%$$

The statistical test of the null hypothesis for the primary safety endpoint is based on a one-sided, upper 95% confidence limit for device or procedural related death and/or reoperation at 1 year. If the upper 95% confidence limit is less than 25%, the acceptance criterion for the primary safety endpoint will have been met.

Based on a simulation, the power of the confidence interval above to reject the null hypothesis is 90% for the sample size of 100 patients receiving the 1-year visit. For the purposes of power calculation, the simulation assumes an exponential survival model with a constant hazard rate of device or procedure-related death or reoperation at 1 year of 15%; if a smaller rate is assumed, the power of the statistical test would be higher.

Reoperation is defined as any operation that repairs, alters or replaces the study valve, which occurs after the completion of the procedure and the transfer out of the procedure room.

9.3.1.2 Secondary Safety Endpoints

The secondary safety endpoints listed in 7.3 will be analyzed using the investigational valve population. Early adverse events within 30 days of procedure will be reported as the number of events divided by the

number of enrolled subjects. Percentages for the early events will also be calculated for all other complications observed in the trial, including reoperation and/or death.

Actuarial rates based on the method of Kaplan - Meier will be calculated for the primary safety endpoint, and for each of the safety events in Section 7.3 at each of the follow-up time points; the number of subjects at risk of the event will be reported at each of these intervals.

A sub-analysis for patients receiving valve-in-valve procedures will be made via descriptive method.

9.3.2 **EFFECTIVENESS ANALYSIS**

The following effectiveness endpoints will be analyzed using the investigational valve population.

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

- Peak pressure gradient
- Mean pressure gradient
- TR gradient
- Valvular regurgitation
- Peak Velocity
- Doppler Velocity Index (DVI)
- Transvalvular VTI

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

9.3.3 **NYHA CLASS**

A comparison of preoperative and postoperative NYHA functional class (presented as the percentage of subjects in each class at baseline, at each follow-up time-point, and as the percentage of subjects at each follow-up time-point who improved, worsened, or did not change in class) will be presented for all subjects greater than 12 years old. This comparison will be based on the investigational valve population. Additionally, a cross-tabulation of baseline vs. POD 390 NYHA will be presented for all subjects in the investigational valve population with both baseline and POD 390 NYHA data. Additionally, the summaries described above will be presents using the Modified Ross Heart Failure Classification for subjects aged 12 and under.

9.4 ADDITIONAL MEASURES

9.4.1 **BLOOD DATA**

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

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

9.5 POOLABILITY

Subject baseline risk will be statistically compared among centers for the enrolled population. Chi-square tests will be used to compare categorical risk factors while analysis of variance will be used to compare continuous risk factors. Comparisons will be based on the following demographic and pre-operative variables: age, sex, and pre-operative NYHA or Modified Ross Heart Failure Classification.

Early and late adverse event rates for the investigational valve population will be compared between the sites for each of the adverse events listed in the **Safety Endpoints Section 7.3.1**. Early event rates will be compared with a logistic regression model; late event rates will be compared with an exponential hazards regression model.

9.6 ANALYSIS OF COVARIATES

A hazard regression analysis will be performed to test for the effect of gender, age at implant, pre-operative NYHA functional classification or Modified Ross Heart Failure Classification, previous valve surgery, right ventricular function, BMI, and implant size on survival. This analysis will be performed by using a Cox proportional hazards model and will be based on the enrolled population. Additionally, the rate for each of the adverse events listed in the **Safety Endpoints Section 7.3.1** will be compared between the genders via a Cox regression analysis.

Finally, the effect of gender on each of the following effectiveness endpoints at POD 390 (1 year) will be investigated with a linear regression model: peak gradient, mean gradient, and TR gradient. These linear regression models will be adjusted by BSA (to adjust for the effect of body size), and by valve size. The effect of gender on all valvular regurgitation at POD 390 (1 year) will be investigated via a proportional odds model; this model also will be adjusted by BSA, and by valve size.

9.7 MISSING DATA

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

9.8 FOLLOW-UP AND COMPLIANCE DATA

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

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

10. TRIAL PROCEDURES

The following section provides a summary of the tests and measurements to be conducted at baseline/screening, operatively, prior to discharge, and during follow-up. [redacted].

10.1 SUBJECT SCREENING

All subjects requiring pulmonary valve replacement as assessed by cardiac surgeon participating in this clinical trial should be screened for eligibility. Subjects who may meet eligibility requirements will be asked to participate.

A "Screening Log" is provided to the investigational sites to maintain a cumulative log of all screened subjects. For subjects who are ineligible for participation in the clinical investigation, a reason supporting the disqualification of the subject must be entered on the Screening Log. Any subject deemed ineligible due to active or recent endocarditis, acute anemia, pregnancy, or participation in another clinical investigation may be re-screened later. Re-screened subjects will be assigned another unique subject ID number and must be re-entered on the Screening Log.

10.2 INFORMED CONSENT

Written informed assent and/or consent, in accordance with FDA and IRB regulations shall be obtained from each subject and/or or the subject's legal representative prior to ***research related*** procedures. The

investigator retains a copy of the signed informed consent document in each subject's record, and provides a copy to the subject.

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

[redacted]

10.3 SCREENING/BASELINE ASSESSMENT

Sponsor allows standard of care tests to be used for screening/baseline data collection provided they are performed within 60 days before implant date and there are no significant changes in subject's condition that would invalidate the results. Standard of care tests are performed for all valve patients scheduled for valve replacement surgery whether or not being considered for the trial. If the patient agrees to participate in the trial, they are then consented and any ***trial related*** tests are performed post consent.

The following baseline data is obtained as noted in **Table 2** below. This data includes physical assessment, demographic and medical history, 12-lead electrocardiogram (ECG), echocardiogram, blood studies, an assessment of NYHA or Modified Ross Heart Failure Classification, and INR or PTT.

Table 2. Screening/Baseline Assessment

Clinical/Physical Assessment		**Blood Studies**	**Echocardiography (TTE or TEE)**
Date of Assessment Date of Birth Sex/Gender Height Weight Heart Rate Blood Pressure Cardiac Rhythm (12-lead ECG) NYHA Classification or Modified Ross Heart Failure Classification	Anti-thromboembolic Therapy (cardiac medications) Cardiovascular Risk Factors Cardiovascular Conditions Previous Procedures / Interventions Non-Cardiovascular Conditions Pregnancy Test* * negative urine or serum pregnancy test ≤ **7 days prior to procedure** in female patients of child bearing potential is required	Blood Draw Date White Blood Cell Count Red Blood Cell Count Hemoglobin Hematocrit Platelet Count Plasma Free Hemoglobin or Haptoglobin or Serum LDH Serum Creatinine INR/PTT* *INR/PTT will be determined for subjects on anticoagulant therapy only.	Date of Exam ***REFER TO ECHO MANUAL***

10.4 VALVE REPLACEMENT PROCEDURE

All procedures are performed in an operating room, or a surgical suite having cardiac surgery and anesthesia services. The surgical approach used is at the discretion of the Investigator's routine surgical practice. TEE will be performed unless contraindicated (e.g., in the event of esophageal varices) to assess valve placement and function, including PVL.

Note: The INSPIRIS RESILIA Pulmonary Valve, Model 11500P does not require rinsing prior to implant. ***Note:*** If the valve is rinsed prior to implant, it must be kept hydrated with sterile physiological solution throughout the remainder of the surgical procedure. Rinsing every 1-2 minutes is recommended. ***Caution:*** Contact of the leaflet tissue with any articles or sources of particulate matter should be avoided.

Procedural information, findings, results and device identification information to be recorded are identified in **Table 3.**

Table 3. Procedural Information

General Information	Clinical Information	Device Information	Echocardiography (TEE)
Date of Admission Date of Procedure Implanting Surgeon Adverse Events	Etiology Diagnosis for Replacement Valve Implant/ Valve Position Sizing Condition of the Native Valve Concomitant Procedures Intra-operative Adverse Events	Valve Size and Serial Number Valve Performance	Post-operative TEE **REFER TO ECHO MANUAL**

10.5 POST INDEX VALVE IMPLANT

At the discretion of the investigator, bioprosthetic heart valve recipients should be maintained on antithrombotic therapy (except when contraindicated) after implant, in accordance with current American College of Cardiology/American Heart Association (ACC/AHA) Guidelines/ American College of Chest Physicians (ACCP) Guidelines. Therefore, the appropriate antithrombotic therapy must be determined by the physician on an individual basis. Additionally, bioprosthetic heart valve recipients should have antibiotic prophylaxis at the time of all dental procedures per current AHA Guidelines.

Patients should be encouraged to carry their Patient Identification Card at all times and to inform their healthcare providers that they have an implant when seeking care.

10.6 DISCHARGE

The medical information and clinical evaluation of trial subjects at discharge is identified in **Table 4.** Subjects not discharged within 10 days post procedure must have an echocardiogram completed, before or on day 10, to assess placement and performance of the index valve. This echocardiogram is required to complete the evaluation of short-term valve function. Those subjects will not require an additional echocardiogram on the day of discharge.

Table 4. Discharge Information

Clinical/Physical Assessment	Blood Studies	Echocardiography (TTE)
Date of Discharge Weight Heart Rate Blood Pressure Cardiac Rhythm (12-lead ECG) Anti-thromboembolic Therapy (cardiac medications) Adverse Events	Blood Draw Date White Blood Cell Count Red Blood Cell Count Hemoglobin Hematocrit Platelet Count Plasma Free Hemoglobin or haptoglobin or serum LDH INR/PTT* *INR/PTT will be determined for subjects on anticoagulant therapy only. Blood Labs and INR/PTT may be omitted (if not clinically indicated) in children (subjects 12 years and under) but must be substituted with spot urine urobilinogen for hemolysis evaluation.	Date of Exam **REFER TO ECHO MANUAL**

10.7 POST DISCHARGE FOLLOW-UP ASSESSMENTS

Post-procedure clinical evaluation is performed on all trial subjects at the investigational site. Information to be recorded at scheduled visits is further detailed in **Table 5.**

During each postoperative follow-up visit, the investigator(s) will determine the subject's availability for future follow-up visits. If any subject needs to be seen at a time other than a regularly scheduled follow-up visit, the required data collection would be the same as the 6 month follow-up evaluation and the data recorded as an interim visit.

Table 5. Follow-Up Information at all Post-Discharge Visits

Visit	Clinical/Physical Assessment	Blood Studies	Echocardiography (TTE)
30 Day Follow Up Visit	NYHA Classification or Modified Ross Heart Failure Classification Anti-thromboembolic Therapy (cardiac medications) Adverse Events	Not required	*only if clinically indicated
Each visit at 6 mos and annual visits	Weight Heart Rate Blood Pressure Cardiac Rhythm (12-lead ECG) NYHA Classification or Modified Ross Heart Failure Classification Anti-thromboembolic Therapy (cardiac medications) Adverse Events	Blood Draw Date White Blood Cell Count Red Blood Cell Count Hemoglobin Hematocrit Platelet Count Plasma Free Hemoglobin or haptoglobin or serum LDH INR/PTT* *INR/PTT will be determined for subjects on anticoagulant therapy only. Blood Labs and INR/PTT may be omitted (if not clinically indicated) at Day 30 in children (subjects 12 years and under) but must be substituted with spot urine urobilinogen for hemolysis evaluation.	**REFER TO ECHO MANUAL**

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

10.8 MISSED FOLLOW-UP

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

If a subject cannot be reached for a follow-up visit, the site will document on the CRF, the efforts

undertaken to contact the subject or the subject's primary health care provider. These efforts should include three (3) attempts of telephone contact (telephone attempts should include next of kin or care giver if available) at least one month apart and a registered letter sent before the end of the follow-up window. Subjects who miss two (2) sequential follow-up visits will be considered lost to follow-up at the second missed visit and exit from the trial. After the subject is exited from the trial, the Investigator/designee will attempt to determine if the subject is alive, including searching national mortality registries as permitted by local laws.

10.9 STUDY EXIT

Trial subjects exit the trial when no additional follow-up visits, procedures, or data collection are required. A subject is exited from the trial in the following instances:

- Fails enrollment criteria after written consent
- Is Lost-to-follow-up (LTFU)
- Voluntarily withdraws from the trial
- Death
- Explant
- Valve-in-Valve*
- Does not retain trial valve after attempt to implant
- Completes five (5) year follow-up visit (at POD 1825)
- Investigator withdraws the subject from the trial

* Enrolled subjects implanted with the study valve requiring valve-in-valve (ViV) reoperation will be assessed at day 30 post ViV procedure date for assessment of device related events. Subjects will be monitored up to 90 days post ViV procedure.

- If no device related adverse events are observed per CEC determination, patients will be exited from the trial at day 90 post ViV.
- If there are device related adverse events observed per CEC determination, subjects will be continued to be followed until resolution of event(s).

Valve-in-valve data will be captured as part of the Case Report Form process.

10.10 EXPLANT

Implantation of the investigational valve is considered complete once proper placement of the valve is

confirmed and patient leaves the procedure room. Proper placement of the valve will be confirmed by surgeon and echocardiologist by means of an intra-op transesophageal echocardiogram (TEE) confirming normal leaflet mobility and clinically acceptable study valve regurgitation. If removal is required from this point forward, it will be considered an explant.

In the event a valve is explanted, a copy of the procedure report must be provided to the trial Sponsor. Information on the cause of explant and its relationship to the valve will be provided by the investigator(s). Explanted valves must be returned to the trial Sponsor for analysis. Return kits for devices will be provided by the trial Sponsor.

11.ADVERSE EVENTS

11.1 REPORTING

Adverse event (AE) information is reported throughout the clinical investigation. AEs are reported from the time of the valve implant procedure (index procedure) until subject participation has ended (study exit). At each evaluation, the Investigator will determine whether any adverse events (AEs) have occurred. For the purpose of this protocol, an adverse event is any undesirable medical occurrence in a subject. This definition does not depend on a causal relationship with the device or the protocol requirements. Adverse events are followed until they are adequately resolved.

Adverse events may be volunteered by subjects, elicited from questioning or collected via observation. The Investigator or designee will determine whether or not the event is related to the device and/or procedure, and whether or not the event meets seriousness criteria. If it is determined that an AE has occurred, the Investigator should obtain all the information required to complete the AE Case Report Form. In addition, subjects will be instructed to contact the Investigator, and/or study coordinator if any significant adverse events occur between study evaluation visits.

Each event shall be assessed for severity using the definition of a serious adverse event (SAE) or not and SAE (see section 11.1.1). Each event shall be assessed for causality (see section 11.1.2) and if the event is anticipated or unanticipated, as described in section 11.1.3 and 11.1.4.

Pre-existing medical conditions or symptoms reported prior to device implantation will not be recorded as an AE. In the event there is a change in the pre-existing medical condition or symptoms due to the device or related procedure, then an AE must be recorded.

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. 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.

11.1.1 **SERIOUS ADVERSE EVENTS**

An Adverse Event is considered serious if the event results in or is:

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

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

11.1.2 **CAUSALITY**

For the adverse events reported from the sites, the causal relationship to the device and the procedure should be rated as follows:

- **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.
- **Not Related:** There is no relationship between the event and the device or procedure. 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, intercurrent illness, or concomitant medication) and does not meet any other criteria listed.
- **Undetermined:** There is no evidence or relevant data available to assess the relationship between the event and the device or procedure.

11.1.3 **ANTICIPATED ADVERSE EVENTS**

Anticipated adverse events are AEs that have been identified as possible adverse events associated with the investigational device, or procedure. [redacted]

11.1.4 **UNANTICIPATED ADVERSE DEVICE EFFECTS**

An ***unanticipated adverse device effect (UADE)*** is any serious adverse effect (SAE) on health or safety or any life threatening problem or death caused by or associated with the device, if that effect, problem, or death was not previously identified in nature, severity, degree of incidence in this Investigational Plan (including a supplementary plan or application)- see Risk Section 6.2 and IFU for a list of anticipated events. Additionally, an unanticipated adverse event includes any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects.

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

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

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

Notification of UADE and serious device related adverse effects should be done via RDC entry and phone call to Trial Manager.

11.3 DEATH AND EXPLANTS

11.3.1 DEATHS

The site will send the Sponsor copies of an autopsy report, if available, and/or a death summary. The Investigator/designee will provide information about the cause of death and will determine relationship to the clinical investigational device. Deaths and UADEs will be reported to the DMC within five (5) business days after Edwards Lifesciences or its designee first receives notice of the event. The Clinical Events Committee (CEC) will also adjudicate each death for device relatedness and procedure relatedness.

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.

11.3.2 EXPLANT REPORTING

In the event a trial valve is explanted in the intra-operative or early post-operative period (i.e., while the subject is hospitalized at the investigational center), a copy of the procedure report must be provided to the Sponsor. Information on the cause of the explant and its relationship to the valve will be determined by the Investigator/designee. Explanted trial valves during this period must be returned to the Sponsor for analysis. Return kits for explanted devices will be provided upon request by the clinical site manager.

In the event a trial valve is explanted in the late post-operative period, the Investigator/designee 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.

11.4 DATA MONITORING COMMITTEE

The trial Sponsor will appoint a Data Monitoring Committee (DMC) composed of two or more independent physicians including a cardiothoracic surgeon and a cardiologist, and a statistician. Members of the DMC will not have scientific, financial, or other conflict of interest related to the Sponsor or the Investigators. DMC members must sign a non-conflict-of-interest statement in this regard. The primary purpose of the DMC is to ensure a consistent, independent review of aggregate safety data during the enrollment period to determine if the trial is being conducted safely and will decide if the clinical investigation should be modified, suspended, and/or stopped. The DMC will establish guideline criteria for recommending trial

termination. The DMC activities and meeting schedule is regulated by the DMC Charter. The DMC will meet at least yearly or more often as determined by the Chairperson and possibly on an *ad hoc* basis to evaluate trial progress and results during the enrollment phase.

11.5 CLINICAL EVENTS COMMITTEE (CEC)

The Clinical Events Committee (CEC) is an independent institutional adjudicator which evaluates the adverse events that are endpoint related as well as those resulting in death. The CEC adjudicates early and late events for their relatedness to the investigational device and/or the valve implant procedure. The CEC activities and adjudication process is described in the CEC Adjudication Charter.

The trial Sponsor will provide the CEC completed case report forms and any relevant source documentation/ subject information as provided by the clinical site investigators. The trial Sponsor will ensure that all information is de-identified before presenting to the committee.

12.TRIAL AND DATA MANAGEMENT

12.1 ECHOCARDIOGRAPHY CORE LAB

The Echocardiography Core Lab is responsible for independently evaluating echocardiograms submitted preoperatively and postoperatively by trial sites, and for reporting of hemodynamic and other valvular function results. The purpose of the Echocardiography Core Lab is to ensure unbiased, timely and consistent analysis of the diagnostic data, and for evaluating changes in subject status over the course of the trial based on serial echocardiographic studies conducted on the same subject.

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

12.2 DEVICE ACCOUNTABILITY

An initial set of trial valves are shipped to the clinical site once the following conditions are met: FDA approval has been obtained, the site obtained regulatory approval (Institutional Review Board), and a signed Clinical Trial Agreement is in place. Additional devices are sent to the clinical site as devices are used or as needed.

12.2.1 INVENTORY AND ACCOUNTABILITY RECORDS

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

All device shipments include inventory and shipment records (packing slip). The Principal Investigator or designee will take inventory of the product, complete the delivery documentation with receipt date, note the condition of the device(s), and complete the delivery documentation by signing the packing slip and dating with the receipt date. Both the investigational site and the trial Sponsor retain copies of the packing slips and the Device Accountability Log.

12.2.2 DEVICE STORAGE

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

12.2.3 DEVICE RETURN

The Principal Investigator(s) is notified in writing upon termination of the clinical trial. All unused devices in original package and/or those in opened packages will be returned upon receipt of this notice as described in the IFU. The Investigator's copy of the Device Accountability Log must document any unused devices that are returned. The trial Sponsor will provide shipping instructions.

12.3 PROTOCOL DEVIATIONS

A protocol deviation is defined as an event where the Investigator or trial personnel did not conduct the trial according to the clinical protocol or the Clinical Trial Agreement.

Deviations shall be reported to the trial Sponsor regardless of whether medically justifiable or taken to protect the subject in an emergency. Subject specific deviations and non-subject specific deviations, (e.g. unauthorized use of a trial device outside the trial, unauthorized use of a trial device by a physician who is not listed in the Clinical Trial Agreement, etc.) will be reported to Sponsor. Investigators will adhere to procedures for reporting trial deviations to the IRB/EC/REB in accordance with their specific reporting policies and procedures.

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

Major deviations – Major deviations will be documented on the appropriate case report form provided and reported to the trial Sponsor within 3 business days of awareness. Additionally, these deviations will be reported to the IRB/REB/EC per institutional guidelines. A major deviation is one that impacts subject safety, may affect the quality/integrity of study data, or leads to failure of meeting regulatory commitments. Examples include:

- Subject enrolled not meeting enrollment criteria
- Informed consent not obtained
- Loss or theft of data or breach of data security
- UADE not reported to IRB/Sponsor within the required timeframe
- Unauthorized use/implant of an investigational device

The following escalation process will be followed for major deviations:

- Investigator/Sponsor will promptly investigate root cause and secure compliance
- Formulate corrective actions
- Verify effectiveness of the corrective actions

Minor deviations – Minor deviations do not pose a risk to subject safety; data integrity; study endpoints; or regulatory commitments. Minor deviations will be reported to the trial Sponsor on the appropriate case report form provided; and to the IRB/REB/EC per their guidelines. Examples include:

- Deviation from a protocol requirement such as incomplete/inadequate testing procedures (if this type of deviation does not pose a risk to subject safety);
- Follow-up performed outside specified time windows in the protocol

12.4 TRAINING AND MONITORING

12.4.1 TRAINING

12.4.1.1 SPONSOR TRAINING RESPONSIBILITIES

Sponsor will provide training on device usage, the protocol, the Electronic Data Capture (EDC) system, and Investigator/Designee Responsibilities per applicable country regulation (i.e., FDA CFRs for US Sites; ISO14155 for EU Sites). Training methods include live or online training sessions, teleconference, WebEx,

and/or read and review. Site personnel training requirements will be dependent on study role/delegated tasks defined in the site's Delegation of Authority Log (DOA).

A Training Matrix will outline the training requirements based on study roles and delegated tasks and/or nature of document revision (i.e., protocol amendment). The Training Matrix will be filed in the study master file.

12.4.2 SITE TRAINING RESPONSIBILITIES

A Delegation of Authority Form (DOA) is completed by Investigator designating which individuals are allowed to perform specific clinical trial related tasks. Investigator or designee will be responsible for communicating/documenting site personnel changes from the Delegation of Authority (DOA) to the Sponsor.

Investigators (Principal Investigators, PI) who conduct clinical investigations of medical devices under 21 CFR Part 812, commit themselves to conducting the investigation in accordance to the Clinical Study Agreement, protocol, and applicable FDA regulations for patient safety and control of the investigational devices. When tasks are delegated by an Investigator, the PI should ensure that any individual to whom a task is delegated is qualified by education, training, and experience to perform the delegated task.

Site personnel training is documented on a "Training Log" provided by the trial Sponsor, which the trainee must sign and date.

12.4.3 MONITORING

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

A pre-trial monitoring visit or meeting will be conducted to ensure that the Investigator clearly understands and accepts the obligations incurred in undertaking the clinical investigation as listed in **Table 6** (Regulations and Guidelines), and that the facilities are acceptable. Periodic monitoring visits will be conducted with adequate frequency to ensure that the Investigator's obligations as set forth in 21 CFR Parts 50, 56 and Part 812 are being fulfilled and that the facilities continue to be acceptable.

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

The Sponsor may perform Investigator audits to evaluate compliance with regulatory requirements, the protocol, study agreement, and IRB policy and procedures.

12.5 DOCUMENTATION REQUIREMENTS

12.5.1 SOURCE DOCUMENTS

Clinical regulations require that Investigators maintain information in the clinical trial subject's medical records that corroborate data collected on the eCRF. Certain data elements (e.g., blood pressure, weight, temperature, resolution of a symptom or sign) in a clinical investigation can be obtained at a study visit and can be entered directly into the eCRF by an authorized data originator. This direct entry of data can eliminate errors by not using a paper transcription step before entry into the eCRF. For these data elements, the eCRF is the source. If a paper transcription step is used, then the paper documentation should be retained and made available for FDA inspection and Sponsor Monitoring. Sites will identify data elements entered directly in the eCRF (e.g., blood pressure, weight, temperature, resolution of a symptom or sign).

To protect subject confidentiality, the subject's name must not appear anywhere on the imaging media sent to trial Sponsor e.g. for reporting serious adverse device effects (SADE), or prepared for evaluation by the core lab. Each page should be identified with the subject's unique trial ID number. All other subject identifiers (i.e. medical record number, personal number) are to be obscured. Original copies of all data must be kept at the site.

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

12.5.2 **TRIAL DOCUMENTS**

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

- Investigator and site training to the protocol (Training Log)
- Authorized trial site personnel (Delegation of Authority)
- Subject consent and screening (Screening and Enrollment Log)
- Monitoring visit tracking (Site Visit Log)
- Investigational Device Accountability (Investigational Device Accountability Log)

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

During the course of the clinical trial, all correspondence (letters, records of telephone calls, emails and faxes) regarding the trial must be maintained in the regulatory binder provided by the trial Sponsor. This binder must be made available for monitoring visits and audits.

12.6 DATA COLLECTION

All required data for this trial are to be collected with standardized Case Report Forms (CRF) for individual subjects; [redacted]. Electronic CRF (eCRF) will be utilized for this trial. Each eCRF must be signed electronically by the Principal Investigator listed in the Clinical Trial Agreement and Delegation of Authority Log. If for any reason an eCRF is unavailable and/or inaccessible, a paper CRF will be provided by the trial Sponsor to be completed, signed by the Principal Investigator or designee and submitted to the trial Sponsor.

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

The Sponsor's data management group is responsible for database development and validation, database maintenance, control and management of data collected from CRFs, data validation, and statistical support. The Data Management team will employ a full-featured relational database application (or equivalent) on a central server, and the system is fully compliant with 21 CFR Part 11 regulations. The application provides the capability of secured data collection remotely through the Internet so authorized personnel at participating sites may log on to the system and enter the data. Other data management programming and/or data analyses activities will be done within the trial Sponsor's internal network.

12.7 DATA AND DOCUMENT RETENTION

Trial-related correspondence, subject records, consent forms, records of device implant, and source document worksheets are to be maintained on file by the trial site. The trial Sponsor requires that it be notified in writing if the Principal Investigator wishes to relinquish ownership of the data and information so that mutually agreed upon arrangements can be made for transfer of ownership to a qualified entity. Per FDA regulation 21 CFR 812.140, records of each subject's participation in the trial must be maintained for a period of two (2) years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

12.8 TRIAL PROTOCOL AMENDMENTS

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

12.9 TRIAL COMPLETION

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

A final clinical report shall be compiled once data collection is complete. Such reports include all

information required and outlined in this protocol. The final report will be provided to regulatory agencies and/or institutional review boards/independent ethics committees and other regulatory agencies as per applicable laws. The final clinical report will be filed in the clinical trial master file.

12.10 FUTURE PLANS

No changes are planned at this time.

13.STATEMENTS OF COMPLIANCE, CONFIDENTIALITY AND RESPONSIBILITIES

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

13.1 PROTECTION OF SUBJECT CONFIDENTIALITY

Subject confidentiality will be maintained in accordance with applicable governmental regulations, HIPAA, and institutional policies.

13.2 REGULATIONS AND GUIDELINES

The regulations listed in **Table 6** must be observed to comply with the trial Sponsor's policy for conduct of clinical studies; they represent good clinical practice. It is the responsibility of the investigator(s) to comply with the requirements.

Table 6. FDA Regulations

FDA Regulations
- Investigational Device Exemption (IDE), 21 CFR Part 812 - Protection of Human Subjects, 21 CFR Part 50 - Financial Disclosure, 21 CFR part 54 - Institutional Review Board (IRB), 21 CFR Part 56

13.3 INVESTIGATOR RESPONSIBILITIES

Trial Investigators (Principal Investigators, PI) who conduct clinical investigations of medical devices commit themselves to conducting the investigation in accordance to the Clinical Study Agreement, trial protocol, and in compliance with applicable governmental and institutional regulations. The trial Investigator(s) is responsible for obtaining proper institutional approvals, and reporting to regulatory authorities per all applicable regulations. An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation. The PI must ensure that any individual to whom a task is delegated is qualified by education, training, and experience to perform the delegated task. Upon completion or termination of the trial, the Principal Investigator must submit a final written report to Edwards Lifesciences and the IRB as required by the regulations. The report must be submitted within 3 months (90 days) of completion or termination of the trial. [redacted]

13.4 SPONSOR RESPONSIBILITIES

The trial Sponsor will adhere to the trial protocol and compliance with applicable government and institutional regulations. The trial Sponsor is responsible for obtaining proper regulatory approvals, and reporting to regulatory authorities per applicable country regulations. A sponsor shall notify FDA and all reviewing IRB's and participating investigators of any withdrawal of approval of an investigation or a part of an investigation by FDA or a reviewing IRB within 5 working days after receipt of the withdrawal of approval. [redacted]

14. PUBLICATIONS

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

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