



TRITON Trial

Surgical Treatment of Aortic Stenosis With a Next Generation Surgical Aortic Valve (TRITON)

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September 15, 2011



TRITON
Surgical Treatment of Aortic Stenosis with a Next Generation Surgical
Aortic Valve

CLINICAL PROTOCOL
(Clinical Investigational Plan)

Clinical Investigation Number: 2009-01
Revision: E
Effective Date: September 15, 2011



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Investigation Sponsor:
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1 SYNOPSIS

Investigation Number: 2009-01

Title: TRITON
Surgical Treatment of Aortic Stenosis with a Next Generation Surgical Aortic Valve

Investigation Sponsor: Edwards Lifesciences LLC
One Edwards Way,
Irvine, CA 92614 USA
[REDACTED]
[REDACTED]

Principal Investigator¹: [REDACTED]

Investigation Purpose: The purpose of this clinical investigation is to confirm that the safety and performance of the EDWARDS INTUITY Valve System, INTUITY Aortic Valve Models 8300ACA and 8300ACB used with the INTUITY Delivery System Models 8300DCA and 8300DCB respectively, are not adversely affected by the addition of a balloon expandable frame.

Data collected in this clinical investigation will include short-term safety and performance of the device deployment and delivery systems as well as long-term clinical outcomes comparable to the other currently marketed aortic bioprosthesis. Results of this clinical investigation will be used to support a CE Marking application in Europe and other global product registrations.

Investigation Devices: The following two models are included in the study.

Edwards INTUITY Valve System:	EDWARDS INTUITY Valve System:
INTUITY Aortic Valve, Model 8300ACA	INTUITY Aortic Valve, Model 8300ACB
and	and
INTUITY Delivery System, Model 8300DCA	INTUITY Delivery System, Model 8300DCB

¹ Refer to the "List of Investigation Centers" for a complete list of Principal Investigators.



Intended Use The devices together (EDWARDS INTUITY Aortic Valves and Delivery Systems) are intended for use in subjects with aortic stenosis or stenosis-insufficiency requiring primary replacement of the native aortic valve.

Investigation Design: This is a two-phase, non-randomized, prospective, single arm, multi-center clinical investigation.

In **Phase I**, a total of 10 subjects will be enrolled at up to 2 participating investigational centers. Safety data will be reviewed by the Data Monitoring Committee (DMC) after 10 subjects have completed 1-month follow-up.² Following recommendation by the DMC, enrollment will proceed to Phase II. (Section 4.1)

In **Phase II**, 340 additional subjects will be enrolled in up to 8 participating investigational centers. Combined enrollment in Phase I and Phase II of this investigation will be 350 subjects.

Each subject in Phase I and Phase II is consented for a period of 5 years. All subjects will be assessed for clinical follow-up at the following intervals: Discharge, 1 month, 3 months, 1 year and annually thereafter until 5 years of follow-up is achieved per subject. (Section 4.2)

Population: Adult male and female subjects diagnosed with aortic stenosis or stenosis-insufficiency requiring replacement of the native aortic valve.

Enrollment Criteria: **Pre-operative criteria**

Inclusion Criteria

1. Subject is 18 years or older
2. Subject has aortic stenosis or stenosis-insufficiency of an aortic valve requiring a planned replacement as indicated in the preoperative evaluation.
3. Subject is scheduled to undergo planned aortic valve replacement with or without concomitant coronary bypass surgery, MAZE procedure, septal myectomy, pacemaker/ICD implant and or atrial appendage occlusion/removal.
4. Subject has signed and dated the investigation informed consent form prior to investigation procedures.
5. Subject is geographically stable and agrees to attend follow-up assessments at the hospital of surgical services for a maximum of 5 years.

Exclusion Criteria

1. Subject with pure aortic insufficiency.
2. Subject requires emergency surgery.
3. Subject with an aneurysm of the aortic root and / or ascending aorta requiring surgical intervention).
4. Subject with a left ventricular ejection fraction of $\leq 25\%$

² This may include subjects who expired or had the valve explanted prior to 1 month.



5. Subject with a congenital bicuspid or unicuspid aortic valve.
6. Subject had active endocarditis within 3 months prior to the scheduled aortic valve replacement surgery.
7. Subject with concomitant valve (mitral, tricuspid, or pulmonic) disease requiring repair with an annuloplasty ring or replacement with prosthesis.
8. Subject had prior mitral, tricuspid or pulmonic valve surgery, which included implantation of a bioprosthetic valve, mechanical valve, or annuloplasty ring that will remain *in situ*.
9. Subject had a myocardial infarction within 1 month prior to the scheduled aortic valve replacement surgery.
10. Subject has a disease limiting life expectancy to less than 12 months.
11. Subject was previously implanted with EDWARDS INTUITY Aortic Valve³.
12. Subject is an alcohol and/or drug abuser.
13. Female subject is pregnant or lactating.
14. Subject is currently participating in another drug or device clinical investigation.
15. Subject with documented leukopenia ($WBC < 3.5 \times 10^3/\mu L$), acute anemia ($Hgb < 10.0 \text{ gm/dL}$ or $< 6.2 \text{ mmol/L}$), thrombocytopenia (platelet count $< 100 \times 10^3/\text{mL}$), or history of bleeding diathesis or coagulopathy⁴.
16. Subject who requires a non-cardiac procedure such as carotid procedures or mediastinal tumor removal.
17. Subject had a stroke or transient ischemic attack within six months prior to scheduled aortic valve replacement surgery.
18. Study site pre-operative echocardiographic assessment shows evidence of an intracardiac mass, thrombus, or vegetation.
19. Subject has hemodynamic or respiratory instability requiring inotropic support, mechanical circulatory support, or mechanical ventilation within 30 days of procedure.
20. Subject with documented renal insufficiency as determined by Serum creatinine $\geq 200 \mu\text{mol/L}$ (2.27 mg/dL) at screening or end-stage renal disease requiring chronic dialysis.
21. Subject with documented hyperparathyroidism.

Intra-operative criteria

Exclusion Criteria

1. Participation in the clinical investigation may be contrary to the subject's medical treatment;

³ Previously implanted means that the EDWARDS INTUITY Aortic Valve implant procedure was completed. The INTUITY Aortic Valve procedure is complete when the surgeon takes the patient off cardiopulmonary bypass and restarts the heart

⁴ WBC: White Blood Cells; Hgb: Hemoglobin



2. Any anatomical findings that would not be suitable for implantation of the EDWARDS INTUITY Aortic Valve or use of the EDWARDS INTUITY Delivery System and which are discovered, intraoperatively. These may include findings such as:
 - a. Significant calcium on the anterior mitral leaflet which cannot be removed,
 - b. Septal hypertrophy that will not be corrected by myectomy, or pronounced septal calcification,
 - c. The position of the coronary ostia relative to the EDWARDS INTUITY Aortic Valve Models 8300ACA and/or 8300ACB would result in obstruction of blood flow,
 - d. Extensive calcification of the aortic root,
 - e. Left atrial thrombus,
 - f. The subject is hemodynamically unstable during the procedure requiring the procedure to be aborted prior to insertion of the investigational bioprosthesis and delivery system,
 - g. A device is not available in the correct size for the subject,
 - h. Annular deformation which may or may not be caused by too extensive decalcification of the aortic annulus;
3. It is discovered that the subject is participating in a clinical investigation of another drug or device prior to insertion of the investigational bioprosthesis and delivery system

Safety Endpoints: The following primary safety endpoints will be assessed throughout each subject's participation in the investigation:

- Study valve-related mortality
- Thromboembolic events
- Study valve thrombosis
- Major bleeding events
- Study valve paravalvular leakage
- Study valve-related endocarditis

In addition, the following safety endpoints will also be assessed throughout each subject's participation in the investigation:

- All-cause mortality
- Study valve structural valve deterioration
- Hemolysis
- Study valve-related reoperation
- Study valve explant
- All adverse events



Performance Endpoints:

The following performance endpoint will be assessed when the investigation procedure is performed:

- Device technical success (successful delivery and deployment of one bioprosthesis with one delivery system)

The following performance endpoint will be determined when the subject is discharged from the hospital or 10 days post implant, whichever occurs first:

- Procedure success defined as device technical success followed by the absence of adverse events requiring device reoperation, requiring implantation of permanent pacemaker (with baseline sinus rhythm and no other conduction issues), or subject death

The following performance endpoints will be assessed at each scheduled follow-up visit:

- Improvement in NYHA functional class
- Hemodynamic performance (mean gradient, effective orifice area, regurgitation by echocardiogram)

Other data:

The following data also will be collected:

- EQ-5D Quality of Life questionnaire (baseline and 1 year only)
- Blood data (White Blood Cell Count, Red Blood Cell Count, Hemoglobin, Hematocrit, Haptoglobin, Reticulocytes, Platelet Count, Serum Lactate Dehydrogenase)
- New onset or worsening of conduction disturbances

Investigation Committees:

Data Monitoring Committee
Clinical Events Committee

Echocardiography Core Lab:



2 INTRODUCTION

2.1 BACKGROUND

Aortic Valve Replacement (AVR) surgery is considered to be a class I indication for symptomatic patients with severe calcific AS. Braunwald advocates AVR surgery as the treatment of choice in most adults with calcific AS. The aortic valve should be replaced in symptomatic patients with hemodynamic evidence of severe aortic obstruction. The same applies to asymptomatic patients with progressive left ventricular dysfunction and/or significant ventricular ectopic activity at rest, or an abnormal hemodynamic response (inadequate elevation of systolic arterial pressure) to exercise [13]. Apart from symptomatic relief, the operation improves long-term survival. In one series, three-year survival was 87% in operated and 21% in non-operated patients [54].

Traditionally aortic valve replacement surgery is performed via a full sternotomy. However with the introduction of minimally invasive aortic valve surgery in 1996 [1, 2] this surgical approach is gaining in acceptance. Many studies show that it can be done safely with mortality and morbidity similar to conventional full sternotomy aortic valve surgery [3–15]. Several studies also show that the minimal access approach contributes to better surgical outcomes compared to a full sternotomy [3–5, 14–16] although this is still controversial. Published studies show that minimal access approaches have shorter length of stay [3–5, 15, 16], more home discharge [3–5, 15], less incisional pain [6, 20], shorter duration of ventilation [4–6], less blood loss [4–6, 11, 16] and less blood transfusion [5], compared to a full sternotomy. Advances in technology are designed to facilitate minimally invasive aortic valve surgical techniques and reduce the risks associated with longer pump and coagulation times. One of these advances is the Model 8300TFX bioprosthesis.

2.2 PURPOSE

The purpose of this clinical investigation is to confirm that the safety and performance of the EDWARDS INTUITY Valve System, INTUITY Aortic Valve Models 8300ACA and 8399ACB, respectively used with the EDWARDS INTUITY Valve System, INTUITY Delivery System Models 8300DCA and 8300DCB are not adversely affected by the addition of a balloon expandable frame.

Data collected in this clinical investigation will include short-term safety and performance of the devices deployment and delivery systems as well as long-term clinical outcomes comparable to the other currently marketed aortic bioprosthesis. Results of this clinical investigation will be used to support a CE Marking application in Europe and other global product registrations.

2.2.1 HYPOTHESIS

Success of this investigation will be determined at each phase of the investigation:

- Phase I will be considered successful when the Data Monitoring Committee (DMC) (Section 14.1) determines that the investigation can proceed to enrollment in Phase II

- Phase II will be considered successful when the DMC reviews 3 month data and determines that use of the EDWARDS INTUITY Aortic Valve and the EDWARDS INTUITY Delivery System is clinically safe.

2.3 DEVICES

2.3.1 BIOPROSTHESES

The EDWARDS INTUITY Valve System, INTUITY Aortic Valve Models 8300ACA and 8300ACB (also referred to as EDWARDS INTUITY Aortic Valve) is a stented trileaflet bioprosthesis comprised of bovine pericardium that has been preserved in a buffered glutaraldehyde solution and mounted on a balloon expandable frame. It is available in sizes 19, 21, 23, 25, and 27 mm. To facilitate implantation in subjects with small aortic roots, the EDWARDS INTUITY Aortic Valve has a low supra-annular profile height.

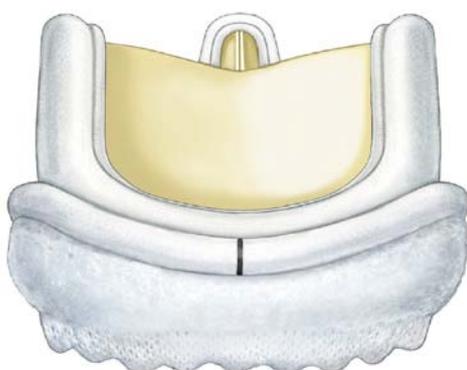


Figure 1: EDWARDS INTUITY Aortic Valve Model 8300ACA

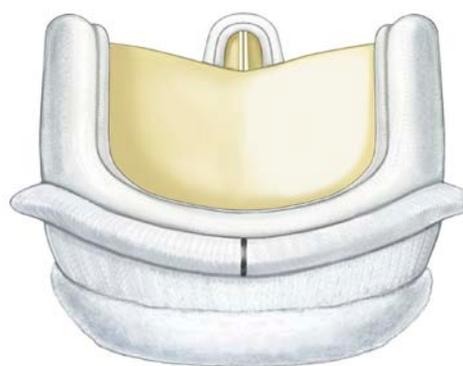


Figure 2: EDWARDS INTUITY Aortic Valve Model 8300ACB

Both Models 8300ACA and 8300ACB are treated with the Carpentier-Edwards ThermoFix process, which involves heat treatment of the tissue in glutaraldehyde and uses ethanol and polysorbate-80 (a surfactant). The bioprosthesis is packaged and terminally sterilized in glutaraldehyde. Glutaraldehyde is shown to both reduce the antigenicity of tissue xenograft bioprostheses and increase tissue stability.

The wireform is designed to be compliant at the orifice as well as at the commissures. The compliance of the commissure supports is intended to reduce the loading shock at the valve commissures and free margin of the leaflets. The compliance of the orifice is intended to reduce the stress on the leaflets. The compliant orifice concept is based on the physiology and mechanics of natural heart valves and reported experience with implantation of unstented homografts.

The wireform is made of cobalt-chromium alloy, a corrosion-resistant alloy, chosen because of its superior spring efficiency and fatigue-resistant characteristics, and is covered with a woven polyester fabric. A thin, cobalt-chromium alloy/polyester film laminate band surrounds the base of the wireform providing structural support for the orifice.

A soft, silicone-rubber sewing ring, which is covered with a porous, seamless polytetrafluoroethylene (PTFE) cloth to facilitate tissue ingrowth and encapsulation, is attached to the wireform. The sewing ring is scalloped to conform to the natural aortic annulus. The compliant nature of the sewing ring facilitates coaptation between the bioprosthesis and an often irregular or calcific tissue bed. The sewing ring has three, equally spaced suture markers at the cusp centers to aid in bioprosthesis orientation and suture placement.

The balloon expandable frame is made of stainless steel and is attached to the inflow aspect of the bioprosthesis. In the EDWARDS INTUITY Aortic Valve Model 8300ACA the balloon expandable frame is covered with a knitted PTFE cloth and a layer of polyester cloth covering the external outflow end of the balloon expandable frame. In the EDWARDS INTUITY Aortic Valve Model 8300ACB the knitted PTFE cloth covering the balloon expandable frame is folded over to the distal end of the frame. The purpose of the cloth frame coverage is to help prevent paravalvular leaks.

An integral bioprosthesis holder is attached to the bioprosthesis by means of sutures to facilitate handling, deployment, and suturing the bioprosthesis during implantation. The holder is easily detached by the surgeon. In the EDWARDS INTUITY Aortic Valve Model 8300ACA the holder is mounted on the commissure posts; in Model 8300ACB the holder is mounted on the cusps nadir.

Please refer to the EDWARDS INTUITY Valve System, Aortic Valve Models 8300ACA and 8300ACB Instruction for Use for further details.

2.3.2 DELIVERY SYSTEMS

The EDWARDS INTUITY Delivery System Models 8300DCA and 8300DCB are used with the EDWARDS INTUITY Aortic Valve Models 8300ACA and 8300ACB respectively. They are not interchangeable.

The EDWARDS INTUITY Delivery System Model 8300DCA consists of the following components: (see Figure 3)

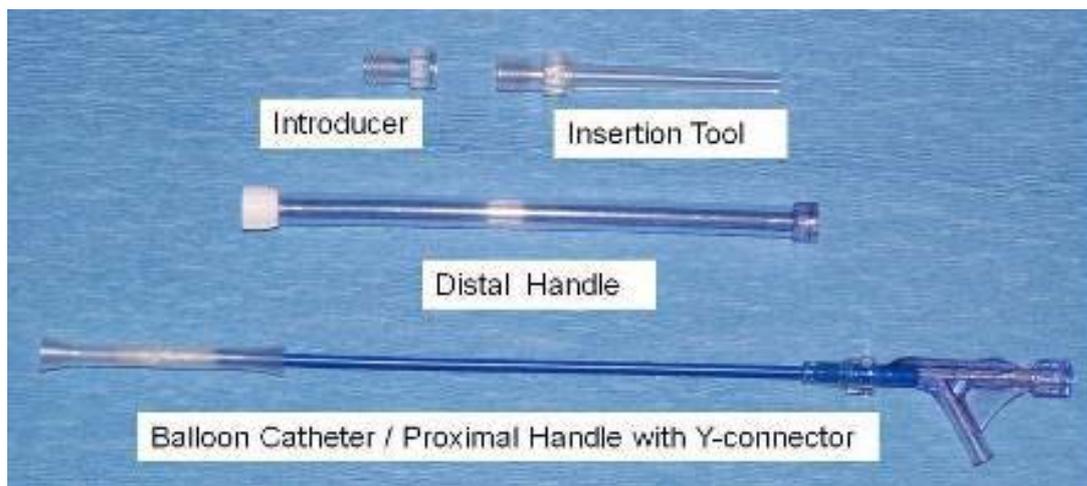


Figure 3: EDWARDS INTUITY delivery system model 8300DCA

- Introducer
- Insertion Tool
- Distal Handle
- Balloon Catheter / Proximal Handle with Y-connector

The assembled Balloon Introducer and Insertion tool is used to remove the EDWARDS INTUITY Aortic Valve Model 8300ACA from the packaging jar and to enable connection of the distal handle to the proximal threaded section of the balloon introducer that extends beyond the valve holder. This assembly facilitates removal of the packaging sleeve from the bioprosthesis. Upon removal of the sleeve, the insertion tool is removed from the balloon introducer and the distal handle/bioprosthesis assembly is ready for deployment.

The Distal Handle is used to hold the bioprosthesis while the nadir sutures are placed through the sewing ring and to facilitate parachuting the implant down into the native valve annulus. When connected to the Proximal Handle, the Distal Handle also controls the position of the expanding balloon with regard to the bioprosthesis.

The Balloon Catheter / Proximal Handle with Y-connector is connected to the Distal Handle and used to expand the EDWARDS INTUITY Aortic Valve expandable frame by using an inflation device. The Balloon Catheter/Proximal Handle with Y-connector (in the figure above) is a coaxial-designed catheter with a distal inflatable balloon. At the proximal end of the catheter, there is a standard Y-connector with an inflation port (marked "BALLOON") used for balloon inflation. The balloon is inflated by injecting a saline solution through the luer port (marked "BALLOON") on the Y connector. An inflation device filled with saline solution is connected to the inflation port to pressurize and expand the balloon.

A delivery system is available for each size of the EDWARDS INTUITY Aortic Valve Model 8300ACA (19, 21, 23, 25 and 27 mm).

The EDWARDS INTUITY delivery system model 8300DCB consists of the following components (see Figure 4):

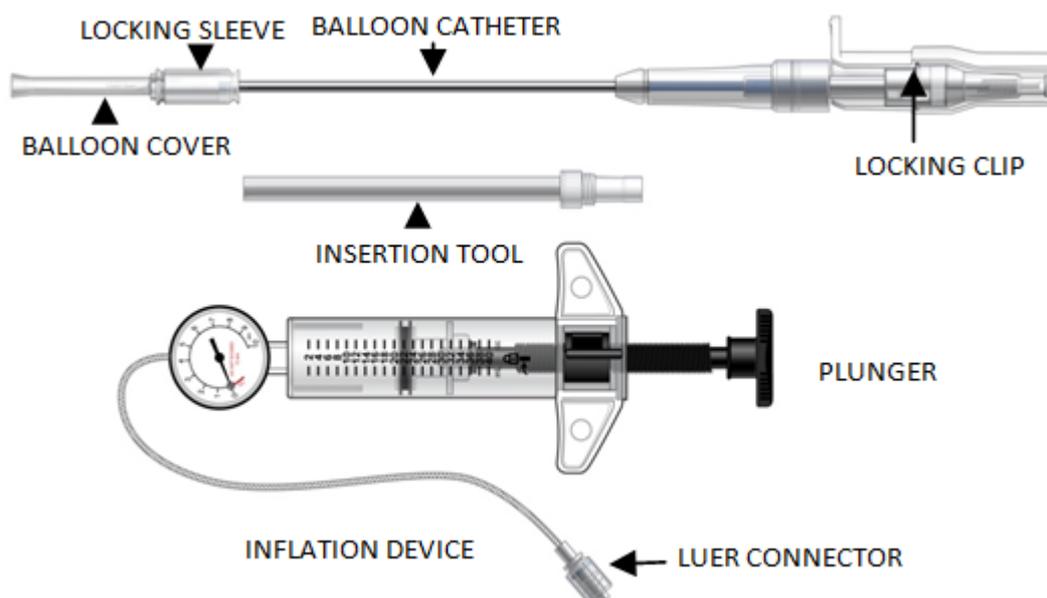


Figure 4: EDWARDS INTUITY delivery system model 8300DCB & Atrion Inflation Device, QL2540 – Model 96417

The EDWARDS INTUITY delivery system model 8300DCB is designed to introduce the model 8300ACB valve to the surgical site after removal of the diseased native leaflets.

The delivery system includes an integrated balloon catheter and tubular handle shaft through which the catheter extends. The distal end of the handle shaft includes an adapter, which mates with the holder of the valve, and a locking sleeve for rapidly connecting the delivery system to the valve holder. The balloon portion of the delivery system resides within the adapter, and advances distally into position for expanding the inflow frame. A tubular balloon introducer sleeve attached when removing the valve from a storage jar facilitates passage of the balloon through the valve.

A size-specific delivery system is available for each size of the EDWARDS INTUITY Aortic Valve Model 8300ACB (19, 21, 23, 25 and 27 mm).

Please refer to the EDWARDS INTUITY Valve System, Delivery System Models 8300DCA and 8300DCB Instruction for Use for further details.

2.3.3 ANCILLARY PRODUCTS

The Carpentier-Edwards aortic sizers, model 1133 are used to size the native annulus determining the appropriate bioprosthesis size (EDWARDS INTUITY Aortic Valve Model 8300ACA and Model 8300ACB). Model 1133 sizers are fabricated from translucent Polysulfone plastic to permit direct observation of their fit within the annulus. Each sizer consists of a handle with a different sizing configuration at each end. On one side of the handle is a cylindrical end with an integrated lip that reflects the bioprosthesis sewing ring geometry. On the other side of the handle is a bioprosthesis replica end that reflects the bioprosthesis sewing ring geometry as well as the height and location

of the stent posts. A sizer is available for each size of the aortic bioprosthesis (19, 21, 23, 25 and 27 mm).

2.3.4 INTENDED USE

The EDWARDS INTUITY Valve System, INTUITY Aortic Valve Models 8300ACA and 8300ACB and INTUITY Delivery System Models 8300DCA and 8300DCB are intended to be used in subjects with aortic stenosis or stenosis-insufficiency who require replacement of their native aortic valve.

Refer to the Instructions for Use in the Clinical Investigator's Brochure (CIB) for contraindications, procedure steps, and cautions.

2.3.5 PRIOR TESTING

A Clinical Investigator's Brochure (CIB) has been prepared for both the EDWARDS INTUITY Aortic Valve and the EDWARDS INTUITY Delivery System. The CIB includes the non-clinical testing results for the Magna Ease, the valved component of the EDWARDS INTUITY Aortic Valve.

2.3.6 PRIOR CLINICAL STUDIES

No prior clinical studies have been conducted for the EDWARDS INTUITY Aortic Valve or the EDWARDS INTUITY Delivery System.

A summary of prior clinical studies on similar pericardial valves, the Carpentier-Edwards PERIMOUNT Aortic bioprosthesis (model 2700) and the Carpentier-Edwards PERIMOUNT Magna Aortic bioprosthesis (model 3000/3000TFX) are included in the Clinical Investigator's Brochure.

3 RISK ANALYSIS

3.1 RISKS

As with all prosthetic heart valves, serious complications, sometimes leading to death, may be associated with the use of tissue valves. In addition, complications due to individual 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

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

- Stenosis
- Regurgitation through an incompetent valve
- Perivalvular leak
- Endocarditis
- Hemolysis
- Thromboembolism
- Thrombotic obstruction
- Bleeding diatheses related to the use of anticoagulant therapy

- Malfunctions of the valve due to distortion at implant, fracture of the cobalt chromium alloy wireform, or physical or chemical deterioration of valve components
- Tissue deterioration including infection, calcification, thickening, perforation, degeneration, suture abrasion, instrument trauma, and leaflet detachment from the valve stent posts

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

- Angina
- Cardiac arrhythmias
- Heart failure
- Hemolysis
- Hemolytic anemia
- Hemorrhage
- Myocardial infarction
- Prosthesis leaflet entrapment (impingement)
- Prosthesis nonstructural dysfunction
- Prosthesis pannus
- Prosthesis perivalvular leak
- Prosthesis regurgitation
- Prosthesis structural deterioration
- Prosthesis thrombosis
- Prosthesis frame malformation (from chest compression or trauma)
- Prosthesis transvalvular leak
- Stroke
- Transient Ischemic Attack (TIA)

Potential risks associated with aortic valve replacement surgery include:

- Procedural bleeding
- Post-procedural bleeding
- Anticoagulant related bleeding
- Disseminated Intravascular Coagulation (DIC)
- Heparin Induced Thrombocytopenia (HITs)
- Hematoma
- Pericardial Tamponade
- Annular Dissection/Tear
- Aortic Dissection/Tear
- Arterial Dissection
- Cardiac Arrest
- Cardiogenic Shock
- Heart Failure
- Hypotension
- Hypertension
- Pericardial Effusion
- Perforation of free myocardial wall
- Myocardial Infarction
- Peripheral Embolic Event
- Pulmonary Embolism
- Esophageal rupture
- Bacteremia
- Pneumonia
- Sepsis/Septicemia
- Sternal Wound Infection
- Infection, local
- Infection, systemic
- Vascular Access Site Complication
- Deep Vein Thrombosis (DVT)
- Allergic reaction
- Pleural effusion

Potential Risks associated with EDWARDS INTUITY Aortic Valves and Delivery Systems may be found in the respective IFU. Based on a review of scientific literature, preliminary animal studies, risk analysis and a Failure Modes and Effects Analysis (FMEA) potential risks associated with the use of the EDWARDS INTUITY Aortic Valves may include:

- Loss of frame structural integrity resulting in damage to aortic wall or aortic annulus
- Delivery system impingement resulting in mitral chordae trauma or damage
- Frame damage or flaring resulting in a reduction of effective orifice area
- Hemolysis
- Frame expansion resulting in conduction interruptions or disturbances (i.e. arrhythmia)
- Frame expansion resulting in mitral valve impingement or abrasion with or without mitral regurgitation
- Insufficient frame expansion/suturing resulting in paravalvular leak requiring intervention or reoperation to resolve
- Device malpositioning resulting in ostial blockage
- Device embolization into the aorta/ ventricular due to suture failure

Some or all of these risks could require a need for reoperation or explant, and may lead to permanent disability or death.

There may be other risks that are unknown at this time. All safety events will be collected and reviewed throughout the entire investigation and follow-up period. Investigators will be notified of any additional risks identified that could affect the health, safety or welfare of the investigation subjects.

3.2 BENEFITS

There are no guaranteed benefits from participation in this clinical investigation. Aortic valve replacement with the EDWARDS INTUITY Aortic Valve may result in one or more of the following benefits: improved valvular function, acute alleviation of symptoms related to aortic stenosis, and/or improved morbidity and mortality.

Additionally, information gained from the conduct of this investigation may be of benefit to other people with the same medical condition in the future. The long-term results of using the investigation valve are not known at the present time. Alternative treatments may include palliative medical therapy, aortic balloon valvuloplasty and replacement of the aortic valve with prosthesis other than the EDWARDS INTUITY Aortic Valve.

3.3 JUSTIFICATION

Aortic stenosis is progressive degenerative disease that decreases systemic and coronary blood flow, valvular and ventricular function. Many patients are asymptomatic until the disease is well-advanced and once diagnosed have a poor prognosis (onset of symptoms to the time of death of approximately two years in patients with heart failure, three years in those with syncope, and five years in those with angina [31]). Other studies have reported that among symptomatic patients with medically treated moderate-to-severe AS, mortality rates after the onset of symptoms were approximately 25% at one year and 50% at two years.

Aortic Valve Replacement (AVR) surgery is the current procedure of choice for symptomatic adult patients with severe calcific AS, symptomatic patients with evidence of severe aortic obstruction, progressive left ventricular dysfunction,



ventricular ectopy at rest, or an abnormal hemodynamic response when exercising. One series reported that patients undergoing AVR had improved long-term survival rate, with a three-year rate of 87% in operated patients versus a 21% rate in non-operated patients [54].

At most centers, the reported operative mortality rate for AVR procedures ranges from 2 to 8% [4, 54, 61] increasing in patients over 70 years of age, and up to 30% , patients 80 years or older, or patients presenting in advanced heart failure with left ventricular dysfunction. Despite the poor outcomes reported for these severely compromised patients, AVR surgery still appears to have a survival benefit in patients with early diagnoses and surgical intervention compared medical therapy or no intervention [25, 48].

Since the risks associated with use of the EDWARDS INTUITY Aortic Valve are expected to be similar in nature and rate to those of other aortic bioprostheses, the Sponsor considers the risk of use of EDWARDS INTUITY Valve System to outweigh the risks of medical therapy or no surgical intervention in the defined subject population.

Over the past decade there is a trend towards less invasive medical procedures in virtually all medical specialties. Clinical outcome studies have now shown that less invasive procedures can provide reductions in procedure and hospitalization times, cost savings and improvements in subject recuperation and outcomes [73, 74].

Edwards developed the EDWARDS INTUITY Valve System, INTUITY Aortic Valve Models 8300ACA and 8300ACB to facilitate less invasive surgical approaches requiring fewer suture placements.

The Models 8300ACA and 8300ACB valve use the commercially available Magna Ease valve with a modified balloon expandable annular frame. The Models 8300DCA and 8300DCB delivery system allows for less invasive valve replacement.

The potential advantage of the Models 8300ACA and 8300ACB design is a balloon expandable frame reducing the number of sutures required without increasing the risk for paravalvular leak.

4 CLINICAL INVESTIGATION DESIGN

This is a two-phase, non-randomized, prospective, single arm, multi-center clinical investigation.

4.1 PHASE I

In **Phase I**, a total of 10 subjects will be enrolled at up to 2 participating investigational centers. Safety data will be reviewed by the Data Monitoring Committee (DMC) after 10 subjects have completed 1-month follow-up⁵. Following recommendation by the DMC, enrollment will proceed to Phase II. (Refer to Section 14.1 for DMC.)

4.2 PHASE II

In **Phase II**, 340 additional subjects will be enrolled in up to 8 participating investigational centers. Combined enrollment in Phase I and Phase II of this investigation will be 350 subjects.

Each subject in Phase I and Phase II is consented for a period of 5 years. All subjects will be assessed for clinical follow-up at the following intervals: Discharge, 1 month, 3 months, 1 year and annually thereafter until 5 years of follow-up is achieved per subject.

5 ENDPOINTS

5.1 SAFETY ENDPOINTS

The following primary safety endpoints will be assessed throughout each subject's participation in the investigation:

- Study valve-related mortality
- Thromboembolic events
- Study valve thrombosis
- Major bleeding events
- Study valve paravalvular leakage
- Study valve-related endocarditis

In addition, the following safety endpoints will also be assessed throughout each subject's participation in the investigation:

- All-cause mortality
- Study valve structural valve deterioration
- Hemolysis
- Study valve-related reoperation
- Study valve explant
- All adverse events

⁵ This may include subjects who expired or had the valve explanted prior to 1 month.

5.2 PERFORMANCE ENDPOINTS

The following performance endpoint will be assessed when the investigation procedure is performed:

- Device technical success (successful delivery and deployment of one bioprosthesis with one delivery system)

The following performance endpoint will be determined when the subject is discharged from the hospital or 10 days post implant, whichever occurs first:

- Procedure success defined as device technical success followed by the absence of adverse events requiring device reoperation, requiring implantation of permanent pacemaker (with baseline sinus rhythm and no other conduction issues), or subject death

The following performance endpoints will be assessed at each scheduled follow-up visit:

- Improvement in NYHA functional class
- Hemodynamic performance (mean gradient, effective orifice area, regurgitation by echocardiogram).

5.3 OTHER DATA

The following data also will be collected:

- EQ-5D Quality of Life questionnaire at baseline, 3-months and 1-year only,
- Blood data (White Blood Cell Count, Red Blood Cell Count, Hemoglobin, Hematocrit, Haptoglobin, Reticulocytes, Platelet Count, Serum Lactate Dehydrogenase) at baseline, 3-months, 1- and 5-years only,
- New onset or worsening of conduction disturbances.

6 SUBJECT POPULATION

6.1 DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Adult male and female subjects diagnosed with aortic stenosis or stenosis-insufficiency and scheduled to undergo aortic valve replacement are eligible for participation in the clinical investigation.

6.2 PRE-OPERATIVE CRITERIA

6.2.1 INCLUSION CRITERIA

The principal investigator at the investigational center has the responsibility of screening potential subjects to determine if the subjects meet all the inclusion criteria. The following are requirements for entry into Phase I or Phase II of the clinical investigation:

1. Subject is 18 years or older
2. Subject has aortic stenosis or stenosis-insufficiency of an aortic valve requiring a planned replacement as indicated in the preoperative evaluation.

3. Subject is scheduled to undergo planned aortic valve replacement with or without concomitant coronary bypass surgery, MAZE procedure, septal myectomy, pacemaker/ICD implant and or atrial appendage occlusion/removal.
4. Subject has signed and dated the investigation informed consent form prior to investigation procedures.
5. Subject is geographically stable and agrees to attend follow-up assessments at the hospital of surgical services for a maximum of 5 years.

6.2.2 EXCLUSION CRITERIA

The principal investigator at the investigational center must exclude subjects if any of the exclusion criteria is present. The following are the criteria for exclusion from participating in Phase I or Phase II of the clinical investigation:

1. Subject with pure aortic insufficiency.
2. Subject requires emergency surgery.
3. Subject with an aneurysm of the aortic root and / or ascending aorta requiring surgical intervention).
4. Subject with a left ventricular ejection fraction of $\leq 25\%$.
5. Subject with a congenital bicuspid or unicuspid aortic valve.
6. Subject had active endocarditis within 3 months prior to the scheduled aortic valve replacement surgery.
7. Subject with concomitant valve (mitral, tricuspid, or pulmonic) disease requiring repair with an annuloplasty ring or replacement with prosthesis.
8. Subject had prior mitral, tricuspid or pulmonic valve surgery, which included implantation of a bioprosthetic valve, mechanical valve, or annuloplasty ring that will remain *in situ*.
9. Subject had a myocardial infarction within 1 month prior to the scheduled aortic valve replacement surgery.
10. Subject has a disease limiting life expectancy to less than 12 months.
11. Subject was previously implanted with EDWARDS INTUITY Aortic Valve⁶.
12. Subject is an alcohol and/or drug abuser.
13. Female subject is pregnant or lactating.
14. Subject is currently participating in another drug or device clinical investigation.
15. Subject with documented leukopenia ($WBC < 3.5 \times 10^3/\mu L$), acute anemia ($Hgb < 10.0 \text{ gm/dL}$ or $< 6.2 \text{ mmol/L}$), thrombocytopenia (platelet count $< 100 \times 10^3/\text{mL}$), or history of bleeding diathesis or coagulopathy⁷.
16. Subject who requires a non-cardiac procedure such as carotid procedures or mediastinal tumor removal.

⁶ Previously implanted means that the EDWARDS INTUITY Aortic Valve implant procedure was completed. The EDWARDS INTUITY Aortic Valve procedure is complete when the surgeon takes the patient off cardiopulmonary bypass and restarts the heart.

⁷ WBC: White Blood Cells; Hgb: Hemoglobin

17. Subject had a stroke or transient ischemic attack within six months prior to scheduled aortic valve replacement surgery.
18. Study site pre-operative echocardiographic assessment shows evidence of an intracardiac mass, thrombus, or vegetation.
19. Subject has hemodynamic or respiratory instability requiring inotropic support, mechanical circulatory support, or mechanical ventilation within 30 days of procedure.
20. Subject with documented renal insufficiency as determined by Serum creatinine ≥ 200 $\mu\text{mol/L}$ (2.27 mg/dL) at screening or end-stage renal disease requiring chronic dialysis.
21. Subject with documented hyperparathyroidism.

6.3 INTRA-OPERATIVE CRITERIA

6.3.1 EXCLUSION CRITERIA

These exclusion criteria will be determined after subject consent, intraoperatively and before any attempt with an EDWARDS INTUITY valve is performed.

The Investigator may exclude any subject due to any of the following conditions:

1. Participation in the clinical investigation may be contrary to the subject's medical treatment;
2. Any anatomical findings that would not be suitable for implantation of the EDWARDS INTUITY Aortic Valve or use of the EDWARDS INTUITY Delivery System and which are discovered, intraoperatively. These may include findings such as:
 - a. Significant calcium on the anterior mitral leaflet which cannot be removed,
 - b. Septal hypertrophy that will not be corrected by myectomy, or pronounced septal calcification,
 - c. The position of the coronary ostia relative to the EDWARDS INTUITY Aortic Valve Models 8300ACA and/or 8300ACB would result in obstruction of blood flow,
 - d. Extensive calcification of the aortic root,
 - e. Left atrial thrombus,
 - f. the subject is hemodynamically unstable during the procedure requiring the procedure to be aborted prior to insertion of the investigational bioprosthesis and delivery system,
 - g. A device is not available in the correct size for the subject,
 - h. Annular deformation which may or may not be caused by too extensive decalcification of the aortic annulus;
3. It is discovered that the subject is participating in a clinical investigation of another drug or device prior to insertion of the investigational bioprosthesis and delivery system.

The Investigator will document the exclusion of investigation subjects and notify the Investigation Sponsor within 5 working days. Additional subjects will be screened to



replace those subjects who are excluded by the Investigator during the surgical procedure prior to implantation.

6.4 WITHDRAWAL CRITERIA AND PROCEDURES

Subjects may voluntarily withdraw consent at any time during Phase I or Phase II of the clinical investigation with no loss of benefit or penalty. Subjects will be exempt from follow-up after withdrawing from the clinical investigation. For subjects who are consented but have withdrawn, the investigational center must retain the subject's informed consent and all documents pertaining to the subject prior to the subject's withdrawal. Additional subjects will not be enrolled to replace those subjects implanted with the bioprosthesis who chose to withdraw from the clinical investigation.

7 INVESTIGATIONAL DEVICE MANAGEMENT

7.1 DEVICE SHIPMENTS

An initial set of EDWARDS INTUITY Aortic Valves and EDWARDS INTUITY Delivery Systems will be shipped to the investigational center once the following conditions are met: the investigational center has obtained Ethics Committee approval, a signed Clinical Investigational Agreement is in place, and the Site Initiation Visit, including Principal Investigator training, has been completed. Additional devices will be sent to the investigational center as devices are used or as needed.

7.2 INVENTORY AND ACCOUNTABILITY RECORDS

All device shipments will have inventory and shipment records. Devices may be hand carried to participating investigational centers by Investigational Sponsor personnel and will be accompanied by delivery of investigational device documentation. The principal investigator(s) or designee will take inventory of the product and complete the delivery documentation with receipt date, condition of the device and signature. Both the investigational center and the Investigation Sponsor will retain copies of these documents.

The investigator will maintain a Device Accountability Log of all investigational devices received for use during this clinical investigation. The log will be kept with the documents for the clinical investigation and will be available for review during Investigational Sponsor monitoring visits. Documentation on the log will include:

1. Valve Model number
2. Valve serial number
3. Valve size
4. Delivery system Model number
5. Delivery system lot number
6. Delivery system size
7. Subject identification number for the clinical investigation, if device was used or opened



8. Date of use or if not used, date of return and Returned Goods Authorization (RGA) number (if applicable), or date of discard⁸.

7.3 DEVICE STORAGE

The device inventory will be stored in a locked, controlled, cool, dry and clean area as described in the Instructions for Use (IFU). This storage area shall be accessible only to the principal investigator(s), his/her co-investigator or approved designee. Only cardiac surgeons identified in the Clinical Investigational Agreement and the Delegation of Authority form on file at the Investigation Sponsor may use the investigational device.

7.4 DEVICE RETURN

The principal investigator(s) will be notified in writing upon termination of the clinical investigation. All unused devices in original package and/or those in opened packages as well as those removed from the original package will be returned upon receipt of this notice. The Investigator's copy of the Device Accountability log must document any unused devices that have been returned. In the event that the EDWARDS INTUITY Aortic Valve is removed from the package, the bioprosthesis should be placed in a container with a suitable histological fixative such as 10% formalin or 2% glutaraldehyde immediately and returned to the Investigation Sponsor. Refrigeration is not necessary under these circumstances. Contact Edwards the Investigation Sponsor for additional instructions.

8 TRAINING

8.1 TRAINING OF INVESTIGATIONAL CENTER PERSONNEL

Principal investigator(s) and support staff will be trained by the Investigation Sponsor on the use of the EDWARDS INTUITY Aortic Valve and the EDWARDS INTUITY Delivery System, the Protocol, the Clinical Investigator's Brochure, electronic Case Report Forms (eCRF) and Electronic Data Capture (EDC) system, device accountability procedures, GCP (Good Clinical Practices) Guidelines and other investigation documents as applicable. A "Delegation of Authority Form" will be completed at each investigational center designating which individuals are allowed to perform specific clinical investigation related tasks. The delegated tasks will determine what the training requirements are for each member of the investigation support staff.

8.2 DEVICES

Each cardiac surgeon participating in the clinical investigation must be trained on the use of the devices before screening potential subjects or using the EDWARDS INTUITY Aortic Valve and the EDWARDS INTUITY Delivery System.

8.3 ECHOCARDIOGRAPHIC EXAMINATIONS

Each sonographer participating in the clinical investigation must be trained on the requirements of the Echo Manual.

⁸ Bioprostheses must be returned to the Sponsor. It is preferable that delivery systems are returned also, but they may be discarded as described in the IFU.

8.4 DOCUMENTATION

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

9 PROCEDURES AND METHODS

9.1 BASELINE EVALUATION

The Phase I or Phase II baseline evaluation will include:

1. Initial screening for the clinical inclusion and exclusion criteria,
2. Informed consent discussion and dated signature
3. History and physical examination,
4. Baseline blood studies per protocol, Section 9.1.3
5. Baseline transthoracic echocardiogram (TTE) per protocol (Section 9.5)
6. Baseline 12 lead electrocardiogram
7. NYHA Functional Class
8. Quality of Life Survey (EQ-5D)

9.1.1 SUBJECT SCREENING

All subjects diagnosed with aortic stenosis requiring aortic valve replacement seen by cardiac surgeons participating in this clinical investigation should be screened for eligibility. All subjects who meet eligibility requirements will be asked to participate. A Screening Log will be provided to the investigational centers to maintain a cumulative log of all screened subjects admitted for aortic valve replacement by the cardiac surgeons participating in this investigation. For subjects listed as not eligible for participation in the clinical investigation, a reason supporting the disqualification of the subject must be entered on the screening log. The Screening Log shall be duly completed and faxed to the Investigation Sponsor regularly (at least once per month). Any subject deemed ineligible due to active endocarditis, recent myocardial infarction, pregnancy or lactating, or due to participation in another clinical investigation may be re-screened at a later time. Re-screened subjects must be re-entered on the Screening Log.

9.1.2 INFORMED CONSENT

Subjects who are eligible for participation in the clinical investigation shall be provided at a minimum with the following explanation:

1. background of the clinical investigation;
2. potential benefits and risks of the procedures involved;
3. follow-up visit requirements per the clinical investigation.

Each subject shall be given ample time to read the Informed Consent in its entirety and ask questions to make an informed decision. The subject must sign and date the investigational center's Ethics Committee (EC) approved Informed Consent before any clinical investigation specific procedure is applied to the subject. Subjects who provide



informed consent will be assigned a unique investigation subject identification number that will be recorded on the Screening Log. The Investigator, or designee, and any witnesses shall also sign and date the consent form, as indicated. Failure to provide Informed Consent renders the subject ineligible for participation in the clinical investigation including undergoing treatment with the investigational devices. Subjects who do not provide informed consent also are recorded on the Screening Log.

For subjects who are not able to read or write and or are blind, a legal representative who is authorized to sign and date the consent on the subject's behalf will do so, but only after the informed consent is read and explained, all questions answered and understood by the subject and legal representative and the subject has given verbal agreement to volunteer for the clinical investigation. An independent witness (other than the subject's legal representative or the consenting physician) shall be present throughout the process. A note will be made of the subject's verbal agreement to participate; furthermore the witness shall also sign and personally date the informed consent form attesting that the information was accurately explained and that informed consent was freely given.

9.1.3 BASELINE ASSESSMENT

After a written informed consent has been obtained from the subject the following baseline tests and exams will be conducted: transthoracic echocardiography (TTE) per protocol (Section 9.5); 12-lead electrocardiogram; blood studies per protocol; an assessment per NYHA Functional Classification; completion of a Quality of Life Survey (EQ-5D); a pregnancy test (not applicable if subject is male or female who is post-menopausal / surgically sterile). Test results conducted within 30 days before aortic valve surgery may be used for this investigation if all values per protocol are available. Baseline information to be documented is further detailed in Table 1.



Table 1: Baseline Assessment

General information	Clinical information	Blood studies	Echocardiography ⁹
Birth Date Subject Sex Height Weight Heart rate	Cardiac Rhythm (12-lead EKG) NYHA Classification Cardiovascular Risk Factors Cardiovascular Conditions Previous Procedures / Interventions Non-Cardiovascular Conditions Quality of Life	Blood Draw Date White Blood Cell Count Red Blood Cell Count Hemoglobin Hematocrit Haptoglobin Reticulocytes Platelet Count Serum Lactate Dehydrogenase	Date of exam 2D measurements Ejection fraction Aortic bioprosthesis assessment LVOT assessment Mitral Valve assessment Other Variables Left Ventricular Assessment

9.2 SURGICAL PROCEDURE

9.2.1 PROCEDURE PREPARATION

The surgical approach used will be at the discretion of the investigator in his/her routine surgical practice. At the time of aortic valve replacement a transesophageal echocardiogram to further assess the anatomy (See Intra-operative Exclusion criteria section 6.3) is recommended prior to aortic valve replacement with the EDWARDS INTUITY Aortic Valve. After performing the aortotomy, the native valve and surrounding anatomy should be examined for compatibility with the devices (See Intra-operative Exclusion criteria section 6.3).

9.2.2 EDWARDS INTUITY AORTIC VALVE IMPLANTING PROCEDURE

A detailed description of device preparation and use is provided in the Instructions for Use (IFU) of both Models 8300ACA and 8300ACB, (See Clinical Investigator’s Brochure). Investigators must be familiar with Precautions and Technique information described in the IFU prior to use of the bioprosthesis and the delivery system. The EDWARDS INTUITY Valve System implanting procedure uses one bioprosthesis and one delivery system. A second attempt, with new devices, is permitted. If the second attempt is not successful, no further attempts are permitted and the subject should be treated with another surgical valve. [REDACTED]

A Transesophageal echo (TEE) should be performed after the bioprosthesis is implanted to assess placement, potential paravalvular leak, and mitral valve function.

Procedural information, findings, results and device identification information to be recorded is identified in Table 2.

⁹ Data evaluation to be performed by a Core Lab as described in the Echo Manual.



Table 2: Procedural information

General information	Clinical information	Device performance
Date of Admission Date of Procedure Implanting Surgeon Type of Operation	Etiology Diagnosis for replacement Valve implantation Condition of the native aortic valve Sizing Concomitant procedures Intraoperative Adverse Events	Bioprosthesis size and serial number Delivery system size, lot, and components used Device technical success

9.3 SUBJECT ENROLLMENT

Subjects will be considered enrolled into the clinical investigation after meeting all the enrollment criteria, signing the informed consent, and after the surgeon sizes the aortic annulus, and determines that the bioprosthesis can be implanted. The point of enrollment in Phase I and Phase II of the clinical investigation is established in the Operating Room when the investigator sizes the aortic annulus and confirms that the subject is an appropriate candidate for the investigation device(s)¹⁰. All subjects enrolled in this clinical investigation must be followed as described in section 9.4 and section 9.5

Adverse events are collected from the time the subject provides consent.

9.4 POST-PROCEDURE

9.4.1 POST-PROCEDURE CARE

Bioprosthetic heart valve recipients should be maintained on anticoagulant therapy (except when contraindicated) during the initial healing stages after implantation, approximately 2 to 3 months in accordance with the ACC/AHA 2006 Guidelines for the Management of Patients with Valvular Heart Disease [8]. Anticoagulants should then be discontinued over a period of 10 days, except in those subjects for whom ongoing anticoagulant protection is indicated, i.e., in the absence of sinus rhythm and in subjects with a dilated left atrium, calcification of the atrial wall, history of previous atrial thrombus, or any other medical condition requiring anticoagulation therapy. However, the appropriate anticoagulation therapy must be determined by the physician on individual basis.

It is recommended to collect post-operative telemetry on all subjects for a minimum of five (days) after aortic valve replacement.

9.4.2 DISCHARGE

A clinical evaluation of Phase I or Phase II subjects, including an echocardiogram (refer to Section 9.5), will be performed at the time of hospital discharge. Medical information, findings, and results to be recorded are identified in Table 3.

¹⁰ The bioprosthesis and the delivery system must be used.



Table 3: Discharge Evaluation

General information	Clinical information	Echocardiography ¹¹
Date of Discharge	Weight Heart rate Cardiac Rhythm (12-lead EKG) Anti-thromboembolic therapy Adverse Events Coagulation Profile	Date of exam 2D measurements Ejection fraction Aortic bioprosthesis assessment LVOT assessment Mitral Valve assessment Other Variables Left Ventricular Assessment

Subjects, who are not discharged within 10 days post procedure must have an echocardiogram (refer to Section 9.5) to further assess placement and performance of the bioprosthesis. This echocardiogram is required to complete the evaluation of procedural success. Those subjects will not require an additional echocardiogram at discharge.

9.4.3 FOLLOW-UP ASSESSMENTS

Post-procedure clinical evaluation will be performed on all Phase I or Phase II of enrolled subjects at 1 month, 3 months, 1 year and annually thereafter until 5 years of follow-up is achieved. The follow-up windows are listed in Table 4.

Table 4: Follow-up Windows

Follow-up Assessment ¹²	Assessment Window
1-month	± 1 week
3-months	+ 1 month
1-year	± 1 month
2-year	± 1 month
3-year	± 1 month
4-year	± 1 month
5-year	± 1 month

During the Phase I 1-month evaluation of the subject a 12 lead electrocardiogram and a Transthoracic echocardiography (TTE) per protocol (Section 9.5) is required. Medical information and findings to be recorded are identified in Table 5.

¹¹ Data evaluation to be performed by a Core Lab as described in the Echo Manual.

¹² 1 week = 7 days; 1 month = 30 days; 3 months = 90 days; 1 year = 365 days.



Table 5: Phase I Follow-up Evaluation at 1 Month

General information	Clinical information	Echocardiography ¹³
Date of Evaluation	Cardiac Rhythm Weight Heart rate Adverse Events	Date of exam 2D measurements Ejection fraction Aortic bioprosthesis assessment LVOT assessment Mitral Valve assessment Other Variables Left Ventricular Assessment

During the Phase II 1-month evaluation subject will be contacted to assess his/her current status. Medical information and findings to be recorded are identified in Table 6. It is acceptable to obtain the information through an evaluation conducted via telephone. Should the subject return, for any reason, to the investigational center for the Phase II 1-month evaluation, assessments of the cardiac rhythm, weight, heart rate, NYHA functional classification and a Transthoracic echocardiography (TTE) are requested.

Table 6: Phase II Follow-up Evaluation at 1 Month

General information	Clinical information
Date of Evaluation	Adverse Events

During the subsequent 3 months, and annual visits, for Phase I or Phase II of the study, the subject returns to the investigational center for the evaluations listed in Table 7



At each postoperative assessment, the investigator(s) will determine the subject's availability for future follow-up visits. If any subject is seen at a time other than a regularly scheduled follow-up visit (called an interim visit), the same information as described in Table 7 will be collected and documented by the investigator.

¹³ Data evaluation to be performed by a Core Lab as described in the Echo Manual.



Table 7: Follow-up evaluations

General information	Clinical information	Blood studies	Echocardiography ¹⁴
Date of Evaluation	Cardiac Rhythm Physical Assessment NYHA Classification Coagulation Profile Anti-thromboembolic therapy Adverse Events Quality of Life (at 3-months and 1-year)	Blood Draw Date White Blood Cell Count Red Blood Cell Count Hemoglobin Hematocrit Haptoglobin Reticulocytes Platelet Count Serum Lactate Dehydrogenase	Date of exam 2D measurements Ejection fraction Aortic bioprosthesis assessment LVOT assessment Mitral Valve assessment Other Variables Left Ventricular Assessment

9.5 ECHOCARDIOGRAM

All echocardiograms will be independently analyzed by the Echocardiography Core Lab as described in the Echo Manual [REDACTED]. Each investigation echocardiogram is to be recorded individually on a computer disc (CD) with the individual subject investigation number provided on the examination screen.

9.6 DEVICE REMOVAL / EXPLANT PROCEDURE

Subjects with device removal or explant will be followed as described in section 9.4 and section 9.5; however neither echocardiography nor blood tests will be performed after discharge, unless required to better assess subject's health status.

9.6.1 INTRA-OPERATIVE REMOVAL

Intra-operative removal is the excision of the investigation bioprosthesis before the EDWARDS INTUITY Valve System procedure was completed. The heart was not restarted with the bioprosthesis implanted. During the aortic valve replacement (AVR) procedure, should removal of the bioprosthesis be required after the frame was expanded, use of a nerve hook is recommended. Using a scalpel the operator shall carefully cut the bioprosthesis holder retaining sutures and remove the complete delivery system. Then, insert the nerve hook through the outflow aspect of the bioprosthesis. Operator is to engage the expanded frame with the nerve hook and gently pull the frame inward. Then, operator is to disengage the collapsed portion of the frame and engage the expanded frame at another location, gently pulling the frame inwards. The expanded frame should be engaged and collapsed at least at 3 radial locations. Once the frame is collapsed, the operator shall cut the nadir sutures and remove the bioprosthesis with forceps.

9.6.2 INTRA-OPERATIVE OR EARLY POST-OPERATIVE EXPLANT

Intra-operative explant is the excision of the investigation bioprosthesis, or part of the investigation bioprosthesis, after the EDWARDS INTUITY Valve System procedure was completed and the heart was restarted with the bioprosthesis implanted. The

¹⁴ Data evaluation to be performed by a Core Lab as described in the Echo Manual.

bioprosthesis is explanted by accessing the aortic valve site and excising the valve as described in section 9.6.1.

This procedure is also recommended in the early AVR post-operative period, before substantial ingrowth tissue has occurred.

9.6.3 LATE POST-OPERATIVE EXPLANT

During the late AVR post-operative period, should explantation of the bioprosthesis be required the device and the surrounding anatomy should be assessed (echo/x-ray or visually) to determine the most appropriate course of action.

The bioprosthesis is designed to allow:

- Collapsing of the frame using a nerve hook.
- Removal of the pericardial leaflets only.
- Separation from the frame by severing the connections between the bioprosthesis wireform and the frame.
- Implantation of a transcatheter valve (Per Instructions For Use in regions where such devices are approved for this intended use)

9.7 MISSED SUBJECT VISITS

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

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

9.8 INVESTIGATION SUBJECT EXIT

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

- Subject fails enrollment criteria after written consent (section 6)

- Subject is excluded intra-operatively by investigator prior to attempted placement of the investigational device (section 6.3)
- Subject is Lost-to-follow-up (section 9.7)
- Subject withdraws from the investigation (section 6.3)
- Subject Death (section 11.3.1)
- Subject completes investigation follow-up (section 9.4.3)

9.9 CLINICAL INVESTIGATION TERMINATION

The principal investigator(s) will be notified in writing upon termination of the clinical investigation. The Investigation Sponsor retains the right to suspend or terminate this clinical investigation at any time. Safety review committees associated with the clinical investigation may recommend termination should safety concerns warrant such action. Upon investigation termination, the Investigator will contact the investigation subjects to perform a final follow-up assessment within 2 months of investigation termination. If a subject completed a protocol scheduled clinical evaluation within 6 months prior to investigation termination, the final follow-up assessment may be completed by telephone. Subjects should continue seeing their physicians as part of routine clinical follow-up after heart valve replacement surgery.

10 DATA COLLECTION AND REPORTING

10.1 DATA COLLECTION METHODS

All required data for this investigation are to be collected with standardized Case Report Forms (CRFs) for individual subjects; samples are provided in Section 17.8. Electronic CRFs (eCRFs) will be utilized for this investigation. eCRFs must be electronically signed by the Principal Investigator or co-Investigator listed in the Clinical Studies Agreement and Delegation of Authority Log. If for any reason the eCRFs are unavailable and/or inaccessible, paper CRFs will be provided by the Investigation Sponsor to be completed, signed by the Principal Investigator or designee and submitted to the Investigation Sponsor.

Primary data collection should be drawn from hospital chart and operator worksheet (source document) reviews. eCRFs must be kept current to reflect subject status during the course of the investigation.

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

10.2 SOURCE DOCUMENTATION REQUIREMENTS

Regulations require that Investigators maintain information in the clinical investigation subject's medical records that corroborate data collected on the eCRFs. In order to comply with these regulatory requirements, the following information will be maintained as required by the Investigation Sponsor monitors and/or regulatory inspectors:



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

10.3 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

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

Data Management personnel will employ a full-featured relational Oracle database application on a central server. The application provides the capability of data collection remotely through the Internet so the participating site personnel may log on the system securely and enter the data. Other data management programming and/or data analyses will be done in the database system through the sponsor's internal network. All subjects' data collected in the system will be extensively verified through data validation programs, database integrity rules, and investigation-specific data entry conventions for data accuracy and logical meaningfulness. Periodic analysis of all subjects' collected data will be performed in order to examine the expected distributions of data and to identify outliers for possible data entry errors.

11 REPORTABLE EVENTS / EFFECTS

Reportable event codes are provided in the eCRF synopsis for this investigation.

11.1 REPORTING PROCEDURE

Adverse event information will be reported throughout the clinical investigation as they occur. Adverse events will be followed until they are adequately resolved or explained. The investigator(s) will report any serious adverse event to the Investigation Sponsor's Clinical Research department no later than three calendar days after the Investigators first learns of the event, followed by relevant source documents in ten working days. It is preferable for the investigator to notify the Investigation Sponsor's Clinical Research department within 24 hours of occurrence or knowledge of the device related event. **Notification should be done via email to HVTClinicalEU@edwards.com or faxed to +41-22-787-4324.** In addition, investigational centers will report all serious adverse events to their local EC and National Competent Authority in accordance with the review committee's and national requirements.

11.2 DEFINITIONS

For purposes of this protocol adverse event definitions are taken from the guidance ISO document; please refer to ISO 14155:2011.

11.2.1 ADVERSE EVENT

An adverse event (AE) is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

NOTE 1: *This definition includes events related to the investigational medical device or the comparator.*

NOTE 2: *This definition includes events related to the procedures involved.*

NOTE 3: *For users or other persons, this definition is restricted to events related to investigational medical devices.*

11.2.2 ADVERSE DEVICE EFFECT

An adverse device effect (ADE) is defined as any adverse event related to the use of an investigational medical device.

NOTE 1: *This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.*

NOTE 2: *This definition includes any event resulting from use error or from intentional misuse of the investigational medical device .*

11.2.3 SERIOUS ADVERSE EVENT

A serious adverse event (SAE) is defined an adverse event that:

- a. led to death,
- b. led to a serious deterioration in the health of the subject, that either resulted in:

1. a life-threatening illness or injury, or
 2. a permanent impairment of a body structure or a body function, or
 3. in-patient or prolonged hospitalization, or
 4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function,
- c. led to fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

11.2.4 SERIOUS ADVERSE DEVICE EFFECT

A serious adverse device effect (SADE) is defined as an adverse device effect that results in any of the consequences characteristics of a serious adverse event.

11.2.5 UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE)

Serious Adverse Device Effect which by its nature, incidence, severity or outcome, has not been identified in the current version of the risk analysis.

Note: Anticipated serious device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

11.3 DEATHS AND EXPLANTS

11.3.1 SUBJECT DEATHS

In the event of subject death, every effort should be made to obtain a copy of the death certificate, the autopsy report and/or the death summary. Information on the cause of death and its relationship to the device used in this clinical investigation will be determined by the principal investigator. Copies of an autopsy report, if available, and/or a death summary are to be sent to the Investigation Sponsor.

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

11.3.2 DEVICE EXPLANTS

In the event a bioprosthesis 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 Investigation Sponsor. Information on the cause of explant and its relationship to the bioprosthesis will be determined by the principal investigator. Explanted bioprostheses during this period must be returned to the Investigation Sponsor for analysis. Return kits for devices will be provided upon request by the clinical monitor.

In the event a bioprosthesis is explanted in the late post-operative period, every effort should be made to obtain a copy of the explant procedure report, as applicable. Information on the cause of explant and its relationship to the bioprosthesis will be determined by the principal investigator. Copies of an explant report, if available, are

to be sent to the Investigation Sponsor. Explanted bioprostheses during this period should be returned to the Investigation Sponsor for analysis. Return kits for devices will be provided upon request by the clinical monitor.

12 STATISTICAL ANALYSIS

12.1 SAMPLE SIZE PHASE I

The Phase I investigation will enroll 10 subjects for feasibility. No statistical justification is established.

12.2 SAMPLE SIZE PHASE II

Phase II will enroll up to 340 subjects. The sample size is determined based on ISO5840 requirements. The rationale for the increase is based on estimation of the number of additional subjects required in order to reach a minimum of eight subjects implanted with the smallest valve size tested (19 mm valves) and a minimum of fifteen subjects implanted with the larger 27mm valve size tested to meet ISO5840 requirements.

12.3 PHASE I ANALYSIS

Phase I consists of the first 10 subjects enrolled to the investigation.

The following primary safety endpoints will be summarized by counts and percentages based on 30-day follow-up:

- study valve-related mortality,
- thromboembolic events,
- study valve thrombosis,
- major bleeding events,
- study valve paravalvular leakage, and
- study valve endocarditis.

In addition, the following safety endpoints will also be summarized by counts and percentages based on 30-day follow-up:

- all-cause mortality,
- study valve structural valve deterioration,
- hemolysis,
- study valve-related reoperation,
- study valve explantation, and
- all adverse events.

12.4 PHASE II ANALYSIS

12.4.1 ANALYSIS POPULATION

The primary safety analysis will include all the enrolled subjects including those enrolled in Phase I. The performance analysis will include the subjects who survived at least 30 days post implant.

12.4.2 SAFETY ANALYSIS

For reporting purposes, the percent of subjects who experience an early adverse event within 30 days of implant for the events listed in the primary safety endpoints will be summarized. Linearized rates will be used to summarize adverse events for the late (>30 days) post-operative period for the events listed in the primary safety endpoints. The linearized rates will be reported as the number of events occurring after the early post-operative period per year of subject survival.

Actuarial analysis according to Kaplan-Meier will be used to estimate probability of freedom from each adverse event listed in the primary safety endpoint.

The percentages for the early events and linearized rates for the late events will also be calculated for the other complications.

Blood data (red blood count, white blood count, hematocrit, hemoglobin, platelet count, serum lactate dehydrogenase, haptoglobin, and reticulocytes) will be collected preoperatively, at 6-months, 1-years, and 5-years post implant. Data will be reported as the percent of subjects with results within the normal ranges at each time interval.

12.4.3 PERFORMANCE ANALYSIS

The device technical success and procedure success will be summarized by counts and percentages.

Subjects will be analyzed according to the NYHA classification preoperatively, at 3 months and annually post implant for 5 years. The distribution (numbers of subjects and percentages) in the various NYHA classes will be tabulated at each follow-up interval.

Echocardiography data will be obtained preoperatively, at discharge (or 10-days post implant, whichever occurs first), at 6-months and at 1, 3, and 5 year follow-ups. Descriptive statistics for the continuous echo variables and change from baseline (e.g. mean, standard deviation, and range) will be categorized by time interval and size. Regurgitation data will be summarized using frequency at each severity level.

Improvement in regurgitation at one year will be analyzed via the Wilcoxon Signed-Rank test. Change at one year from baseline for all other hemodynamic outcomes will be analyzed using paired *t*-tests.

12.4.4 MISSING DATA

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

13 MONITORING

13.1 MONITORING METHODS

The Investigation Sponsor will assign a monitor to monitor 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) or answer any questions. The monitor will be responsible for verifying that the subject signed the consent, reviewing data recorded on the eCRFs, and visiting each investigational center periodically to observe investigation progress and compliance with clinical protocol and regulations applicable to this clinical investigation.

Monitoring visits will be scheduled throughout the duration of the clinical investigation between the monitor and the principal investigator at a mutually convenient and available time. These visits will assure that the facilities are still acceptable, the protocol and investigational plan are being followed, the EC is notified of approved protocol changes as required, complete records are being maintained, appropriate timely reports have been made to the Investigation Sponsor the EC and the Competent Authority (as applicable), device and device inventory are controlled and the investigator is carrying out all agreed activities. Any personnel changes must be reported to the monitor immediately and a training program scheduled and documented. Additionally, the monitor will do source data verification to assure CRF data accuracy and completeness. The scope of monitoring is defined and will be conducted in accordance with the TRITON Study Monitoring Plan.

To protect subject confidentiality, the subject's name must not appear anywhere on the imaging media sent prepared for evaluation by the core lab, or supporting documentation removed from the investigational center. Each page should be identified with the subject's ID number only. All other subject identifiers (i.e., medical record number, personal number) are to be obscured.

13.2 MONITORING PLAN

Prior to subject enrollment, an initiation visit will be completed at each investigational center to ensure the following:

1. Ethics Committee and applicable regulatory body approvals have been obtained and documented,
2. The investigators and clinical investigation personnel are appropriately trained and clearly understand the investigation,
3. The investigators and clinical investigation personnel accept the obligations incurred in undertaking this clinical investigation.
4. The Delegation of Authority form has been completed properly

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

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

Monitoring activities are further described in the TRITON Study Monitoring plan for this investigation.

13.3 PROTOCOL DEVIATION

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

Deviations shall be reported to the Investigation 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 an investigational device outside the investigation, unauthorized use of an investigational device by a physician who is not listed in the Clinical Investigation Agreement, etc.) will be reported in writing. Investigators will also adhere to procedures for reporting investigation deviations to their EC in accordance with their specific EC's reporting policies and procedures.

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

1. Major deviations:
 - a. Any deviation from subject inclusion and exclusion criteria;
 - b. Any deviation from subject informed consent procedures;
 - c. Unauthorized use of an investigational device outside the investigation;
 - d. Unauthorized use of an investigational device by a physician who is not listed in the Clinical Investigation Agreement.
2. Minor deviations:
 - a. Deviation from a protocol requirement such as incomplete/inadequate testing procedures (unless procedure is optional or deemed medically inadvisable to perform on subject);
 - b. Follow-up performed outside specified time windows.

13.3.1 EXCEPTIONS

Some information in this investigation is collected for Investigation Sponsor research purposes and is therefore not a reportable protocol deviation if absent.

At Baseline this includes:

- Blood pressure
- Pre-operative risk scores
(Additive euroSCORE, Logistic euroSCORE, STS risk score)
- Type of medication currently in use (ACE or ARB Inhibitors, ADP inhibitors, Antiarrhythmics, Anticoagulants, Antiplatelets, Beta Blocker, Glycoprotein IIb/IIIa inhibitor, Inotropes, Lipid Lowering, Nitrates, or Steroids)

During the investigation procedure this includes:

- Surgical approach
- Suture technique
- Debridement procedure
- Surgical procedure timing
- Device procedure timing
- Inflation device used
- Balloon inflation pressure and number of inflations
- User assessment: device ease of use

At hospital discharge this includes:

- Blood pressure
- Subject discharged to: home, another hospital, extended care
- Current medications
- Post-operative hospitalization
(time in intensive care unit, intermediate care, general ward)
- Ventilation time
- Post-operative blood replacement, including Cell Saver amount auto transfused
(in intensive care unit, intermediate care, general ward)

At follow-up evaluation this includes:

- Visit type (Hospital/Clinic, In-patient admission, phone)
- Current medications

13.4 COMMUNICATION PROCEDURES

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

14 COMMITTEES

14.1 DATA MONITORING COMMITTEE

The Investigation Sponsor will appoint a Data Monitoring Committee (DMC) whose members will be independent of both the Investigation Sponsor and the Investigators. The role and composition of the DMC is described in the DMC Charter for this clinical investigation.

14.2 CLINICAL EVENTS COMMITTEE

The Investigation Sponsor will appoint a Clinical Events Committee (CEC) whose members will be independent of both the Investigation Sponsor and the Investigators. The role and composition of the CEC is described in the CEC Charter for this clinical investigation.



15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 APPLICABLE REGULATIONS AND GUIDELINES

The clinical investigation will be conducted in compliance with the regulations set forth in Table 8. It is the responsibility of the investigator(s) and Sponsor to comply additionally with country specific regulations.

Table 8: Applicable Regulations and Guidelines

Region	Regulation / Guideline
Europe	<ul style="list-style-type: none"> - 2007/47/EC European Medical Device Directive (MDD) - ISO 14155:2011 (Clinical investigation of medical devices for human subjects – Good clinical practice) - ISO 5840: 2005 (Cardiovascular implants-Cardiac valve prostheses) - Declaration of Helsinki - ISO 14971:2007 (Medical Devices – application of risk management to medical devices)

Furthermore, the investigator will use as guidance pertinent sections of ICH E6 GCP or will comply with the laws of the applicable country, whichever will afford greater protection to subjects screened for participation in the clinical investigation and subjects who participate in the investigation.

Principles protecting the rights, safety and well-being of human subjects, which are the most important considerations and shall prevail over interests of science and society, shall be understood, observed, and applied at every step in the clinical investigation.

15.2 IMPROPER INFLUENCE

The Sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s) or other parties participating in, or contributing to, the clinical investigation. The Investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s) or other parties participating in or contributing to the clinical investigation

15.3 DATA PROTECTION AND SUBJECT CONFIDENTIALITY

The Investigation Sponsor is dedicated to maintaining the confidentiality and privacy of subjects who volunteer to participate in the clinical investigation. Passwords are issued to appropriate personnel to insure confidentiality and protection of the database by allowing variable levels of access to the computer system. In addition, the principal investigator is responsible for maintaining confidentiality throughout the clinical investigation. The hard copies of the source documentation are to be maintained in a secure area with limited access. All subject identifiers will be obliterated from all photocopies of source documents that have been removed from the investigational center. Subject identifiers include, but are not limited to: subject's name, social security number or equivalent, and medical / hospital number. All documents for the clinical investigation will identify the subject by a subject identification number assigned by the Investigation Sponsor.

15.4 INFORMED CONSENT AND REVIEW COMMITTEES

All subjects must provide written informed consent in accordance with the local investigational center's EC rules and regulations. A copy of the consent form from each center must be forwarded to the Investigation Sponsor for review and approval prior to submitting it to the institutional review committee. Each center must provide the Investigation Sponsor with a copy of the investigational center's EC approval letter (stating at a minimum, the clinical investigation name or identification number, protocol revision being approved and an approval date) and the informed consent prior to the initiation of enrollment at that center. If yearly approvals for the continuation of the investigation at each investigational center are required, they must also be forwarded to the Investigation Sponsor.

If national or regional EC requirements are less strict than the requirements of ISO 14155:2011, the Sponsor will apply the ISO14155:2011 requirements to the greatest extent possible, irrespective of any lesser requirements, and shall record such efforts.

15.5 INVESTIGATOR RESPONSIBILITIES

15.5.1 GENERAL DUTIES

The investigator shall ensure that all work and services described herein, or incidental to those described herein, shall be conducted in accordance with the highest standards of medical and clinical research practice and the applicable regulations. The investigator shall be responsible for the day to day conduct of the clinical investigation and for the safety and well-being of human subjects enrolled. The investigator will provide copies of the current clinical protocol to all staff responsible for conduct of the clinical investigation.

The principal investigator is responsible for obtaining EC approval to start the clinical investigation at his/her investigational center.

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

15.5.2 INVESTIGATOR RECORDS

The principal investigator will maintain the accurate, complete, and current records relating to participation in this clinical investigation. Records including eCRFs and supporting data including hardcopies of all blood and diagnostic exams, signed Clinical Investigation Agreement, protocols and protocol amendments, signed informed consents, use of devices, EC approval letters, EC submissions, correspondence, including required reports and other documents pertaining to the conduct of the clinical investigation must be kept on file by the investigator. If the investigator(s) wishes to assign the files to someone else or remove them to another location, he/she should consult with the Investigation Sponsor in writing as to this change. Files for the clinical investigation must be maintained in a known location until the Investigation Sponsor notifies the investigator in writing that he/she may discard them.

15.5.3 INVESTIGATOR REPORTS

The principal investigator will prepare and submit the following accurate and complete reports to the Investigation Sponsor and EC in a timely manner:

- Unanticipated adverse device effects (UADE) occurring during the clinical investigation will be reported as soon as possible, but no later than 10 working days after the principal investigator first learns of the event.
- Serious adverse device effects (SADE) occurring during the clinical investigation will be reported as described in Section 11.1.
- Deviation from the clinical protocol (investigational plan) to protect the subject's life or physical well-being in an emergency will be reported to the Investigation Sponsor and the EC within 5 working days.
- Use of devices without informed consent will be reported to the Investigation Sponsor within 5 working days after the use occurs.
- Investigator will inform Edwards of any new information about the investigation that may affect the health, safety or welfare of the subjects or which may influence their decision to continue participating in the investigation. Investigator is also responsible to inform the affected subject in writing. If relevant, all affected subjects will be asked to confirm their continuing informed consent in writing.
- A final written report is submitted to the Investigation Sponsor and the EC within three months of completion or termination of the investigation.
- Upon request by a reviewing EC or the pertinent regulatory agencies, the principal investigator will provide current information about any aspect of the investigation.

15.6 INVESTIGATION SPONSOR RESPONSIBILITIES

15.6.1 GENERAL DUTIES

As the sponsor of this clinical investigation, Edwards Lifesciences has the overall responsibility for the conduct of the clinical investigation, including assurance that the investigation meets the regulatory requirements of the pertinent regulatory agencies. In this clinical investigation, Edwards Lifesciences will have certain direct responsibilities and will delegate other responsibilities to an Echocardiography Core Laboratory.

15.6.2 SELECTION OF INVESTIGATORS

Edwards Lifesciences will select qualified investigators and will ship investigational devices to participating investigational centers only. Edwards Lifesciences will obtain signed investigator agreements and provide the Investigators with the information and supplies necessary to conduct the clinical investigation.

15.6.3 MONITORING THE CLINICAL INVESTIGATION

Edwards will ensure compliance with the signed investigator's agreement, the protocol (investigational plan), the requirements of applicable regulations and guidelines (see section 15.1), and any conditions of clinical investigation approval by the EC and regulatory bodies per written monitoring procedures.

Edwards will conduct and immediate investigation of any unanticipated adverse device effects (UADE) and if an event is found to present an unreasonable risk to subjects participating in this clinical investigation. Edwards will inform the Investigator of any new information about the investigation that may affect the health, safety or welfare of the subjects or which may influence their decision to continue participating in the investigation. Investigator will be responsible to inform the affected subject in writing. If relevant, all affected subjects will be asked to confirm their continuing informed consent in writing.

15.6.4 SPONSOR RECORDS

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

15.6.5 SPONSOR REPORTS

Edwards Clinical Research will prepare and submit the following accurate and complete reports to the EC and the pertinent regulatory agencies in a timely manner:

- Withdrawal of EC approval will be reported to all EC and the pertinent regulatory agencies within 5 working days of receipt of withdrawal of approval.
- Withdraw of the pertinent regulatory agencies approval will be reported to investigational centers and EC within 5 working days after receiving the notice of approval withdrawal.
- Current investigator list will be submitted to the pertinent regulatory agencies at 6-month intervals.
- Progress reports to the EC at least annually and to the pertinent regulatory agencies as required.
- A final written report is to be completed and submitted to the EC and the pertinent regulatory agencies within six months after completion or termination of the investigation.
- Use of the devices without informed consent will be reported to regulatory authorities within 5 working days after notification of device use.
- Upon request by a reviewing EC or the pertinent regulatory agencies, Edwards will provide current information about any aspect of the investigation.

15.7 MODIFICATIONS

Changes in the protocol may be made only by written amendment agreed upon by the sponsor, the regulatory agency, and if pertinent, the EC. As appropriate, the Investigation Sponsor will submit changes in the protocol to the pertinent regulatory agencies and investigators to obtain EC re-approval.



15.8 CLINICAL INVESTIGATION COMPLETION OR TERMINATION AND CLOSE-OUT

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

15.9 AUDITS AND INSPECTIONS

In the event that audits are initiated by the sponsor or national/international regulatory authorities, the investigator shall allow access to the original medical records and provide all requested information.

15.10 PUBLICATION POLICY

At various milestones in the TRITON investigation, including the conclusion, it is intended that multi-center papers will be published, in peer-reviewed scientific journals and scientific meetings. These publications/presentations will be co-ordinated by Edwards via the Principal Investigator.

Publication or presentations of the investigators site-specific study results of devices which have not been market released will require the review of Edwards regarding proprietary information which shall not be divulged. If requested by Edwards, investigator will delay submission of such manuscripts for publication to permit preparation and filing of related patent applications. **Publication (abstracts and manuscripts) or presentation of the study results of market approved devices are subject to review by Edwards prior to submission or presentation. Edwards will review the manuscript within sixty (60) days after receipt.** If a multi-center publication is not issued after 1 year from the conclusion of the TRITON investigation (final database closure), single-center results may be published with review by Edwards within 30 days of submission. Exceptions to this rule require prior approval from Edwards.

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