



## MISSION Registry

Assessing clinical outcomes using the EDWARDS  
INTUITY Elite Valve System in isolated AVR using  
**Minimally InvaSive Surgery In a EurOpean multi-  
ceNter**, active, post-market registry

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October 12, 2016



## CLINICAL PROTOCOL

### MISSION Registry

Assessing clinical outcomes using the EDWARDS INTUITY Elite Valve System in isolated AVR using Minimally Invasive Surgery In a European multi-center, active, post-market registry.

**Protocol No:** 2015-05  
**Protocol Revision:** C  
**Protocol Date:** 12 Oct 2016

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## SIGNATURE PAGE

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**Prepared by**

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## INVESTIGATOR SIGNATURE PAGE

### MISSION Registry

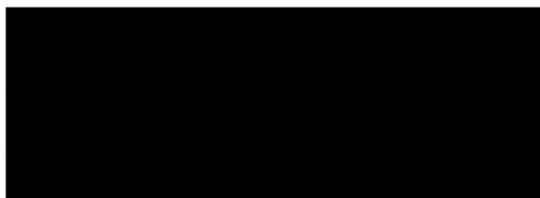
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#### Investigator's Signature

I have read and understand the contents of the attached clinical protocol, and agree to follow and abide by the guidelines set forth in this document.

#### Registry Principal Investigators:



20.10.2016

Date Signed



Date Signed

## INVESTIGATOR SIGNATURE PAGE

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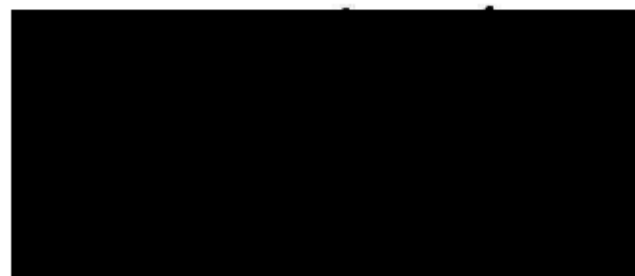
#### Investigator's Signature

I have read and understand the contents of the attached clinical protocol, and agree to follow and abide by the guidelines set forth in this document.

#### Registry Principal Investigators:



Date Signed



13.10.2016

Date Signed

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## 1. REGISTRY SYNOPSIS

REGISTRY NUMBER	2015-05
REGISTRY TITLE	Assessing clinical outcomes using the EDWARDS INTUITY Elite Valve System in isolated AVR using <u>Minimally Invasive Surgery</u> In a <u>EurOpean</u> multi-center, active, post-market registry (MISSION Registry)
PRODUCT NAMES	EDWARDS INTUITY Elite Valve System: EDWARDS INTUITY Elite Aortic Valve, Model 8300AB EDWARDS INTUITY Elite Delivery System, Model 8300DB
REGISTRY SPONSOR	[REDACTED]
SPONSOR REPRESENTATIVE	[REDACTED]
PRINCIPAL INVESTIGATOR	[REDACTED]

<b>DEVICE INTENDED USE</b>	The EDWARDS INTUITY Elite Valve System is indicated for patients whose aortic valvular disease is sufficiently advanced to warrant replacement of their native valve with a prosthetic valve.
<b>REGISTRY PURPOSE</b>	<p>This active, observational, open-label, non-randomized, post-market registry will describe in a real world cohort, procedural, clinical and hemodynamic outcomes of Minimally Invasive Surgery (MIS) for isolated Aortic valve Replacement (AVR) in the context of EDWARDS INTUITY Elite Valve System.</p> <p>Patient assessments will be done according to the sites standard of care.</p> <p>The MISSION registry will collect data only from patients receiving EDWARDS INTUITY Elite Valve System.</p> <p>The EDWARDS INTUITY Elite System has been designed to facilitate minimally invasive surgery (MIS) introduction of the bioprosthetic valve since there are only 3 guiding sutures and an expandable stent frame which contrast with conventional valves (e.g. Edwards Perimount or Edwards Magna Ease) which have multiple sutures and no expandable stent frame</p> <p>A previous study (CADENCE MIS) has compared MIS in the context of EDWARDS INTUITY Valve System with the use of conventional valves and full sternotomy approach. To date, there is no direct comparison available between EDWARDS INTUITY Elite Valve System and conventional valve in the MIS approach. The data from this one-arm registry with EDWARDS INTUITY Elite Valve System in MIS will be compared to a larger published cohort of patients who underwent AVR with conventional valve in the MIS approach (Merck<sup>21</sup>).</p> <p>The primary hypothesis of the registry is that EDWARDS INTUITY Elite reduces cross clamp time (XCT) as compared to conventional valves in MIS setting when compared to published data with a conventional valve in the same setting.</p>

<p><b>REGISTRY OBJECTIVES</b></p>	<p><b>Primary Objective:</b></p> <ul style="list-style-type: none"> <li>To describe procedural time (Cross Clamp Time) and to compare the Cross Clamp Time collected with EDWARDS INTUITY Elite in this registry to the largest published dataset with conventional valves within the MIS setting (Merck et al<sup>21</sup>). The published dataset will be used as a control group.</li> </ul> <p><b>Secondary Objectives:</b></p> <ul style="list-style-type: none"> <li>To describe short term (30 days) and long term (6 months) clinical safety</li> <li>To assess and compare hemodynamic data with EDWARDS INTUITY Elite to a conventional valve at discharge and at 6 months post AVR</li> <li>To assess Quality of Life at baseline and at 6 months post AVR</li> <li>To assess NYHA functional class at baseline, discharge and at 6 months post AVR</li> <li>To assess Fitness for hospital discharge</li> </ul>
<p><b>REGISTRY DESIGN</b></p>	<p>This multi-center registry is open-label, prospective, single arm and non-randomized.</p> <p>Baseline characteristics of subjects shall be collected. Risk scores (Euroscore I and II) will be collected by registry sites.</p> <p>Intra-operative data including cross-clamp time (XCT), bypass times, procedure times and first implant success will be recorded. The intensive care unit (ICU), total hospital durations and fitness to hospital discharge will be recorded. All adverse events will be recorded.</p> <p>Early postoperative (<math>\leq 30</math> days) safety data will be collected to evaluate short term outcomes.</p> <p>Quality of Life will be collected at baseline and 6 months (EQ-5D and SF-36).</p> <p>Follow-up data will be collected and evaluated at 6 months.</p> <p>All patient assessments will be done according to the sites standard of care.</p>

<b>NUMBER OF SUBJECTS</b>	Up to three hundred (300) subjects at up to thirty (30) investigational centers experienced with EDWARDS INTUITY ELITE.
<b>REGISTRY DURATION</b>	Estimated patient enrollment Start Date: February 2016  Enrollment period: February 2016- April 2017  Estimated patient Follow-up completion Date (6 months): October 2017
<b>REGULATORY STATUS</b>	CE-mark
<b>STUDY POPULATION</b>	Adult subjects with aortic stenosis or stenosis-based insufficiency that are scheduled to undergo elective isolated AVR by MIS procedure with EDWARDS INTUITY Elite.
<b>SURGEON and CENTER SELECTION CRITERIA</b>	<p>The data shall be collected during feasibility, and confirmed at the initiation visit:</p> <ul style="list-style-type: none"> <li>During the last 12 months (prior to initiation of the registry), Surgeon investigator will be required to have performed at least thirty (30) isolated AVR via MIS</li> </ul> <p><b>AND</b></p> <ul style="list-style-type: none"> <li>During the last 6 months (prior to initiation of the registry), surgeon investigator will be required to have performed at least five (5) MIS isolated AVR <u>or combined AVR</u> cases with EW Intuity Elite as primary operator</li> </ul>

<p><b>ELIGIBILITY INCLUSION CRITERIA</b></p>	<p>Subjects will be required to meet all inclusion criteria:</p> <ol style="list-style-type: none"> <li>1. Subject is 18 years or older</li> <li>2. Subject is symptomatic for aortic stenosis (AS) or mixed aortic stenosis and aortic insufficiency (AS/AI) disease for which isolated surgical aortic valve replacement without concomitant procedures is indicated according to International guidelines.</li> <li>3. Surgery starts with and is intended to be completed via a minimal invasive surgical approach. MIS is defined as a non-full sternotomy approach such as partial hemi-sternotomy, right anterior thoracotomy.</li> <li>4. Surgery is intended to be completed with an EDWARDS INTUITY Elite</li> <li>5. Subject has signed and dated the investigation informed consent forms prior to any registry-specific procedures are performed.</li> <li>6. Subject is geographically stable and agrees to attend follow-up assessments as specified in the protocol and informed consent.</li> </ol>
<p><b>ELIGIBILITY EXCLUSION CRITERIA</b></p>	<p>Subjects will not be eligible for registry participation if any of the following, or any contra-indications for use for the model 8300AB valve or model 8300DB delivery system, are present:</p> <ol style="list-style-type: none"> <li>1. Subject is diagnosed with pure aortic insufficiency.</li> <li>2. Subject requires multiple valve replacement/repair</li> <li>3. Subject has Type 0 congenital true bicuspid aortic valve (i.e. absence of raphe and commissures are positioned about 180 degrees apart) or unicuspid aortic valve.</li> <li>4. Subject has severe ventricular dysfunction defined as LVEF &lt; 25%.</li> <li>5. Subject has a history of active endocarditis and/or myocarditis <math>\leq</math> 3 months before the intended treatment/scheduled surgery.</li> <li>6. Subject has had an acute MI <math>\leq</math> 3 months before the intended treatment.</li> </ol>

	<ol style="list-style-type: none"> <li>7. Subject had a stroke or transient ischemic attack within six months prior to scheduled aortic valve replacement surgery.</li> <li>8. Subject is oxygen or ventilator dependent.</li> <li>9. Subject has life expectancy &lt; 12 months.</li> <li>10. Female subject is pregnant or lactating.</li> <li>11. Subject with documented leukopenia (WBC &lt; <math>3.5 \times 10^3/\mu\text{L}</math>), anemia (Hb &lt; 10.0 gm/dL or &lt; 6.2 mmol/L), thrombocytopenia (platelet count &lt; <math>100 \times 10^3/\text{mL}</math>), or history of bleeding diathesis or coagulopathy.</li> <li>12. Subject has renal insufficiency as determined by Serum creatinine <math>\geq 200 \mu\text{mol/L}</math> (2.27 mg/dL) at screening or end-stage renal disease requiring chronic dialysis.</li> <li>13. Subject is currently participating in an investigational drug or device trial for which follow-up has not yet been completed.</li> <li>14. Minimally Invasive access to the heart is not possible due to anatomical constraints or any other pre-existing condition.</li> <li>15. Aneurysm of the aortic root and/or ascending aorta</li> </ol>
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<b>INTRA-OPERATIVE EXCLUSION CRITERIA</b>	<ol style="list-style-type: none"> <li>1. Subject has Type 0 congenital true bicuspid aortic valve (i.e. absence of raphe and commissures are positioned about 180 degrees apart) or unicuspid aortic valve. (A non-congenital bicuspid valve without a distorted annulus would not be cause for exclusion.)</li> <li>2. Subject has calcium on the anterior mitral leaflet which cannot be removed.</li> <li>3. Subject has extensive calcification of the aortic root.</li> <li>4. Annular deformation which may or may not be caused by too extensive decalcification of the aortic annulus.</li> <li>5. The position of the coronary ostia relative to the EDWARDS INTUITY Elite Aortic Valve could result in obstruction of blood flow.</li> <li>6. Minimally Invasive access to the heart is not possible due to anatomical constraints or any other condition (including patient switched to a full sternotomy approach).</li> <li>7. The device is not available in the correct size for the subject.</li> </ol>
<b>SCHEDULE OF VISITS</b>	<ul style="list-style-type: none"> <li>• Pre-operative screening (Day -30 to Day -1)</li> <li>• Operative procedure (Day 0)</li> <li>• Discharge</li> <li>• Postoperative Day (POD) 30 (+/- 7days; by phone)</li> <li>• POD 180 (+/- 45 days), if applicable</li> </ul> <p>Patient assessments will be done according to the sites standard of care.</p>



<p><b>STUDY ENDPOINTS</b></p>	<p><b><u>Primary endpoint:</u></b></p> <ul style="list-style-type: none"> <li>• Cross clamp time</li> </ul> <p><b><u>Secondary endpoints:</u></b></p> <ul style="list-style-type: none"> <li>• Cardiopulmonary bypass time</li> <li>• Device technical success (defined as the successful delivery and deployment of a registry valve and delivery system and subject leaving the operating room with valve in place)</li> <li>• First Attempt Success Rate</li> <li>• ICU and Hospital Length of Stay</li> <li>• Hemodynamic performance (mean gradient, peak gradient, effective orifice area [EOA], EOA index, performance index, cardiac output [CO], cardiac index [CI], valvular regurgitation [including paravalvular leak] confirmed by an Echocardiographic Core Laboratory) at Discharge and 6 months (if available)</li> </ul> <p><b><u>Patient related endpoints:</u></b></p> <ul style="list-style-type: none"> <li>• NYHA functional class compared to baseline</li> <li>• Change in Quality of Life questionnaire SF-36 and EQ-5D from Baseline to 6 months (if available)</li> <li>• Fitness for hospital Discharge</li> </ul>
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	<p><b><u>Safety endpoints:</u></b></p> <p>Complication rates at 30 days (early rates) and at 6 months :</p> <ul style="list-style-type: none"> <li>• All cause mortality <ul style="list-style-type: none"> <li>○ Study valve-related mortality</li> </ul> </li> <li>• Thromboembolism <ul style="list-style-type: none"> <li>○ Stroke</li> <li>○ TIA</li> <li>○ Non cerebral embolism</li> </ul> </li> <li>• Valve Thrombosis</li> <li>• Major Bleeding event</li> <li>• Endocarditis (study valve)</li> <li>• Structural valve deterioration</li> <li>• Non Structural valve deterioration <ul style="list-style-type: none"> <li>○ Paravalvular Leak minor</li> <li>○ Paravalvular Leak major</li> <li>○ Other non SVD</li> </ul> </li> <li>• Hemolysis</li> <li>• Reoperation <ul style="list-style-type: none"> <li>○ Trial valve reoperation</li> </ul> </li> <li>• Study valve explants</li> <li>• Implant-related new or worsened cardiac conduction disturbance requiring permanent pacemaker implant</li> <li>• Renal Failure</li> <li>• Respiratory Failure</li> <li>• Deep Sternal Wound infection</li> </ul> <p>The Clinical Events Committee (CEC) will adjudicate the adverse events including adverse events resulting in death as outlined in their charter and adjudicate these events for their relatedness to the investigational device, and the investigational device procedure.</p>
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## 2. Introduction

### 2.1. Background

Aortic valve replacement with mechanical or biological heart valves is the treatment of choice for aortic valve stenosis. Over the past several years, life expectancy has increased in industrial nations, but this has been accompanied by a rising rate of elderly patients with multiple illnesses<sup>1</sup>.

Aortic stenosis remains the most common cause of adult valvular heart disease, the prevalence increasing with age<sup>2,3</sup>. Average survival of patients treated conservatively has historically been reported as 2–5 years from the onset of symptoms<sup>4</sup>. More recent studies have confirmed the dismal prognosis of severe aortic stenosis. Advanced age, reduced left-ventricular ejection fraction, congestive heart failure and renal insufficiency appear to be independent predictors of reduced survival<sup>5</sup>. Asymptomatic patients with very severe aortic stenosis also share a poor prognosis with a high event rate and a risk of rapid functional deterioration<sup>6</sup>. Early surgery offers a therapeutic option to improve clinical outcomes via decreasing cardiac mortality and improving symptoms<sup>7</sup>.

Bioprostheses offer several advantages over mechanical bioprostheses, the most important being freedom from anticoagulation with a low rate of thromboembolic accidents<sup>8</sup>. With increasing patient comorbidity and age, there is a tendency toward biological valve implants avoiding long-term anticoagulation.

Although conventional aortic valve replacement surgery is mostly performed via a full sternotomy surgical approach, minimally invasive aortic valve surgery, since its introduction in 1996<sup>9</sup>, has been gaining acceptance. Several studies have demonstrated reductions in hospital stay, duration of ventilatory support, incisional pain, blood loss and need for blood transfusions in patients undergoing minimally invasive AVR procedures<sup>10-17</sup>.

In response to clinical need and in support of advances in minimally invasive surgical approaches to conventional AVR, Edwards Lifesciences developed the EDWARDS INTUITY Valve System to achieve clinical benefits by reducing cardiopulmonary bypass and cross clamp times, while facilitating a less invasive approach to aortic valve replacement.

The system includes the EDWARDS INTUITY Elite Valve System, Model 8300AB and the EDWARDS INTUITY Elite Delivery System, Model 8300DB; the valve is based on prior heart valve designs which have a long history of safety and effectiveness and have incorporated additional features designed to improve patient outcomes and safety.

With only 3 guiding sutures and secure balloon expandable frame, the EDWARDS INTUITY Elite Valve system is well suited for smaller incisions and tight access, with an emphasis on procedural efficiency within existing operating suite of the surgeon.

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The EDWARDS INTUITY valve system facilitated AVR safely and effectively in multiple patient groups<sup>20</sup>. The successor valve system, EDWARDS INTUITY Elite, obtained CE mark in April 2014 and is the subject of this registry.

EDWARDS INTUITY has demonstrated in clinical trials safety and performance (TRITON study<sup>20</sup> and CADENCE-MIS study<sup>18</sup>). The CADENCE-MIS has compared EDWARDS INTUITY in MIS to conventional valves in FS. The results showed that RDAVR with EDWARDS INTUITY by the MIS approach was associated with significantly reduced myocardial ischemic time and better valvular hemodynamic function than FS-AVR with a conventional stented bioprosthesis<sup>18</sup>. Still there are no data comparing EDWARDS's INTUITY safety and performance in MIS to conventional valves in MIS.

## 2.2. Registry Purpose

This active, observational, open-label, non-randomized, post-market registry will describe in a real world cohort, procedural, clinical and hemodynamic outcomes of Minimally Invasive Surgery (MIS) for isolated Aortic valve Replacement (AVR) in the context of EDWARDS INTUITY Elite Valve System.

Patient assessments will be done according to the sites standard of care.

The MISSION registry will collect data only from patients receiving EDWARDS INTUITY Elite Valve System

A previous study (CADENCE MIS) has compared MIS in the context of EDWARDS INTUITY Valve System with the use of conventional valves and full sternotomy approach. To date there is no direct comparison available between EDWARDS INTUITY Elite Valve System and conventional valve in the MIS approach. The data from this one-arm registry with EDWARDS INTUITY Elite Valve System in MIS will be compared to a larger published cohort of patients who underwent AVR with conventional valve in the MIS approach (Merck et al<sup>21</sup>).

The primary hypothesis of the registry is that EDWARDS INTUITY Elite reduces cross clamp time (XCT) as compared to conventional valves in MIS setting, when compared to published data with a conventional valve in the same setting.

The data from this registry will be used to support submissions to articles and presentation in scientific journals and congresses, to support marketing information on the EDWARDS INTUITY Elite Valve system and to supplement post-market information on the EDWARDS INTUITY Elite Valve system when used as intended.

### 3. REGISTRY DEVICE

#### 3.1. Bioprosthesis

As seen in Figure 1, the EDWARDS INTUITY Elite Valve System (EDWARDS INTUITY Elite Valve System, Model 8300AB, also referred to as EDWARDS INTUITY Elite 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 patients with small aortic roots, the EDWARDS INTUITY Elite Valve has a low supra-annular profile height.



Figure 1 - EDWARDS INTUITY ELITE Valve System, Model 8300AB

As referenced in Figure 2, the bioprosthesis is 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 of the valve 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 of the valve is made of a cobalt-chromium alloy, a corrosion-resistant alloy, chosen because of its 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 in-growth 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. 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 to help prevent perivalvular leaks.

A holder is attached to the bioprosthesis by means of sutures to facilitate handling, attachment of the delivery system and valve deployment during implantation. The holder and delivery system are easily detached by the surgeon.

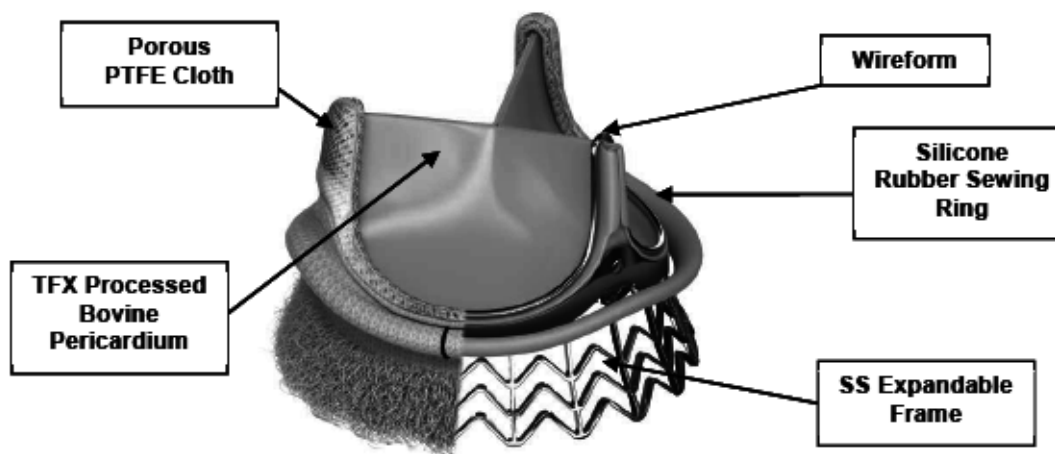


Figure 2 - COMPONENTS OF THE EDWARDS INTUITY ELITE VALVE

### 3.2. Delivery System

As seen in Figure 3, the EDWARDS INTUITY ELITE Delivery System, Model 8300DB consists of the 3 major components listed below:

- Insertion Tool/Balloon Introducer

- Balloon Catheter / malleable tubular handle shaft
- Inflation Device with Luer Connector

The Balloon Introducer and Insertion tool comes assembled and is used to remove the EDWARDS INTUITY Elite Valve 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.



Figure 3 - EDWARDS INTUITY ELITE Delivery System, Model 8300DB

The delivery system includes an integrated balloon catheter and malleable 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 frame. A tubular balloon introducer is attached when removing the valve from a storage jar and facilitates passage of the balloon through the valve. The malleable handle is made of aluminum and has chromate conversion coating applied over the entire surface of the part. The inflation device is used to pressurize and expand the balloon.

The balloon is inflated by injecting a saline solution through the luer. 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 aortic bioprosthesis (19, 21, 23, 25 and 27 mm).

### 3.3. Ancillary Products

The Carpentier-Edwards aortic valve sizer, Model 1133 is used to size the native annulus determining the needed bioprosthesis size. Model 1133 sizer is fabricated from translucent plastic to permit direct observation of their fit within the annulus. Each sizer consists of a handle with a barrel shaped configuration. 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).

### 3.4. Materials

All materials intended to come into contact with human subjects have been tested in accordance with ISO 10993 and are appropriate for their intended use.

## 4. RISK ANALYSIS

### 4.1. Potential Risks

The potential risks for the registry are the same as those for patients undergoing conventional AVR surgery. Key risks are listed below. Anticipated risks include listed complications and associated symptoms. As with all cardiac surgeries, serious complications, which can lead to death, may be associated with the procedure or use of the products, such as bioprosthetic heart valves and the heart valve replacement procedure. In addition, complications due to individual patient reaction to an implanted device, or to physical or chemical changes in the components, particularly those of biological origin, may occur at varying intervals (hours or days) necessitating reoperation and replacement of the prosthetic device. Risks associated with the use of the devices applicable in the registry can be found in the specific products Instructions For Use.

Risks associated with surgical replacement of the aortic valve may include but are not limited to the following:



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

- |   |  |
|---|--|
| <ul style="list-style-type: none"> <li>• Allergic reaction to valve materials</li> <li>• Angina</li> <li>• Annulus (damage, dissection, tear)</li> <li>• Aortic Insufficiency—Regurgitation/Stenosis</li> <li>• Aorta (damage, dissection, tear)</li> <li>• Blood - Coagulopathy</li> <li>• Blood - Hemolysis</li> <li>• Blood - Hemorrhage/anemia</li> <li>• Blood Pressure alteration (hypotension, hypertension)</li> <li>• Cardiac Arrest</li> <li>• Cardiac Arrhythmias/conduction disturbances</li> <li>• Cardiac Failure (heart failure)</li> <li>• Chordae Tendineae damage (Mitral valve)</li> <li>• Coronary artery Ostia blockage</li> <li>• Death</li> <li>• Endocarditis</li> <li>• Explant</li> <li>• Infection – local</li> <li>• Neurologic Events                         <ul style="list-style-type: none"> <li>– Stroke (CVA)</li> <li>– Transient Ischemic Attack (TIA)</li> </ul> </li> <li>• Reduced exercise tolerance</li> <li>• Thromboembolism</li> </ul> | <ul style="list-style-type: none"> <li>• Transvalvular or Valvular Leaking</li> <li>• Valve instability/ migration/ embolization</li> <li>• Valve dislodgement</li> <li>• Valve - Non structural dysfunction                         <ul style="list-style-type: none"> <li>– Paravalvular Leak</li> <li>– Leaflet impingement (Aortic or Mitral valve)</li> <li>– Leaflet tissue damage (instruments /sutures or pannus)</li> <li>– Subject Prosthesis Mismatch (PPM) (due to inappropriate sizing)</li> <li>– Distortion at implant</li> </ul> </li> <li>• Valve Structural dysfunction/deterioration (e.g., wear, leaflet tear, calcification, leaflet detachment from stent posts, component deterioration – physical or chemical)</li> <li>• Valve Thrombosis</li> <li>• Valve Wireform and or Frame Fracture or Distortion (from chest compression or trauma)</li> <li>• Valve stent fracture</li> <li>• Valve stent separation</li> <li>• Annulus frame fracture</li> <li>• Annulus frame separation</li> </ul> |
|---|--|

**Potential risks associated with aortic valve replacement surgery include:**

- |  |   |
|--|---|
| <ul style="list-style-type: none"> <li>• Allergic reaction</li> <li>• Annular dissection</li> <li>• Aortic or arterial dissection</li> <li>• Asystole and/or cardiac arrest</li> <li>• Bleeding                         <ul style="list-style-type: none"> <li>– Peri or post-procedural</li> <li>– Anticoagulant related</li> <li>– Pericardial tamponade</li> <li>– Hematoma</li> <li>– Cerebral vascular</li> </ul> </li> <li>• Cardiogenic shock</li> <li>• Disseminated intravascular coagulation (DIC)</li> <li>• Embolism, pulmonary</li> <li>• Esophageal tear/rupture</li> <li>• Heart failure</li> <li>• Hypo- or hypertension</li> <li>• Hypoxemia</li> </ul> | <ul style="list-style-type: none"> <li>• Infection: local, wound or systemic</li> <li>• Infection Septicemia: bacterial, viral, fungal</li> <li>• Myocardial infarction</li> <li>• Myocardial perforation, free wall</li> <li>• Multi-system organ failure (MOF)</li> <li>• Pericardial effusion</li> <li>• Pleural effusion</li> <li>• Pulmonary edema</li> <li>• Pneumonia</li> <li>• Renal failure, acute</li> <li>• Respiratory failure</li> <li>• Thrombocytopenia, (Non-HIT)</li> <li>• Thrombocytopenia, heparin induced (HIT)</li> <li>• Thromboembolism                         <ul style="list-style-type: none"> <li>– Venous, peripheral or central</li> <li>– Arterial, peripheral or central</li> <li>– Pulmonary, thrombus or other</li> </ul> </li> </ul> |
|--|---|

In addition to the above, the following are potential risks that could be uniquely associated with the EDWARDS INTUITY Elite Valve System:

- Trauma to the mitral chordae resulting from the delivery system
- Frame damage or under-flaring resulting in a reduction of effective orifice area
- Loss of frame structural integrity resulting in damage to aortic wall or aortic annulus
- 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 resulting in perivalvular leak requiring intervention or reoperation

Some or all of these risks may require reoperation, valve explantation, or may lead to permanent disability or death. All events related to the registry medical procedure or the valve and any post-operative cardiac related events will be collected and reviewed throughout the registry duration and follow-up period. Investigators will be notified of any additional risks identified during the registry that could affect the health, safety or welfare of the subjects in the investigation.

#### 4.2. Benefits

There are no guaranteed benefits to participation in this registry. Potential benefits associated with the use of the EDWARDS INTUITY Elite Valve above those for standard aortic valve replacement with any other commercially available valve may include:

- Reduction in morbidity and mortality
- Reduction in procedure time, cardiopulmonary bypass and aortic cross clamp time
- Reduction in procedure related complications
- Reduction in short and long term complications of AVR surgery

Additionally, information gained from participation in this registry may benefit other people with the same medical condition in future.

### 5. CLINICAL REGISTRY DESIGN

The registry is designed as active, multicenter, open label, and non-randomized. It will involve collection of prospective parameters routinely recorded during isolated aortic valve replacement (AVR) surgery.

All enrolled subjects will have assessment at the following intervals: pre-operative, operative, discharge, 30 days and 6 months post-implantation. A description of the follow-up visits and required registry procedures is included in sections 9 and 10 of this protocol.

Patient assessments will be done according to standard of care.

## 6. REGISTRY OBJECTIVES

### Primary Objective:

- To describe procedural time (Cross Clamp Time) and to compare the Cross Clamp Time collected with EDWARDS INTUITY Elite in this registry to the largest published dataset with conventional valves within the MIS setting (Merck et al <sup>21</sup>). The published dataset will be used as a control group.

### Secondary Objectives:

- To describe short term (30 days) and long term (6 months) clinical safety
- To assess and compare hemodynamic data with EDWARDS INTUITY Elite to a conventional valve at discharge and at 6 months post AVR
- To assess Quality of Life at baseline, and at 6 months post AVR
- To assess NYHA functional class at baseline, discharge and at 6 months post AVR
- To assess Fitness for hospital discharge

## 7. REGISTRY ENDPOINTS

### 7.1. Primary endpoint:

- Cross clamp time (cumulative XCT during the SAME operation should be recorded)

### 7.2. Secondary endpoints:

- Cardiopulmonary bypass time
- Device technical success rate (defined as the successful delivery and deployment of the valve and delivery system and subject leaving the operating room with valve in place)
- First attempt success rate
- ICU and Hospital Length of Stay
- Hemodynamic performance (mean gradient, peak gradient, effective orifice area [EOA], EOA index, performance index, cardiac output [CO], cardiac index [CI], valvular regurgitation [including paravalvular leak] confirmed by and Core lab evaluation) at Discharge and 6 months (if available)

### 7.3. Patient related endpoints:

- NYHA functional class compared to baseline
- Change in Quality of Life questionnaire SF-36 and EQ-5D from Baseline to 6 months, if applicable
- Fitness for hospital discharge.
  - The criteria for Fitness for hospital discharge <sup>19</sup> are:
    - Hemodynamic stability
    - Independent ambulation
    - No fever or obvious infections and wound clean
    - Independent feeding
    - Normal voiding
    - Pain control on oral medications
  - Meeting one criteria will provide one point to the score. The maximum is 6 points. According to this scoring system, the patient will be considered fit for discharge when the score is the maximum (i.e. 6). The post-operative day on which the patient meets the maximum score (i.e. 6) will be considered as the day at which the patient was fit for hospital discharge and will be recorded.
  - The composite score will be assessed on the day of discharge based on chart data.

### 7.4. Safety endpoints:

The safety endpoints consist of:

- All cause mortality
  - Study valve-related mortality
- Thromboembolism:
  - Stroke
  - TIA
  - Non cerebral embolism
- Valve Thrombosis
- Major Bleeding event
- Endocarditis (study valve)
- Structural valve deterioration
- Non Structural valve deterioration
  - Paravalvular Leak minor
  - Paravalvular Leak major
  - Other non SVD
- Hemolysis
- Reoperation
  - Trial valve reoperation
- Study valve explants

- Implant-related new or worsened cardiac conduction disturbance requiring permanent pacemaker implant
- Renal Failure
- Respiratory Failure
- Deep Sternal Wound infection

## 8. REGISTRY POPULATION

### 8.1. Demographic and clinical characteristics

Adult subjects, age 18 or older, that have been diagnosed with aortic stenosis or stenosis-based insufficiency and are scheduled to undergo surgical aortic valve replacement by MIS procedure are eligible for participation in this registry. Registry subjects shall be drawn from the general patient populations served by each investigational center. Candidates for this registry must meet all of the following inclusion criteria and none of the exclusion criteria.

### 8.2. Eligibility Inclusion Criteria

Subjects will be required to meet all inclusion criteria:

1. Subject is 18 years or older
2. Subject is symptomatic for aortic stenosis (AS) or mixed aortic stenosis and aortic insufficiency (AS/AI) disease for which isolated surgical aortic valve replacement without concomitant procedures is indicated according to International guidelines.
3. Surgery starts with and is intended to be completed via a minimal invasive surgical approach. MIS is defined as one of the following approaches: upper hemi-sternotomy and right anterior thoracotomy.
4. Surgery is intended to be completed with an EDWARDS INTUITY Elite
5. Subject has signed and dated the investigation informed consent forms prior to registry-specific procedures are performed.
6. Subject is geographically stable and agrees to attend follow-up assessments as specified in the protocol and informed consent.

### 8.3. Eligibility Exclusion Criteria

Subjects will **not** be eligible for registry participation if any of the following, or any contra-indications for use for the model 8300AB valve or model 8300DB delivery system, are present:

1. Subject is diagnosed with pure aortic insufficiency.
2. Subject requires multiple valve replacement/repair.

3. Subject has Type 0 congenital true bicuspid aortic valve (i.e. absence of raphe and commissures are positioned about 180 degrees apart) or unicuspid aortic valve.
4. Subject has severe ventricular dysfunction defined as LVEF < 25%.
5. Subject has a history of active endocarditis and/or myocarditis  $\leq$  3 months before the intended treatment/scheduled surgery.
6. Subject has had an MI  $\leq$  90 days before the intended treatment.
7. Subject had a stroke or transient ischemic attack within six months prior to scheduled aortic valve replacement surgery.
8. Subject is oxygen or ventilator dependent.
9. Subject has life expectancy < 12 months.
10. Female subject is pregnant or lactating.
11. 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  $< 50 \times 10^3/\text{mL}$ ), or history of bleeding diathesis or coagulopathy.
12. Subject has 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.
13. Subject is currently participating in an investigational drug or device trial for which follow-up has not yet been completed.
14. Minimally Invasive access to the heart is not possible due to anatomical constraints or any other pre-existing condition.
15. Aneurysm of the aortic root and/or ascending aorta

#### 8.4. Intra-operative Exclusion criteria

1. Subject has Type 0 congenital true bicuspid aortic valve (i.e. absence of raphe and commissures are positioned about 180 degrees apart) or unicuspid aortic valve. (A non-congenital bicuspid valve without a distorted annulus would not be cause for exclusion.)
2. Subject has calcium on the anterior mitral leaflet which cannot be removed.
3. Subject has extensive calcification of the aortic root.
4. Annular deformation which may or may not be caused by too extensive decalcification of the aortic annulus;
5. The position of the coronary ostia relative to the EDWARDS INTUITY Elite Aortic Valve could result in obstruction of blood flow.
6. Minimally Invasive access to the heart is not possible due to anatomical constraints or any other condition (including patient switched to a full sternotomy approach).
7. The device is not available in the correct size for the subject.

#### 8.5. Surgeon and center selection criteria

The data shall be collected during feasibility, and confirmed at the initiation visit:

1. During the last 12 months (prior to initiation of the registry), Surgeon investigator will be required to have performed at least thirty (30) isolated AVR via MIS

AND

2. During the last 6 months (prior to initiation of the registry), surgeon investigator will be required to have performed at least five (5) MIS isolated AVR or combined AVR cases with EW Intuity Elite as primary operator

### 9. REGISTRY PROCEDURES

#### 9.1. General

An overall summary of required procedures and evaluations can be found in Appendix A, "Table of Procedures and Flowchart". All registry data must be documented in the subject's medical records and will be transcribed on the standardized Case Report Forms.

#### 9.2. Surgeon and center selection criteria

The surgeon and center data shall be collected during feasibility, and confirmed at the initiation visit:

- Number of isolated AVR operations with EDWARDS INTUITY Elite as primary operator in the last 12 months.
- Number of minimally invasive isolated AVR operations as primary operator in the last 6 months.
- Number of MIS isolated AVR with EW Intuity Elite as primary operator in the last 6 months.

#### 9.3. Subject screening

The following subjects' information will be screened for eligibility:

- Subjects who have been diagnosed with aortic stenosis or stenosis-based insufficiency requiring isolated aortic valve replacement

- Subjects whose medical records indicate they are a suitable candidate for minimally invasive surgery
- Subjects whose treating physician is the Principle Investigator or a Sub-Investigator participating in the registry and has been trained on the EDWARDS INTUITY Elite Valve System

If all of the above criteria are met, a detailed review of the subjects' medical records will be performed to assess inclusion/exclusion criteria. This will be done before obtaining an informed consent from eligible patients or performing any registry-specific procedures.

A Screening/Enrolment Log will be provided to the registry centers to document all suitable consented and screened subjects (per the above 3 criteria) who were not eligible for the registry, specifying which inclusion or exclusion criteria was not met. The current Screening/Enrolment Log shall be submitted to the Sponsor at least once a month for the duration of the enrolment period.

#### 9.4. Informed Consent Process

The investigational center's Ethics Committee (EC) approved Informed Consent must be obtained from an eligible subject prior to collecting any registry-specific data. A sample informed consent is included in Appendix D.

Subjects who are eligible for participation in the registry shall be provided with the following explanations:

1. Background of the registry
2. Potential benefits associated with the use of the EDWARDS INTUITY Elite Valve and risks of the procedures involved
3. Follow-up visit requirements per the registry protocol

Each subject shall be given ample time to read the Informed Consent in its entirety and ask questions to make an informed decision.

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.

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.

The original signed informed consent will be retained by the investigator in the patient's hospital file. A copy will be provided to the patient.

A subject will be considered enrolled into the registry when he/she has signed the informed consent, met all the registry eligibility criteria.

At this point the patient will be assigned a unique identification number that must be entered on the registry Enrollment Log and this will be used on all registry documentation for that patient. Once a subject number has been assigned to a subject, it will not be reassigned to any other subject.

At this time point, data will be documented into the eCRF.

In the operating room, the intra-operative exclusion criteria will be assessed by careful examination of the valve anatomy, valve condition and associated structures. Any other intra-operative exclusion criteria or eligibility exclusion criteria may be assessed throughout the procedure.

Adverse events for enrolled patients are collected from the time the subject is in the operating room.

Enrolled patients, due to an intra-op Exclusion criteria can be excluded (defined as intra-op screen failure). The reason for ineligibility will be explained to them and will be documented into the eCRF. Subjects will then be followed by their primary health care provider per best medical practice.

#### 9.5. Pre-Operative Evaluations and Data Requirements

After a written informed consent has been obtained from the subject and a unique identification number has been assigned, the following test are conducted according to standard of care.

- **Medical history:** Pre-existing cardiac conditions, previous cardiac surgery, and other relevant medical conditions specifically end stage renal disease (ESRD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), diabetes mellitus, peripheral artery disease (PAD), hypertension
- **Valve pathology:** Stenosis, regurgitation, congenital anomaly, rheumatic, endocarditis, myocarditis
- **Baseline characteristics, vital signs and risk stratification:** height, weight, heart rate, blood pressure, NYHA classification, LVEF , Logistic Euroscore I and II, demographics (DOB, gender)

- Pregnancy Test : Required for female subjects who are not post-menopausal or surgically sterile
- ECG 12 lead
- Echocardiography data will be collected (if available) and CD will be sent to CoreLab
- Anticoagulation therapy
- Coagulation profile if patient is being treated with a Coumadin derivation medication (INR and PT)
- Blood: RBC, WBC, HGB, HCT, Reticulocytes, Platelet counts, Serum Creatinine (if available per standard of care)
- QoL (EQ-5D and SF-36)

#### 9.6. Operative Procedures

In the operating room, the intra-operative and eligibility exclusion criteria will be assessed by careful examination of the valve anatomy, valve condition and associated structures.

All data collected on the operative procedure will be documented into the eCRF. Subjects will be prepped for a minimally invasive surgical approach used for isolated aortic valve replacement. Minimal invasive surgery (MIS) is defined as a non-full sternotomy approach such as partial hemi-sternotomy and right anterior thoracotomy.

A detailed description of device preparation and use is provided in the Instructions for Use (See Appendix I for both the EDWARDS INTUITY Elite Valve, Model 8300AB and EDWARDS INTUITY Elite Delivery System, Model 8300DB. Investigators will be advised of the EDWARDS INTUITY Elite Valve System device preparation and use techniques per the Instructions for Use (IFU) during the mandatory training program.

The procedure will be considered a technical success if the subject leaves the Operating Room with the EDWARDS INTUITY Elite valve in place.

The procedure will be considered a procedural success in case of 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, within discharge or 10 days post index procedure whichever comes first.

The number of attempts (maximum 2) and final outcome of each EDWARDS INTUITY Elite Valve placement attempt shall be documented on the Device Performance form in CRF.

#### 9.6.1. OPERATIVE DATA COLLECTION REQUIREMENTS

The sponsor will provide a worksheet to note the various activities throughout the procedure. These data will be transferred to the procedure CRF.

- Intra-operative eligibility criteria (Aortic valve anatomy, Aortic valve condition (annulus/leaflets), condition of surrounding structures)
- Procedure Date
- Procedure Time: Cross Clamp Time (XCT), Cardiopulmonary Bypass Time(CPB)
- Surgical Approach (partial hemi-sternotomy or right anterior thoracotomy) and whether conversion to full sternotomy was required
- Implant Data: Valve Model, Serial Number and Valve Size
- Delivery System: Model, Serial Number and Size
- Suture Technique
- Implant Attempts
- Technical Success
- Final Device Implanted
- Implant Evaluation
- Intraoperative Adverse Events/ Complications
- Ventilation time

The subjects for which an EDWARDS INTUITY Elite Valve is attempted, but not successfully implanted or the minimally invasive surgical approach is converted to a full sternotomy after the valve implant procedure is initiated will be followed for 30 days post valve implant procedure. The discharge visit, 30 days FU Phone visit and adverse events if applicable will be collected. The subject will be exited from the registry at after the 30 days FU Phone visit or not until all adverse events associated with the above scenarios' are resolved. Once subjects have completed safety follow-up, they should be exited from the registry.

#### 9.6.2. POST PROCEDURE SUBJECT MANAGEMENT

It is recommended that heart valve recipients are maintained on aspirin and oral anticoagulation, except when contraindicated, for 2 to 3 months after the index operation in accordance with the ACC/AHA 2006 Guidelines for the Management of Patients with Valvular Heart Disease [19]. However, the safety of anticoagulant therapy must be determined by the treating physician on an individual basis. Post implantation patient care will be conducted as per the site's routine procedure.

#### 9.7. Hospital Discharge

The clinical evaluation and data requirements for the registry subjects at the time of hospital discharge:

- Fitness for hospital discharge

- Length of stay: Total length of stay in hospital and duration in ICU
- Disposition at hospital discharge: home, rehabilitation unit
- Adverse Events: Post-operative procedure or cardiac related events that resulted in medical or surgical intervention; all other serious adverse events per investigators decision using the available adverse event code list will also be collected
- Medical examination: NYHA classification, weight
- ECG 12 lead
- Echocardiography data will be collected (if available) and CD will be sent to CoreLab
- Anticoagulation therapy
- Coagulation profile, if patient is being treated with a coumadin derivation medication (INR and PT)
- Blood Studies: RBC, WBC, HGB, HCT, Reticulocytes, Platelet counts, Serum Creatinine (if available per standard of care)

## 9.8. Follow-up Visits Registry Procedures

### 9.8.1. FOLLOW-UP VISIT WINDOWS

Post-procedure clinical evaluation will be performed on all enrolled subjects at 30-days and 6-months post-implant date. Follow-up at 30 days- will be conducted by phone. All follow-up data will be documented on the CRF.

Patient assessments will be done according to the sites standard of care.

It is important that the follow-up visit schedule is maintained as closely as possible for all subjects. Edward's recognizes that subjects may not be able to return for all scheduled visits at precisely the date required, and therefore, an acceptable window of time for the 30 day follow-up period is described in Table 1. Registry visits should be scheduled as close to the earliest portion of the window for the follow-up period so that cancellations and visit rescheduling can still be conducted within the required time period.

TABLE 1. SCHEDULED FOLLOW-UP VISIT DAYS AND APPLICABLE VISIT WINDOWS

Visit	Visit Window days	Timing from Implant (Day 0)
Screening		Day -30 to Day -1
Discharge		Post-op - Day of Discharge
POD 30	+/- 7	Day 23 to Day 37
POD 180 (if applicable)	+/- 45	Day 135 to Day 225

Protocol required registry follow-up not performed will be considered a missed visit.

#### 9.8.2. 30 DAYS FOLLOW-UP VISIT: REQUIRED PROCEDURES AND EVALUATIONS

The 30 day follow-up visit shall be performed by phone. The clinical evaluation and data requirements for the registry subjects at POD 30:

- Adverse Events: Post-operative procedure or cardiac related events that resulted in medical or surgical intervention; all other serious adverse events per investigators decision using the available adverse event code list will also be collected.
- NYHA classification

#### 9.8.3. 180 DAYS (6 MONTHS) FOLLOW-UP VISIT: REQUIRED PROCEDURES AND EVALUATIONS

The 6 month follow-up visit shall be performed at the investigational site, if applicable. The clinical evaluation and data requirements for the registry subjects at POD 180:

- Adverse Events: Post-operative procedure or cardiac related events that resulted in medical or surgical intervention all other serious adverse events per investigators decision using the available adverse event code list will also be collected.
- Medical examination: HR, BP, NYHA classification, weight
- ECG 12 lead
- Echocardiography data will be collected (if available and CD will be sent to CoreLab
- Anticoagulation therapy
- Coagulation profile: INR and PT

- Blood Studies: RBC, WBC, HGB, HCT, Reticulocytes, Platelet counts, Serum Creatinine (if available per standard of care)
- QoL (EQ-5D and SF-36)

#### 9.8.4. UNSCHEDULED VISITS

- Clinical follow up completed outside the follow up windows described above in table 1, or per local site standard of care, will be considered unscheduled visits. All available data from registry procedures performed during these visits, including clinical data will be documented on the CRF, as available.
- If a subject requires further evaluation for assessment of a cardiac related event, the visit will also be documented as an Unscheduled Visit. The investigator will determine what procedures are appropriate for adequate assessment of the possible clinical event. Relevant clinical data will be documented on the follow up assessment CRF.

#### 9.8.5. MISSED VISITS

The Investigator will make every attempt to follow the subjects and subjects will be encouraged by the Investigator to report any changes in contact information to the investigational center. Subjects will also be informed of the importance of returning for scheduled follow-up visits even if they are not experiencing any problems.

During the course of the registry, if a subject cannot be reached for a follow-up visit, the Investigator will document the efforts undertaken to contact the subject or the subject's primary health care provider on the CRF. At least three attempts must be made to contact a subject by telephone at different dates and times. 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.

#### 9.9. Subject Registry Exit

A subject may be exited from the investigation for the following reasons:

- Subject completes all investigation or safety follow-up visits
- Subject withdraws consent
- Subject death

- Index valve explant
- Investigator withdraws the subject
- Subject failed INTUITY ELITE attempt (after the 30 days FU phone visit)
- Conversion from MIS to full sternotomy approach (after the 30 days FU phone visit)

#### 9.9.1. SUBJECT REGISTRY COMPLETION

Registry subjects complete and exit from the registry when no additional follow-up visits, procedures, or data collection are required. Once participation is completed subjects will then continue to be followed by their primary health care provider per standard medical practice.

#### 9.9.2. SUBJECT VOLUNTARY WITHDRAWAL

Although all subjects are informed of their right to withdraw from the registry at any time, it is anticipated that such withdrawals will be infrequent. All measures should be taken by the Investigator and their staff to encourage patients to be available for required follow-up visit by phone at 30 days and return for required follow-up visit at 6 months post-procedure. The registry objective may be jeopardized if large numbers of patients are lost to follow-up.

All patients are expected to continue in the registry until Edwards notifies the Investigator in writing that further follow-up is no longer required, except in the event of death or upon the subject's written request for early withdrawal from the registry. A copy of the withdrawal request should be forwarded to sponsor via the monitor for documentation.

#### 9.10. Subject death

In the event of subject death, every effort should be made to obtain a copy of the autopsy report, death certificate and/or death summary, if applicable. Information on the cause of death and its relationship to the registry device will be evaluated and reported by the Investigator.

#### 9.11. Index Valve Explant

Explant is defined as a re-intervention resulting in removal of the implanted valve after the patient left the operating room with an implanted valve, after the index procedure

If a registry subject requires explant of an EDWARDS INTUITY Elite Valve due to a complication, data will be documented on the Device Explant CRF and Adverse Event CRF forms.

After the EDWARDS INTUITY Elite Valve has been explanted, the subject should be followed for safety for 30-days post-explant or until the complication related to the explant is resolved. Once subjects have completed safety follow-up, they should be exited from the registry.

Every effort should be made to return the explanted EDWARDS INTUITY Elite Valve, at autopsy or explantation to Edwards Lifesciences. The explanted valve should be placed in a container with a suitable histological fixative such as 10% formalin or 2% glutaraldehyde immediately after excision. Refrigeration is not necessary under these circumstances. The Investigator should contact the local clinical specialist for further instructions for return of recovered bioprostheses.

#### 9.11.1. EDWARDS INTUITY ELITE VALVE INTRA-OPERATIVE REMOVAL

Intra-operative removal is the removal of the registry valve before the index EDWARDS INTUITY Elite Valve System procedure was completed (the patient was not transported from the operating room after the index implant procedure). The subject will be followed for 30 days post the surgical procedure (including discharge and 30 days FU visits)

During the index operation, should removal of the registry valve be required after the frame was expanded, the surgeon should use a scalpel to cut the retaining sutures on the valve holder to enable removal of the valve holder and complete delivery system. Next, insert a nerve hook through the outflow aspect of the registry valve. The surgeon should engage the expanded frame with the nerve hook and gently pull the frame inward. Then, surgeon should 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.

#### 9.11.2. EDWARDS INTUITY ELITE VALVE EARLY POST-OPERATIVE EXPLANT

Explant of EDWARDS INTUITY Elite Valve is the removal of the registry valve after the index EDWARDS INTUITY Elite Valve System procedure is completed and the patient is physically transported from the operating room with an implanted valve in place. The valve is explanted by accessing the aortic valve site and exposing the valve. Once exposure has been achieved, the surgeon should use a scalpel to cut the three sutures in the inter-commissural region on the sewing cuff of the valve. Once the three sutures have been removed, the surgeon should perform a circumferential blunt dissection around the registry valve. Once a blunt dissection is complete, use forceps to grasp the valve at the commissure and lift the study valve upward from the annulus.



### 9.11.3. EDWARDS INTUITY ELITE VALVE – LATE POST-OPERATIVE EXPLANT (>30 DAYS)

During the late post-operative period, explantation of the study valve may require that the device and surrounding anatomy be assessed using echocardiography, x-ray, or visually to determine the most appropriate course of action.

### 9.12. Reoperation/reintervention on the valve without Valve Explant

Reoperation on the registry valve can also occur without a need of the valve removal.

Any percutaneous interventional procedure that repairs, otherwise alters or adjusts a previously implanted prosthesis (registry valve) after the valve was implanted and the patient left the operating room are considered reoperation. In non-surgical category all enzymatic, balloon dilation, interventional manipulation, prosthetic valve PVL fixation, repositioning, or retrieval, and other catheter-based interventions for valve related complications are also considered re-interventions.

### 9.13. Operative intervention not on the registry valve

If a registry subject experiences complications or otherwise requires additional unplanned operations or interventions, these data should be captured on the Adverse Event CRF forms where applicable in the intervention taken section.

The Adverse Event code should reflect the cause of the intervention

## 10. Data collection and documentation

### 10.1. Data collection methods

All required data for this investigation are to be collected with standardized Case Report Forms (CRFs) for individual subjects. Electronic CRFs will be utilized for this investigation. CRFs must be electronically signed by the Principal Investigator or co-Investigator listed in the Delegation of Authority Log. If for any reason the CRFs 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 patient chart and operation worksheet (source document). CRFs must be kept current to reflect subject status during the course of the investigation.

Data should be captured in the Case Report Form (CRF) **within 2 weeks** of the patient visit.

CRF instructions will be provided to assist the Investigator(s) and appropriate investigation staff in the completion of the required CRFs.

#### 10.2. Source documentation requirements

Regulations require that Investigational centers maintain information about any clinical investigation subject's medical records that reflect the data collected in the CRFs. In order to comply with these regulatory requirements, the following information will be maintained as required by the 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 CRFs for further information, if appropriate (for specific results of procedures and exams).
4. Notations on abnormal lab results and adverse events reported and their resolution.
5. Notes regarding concomitant anticoagulant/antithrombotic medications taken during the clinical investigation
6. Subject's condition upon completion of or withdrawal from the clinical investigation.
7. Source documents related to reported safety endpoints or potential safety endpoints, and device related events, including documentation from outside admissions (admissions not at the enrolling site)

#### 10.3. Quality control and quality assurance procedures

Data Management personnel will employ a full-featured, relational 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 or that of the sponsor's designee.

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. An audit trail will identify all corrections and changes to the electronic data.

Queries or discrepancies will be entered to clarify discrepancies in the data entered on the CRF. Direct queries to the study coordinator via e-mail or phone are also allowed, but should be documented.

#### **10.4. Protocol Deviations**

The protocol deviations are defined as deviations in the informed consent improperly obtained (not signed & dated, not consented); inclusion/exclusion criteria (eligibility and intra-operative criteria); Safety as UADE / USADE not reported within 24 hours of the investigator first learning of the event without documentation.

### **11. Adverse Events**

#### **11.1. General Reporting Requirements**

The EDWARDS INTUITY Elite is CE marked; therefore all adverse events should be recorded in accordance with Medical Device Directive 93/42/EEC, MEDDEV 2.12-1 Guidelines on a Medical Devices Vigilance System, ISO 14155:2011(E), and any other regulations as applicable, and as summarized in Table 2.

Adverse event reporting is an investigator's responsibility and decision. Adverse Events (AE) will be identified and captured on the AE CRF throughout the duration of the registry as they occur and will be followed until they are adequately resolved or explained.

In MISSION Registry, all Serious Adverse Events and Device/Procedure Related Events should be reported as soon as possible but no later than within 72 hours (3 calendar days) after the Investigational center first learns of the event.

All Device-Related Deaths and all Unanticipated Adverse Events (not listed in the risk section of the protocol or IFU) or Serious Device-Related Adverse Events should be reported within 24 hours after the investigational center first learns of the event.

Relevant source documents will be provided to Sponsor for evaluation and endpoints adjudication within 15 working days after the Investigational center first learns of the event. That includes source documents records from outside admissions (hospitalizations out of the enrolling site), which are related to reported adverse events/complications.

Notification to the Sponsor should be done via electronic data system by entering an adverse event into the database or if that's impossible an initial notification can be done by fax or email to the assigned Safety personnel

Fax: 0041 22 787 4324

In addition, investigational centers are responsible for reporting serious adverse events to their local Regulatory Bodies in accordance with the applicable requirements.

## 11.2. ADVERSE EVENTS COLLECTED FOR THIS REGISTRY – REGISTRY ENDPOINTS:

All Registry Endpoints and Potential Endpoints will be adjudicated (reviewed) by an independent CEC committee

TABLE 2. SAFETY ENDPOINTS DEFINITIONS

<u>Complication</u>	<u>Definition</u>
All-cause mortality	All cause mortality includes all expirations of registry subjects as reported from investigational sites/or adjudicated per CEC
Registry valve-related mortality	Any death caused by structural valve deterioration, nonstructural dysfunction, valve thrombosis, thromboembolism, bleeding event, or operated prosthetic valve endocarditis; death related to reintervention on the operated valve; or sudden, unexplained death (when the cause of death has not been determined by clinical investigation or autopsy findings and the relationship to the operated valve is undefined)  Deaths caused by heart failure in patients with advanced myocardial disease and satisfactorily functioning cardiac valves are not counted.
Hemolysis	Plasma-free hemoglobin > 40 mg/dl on two consecutive measurements within 48 hours; or clinical diagnosis of hemolysis evidenced by laboratory testing such as serum hemoglobin, hematocrit, and/or plasma-free hemoglobin (not immunologically based) and/or hemolysis diagnosed elevated serum lactate dehydrogenase ( $\geq 440$ U/L) and/or reduced serum haptoglobin ( $\leq 37$ mg/dL) in the absence of paravalvular leak
Prosthetic Valve Endocarditis	Operated Valve Endocarditis is any infection involving a valve on which an operation has been performed. The diagnosis of operated valve endocarditis is based on one of the following criteria: <ul style="list-style-type: none"> <li>reoperation with evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies</li> </ul>

	<ul style="list-style-type: none"> <li>autopsy findings of abscess, pus, or vegetation involving a repaired or replaced valve; or</li> <li>in the absence of reoperation or autopsy, fulfilling the Duke Criteria for endocarditis (Am J Med 1994; 96:200-9)</li> </ul> <p>Positive blood cultures are not required for the diagnosis of operated valve endocarditis. Culture-negative endocarditis should refer only to negative blood cultures results and not just the absence of any proof of infection. Morbidities associated with active infection, such as valve thrombosis, thrombotic embolus, bleeding event, or paravalvular leak are included under this category, but not counted in other categories of morbidity.</p>
Thromboembolism (Stroke, TIA and Non-Cerebral Thromboembolic Event)	<p>Embolism is any embolic event that occurs in the absence of infection (endocarditis) starting from anesthesia time. Embolism may be manifested by a neurologic event or a non-cerebral embolic event.</p> <p>A neurologic event includes any central, new neurologic deficit, whether temporary or permanent and whether focal or global, that occurs <u>after anesthesia was administered</u>.</p> <p>Stroke is a prolonged (&gt;72 hours) or permanent neurologic deficit that is usually associated with abnormal results of brain magnetic resonance imaging or computed tomography. Patients with minimal, atypical, or protean symptoms that lead to radiographic imaging demonstrating an acute ischemic event are considered to have sustained a stroke.</p> <p><b>Transient Ischemic Attack (TIA)</b> is characterized by fully reversible symptoms of short duration. If radiographic imaging demonstrates an acute central neurologic lesion ("cerebral infarction with transient symptoms"), however, such patients are reclassified as having sustained a stroke. ‡ Multiple or repeated transient events occurring during a short period (a burst or cluster) should be recorded as one event, but documented as a "cluster".</p> <p>The diagnosis of a TIA is defined as complete resolution of new neurological symptoms usually within 1-2 h but always within 24 h and also requires a normal neuroimaging registry and the absence of any other primary medical cause (hypoglycemia, hypoxia, etc.)</p> <p><b>NON-CEREBRAL EMBOLIC EVENT</b></p> <p><b>Non-cerebral embolic event</b> is an embolus documented operatively, at autopsy, or clinically that produces signs or symptoms attributable to complete or partial obstruction of a <u>peripheral artery, excluding deep venous thrombosis (DVT)</u>. Emboli consisting of confirmed/documented nonthrombotic material (e.g., atherosclerosis, myxoma) are not counted. If unable to determine the material then it will be considered embolic.</p>

	Intraoperative myocardial infarctions are <u>not</u> counted. Postoperative myocardial infarction is also not counted unless the infarction is caused by a coronary thromboembolism (as detected by operation, autopsy, or clinical imaging).
Major Paravalvular Leak	Major Paravalvular Leak is any paravalvular leak, exclusive of that associated with thrombosis or infection, that leads to intervention or re-operation (with or without symptoms), or that is graded 3+ or greater (with or without symptoms and with or without intervention/ re-operation), or that results in death, or that is 3+ or greater when diagnosed by autopsy.
Major Bleeding	<p>Major bleeding is bleeding that causes death, hospitalization, or permanent injury (e.g. vision loss) or requires transfusion of 3 or more units of PRBCs.</p> <p>Major bleeding unexpectedly associated with <u>minor trauma</u> should be reported as a bleeding event, but bleeding associated with <u>major trauma</u> or a <u>major operation</u> should not.</p> <p>Minor Trauma examples are subdural hematoma, IC bleed associated with fall, hematuria from catheter</p> <p>Major Trauma/Major Operation examples are a fracture, CT surgery. These will be noted but do not count as events for the analysis.</p> <p>All bleedings requiring hospital admission such as an admission for GI Bleeding, Access Site Hematoma or other source of bleeding should be reported as Major Bleeding.</p>
Reoperation (on the registry valve)	<p>Re-intervention is any surgical or percutaneous interventional procedure that repairs, otherwise alters or adjusts, or replaces a <u>previously</u> implanted prosthesis or repaired valve (registry valve). In addition to surgical reoperations, enzymatic, balloon dilation, interventional manipulation, repositioning, or retrieval, and other catheter-based interventions for valve related complications are also considered re-interventions. Indications for re-interventions must be reported. Open surgical and percutaneous catheter re-interventions should be listed separately.</p> <p><u>An explant</u> is defined as a re-intervention resulting in removal of the implanted valve after the patient leaves the operating room with an implanted valve, after the index procedure.</p>
Renal Failure	An acute event or worsening of renal function resulting in one or more of the following: 1) Increase of serum creatinine to >2.0 mg/dL, and 2x most recent preoperative creatinine level. 2) A new requirement for dialysis postoperatively
Respiratory Failure with need for mechanical ventilation (Post index procedure)	Respiratory event requiring endotracheal reintubation and ventilator support post index procedure.

New or worsening implant related conduction disturbance requiring a permanent pacemaker implantation	Any new or worsened implant-related cardiac conduction disturbance requiring implantation of permanent pacemaker.
Valve thrombosis	Any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Valve thrombus found at autopsy in a patient whose cause of death was not valve related or found at operation for an unrelated indication should also be reported as valve thrombosis.
Deep sternal wound infection	Deep sternal wound infection involving muscle, bone, and/or mediastinal contents confirmed by positive tissue cultures and requiring intervention (wound opening and excision of tissue ; or re-exploration for washout and treatment) and systemic antibiotics.
Structural Valve Deterioration	Structural valve deterioration includes dysfunction or deterioration involving the operated valve (exclusive of infection or thrombosis), as determined by re-operation, autopsy, or clinical investigation. Clinical investigation should include periodic echocardiographic surveillance. Substantially increased regurgitation or stenosis of the operated valve over time should be reported with quantitative or semi-quantitative methods. The term structural valve deterioration refers to changes intrinsic to the valve, such as wear, fracture, poppet escape, calcification, leaflet tear, stent creep, and suture line disruption of components of a prosthetic valve; it also refers to new chordal rupture, leaflet disruption, or leaflet retraction of a repaired valve.
Non Structural Valve Deterioration	Any abnormality not intrinsic to the valve (do not directly involve valve components) itself that results in stenosis or regurgitation of the operated valve or hemolysis (excludes thrombosis and infection). Examples include: Entrapment by pannus, tissue, or suture, paravalvular leak, inappropriate sizing, inappropriate positioning, Regurgitation as a result of technical error, STJ dilation, dilation of the valve annulus, obstruction of the coronary ostia by the registry valve.

### 11.3. Adverse Event Categorization

TABLE 3. ISO 14155:2011- ANNEX F - ADVERSE EVENT CATEGORIZATION

Adverse Event	Non-Device Related	Device or Procedure Related
Non-Serious	Adverse Event (AE)	Adverse Device Effect (ADE)
Serious	Serious Adverse Event (SAE)	Serious Adverse Device Effect (SADE)
		<ul style="list-style-type: none"> <li>Anticipated Serious Adverse Device Effect (ASADE)</li> </ul>

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		<ul style="list-style-type: none"> <li>Unanticipated Serious Adverse Device Effect (USADE)</li> </ul>
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#### 11.4. Adverse Event Definitions

##### 11.4.1. ADVERSE EVENT DEFINITION (AE)

An adverse event (AE) is defined in ISO 14155:2011 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 device.

##### 11.4.2. ADVERSE DEVICE EFFECT (ADE)

An adverse device effect is defined in ISO 14155:2011 as any adverse event related to the use of an investigational medical device. This definition includes:

- Adverse event resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device
- Any event resulting from use error or from intentional misuse of the investigational medical device.

##### 11.4.3. SERIOUS ADVERSE EVENT (SAE)

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

- Led to death
- Led to a fetal distress, fetal death or a congenital abnormality or birth defect
- Led to a serious deterioration in the health of the subject, that either resulted in:
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function, or
  - in-patient hospitalization or prolonged hospitalization of existing hospitalization, or
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function

**NOTE:** Planned hospitalizations and procedures scheduled before the patient is enrolled in the registry for a pre-existing condition without serious deterioration in health should not be reported.

##### 11.4.4. SERIOUS ADVERSE DEVICE EFFECT (SADE)

A serious adverse device effect is defined as an adverse device effect that results in any of the consequences characteristic of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

##### 11.4.5. ANTICIPATED AND UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECTS (ASADE/USADE)

Anticipated adverse events are device- or procedure-related complications that are expected to occur in subjects undergoing aortic valve replacement and concomitant procedures, and that have been identified as potential risks in this investigational



plan, the risk analysis report or in product labeling (Section 4.1: Risks) If these events are deemed to be serious, they should be reported as Anticipated Serious Adverse Device Effects.

Unanticipated adverse device effect (USADE) is defined in ISO 14155:2011 as any serious adverse effect which by its nature, incidence, severity or outcome has not been identified in the risk analysis report.

#### **11.4.6. DEVICE DEFICIENCY AND MALFUNCTION**

Device deficiency is defined in ISO 14155:2011 as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labeling. Device malfunction is defined in ISO 14155:2011 as a failure of an investigational device to perform in accordance with its intended purpose when used in accordance with the Instructions For Use (Appendix I)

## **12.Statistical Analysis**

This trial is a multi-center, active and non-randomized registry, with maximum planned enrollment up to 300 patients to receive the EDWARDS INTUITY Elite Valve System through a minimally invasive incision. The following sections detail the statistical analysis for this registry.

### **12.1. ANALYSIS COHORTS**

There will be two analysis cohorts for this registry: the enrolled and the per protocol cohort. The following two sub-sections contain the definition for these two cohorts.

#### **12.1.1. ENROLLED COHORT**

A subject will be considered enrolled into the registry when he/she has signed the informed consent, met all the registry eligibility criteria.

#### **12.1.2. PER PROTOCOL COHORT**

The per protocol cohort will consist of all enrolled patients that leave the operating room with the registry valve in place and had an AVR MIS surgery procedure. All summaries of the safety endpoints and other safety data will be based on the per protocol cohort. The summaries of the primary, secondary and patient related endpoints will also be based on the per protocol cohort.

## 12.2. PERFORMANCE DATA

### 12.2.1. CROSS CLAMP TIME

Cross clamp time will be summarized by central tendency and variability estimators such as mean, median, standard deviation and interquartile range.

Cross clamp time collected with EDWARDS INTUITY Elite valves from the registry will be compared to cross clamp time derived from published data in conventional valves using an MIS approach via a two-sided student's t-test.

Merck et al<sup>21</sup> have published to date the largest European dataset on Cross Clamp Time with conventional valves within the MIS setting and this dataset will be used as a comparator.

Cross Clamp time will be stratified by surgical approach (i.e. Upper Hemi-Sternotomy and Anterior Right Thoracotomy). If necessary, other potential confounding factors will be adjusted for using appropriate statistical modeling techniques.

### 12.2.2. CARDIOPULMONARY BYPASS TIME

Cardiopulmonary bypass time will be summarized by central tendency and variability estimators such as mean, median, standard deviation and interquartile range.

### 12.2.3. DEVICE TECHNICAL SUCCESS AND PROCEDURAL SUCCESS

The number and percentage of enrolled patients experiencing device technical success and procedural success will be calculated.

### 12.2.4. HEMODYNAMIC PERFORMANCE

The following parameters will be summarized (mean, median, standard deviation and interquartile range) at baseline, Discharge and 6 month Follow up visits for all subjects in the study valve population: mean gradient, peak gradient, effective orifice area (EOA), EOA index, performance index, cardiac output, cardiac index, valvular regurgitation (including paravalvular leak), end systolic and end diastolic left ventricular volumes. Valvular regurgitation will be summarized by the number and percentage of subjects in each level of regurgitation. An analysis stratifying by valve size will also be performed.

### 12.2.5. LENGTH OF HOSPITAL STAY AND TIME IN INTENSIVE CARE UNIT

The length of hospital stay and length of time in intensive care unit will be summarized (mean, median, standard deviation and interquartile range) for the enrolled cohort.

## 12.3. SAFETY DATA

- All cause mortality
  - Study valve-related mortality
- Thromboembolism (Stroke, TIA, and Non cerebral embolism)
- Valve Thrombosis
- Major Bleeding event

- Endocarditis (study valve)
- Structural valve deterioration
- Non Structural valve deterioration
  - Paravalvular Leak minor
  - Paravalvular Leak major
  - Other non SVD
- Hemolysis
- Reoperation
  - Trial valve reoperation
- Study valve explants
- Implant-related new or worsened cardiac conduction disturbance requiring permanent pacemaker implant
- Renal Failure
- Respiratory Failure
- Deep Sternal Wound infection

Early adverse events within 30 days of procedure will be reported as the number of events divided by the number of enrolled subjects. Linearized rates will be used to summarize adverse events for the late (>30 days) post-operative period. The linearized rates will be calculated as the number of late events divided by the total number of late-subject years.

Percentages for the early events and linearized rates for the late events also will be calculated for all other complications observed in the trial.

Actuarial rates based on the method of Kaplan - Meier will be calculated for each of the safety endpoints at thirty days and six months; the number of subjects at risk for death will be reported at each of these intervals.

On top of Implant-related new or worsened cardiac conduction disturbance requiring permanent pacemaker, the counts and percentage of subjects who experience new or worsening cardiac rhythm or conduction disturbances will be calculated at each follow-up visit. The identification of "new and worsening" cardiac rhythm or conduction disturbance will be based on a comparison to the previous visit.

#### 12.4. MISSING DATA

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

#### 12.5. SAMPLE SIZE

The sample size of 300 patients has been calculated to ensure that the test of the primary hypothesis in the registry has sufficient power. For the purposes of a power

calculation, we assume the data follow a t-distribution with a 15 minute reduction in cross-clamp time in the EDWARDS INTUITY ELITE group as compared to the cohort published in Merck et al; if a larger reduction is assumed, the power of the statistical test would of course be higher. The cohort of MIS patients in Merck et al. has a total of 479 patients with a mean cross-clamp time of  $59.4 \pm 16.0$  minutes. Assuming a 5% false positive rate, the test of the primary hypothesis has greater than 90% power.

### **13.EXTERNAL REGISTRY RESOURCES**

#### **13.1. Clinical Events Committee**

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

#### **13.2. Echocardiography Core Laboratory**

An Echocardiography Core Laboratory will be used to evaluate all Doppler Echocardiograms. The purpose of the Core Lab is to ensure unbiased, timely and consistent analysis of this diagnostic data. The Core Lab is responsible for evaluating subject echocardiograms and notifying the site and sponsor of any changes in patient status over the course of the registry based on serial studies in the same patient. The personnel at the Core Lab will have training and experience appropriate for analyzing Doppler echocardiography data. Edwards will ensure that Core Lab personnel are familiar with the valve. Edwards or its designee will perform audits of the Core Lab. Edwards' technical personnel and the CEC will review the data provided by the Core Lab as appropriate.

An echocardiography guideline for this registry will be provided to all participating centers (see Appendix H).

#### **13.3. Electrocardiogram Core Laboratory**

An Electrocardiogram Core Laboratory will be used to evaluate all electrocardiograms done per standard of care. The purpose of the Core Lab is to ensure unbiased, timely and consistent analysis of this diagnostic data. The Core Lab is responsible for evaluating subject electrocardiograms and notifying the site and sponsor of any changes in patient status over the course of the registry based on serial studies in the same patient. The personnel at the Core Lab will have training and experience appropriate for analyzing electrocardiograms' data. Edwards will ensure that Core Lab

personnel are familiar with the valve. Edwards or its designee will perform audits of the Core Lab. Edwards' technical personnel and the CEC will review the data provided by the Core Lab as appropriate.

#### 14. ETHICAL and REGULATORY CONSIDERATIONS

The registry will be conducted in compliance with the regulations set forth in Table 4 and with country specific laws; whichever will afford greater protection to patients screened for participation in the registry and subjects who participate in the investigation.

TABLE 4 APPLICABLE REGULATIONS

Region	Post Market Regulations / Guidelines
Europe	ISO 14155:2011* (Clinical investigation of medical devices for human subjects) 2007/47/EC European Medical Device Directive (MDD) MedDev 2.12-1 Medical Devices Vigilance System Under directives 90/385/EEC and 93/42/EEC, Dec 2010. Med Dev 2.7.4 guidelines on clinical investigation: A guide for manufacturers and notified Bodies, Dec 2010 Med Dev 2.12.2 Guidelines on Post Market Clinical Follow-up Declaration of Helsinki

*\*Exception to ISO 14155:2011: All devices used in this study are CE marked therefore device accountability records will not be maintained.*

Furthermore, ICH E6 GCP Good Clinical Practices will be used for guidance. Principles protecting the rights, safety and well-being of human subjects, shall prevail over interests of science and society, and shall be understood, observed, and applied at every step in the clinical investigation.

The registry shall not begin until the required approval/favorable opinion from the Ethics Committee (EC) and applicable regulatory authorities have been obtained, where appropriate. Any additional requirements imposed by the EC or regulatory authorities shall be followed.

This registry does not include any subjects considered to be part of a vulnerable population (include the economically disadvantaged, racial and ethnic minorities, the uninsured, low-income children, the elderly, the homeless, those with human immunodeficiency virus (HIV), and those with other chronic health conditions, including severe mental illness).

All subjects should have a valid medical insurance coverage.

The process of informed consent shall be conducted per Section 9.4 specified above.

#### **14.1. Patient and Data Confidentiality**

Confidentiality of data shall be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access, and the privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data.

Registry subject identification will be kept confidential by the assignment and use of registry specific identification numbers. Each investigational center may maintain a separate patient identification log, however all registry documentation and/or medical records collected and used for registry purposes will be anonymized with the patient registry ID, so that an individual subject cannot be identified outside the registry.

The principal investigator or Institution shall also provide direct access to source documents from the subjects during and after the registry: for monitoring, audits, EC review and regulatory authority inspections.

Registry subject data may be inspected, reviewed, monitored or audited by the Sponsor, authorized representatives of the Sponsor and/or regulatory authorities.

Registry data may be maintained in a computerized database that shall comply with all applicable and current regulations. When electronic clinical databases or remote electronic clinical data systems are used, written procedures shall be implemented to;

- a) Establish and document requirements for the electronic clinical data system to receive and process data
- b) Verify and validate that the requirements for the electronic clinical data system can be consistently met
- c) Ensure attribute-ability, completeness, reliability, consistency and logic of the data entered
- d) Ensure accuracy of reports
- e) Ensure that data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail),
- f) Maintain a security system that prevents unauthorized access to the data, both internally and externally
- g) Maintain a list of individuals who have access to the electronic data system as well as the dates of access and privileges granted to each user
- h) Ensure that all completed CRFs are signed by the Principal Investigator or authorized designee
- i) Maintain adequate backup, retention and irretrievability of the data, and
- j) Train users on proper use of the system

#### **14.2. Ethical committee review of registry documents**

The registry shall not start until the required approval/favorable opinion from the Ethics Committee (EC) and/or Regulatory Authority has been obtained, where appropriate. Any additional requirements imposed by the EC or Regulatory Authority shall be followed.

A copy of the local consent form from each center must be forwarded to the Investigation Sponsor for review and approval prior to submitting it to the local EC.

Prior to the initiation at each center, a copy of the investigational center's EC approval letter (stating at a minimum, the clinical investigation name or identification number, protocol revision version and date being approved and an approval date) and the relevant information for the associated informed consent must provide the Investigation Sponsor. If yearly approvals for the continuation of the investigation at each investigational center are required, they must also be forwarded to the Investigation Sponsor.

In case of registry documents modifications, a registry amendment is required and the same document process and information must be completed.

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. INVESTIGATOR RESPONSIBILITIES**

#### **15.1. General Responsibilities**

The role of the investigator is to implement and manage the day-to-day conduct of the registry as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the registry. If the sponsor contracts an institution to conduct the clinical investigation, the institution shall appoint an appropriately qualified person to be the principal investigator, as follows:

- The investigators and clinical investigation personnel are assigned, are appropriately qualified, trained and are clearly able to understand the investigation,
- The investigators and clinical investigation personnel accept the obligations incurred in undertaking this clinical investigation.
- The Delegation of Authority form has been completed properly.

## **15.2. Investigator Qualifications**

Investigators shall be qualified by education, training and experience to assume responsibility for the proper conduct of the registry in accordance with ISO 14155:2011; evidence of such qualifications of the principal investigator and key members of the site team shall be provided to the sponsor through up-to-date CVs and other relevant documentation.

Investigators shall disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results. Investigators shall be knowledgeable with the method of obtaining informed consent.

Any personnel changes must be reported to the Sponsor immediately and a training program completed and documented before any registry procedures can be performed.

## **15.3. Site Qualification**

The Investigator shall be able to demonstrate that the proposed investigation site has the required number of eligible subjects needed within the agreed recruitment period and has one or more qualified investigator.

The investigator shall be able to apply to the surgeon and center selection criteria describe in Section 9.2.

In addition, the Investigator shall be able to demonstrate a qualified site team and adequate facilities for hosting regular monitoring visits for the foreseen duration of the registry.

## **15.4. Informed consent process**

The Investigator shall comply with the requirements specified in ISO 14155 Section 4.7, as well as, ensure compliance with the applicable regulatory requirements and ethical principles for the process of obtaining informed consent. In addition, the Investigator or designee shall ensure and document appropriate training to conduct the informed consent process.

## **15.5. Compliance with the Investigational Plan/Protocol**

The investigator shall:

- a) Indicate his/her acceptance of the Clinical Investigation Plan (CIP) in writing
- b) Conduct the clinical investigation in compliance with the protocol



- c) Create and maintain source documents throughout the clinical investigation and make them available as requested during monitoring visits or audits
- d) Ensure that the device is used solely by authorized users, and in accordance with the protocol and instructions for use
- e) Propose to the sponsor any appropriate modification(s) of the CIP or investigational device or of the use of the investigational device, refrain from implementing any modifications to the CIP without agreement from the sponsor, EC and regulatory authorities, if required
- f) Document and explain any deviation from the approved CIP that occurred during the course of the clinical investigation
- g) Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation
- h) Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable
- i) Ensure the accuracy, completeness, legibility and timeliness of the data reported to the sponsor in the CRFs and in all required reports
- j) Allow and support the sponsor to perform monitoring and auditing activities
- k) Allow and support regulatory authorities and the EC when performing auditing activities
- l) Ensure that all clinical-investigation-related records are retained during and after the clinical investigation as required by the applicable regulatory requirement(s) but for a minimum of two years after the clinical investigation is terminated or completed
- m) Sign the clinical investigation report, as specified in ISO 14155 Section 7.3

#### 15.6. Medical care of subjects

The investigator shall;

- a) Provide adequate medical care to a subject during and after a subject's participation in a clinical, investigation in the case of adverse events, as described in the informed consent [see ISO Section 4.7.4. f)]
- b) Inform the subject of the nature and possible cause of any adverse events experienced
- c) Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required
- d) Provide the subject with well-defined procedures for possible emergency situations related to the clinical investigation, and make the necessary arrangements for emergency treatment
- e) Ensure that clinical records are clearly marked to indicate that the subject is enrolled in a particular clinical investigation
- f) If appropriate, subjects enrolled in the clinical investigation shall be provided with some means of showing their participation in the clinical investigation,

together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided)

- g) Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation
- h) Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from the clinical investigation while fully respecting the subject's rights

#### 15.7. Safety reporting

The principal investigator shall;

- a) Record all cardiac-related adverse events and observed device deficiency, together with an assessment
- b) Report to the sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports
- c) Report to the EC serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the national regulations or CIP or by the EC
- d) Report to regulatory authorities' serious adverse events and device deficiencies that could have led to a serious adverse device effect, as required by the national regulations
- e) Supply the sponsor with any additional information related to the safety reporting of a particular event

#### 15.8. Ethics Committee Communication

The investigator shall;

- a) Provide the sponsor with copies of any clinical-investigation-related communications between the principal investigator and the EC
- b) Comply with the requirements described in ISO 14155 Section 4.5
- c) Obtain the written and dated approval/favorable opinion of the EC for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required
- d) Perform safety reporting as specified in ISO 14155 Section 9.8
- e) Promptly report any protocol deviations that affect the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances, if required by the EC or national regulations. In particular circumstances, the communication with the EC can be performed by the sponsor, partly or in full, in which case the sponsor shall keep the principal investigator informed.

## **16. Sponsor Responsibilities**

### **16.1. General Responsibilities**

As the sponsor of this registry, Edwards Lifesciences has the overall responsibility for the conduct of the registry, including assurance that the investigation meets the regulatory requirements of the pertinent regulatory agencies. In this registry, Edwards Lifesciences will have certain direct responsibilities and will delegate other responsibilities to appropriately qualified external resources.

### **16.2. Selection of investigators**

Edwards Lifesciences will select qualified investigators and will obtain signed investigator agreements and provide the Investigators with the information and supplies necessary to conduct the registry.

The sponsor will maintain an updated list of principal investigators, investigational sites, and institutions. This list will be kept separately from the CIP.

### **16.3. Monitoring the registry**

Edwards Lifesciences will ensure compliance with the signed investigator's agreement, the protocol (investigational plan), the requirements of applicable regulations and guidelines (see section 11.1) and any conditions of the registry approval by the EC and regulatory bodies per written monitoring procedures.

### **16.4. Site Initiation**

The monitor and/or Edwards clinical research designee shall initiate each investigation site to ensure that the principal investigator and investigational site team a) have received and understood the requirements and contents of CIP, the informed consent form, CRFs, the instructions for use, any written registry agreements, as appropriate, is familiar with the responsibilities of the principal investigator.

**NOTE** In certain circumstances, an investigator meeting can be conducted instead of, or in addition to, the on-site initiation visit.

### **16.5. Monitoring Visits**

The Investigation Sponsor will assign a clinical research associate to monitor the progress of the registry 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 consent is correctly documented, source verifying the data recorded on the CRFs, and visiting each investigational center periodically to observe investigation progress and compliance with clinical protocol and regulations applicable to this registry. Monitoring visits will be scheduled throughout the duration of the registry between the monitor and the principal investigator at a mutually convenient and available time.

The monitor shall verify that:

- a) Compliance with the protocol, any subsequent amendment(s), applicable Standards and regulatory requirements is maintained; deviations shall be discussed with the principal investigator(s) or authorized designee, documented and reported to the sponsor
- b) Only authorized individuals are participating in the registry, investigation site resources, including laboratories, equipment and the investigation site team, remain adequate throughout the duration of the registry
- c) The Principal Investigator continues to have access to an adequate number of subjects and investigational devices, signed and dated informed consent forms have been obtained from each subject at the point of enrolment or before any clinical-investigation-related procedures are undertaken
- d) Source documents and other registry records are accurate, complete, up to date, stored and maintained appropriately, CRFs and queries are complete, recorded in a timely manner, and consistent with source documents, appropriate corrections, additions or deletions are made to the CRFs, dated, explained if necessary and initialed by the principal investigator or by his/her authorized designee
- e) The monitor does not make corrections, additions or deletions to the CRFs
- f) Ensure safety reporting is performed according to the applicable regulations and requirements documented in this CIP, if required, reports, notifications, applications, submissions and correspondence are maintained in the investigator's files and are accurate, complete, timely, legible, dated and identify the registry
- g) Maintenance and calibration of the equipment relevant to the assessment of the registry is appropriately performed and documented, where applicable, current laboratory normal values, laboratory certifications, accreditations, or other validations are present in the investigator's file, if required
- h) Subject withdrawal has been documented; the monitor shall discuss this with the Principal Investigator or his/her authorized designee,
- i) Subject non-compliance with the requirements stated in the informed consent has been documented; the monitor shall discuss this with the principal investigator or his/her authorized designee,
- j) The Principal Investigator and investigation site team are informed and knowledgeable of all relevant document updates concerning the registry, and any corrective and preventive actions, as needed, have been implemented and are effective.

- k) The monitor will ensure that any new personnel are appropriately trained on registry procedures before participating in the registry and provide documentation of the training.

#### 16.6. Monitor Qualifications

Monitors shall be:

- a) Qualified in the field of the applicable Standards through training and experience as well as scientific or clinical knowledge
- b) Knowledgeable on the use of the investigational devices and relevant requirements, CIP and informed consent process, trained on the sponsor's clinical quality assurance and quality control system as well as any special procedures for monitoring a specific registry

Training shall be documented in the sponsor's files.

#### 16.7. Safety Evaluation and Reporting

The sponsor is responsible for the classification of adverse events and ongoing safety evaluation of the registry and shall;

- a) Review the investigator's assessment of all adverse events and determine and document in writing their seriousness and relationship to the device under registry; in case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to concerned parties
- b) Review all device deficiencies and determine and document in writing whether they could have led to a serious adverse device effect; in case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to concerned parties
- c) Verify or ensure the reporting, to the EC by the Principal Investigator(s), of all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by national regulations or the CIP or by the EC
- d) Report to regulatory authorities, within the required time period, all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by national regulations or the CIP
- e) Ensure that the EC and the regulatory authorities are informed of significant new information about the clinical investigation
- f) In case of serious adverse device effects and device deficiencies that could have led to serious adverse device effects, determine whether the risk analysis needs to be updated and assess whether corrective or preventive action is required

#### 16.8. Protocol 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 approval from the EC.

#### **16.9. Registry completion, termination and close-out**

The registry and site Principal Investigators will be notified in writing upon termination or conclusion of the registry. The Investigation Sponsor retains the right to suspend or terminate this registry at any time. The reason for termination will be communicated to sites and authorities as applicable.

The Sponsor shall;

- a) Ensure all registry close-out activities are properly conducted
- b) Provide a statistical analysis of the data
- c) Produce a registry report and submit it for review
- d) Ensure that the registry report, whether for a completed or prematurely terminated registry, is provided to the EC, participating Investigators and regulatory authorities, as required by national regulations

#### **16.10. Sponsor records**

Edwards Lifesciences will maintain accurate, complete, and current records relating to this registry. Records include CRFs, signed and dated Clinical Investigator Agreement, financial disclosure, protocols and protocol amendments, EC approval letters, EC submissions, correspondence, including required reports, and other documents. Edwards will maintain documentation during and after the registry as required by the applicable regulatory requirement(s) but for a minimum of two years after the registry is terminated or completed. Storage of the records may be designated to a third party.

#### **16.11. 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.

#### **16.12. Sponsor reports**

Edwards Lifesciences will prepare and submit the following accurate and complete reports to the Investigators, 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 as applicable
- Withdraw of the pertinent regulatory agencies approval will be reported to investigational centers and EC as applicable
- A current Investigator list will be submitted to the pertinent regulatory agencies at as applicable



- Progress reports to the Investigator for the EC 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 after completion or termination of the investigation as applicable
- Use of the devices without informed consent will be reported to relevant authorities as applicable
- Upon request by a reviewing EC or the pertinent regulatory agencies, Edwards will provide current information about any aspect of the investigation

#### **16.13. Regulatory Communications**

The sponsor shall, if required:

- a) Notify or obtain approval from regulatory authorities in the country where the registry is conducted, where applicable
- b) Report on the progress and status of the registry
- c) Perform safety reporting



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## 18. Appendices

### 18.1. APPENDIX A: Table of procedures and flowchart

Time Periods and Assessments	Preoperative	Operative	Discharge	30 Days (Phone)	6 Months ( 180 days)
Informed Consent	X				
Medical History Aortic Valve Etiology and diagnosis	X				
Inclusion Criteria / General Exclusion Criteria	X				
Medical Examination	X		X		X
Height	X				
Weight	X		X		X
Heart rate and Blood Pressure	X		X		X
NYHA	X		X	X	X
Demographics (DOB& gender)	X				
LVEF	X				
Logisitic Euroscore I and II	X				
Pregnancy test (If applicable) <sup>1</sup>	X				
Health care utilization (Length of stay ICU and war0064)			X		



Time Periods and Assessments	Preoperative	Operative	Discharge	30 Days (Phone)	6 Months ( 180 days)
Implant Procedural Data and timing		X			
Intra-operative Exclusion criteria evaluation		X			
12 Lead Electrocardiogram (EKG) <sup>2</sup>	X		X		X
Transthoracic Echocardiography and Doppler	X <sup>3</sup>		X <sup>4</sup>		X <sup>4</sup>
Current Anticoagulation Therapy	X		X		X
Coagulation profile: INR and PT <sup>5</sup>	X		X		X
Blood Studies RBC, WBC, HGB, HCT, Reticulocytes, Platelet counts, Serum Creatinine	X		X		X
Fitness for hospital discharge			X		
Quality of Life (QoL): EQ-5D SF-36	X				X
Adverse Events		X	X	X	X

1 - Pregnancy test is required for female subjects who are not post-menopausal or surgically sterile (urine)

2 - For EKG machine generated reports the Investigator must verify that the cardiac rhythm is correct and sign and date the final EKG report

3 - If available Pre-op echocardiography within 3 months of planned implant date and including echocardiographic data in the format required per the echocardiography guidelines

4 – If available echocardiography data will be collected

5 – Required only if patient is being treated with a coumadin derivation medication

## 18.2. APPENDIX B: registry abbreviations

Abbreviations of Terms			
ACC	American College of Cardiology	GCP	Good Clinical Practice
ADE	Adverse Device Effect	ICE	Intra Cardiac Echocardiography
AE	Adverse Event	IFU	Instructions for Use
AHA	American Heart Association		
AI	Aortic Insufficiency	LV	Left Ventricle
AS	Aortic Stenosis	LVEF	Left Ventricle Ejection Fraction
AVR	Aortic Valve Replacement	LVOT	Left Ventricular Outflow Tract
BMI	Body Mass Index	LVMI	Left Ventricular Mass Index
BSA	Body Surface Area	NSVD	Nonstructural Valve Dysfunction
		NYHA	New York Heart Association
		POD	Post Operative Days
CEC	Clinical Events Committee		
CHF	Congestive Heart Failure	PPM	Patient Prosthesis Mismatch
CI	Cardiac Index	PTFE	Polytetrafluoroethylene
CO	Cardiac Output	PVL	Perivalvular Leak
CPBT	Cardiopulmonary Bypass Time	SAE	Serious Adverse Event
eCRF	Electronic Case Report Form	SADE	Serious Adverse Device Effect
XCT	Cross Clamp Time	SF-36	Short Form-36 Health Survey
		SLDH	Serum Lactate dehydrogenase
EC	Ethics Committee	STS	Society of Thoracic Surgeons
ECG/EKG	Electrocardiogram	SVD	Structural Valve Deterioration
EOA	Effective Orifice Area	TEE	Transesophageal echocardiogram
EOAI	Effective Orifice Area Index	TTE	Transthoracic echocardiogram
EQ-5D	EU Quality of Life-5 Dimensions	USADE	Unanticipated Serious Adverse Device Effect
FMEA	Failure Modes and Effects Analysis		

### 18.3. APPENDIX C: Registry Definitions

**Device Explant** - Explant is defined as a re-intervention resulting in removal of the implanted valve after the patient left the operating room with an implanted valve, after the index procedure

**Device Deficiency** - Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. **NOTE:** Device deficiencies include malfunctions, use errors, and inadequate labeling.

**Device Removal** - The excision of the investigation bioprosthesis before the EDWARDS INTUITY Elite Valve System procedure was completed. The heart *was not* restarted with the bioprosthesis implanted. Patient still IN the operating room.

**EDWARDS INTUITY Elite Valve Device Technical Success** - The successful delivery and deployment of a registry valve and delivery system and subject leaving the operating room with valve in place.

**EDWARDS INTUITY Elite Valve Procedural Success** - is 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, within discharge or 10 days post index procedure whichever comes first.

**Enrollment cohort:**

A subject will be considered enrolled into the registry when he/she has signed the informed consent, met all the registry eligibility criteria.

**Implant failure** - is defined as a re-intervention resulting in removal of the implanted valve with the patient still in OR, after the index procedure

**Index Procedure** - Surgical replacement of the aortic valve.

**New York Heart Association Classification**

- Class I: Patients with cardiac disease but without resulting limitations of physical activity.
- Class II: Patients with cardiac disease resulting in slight limitation of physical activity. Patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina pain.
- Class III: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation dyspnea, or angina pain.

**Class IV:** Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

**Protocol deviations** - The protocol deviations are defined as deviations in the informed consent improperly obtained (not signed & dated, not consented); inclusion/exclusion criteria (eligibility and/or intra-operative criteria); safety as UADE / USADE not reported within 24 hours of the investigator first learning of the event without documentation.

**Pre-operative Screen Failure** - A patient with an ID number assigned, and who has signed his/her informed consent and does not meet all eligibility inclusion criteria or who meets at least one of the eligibility exclusion criteria.

**Intra operative Screen Failure** - A patient with an ID number assigned and who meets at least one of the intra-operative exclusion criteria.

**Subject** - A patient that signs an informed consent to participate in a clinical investigation.

**Subject Withdrawal** - A subject that decides not to participate in the investigation after signing an informed consent form.

**Per protocol cohort:** A subject will be considered enrolled into the registry when he/she has signed the informed consent, met all the registry eligibility criteria, and no intra-operative exclusion criteria; and leaves the operating room with the registry valve in place and had an AVR MIS surgery procedure.

**Withdrawal by Investigator** - A subject who consents to participate in the investigation but is withdrawn by the Investigator before or after enrollment in the investigation.

**Withdrawal** - Subjects may discontinue participation at any time by withdrawing informed consent.



## 18.4. APPENDIX D: SAMPLE INFORMED CONSENT FORM

### Master template

#### Patient information

CLINICAL REGISTRY NO. 2015-05:

EDWARDS MISSION Registry

**“Assessing clinical outcomes using the EDWARDS INTUITY Elite Valve System in isolated AVR using Minimally Invasive Surgery In a European multi-center, active, post-market registry”**

You are invited to take part in a clinical registry. This patient information explains why this clinical registry is being conducted and what it would mean for you if you decided to take part. Please read the following information carefully. You can also discuss this registry in detail with your family or your GP. If you are unclear about anything or would like more information, please consult your registry doctor. Give yourself time to decide whether or not you wish to take part. Your participation in this clinical registry is voluntary. If you decide to participate, we will ask you to sign this document in order to clarify your agreement.

This registry has been given a favorable opinion by the “Ethics Committee [enter name of EC]”. It will be conducted according to the regulations governing clinical research.

#### Introduction

The heart is a muscle that works like a pump, carrying the blood into the lungs and the entire body. In the heart there are 4 valves, which control the blood flow through the heart so that it flows in the correct direction. If a heart valve does not work correctly, the heart has to use extra effort in order to pump the normal amount of blood to the body. This may cause symptoms that are different depending on the valve that is affected and the amount of damage. Generally the symptoms are tiredness and difficulty in breathing, or even angina pectoris (heart pain) and fainting. If the damage is serious, surgery to take out the damaged valve and replace it with a new valve is required.

#### What is the purpose of this registry?

The EDWARDS INTUITY ELITE Aortic Valve System is a new biological valve that has recently become commercially available and is designed to be surgically implanted in a shorter time than the existing aortic biological valves. The purpose of this clinical investigation is to collect clinical data in order to confirm the safety and effectiveness of the EDWARDS INTUITY ELITE Valve System in a general patient population requiring aortic valve replacement (AVR).

Data collected in this clinical investigation will be used to support submissions to health economic agencies and to supplement post-market information on the EDWARDS INTUITY ELITE Aortic Valve system when used as intended.

#### Why am I being invited to take part in this clinical registry?



You are being asked to participate in this clinical registry because you have been found to have a damaged aortic valve and, in your doctor's view, could benefit from the implantation of a biological prosthesis.

Various biological heart valve prostheses from various manufacturers are currently available. In this registry, we will evaluate the biological aortic prosthesis "EDWARDS INTUITY ELITE" (already approved/authorized) in a general ('all comers') patient population undergoing aortic valve replacement (AVR) performed in accordance to the current standard of care. The surgical approach is at the discretion of your registry doctor and will be in a minimally invasive approach (MIS)

### Registry design

This clinical registry will be performed in at least 20 European hospitals. Up to 300 patients are planned to be enrolled.

You will be examined by your Registry doctor to determine your eligibility to take part in the Research Registry. The examination includes questions about your medical history, a physical exam and several routine tests that are required for your involvement in this Registry.

Your participation in the registry will last for a maximum of 6 months. All participants must attend registry visits at the hospital where the surgery was done and be checked by the doctor or his colleagues. You are asked to attend a registry visit at the hospital on being discharged and also at 6 months after the heart valve was implanted. A check-up at 1 month will be conducted on the telephone.

### Description of the EDWARDS INTUITY ELITE Aortic Valve prosthesis

The EDWARDS INTUITY ELITE Valve System, INTUITY ELITE Aortic Valve, Model 8300AB, has been approved for use in Europe.

The EDWARDS INTUITY ELITE heart valve combines the properties of two products already approved for the European market (CE mark) and frequently used in Europe: the Carpentier-Edwards PERIMOUNT Magna Ease 3300TFX valve (also known as Magna Ease) and the Sapien Transcatheter Heart Valve model 9000TFX (also known as Sapien). The valve has been designed to be more easily implanted for all aortic valve surgical techniques and in a shorter time than other traditional valves.

The main component of the EDWARDS INTUITY ELITE bioprosthesis is the Magna Ease valve, which obtained approval to be sold in Europe in 2006. Since then almost 14 000 patients have been implanted with this device. The Magna Ease valve consists of three tissue leaflets made of bovine pericardium that have been treated with the Carpentier-Edwards ThermaFix process, a proven treatment to stabilize and preserve the tissue.

The improvement compared with the Magna Ease valve consists of a stainless steel frame; this frame is the same used for the Sapien valve, a device approved to be sold in the European market in 2007 and that has been implanted successfully in more than 2 500 patients in Europe and Canada.

In the EDWARDS INTUITY ELITE valve, the frame, covered with a polyester cloth, is attached at the lower/inflow edge of the Magna Ease valve. This new design allows a faster implant than with the Magna Ease model, and the polyester cloth helps hold the valve firmly in place.





The EDWARDS INTUITY ELITE valve is mounted on a delivery system (a tool that the doctor uses to put the EDWARDS INTUITY ELITE valve in the right place in the heart). This delivery system consists of a handle and a balloon catheter. The balloon catheter is inserted into the handle of the delivery system and is inflated with saline solution in order to expand the EDWARDS INTUITY ELITE valve frame. The delivery system does not stay in your body after the surgery.

### **What will happen to me if I take part?**

If you agree to participate in this registry, you will be treated like any other patients undergoing a similar operation but you will also have some more tests (described below) to collect further information on the heart valve and the operation. Most of the tests and procedures are routine, but you will have them more frequently than normal. These tests are performed in order to assess your heart's condition and function before, during and after the surgery.

Participation is entirely voluntary.

Before your surgery, we will contact you in order to discuss the registry and answer all your questions. If you decide to participate, we will also ask you to sign and date this Patient Information and Informed Consent Form. A copy of this form will be given to you.

Your registry doctor will then ask you questions and perform some tests and procedures to see whether you can participate in the registry. These tests and procedures are described below:

- You will be given a preliminary examination to see whether you can take part in the registry.
- The doctor will go through your patient history with you.
- You will be given a physical examination (a clinical assessment of your condition), and any findings will be written down in the registry patient records.
- The severity of your health impairment will be graded according to your ability to do physical activities. The standardized NYHA classification is used for grading purposes.
- You will complete two questionnaires that will help your doctor determine your quality of life. It takes about 15 minutes to complete the questionnaires.
- You will have an echocardiogram (investigation of the heart by means of a device emitting ultrasound waves; the pictures are taken with a small probe that is put on the outside of your chest).
- You will have an electrocardiogram (ECG; recording of the electrical activity of your heart with an ECG device, with a self-adhesive electrode being attached to your chest).
- Your blood will be collected for laboratory testing. During the collection of blood, a needle will be put into a vein in your arm (or an accessible vein elsewhere). Approximately three teaspoons (15 ml) of blood will be drawn at this visit for routine tests. Any remaining blood sample will be discarded according to hospital regulations.
- If you are a woman of child-bearing age (and are not sterile), you will be asked for a small amount of urine so that a pregnancy test can be performed.

If the results of the tests and examinations do not meet the registry requirements and your doctor considers that you are not suitable to participate in the registry, you will be excluded from the registry and your doctor will discuss alternative treatment with you. No further commitments will then arise from this registry.



If, as a result of the above mentioned tests and examinations, your doctor considers that you are eligible to take part in the registry, an appointment for the operation will then be laid down for you.

The surgical procedure is performed under full anesthesia. The cardiac surgeon reaches the heart by making an incision in the chest and opening the sternum. The beating of the heart is stopped to do the valve implant, and continuation of blood circulation is ensured by a heart-lung machine. During the operation, an ultrasound probe may, prior to implantation of the heart valve, be passed through your mouth and advanced down the esophagus to the area of the heart ("transesophageal echocardiography"). The doctor takes pictures of your heart with this ultrasound device.

If, during surgery, your doctor finds a reason not to implant the EDWARDS INTUITY ELITE heart valve or considers that the requirements for the registry are not met, you will receive another equivalent aortic biological prosthesis approved for commercial use. You will then be excluded from the registry, and no further commitments will arise for you from this registry.

After the operation and before you go home, you will have some more tests and examinations as described below:

- A physical examination will be performed.
- An ECG (electrical recording of the heart)
- Your blood will be collected for laboratory testing in order to determine the best pharmacological treatment for you.
- An echocardiogram (an ultrasound investigation of the heart) will be performed to see that the newly implanted heart valve is in position and is working well.
- You will be asked if you have experienced any unusual symptoms or side effects since the procedure – any findings will be recorded to track your health status.
- An appointment will be scheduled for your next follow-up assessment approximately 1 month after your procedure date. The assessment will be performed via telephone.

At your check-up at one month, you will be asked to undergo the following procedures (this check-up is conducted on the telephone):

- Your health will be graded according to your ability to do physical activities (NYHA class).
- You will be asked if you have experienced any unusual symptoms or side effects since your last assessment.

You will be asked to provide information about your health status at your follow-up visits after 6 months. You will also undergo the following procedures:

- A physical examination
- A blood test
- An ECG (electrical recording of the heart)
- An echocardiogram (an ultrasound investigation of the heart)
- Your health will be graded according to your ability to do physical activities (NYHA class)
- You will complete two questionnaires which will help your doctor assess your quality of life. It takes about 15 minutes to complete the questionnaires

- You will be asked if you have experienced any unusual symptoms or side effects since your last assessment.

### Participant responsibilities

If you decide to participate in this clinical registry, you will have to follow the instructions given by your registry doctor and his colleagues and come back to the hospital for all the follow-up visits up to the six month of follow-up. The investigations after 1 month are conducted over the telephone. It is important that you attend all the registry visits to ensure that the registry results are complete and correct. If you would like to stop taking part in the registry or find that you have not kept to the above instructions, it is important that you inform the registry doctor or the registry personnel.

Your participation in this registry is **entirely voluntary**, and you are entitled to refuse to participate or withdraw your consent at any time without penalty or loss of benefits. You can withdraw from the registry at any time without giving reasons, even if you have consented in writing to take part. Your decision to withdraw will not have any adverse effect whatsoever on your further treatment at our hospital.

**Giving false, incomplete or misleading information about your medical history, including past and present use of medication, could have very serious consequences for your health. It is very important that you give a true and complete medical history.**

### What are the benefits of taking part in this registry?

It cannot be guaranteed that you will benefit from participation in this clinical registry. The following potential benefits may arise from participation in this clinical registry:

- improvement of the valve function
- acute alleviation of symptoms of aortic valve stenosis
- a shorter surgery time than for a procedure using similar/conventional products

Additionally, information gained from the performance of this registry may be of benefit to other people with the same medical condition in the future. Alternative therapies may be palliative drug therapy, balloon valvuloplasty of the aortic valve and surgical replacement of the aortic valve with another prosthesis.

### What are the risks of taking part in this registry?

You must understand that heart valve replacement is the treatment of choice for your condition and that various heart valves are available.

As with all heart valve prostheses, serious complications that can in some cases lead to death may arise. In addition, complications due to individual patient reaction to an implanted product or to physical or chemical changes in the components, particularly those of biological origin, may occur at varying intervals (hours or days) postoperatively that necessitate reoperation and replacement of the prosthetic device. These risks will be explained to you by your registry doctor. Should any side effects occur, they will be fully assessed and you will be monitored closely.

You may experience events and/or outcomes that may include the following:

- Allergic reaction to valve materials
- Angina pectoris (chest pain)
- Damage to the aortic wall or annulus

- Cardiac arrhythmias/disturbance of stimulus conduction (change in heart rhythm)
- Damage or injury to the tendinous cords (damage to the mitral valve structure)
- Occlusion of the coronary orifices
- Embolism of the aorta or the ventricle of the heart due to the bioprosthesis (slippage of the product from the original position in the aorta or in the left ventricle of the heart)
- Endocarditis (inflammation of the heart valve)
- Heart failure
- Hemolysis (rupturing of red blood cells, with the release of hemoglobin)
- Hemolytic anemia
- Bleeding in connection with the use of clotting inhibitors
- Impingement/regurgitation/abrasion of the mitral valve (damage to the mitral valve)
- Myocardial infarction
- Constriction of the prosthesis valve leaflet (hindering of valve closure, known as "impingement")
- Non-structural malfunction of the valve prosthesis
- Pannus formation on the prosthesis (excessive tissue growth around the heart valve)
- Paravalvular leakage from the prosthesis (blood reflux past the closed heart valve)
- Regurgitation at the prosthesis (blood reflux through the closed heart valve)
- Stenosis/reduction in the effective opening surface of the prosthesis (constriction of the heart valve)
- Structural modification of the heart valve (physical or chemical change in heart valve components)
- Prosthetic thrombosis (adherence of blood clots to the heart valve)
- Stroke or transitory ischemic attack (TIA)
- Side effects attributable to tissue changes: infection, calcification, thickening, perforation, degeneration, suture abrasion, damage to the valve by surgical instruments and detachment of a valve leaflet from the heart valve
- Thromboembolism
- Thrombotic occlusion

In addition to the above, the following potential risks uniquely related to the EDWARDS INTUITY ELITE Aortic Valve may include, but are not necessarily limited to, the following:

- Trauma of the mitral chordae resulting from the delivery system
- Frame damage or under-flaring resulting in a reduction of effective orifice area
- 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 resulting in perivalvular leak requiring intervention or reoperation to resolve
- Loss of frame structural integrity resulting in damage to aortic wall or aortic annulus

It is possible that these complications could lead to:

- Reoperation
- Explantation (removal of the heart valve prosthesis)
- Permanent disability
- Death



Where applicable, you will be able to inform the investigator of any new findings that could affect the benefit or safety of the registry and thus your consent to participation in the registry.

**What happens if I decide against participating in the registry?**

If you decide not to participate in the registry, you can discuss with your doctor which options of heart valve replacement best suit your requirements. A decision not to participate will not affect your future medical care in any way.

**What if problems arise?**

Your doctor and Edwards will make all appropriate efforts to prevent any injury or illness as a result of your participation in this registry. If you suffer any injury or illness as a direct result of participating in this registry, you will receive medical care and treatment at this hospital. Signing this consent does not affect any legal rights you have.

A product specific liability insurance has been concluded (Insurance policy number: [enter number]. Insurance company: [enter contact details].

Accordingly, please note the following insurance obligations:

- For the duration of the registry, you may undergo other medical treatment (except in emergencies) only by agreement with the investigational doctor
- Immediately report any deterioration in your health to the doctor, who will assess whether it is health damage that could have arisen as a result of the registry
- In the event of injury, authorize the doctors providing treatment to notify the insurer on request

You must inform the insurance company immediately of any health damage that could have arisen as a result of the registry. Such notification may also be provided by the doctor.

**Will my taking part in this registry be kept confidential?**

This section explains how your medical records and your health data may be used and passed on if you agree to participate in this registry.

All physicians involved in the registry follow a strict clinical protocol. You have the right to determine who has access to your health data. Medical records collected in this registry may include your medical history, the results of physical examinations, laboratory tests and other diagnostic and therapeutic procedures as specified above in this Patient Information, and basic demographic data.

By signing this form:

- You allow the registry staff and/or the registry doctor to use your medical records for the registry and to disclose your health data to the Sponsor, Edwards Lifesciences SA, or to the Sponsor's representatives so that the latter can review the results of the registry and monitor the safety of participants.
- You allow the registry doctor and/or sponsor to publish the results of the registry or discuss the results at conferences. If this is done, no information will be disclosed that would reveal your identity.

The information passed on by the registry doctor and/or registry staff will not include your name, address or any other personal identifiers. The registry doctor will use a coded number for the



records made available to the Sponsor. However, your entire medical records may be reviewed at your registry doctor's practice and/or hospital by the Sponsor and/or Sponsor representatives, by supervisory/government agencies and by the independent ethics committee (EC – a committee that has been formally set up to review and monitor studies involving human subjects). The purpose of these reviews is to ensure the quality of the registry.

The registry doctor and/or registry staff will make every effort to protect the confidentiality of your data. However, absolute confidentiality cannot be guaranteed because of the need to disclose information as described above.

There is no expiry date for this authorization to pass on data. If you do not cancel this authorization, it will remain in effect indefinitely.

You can cancel this authorization at any time by giving a written notice to the registry doctor. If you cancel this authorization, you will no longer be able to participate in the registry, and the data that has been collected prior to withdrawal of the authorization may still be used and disclosed to the above-mentioned parties. You will receive a copy of the signed consent for your records.

All data collected within the scope of this registry may be forwarded only in an anonymized form to other persons or institutions not authorized for direct data inspection.

### **Participation and withdrawal from the registry**

**You have the right to decide not to participate in this registry or to stop taking part in this registry at any time without any consequences for you. This means that you will not suffer any penalty or loss of medical benefits.**

If you stop taking part in this registry, you must first notify the registry doctor immediately so that your continued medical care can be planned. At the time you stop taking part in the registry, you will be asked to come for a final safety evaluation that will include gathering information about your current health and conducting any required procedures. For your own safety, you should go through the registry exit procedures any time you leave the study and make arrangements for your follow-up care.

It is possible that you may be withdrawn from the registry at any time without being asked. This may happen if you do not follow the instructions given by the doctor or if the doctor believes this to be in your best interest. The registry may also be stopped for administrative, medical or other reasons as determined by the doctor, Edwards Lifesciences SA, or the supervisory authorities in the countries in which this registry is conducted. You and your doctor will be notified of any relevant findings made in the course of this registry that might affect your willingness to participate.

While participating in this registry, you must not take part in any other registry. This is to protect you from possible injury that may arise.

### **Who is organizing and funding this registry?**

This registry is organized by Edwards Lifesciences SA the medical technology company manufacturing the EDWARDS INTUITY ELITE heart valve and the Sponsor of this registry.

The registry staff will not be paid for your inclusion in this registry but the hospital will be reimbursed for the costs incurred in conducting this registry.



### Costs and compensation

You will not be charged or compensated for your participation in this registry.

You will be reimbursed for the travel expenses you incur for the hospital follow-up visits required by the registry.

You must still bear the costs of your usual ongoing medical care, including procedures and/or medication not envisaged in the registry protocol. If you have any questions, please ask the doctor or a member of the registry staff.

### Contact details for further information

If you require any further information before or during the registry, or if you have any questions after you have read this Patient Information or in the event of injury, please contact your doctor responsible for you:

Telephone: \_\_\_\_\_

### Further information

**You consent to participate in a scientific registry and to the statistical analysis of the results of that registry. It is understood that your personal data continue to be subject to data protection and shall not be disclosed to any third parties. Participation in this registry is voluntary, and you can discontinue participation at any time without giving reasons, and without penalty. The Principal Investigator or the Sponsor may also decide on your premature withdrawal from this registry.**

### Informed consent form

**“Assessing clinical outcomes using the EDWARDS INTUITY Elite Valve System in isolated AVR using Minimally InvaSive Surgery In a EurOpean multi-ceNter, active, post-market registry.”**

### Signature of patient or his/her legal representative

I have received written information about the clinical trial or the information was read out to me. I had sufficient time to read this information and think about it. I was verbally informed in detail by the doctor about the nature, significance and scope of the clinical trial; in particular about the objectives, conduct, benefit, risk, insurance coverage including the associated obligations. All my questions were answered in an understandable way. I do not have any further questions at the moment but I know that I can ask questions at any time, including during and after the registry.

• I declare my voluntary consent to the clinical trial. I am aware that I can withdraw my consent at any time without incurring any disadvantages to my medical care.

- I confirm to have a personal medical insurance



- I agree that my medical data may be recorded in the context of this registry. I agree that my medical data may be forwarded in anonymized form to authorized specialists for data processing and scientific evaluation and to the competent authorities for review.
- I also agree to my health data being recorded in the context of this clinical trial and to representatives of the Sponsor or the competent authority inspecting these data for review purposes.
- Finally, I agree to scientific publication of the research results in compliance with provisions of data protection legislation.

☐ I agree / ☐ I do not agree that my GP may be informed about my participation in this registry.

<b>Name of registry participant (printed)</b>	<b>Date</b>	<b>Time<sup>1</sup></b>
---	-------------	-------------------------

\_\_\_\_\_  
**Signature of registry participant**

<b>Name of legal representative (if necessary; printed)</b>	<b>Date</b>	<b>Time<sup>1</sup></b>
---	-------------	-------------------------

\_\_\_\_\_  
**Signature of legal representative (if necessary)**

**Signature of investigator**

I have explained the registry to the patient or his/her legal representative and have answered all his/her questions. I have the impression that he/she understands the information contained in this document and gives his/her consent to participate of his/her own free will. The patient was given a copy of the signed consent form.

<b>Name of investigator (printed)</b>	<b>Date</b>	<b>Time<sup>2</sup></b>
---	-------------	-------------------------

\_\_\_\_\_  
**Signature of investigator**

\_\_\_\_\_  
**Clinic**

<sup>1</sup> Required only if the informed consent is signed on the same day as the procedure

<sup>2</sup> Required only if the informed consent is signed on the same day as the procedure



**Please keep a copy in the patient records and give the patient a copy.**

**18.5. Appendix E : Protocol deviation code list**

**1. Screening**

- 1.01 Patient did not meet eligibility inclusion criterion
- 1.02 Patient met eligibility exclusion criterion
- 1.03 Patient met intra-operative Exclusion criterion
- 1.04 Date of Informed Consent is after registry enrollment
- 1.05 Informed Consent was improperly obtained
- 1.06 Person obtaining Informed Consent did not sign /date the consent form
- 1.07 Informed Consent process collection was not properly documented
- 1.08 Screening other deviation, specify

**2. Adverse Events:**

- 2.01 UADE / USADE not reported within 24 hours of the investigator first learning of the event

## 18.6. APPENDIX F : EQ-5D questionnaire



### HEALTH QUESTIONNAIRE

Patient ID number: 2015-05 \_ \_ \_ \_

Date:    \_ \_ \_ / \_ \_ \_ / \_ \_ \_ \_  
          *dd*    *mmm*    *yyyy*

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

**Mobility**

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

**Self-Care**

- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

**Usual Activities** (*e.g. work, study, housework, family or leisure activities*)

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

**Pain/Discomfort**

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

**Anxiety/Depression**

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own  
health state  
today



## 18.7. APPENDIX G: SF 36 Questionnaire

## Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please tick the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year	About the Same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

3. The following questions are about activities you might do during a typical day.

Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, Not limited at all
	▼	▼	▼
• <u>Vigorous activities</u> , such as running, lifting heavy objects, participating in strenuous sports.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
• <u>Moderate activities</u> , such as moving a table, pushing a vacuum cleaner, bowling, or playing golf.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3
• <u>Lifting or carrying groceries</u> .....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3

- d Climbing several flights of stairs..... ☐ 1..... ☐ 2..... ☐ 3  
 e Climbing one flight of stairs..... ☐ 1..... ☐ 2..... ☐ 3  
 f Bending, kneeling, or stooping..... ☐ 1..... ☐ 2..... ☐ 3  
 g Walking more than a mile..... ☐ 1..... ☐ 2..... ☐ 3  
 h Walking several hundred yards..... ☐ 1..... ☐ 2..... ☐ 3  
 i Walking one hundred yards..... ☐ 1..... ☐ 2..... ☐ 3  
 j Bathing or dressing yourself..... ☐ 1..... ☐ 2..... ☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

All of  
the  
time
     
 Most  
of the  
time
     
 Some  
of the  
time
     
 a little  
of the  
time
     
 None  
of the  
time



- a Cut down on the amount of time you spent on work or other activities..... ☐ 1..... ☐ 2..... ☐ 3..... ☐ 4..... ☐ 5  
 b Accomplished less than you would like..... ☐ 1..... ☐ 2..... ☐ 3..... ☐ 4..... ☐ 5  
 c Were limited in the kind of work or other activities..... ☐ 1..... ☐ 2..... ☐ 3..... ☐ 4..... ☐ 5  
 d Had difficulty performing the work or other activities (for example, it took extra effort)..... ☐ 1..... ☐ 2..... ☐ 3..... ☐ 4..... ☐ 5

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

All of the time	Most of the time	Some of the time	a little of the time	None of the time
▼	▼	▼	▼	▼

- a. Cut down on the amount of time you spent on work or other activities..... ☐ 1..... ☐ 2..... ☐ 3..... ☐ 4..... ☐ 5
- b. Accomplished less than you would like..... ☐ 1..... ☐ 2..... ☐ 3..... ☐ 4..... ☐ 5
- c. Did work or other activities less carefully than usual..... ☐ 1..... ☐ 2..... ☐ 3..... ☐ 4..... ☐ 5

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all      Slightly      Moderately      Quite a bit      Extremely

▼	▼	▼	▼	▼
<input type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input type="checkbox"/> 3.....	<input type="checkbox"/> 4.....	<input type="checkbox"/> 5

7. How much bodily pain have you had during the past 4 weeks?

None      Very mild      Mild      Moderate      Severe      Very severe

▼	▼	▼	▼	▼	▼
<input type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input type="checkbox"/> 3.....	<input type="checkbox"/> 4.....	<input type="checkbox"/> 5.....	<input type="checkbox"/> 6

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all      A little bit      Moderately      Quite a bit      Extremely

▼	▼	▼	▼	▼
<input type="checkbox"/> 1.....	<input type="checkbox"/> 2.....	<input type="checkbox"/> 3.....	<input type="checkbox"/> 4.....	<input type="checkbox"/> 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...






	All of the time ▼	Most the time ▼	Some of the time ▼	A little Of the time ▼	None of the time ▼
1. Did you feel full of pep?.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
2. Have you been a very nervous person?.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
3. Have you felt so down in the dumps that nothing could cheer you up?.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
4. Have you felt calm and peaceful?.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
5. Did you have a lot of energy?.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
6. Have you felt downhearted and blue?.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
7. Did you feel worn out?.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
8. Have you been a happy person?.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
9. Did you feel tired?.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5



**11. How TRUE or FALSE is each of the following statements for you?**

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
    					
a I seem to get ill more easily than other people.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
b I am as healthy as anybody I know.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
c I expect my health to get worse.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5
d My health is excellent.....	<input type="checkbox"/> 1	<input type="checkbox"/> 2	<input type="checkbox"/> 3	<input type="checkbox"/> 4	<input type="checkbox"/> 5

***Thank you for completing these questions!***

## 18.8. APPENDIX H: Echocardiography guidelines

### OBJECTIVES of Echocardiographic Imaging Protocol

- The primary objective of the initial echo-Doppler examination is to establish baseline cardiac anatomy and function with an emphasis on the aortic valve, aortic root and left ventricular size and function.
- The primary goals of the follow-up post-implantation studies are to reassess the aortic valve prosthesis (structure and function) and to determine the impact of the implantation on the parameters evaluated.
- Complete Echo-Doppler examinations are required at the time points specified in the table above.
- Two-dimensional ultrasound imaging system with pulsed, continuous wave and colour Doppler capability, and permanent recording capabilities are required.
- The only accepted storage format is DICOM standard digital.  
You should have transducers with both fundamental and harmonic capability with frequency ranges that are suitable for most adult subjects (approximately 2 to 7 MHz).

### EXAMINATION PREPARATION, POSITIONING, AND GENERAL PROCEDURES

- A qualified physician or sonographer must perform all ultrasound exams. If possible, participating sites should attempt to utilize the same person as well as the same machine for image acquisition throughout the trial.
- Prior to starting the registry, the physician/sonographer should provide the patient with an overview of the registry (duration, general procedure etc).
- Patients will typically be studied while they are in the left lateral decubitus position although occasionally the best images will be obtained with the patient supine.
- EKG leads will be applied and the EKG control setting of the machine optimized to ensure a high quality EKG with adequate amplitude QRS complex for reliable digital capture (lead II equivalent preferred).
- Enter the patient ID as specified on the case report form. Please measure and note the blood pressure on the patient ID screen or as an annotation on one or more images.
- All views will be acquired with 2 captures OF EACH VIEW as follows:
  - Sinus rhythm (up to 90 bpm): 3 beat capture
  - Sinus rhythm (> 90 bpm): 5 beat capture
  - Frequent atrial or ventricular ectopy: 3 second capture
  - Atrial fibrillation or flutter, paced rhythm: 5 second capture
- It is essential that the view be optimized and stabilized before recording. Images are typically acquired during quiet respiration. Breath-holding during recording is not

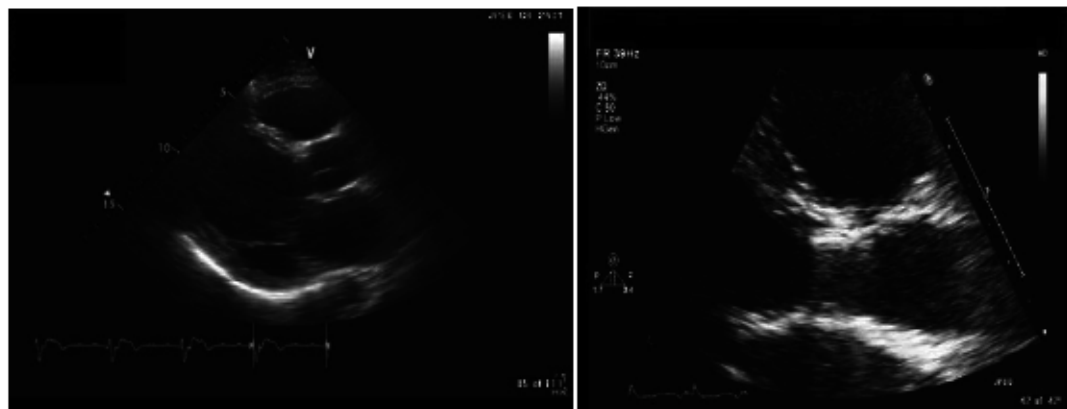
required unless necessary to ensure a stable high quality image.

- The spatial resolution of the images should be optimized using the highest frequencies capable of providing adequate penetration. For each view, the gain and compression and focus should be optimized so that the best echocardiographic image of the endocardial borders is obtained.
- Use echo contrast if available for images with suboptimal endocardial definition.
- The sweep speed for all spectral Doppler and M-mode recordings should be 100 mm/sec. NOTE: at least 3 consecutive sinus beats and at least 5 consecutive “irregular rhythm” beats must be captured, so adjust the number of captures accordingly.
- As defined in the ASE Guidelines for the Quantification of Native Valve Regurgitation, Nyquist settings for color Doppler assessment of the cardiac valves should be 50-60 cm/sec.
- Your performance of measurements is optional. We encourage you to perform measurements as needed for clinical feedback to treating physicians. If you do perform on-line measurements, please do not obscure the flow profiles of subsequent beats. We suggest storing BOTH measured and unmeasured Doppler spectra and images.

## EXAMINATION SEQUENCE

### I. Parasternal Long Axis of LV, LVOT and aortic valve

- 2D (Image A below)
- Colour Doppler of MR
- Colour Doppler of LVOT and aortic valve for aortic insufficiency
- Magnified views of LVOT and aortic valve – to identify the true LVOT dimension, AV annulus and stent diameter. (Image B below)
- High Parasternal View to see ascending aorta
- Off-axis views to search for aortic paravalvular leak



A.

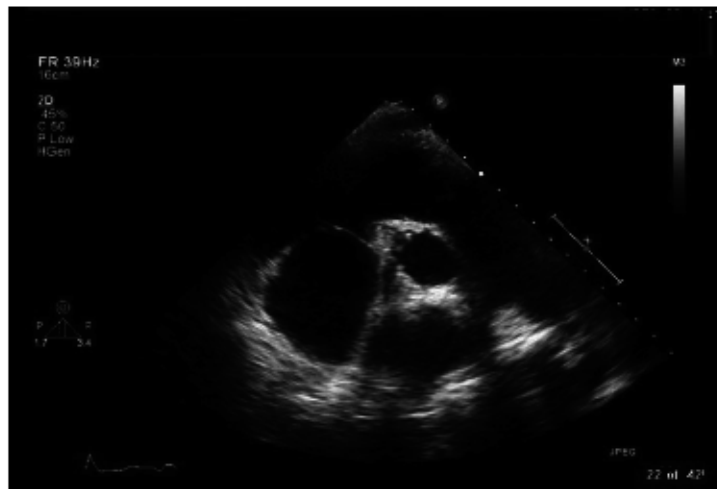
B.

**II. Parasternal Short axis at LV level**

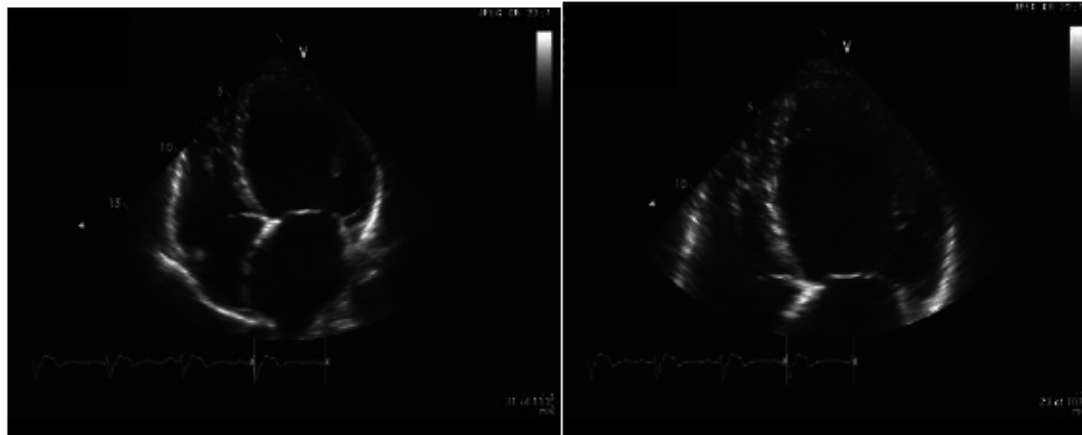
- 2D should be obtained at 3 levels: apex, mid-papillary muscle and base.
- Colour Doppler of MR from the basal view is also required.

**III. Parasternal Short axis at aortic valve level**

- 2D
- Colour Doppler of aortic valve including sewing ring of prosthesis to search for paravalvular leak
- Colour Doppler of TR is optional in this view

**IV. Apical 4 chamber**

- 2D optimizing LV endocardial borders: Need to see all aspects of the lateral wall, septum, and apex
- Show a loop with decreased depth such that LV occupies most of the imaging sector ensuring all walls are visualized
- Colour Doppler of MR showing entire left atrium (to allow jet dimension/LA measurement.
- If there is more than mild MR, provide components for PISA calculation
  - CW of MR jet
  - Zoomed PISA display (baseline shift down to optimize hemispherical PISA shell)
  - If possible, provide split screen (colour suppress) images (i.e. one side with colour, one without)
- Colour Doppler of TR with CW



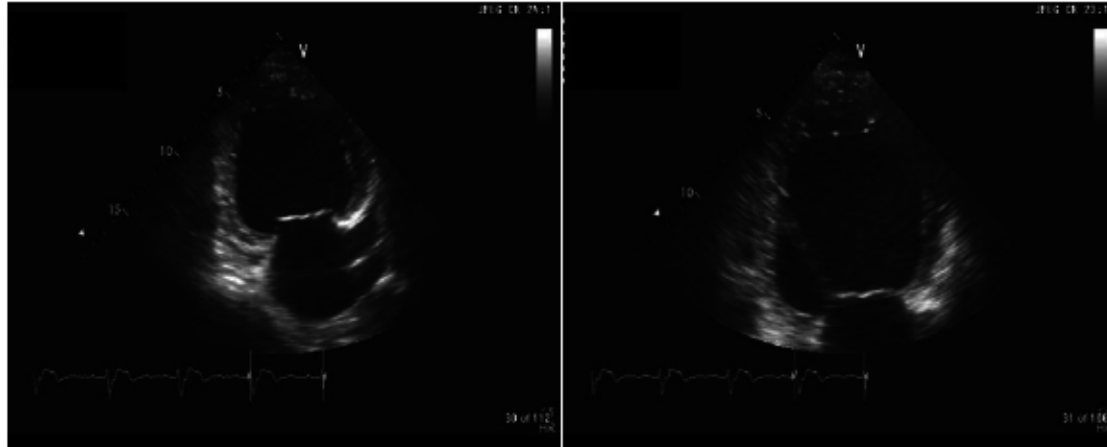
A.

B.

\* Image A shows the traditional 4 chamber while image B shows the 4 chamber with decreased depth.

#### V. Apical 2 chamber

- 2D optimizing LV endocardial borders : Need to see all aspects of the anterior wall, inferior wall, and apex
- Show a loop with decreased depth such that LV occupies most of the imaging sector ensuring all walls are visualized
- Colour Doppler of MR



A.

B.

\* Image A shows the traditional 2 chamber while image B shows the 2 chamber with decreased depth.

#### VI. Apical 5 chamber view

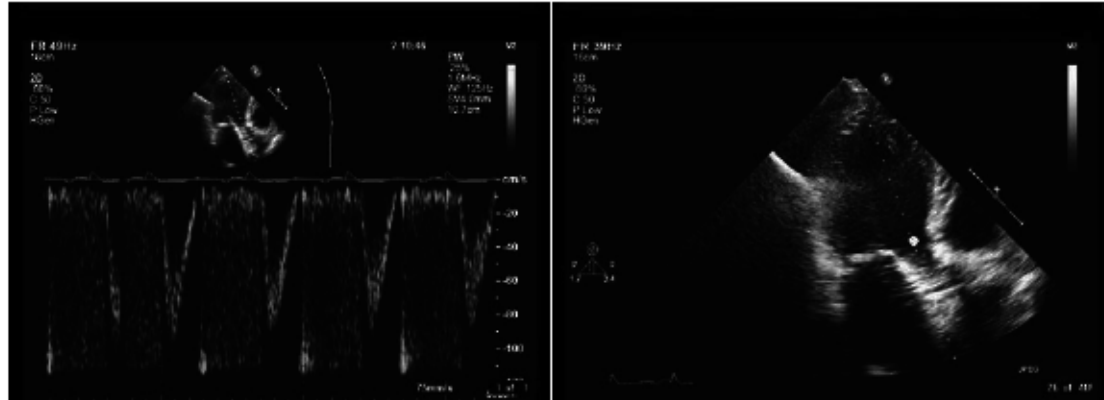
- Pulse wave Doppler of LVOT (to avoid the region of flow acceleration - sample volume should be positioned at valve level and then moved apically until valve noise or "clicks" are no longer detected and then recorded for the baseline registry).
- For post-implantation studies, it is imperative that the sample volume be placed proximal to the valve frame AND at a second position within the valve frame but

**proximal to the valve cusps. Studies in which there are no clips with the sample volume proximal to the valve frame will be considered INADEQUATE.**

- **Note:** record a full screen 2D image showing the pulsed wave sample position (either as moving image or still frame) as well as the Pulse Wave Spectral Doppler for each position. It is very difficult to establish the sample volume position from the small image that is available when image and spectral display are provided simultaneously.
- **Colour Doppler** of LVOT and aortic valve for AI (use off axis views to ensure that all AI jets are demonstrated).
- **Continuous wave Doppler** through the aortic valve.

### VII. Apical long axis view (also known as 3 chamber view)

- **2 D optimizing LV endocardial borders**
- **Show a loop with decreased depth such that LV occupies most of the imaging sector ensuring all walls are visualized**
- **Continuous Wave Doppler through the aortic valve**
- **Colour Doppler of MR**
- **Colour Doppler of LVOT and aortic valve for AI (use off axis views to ensure that all AI jets are demonstrated)**
- **Pulse Wave Doppler just apical to the valve frame as specified in apical 5 chamber view**
- **Note: record a full screen 2D image showing the pulsed wave sample position (either as moving image or still frame) as well as the Pulse Wave Spectral Doppler for each position**



### VIII. Right Parasternal view

- **Continuous Wave Doppler through the aortic valve (Note: this view is particularly useful if you notice an anteriorly-directed transaortic jet from parasternal views)**

### IX. Suprasternal Notch view

- Pulsed Doppler of the descending thoracic aorta from the suprasternal notch should be obtained to assess for reversal of flow if significant (moderate or greater) aortic insufficiency is present (**Note: sample volume is placed in the descending thoracic aorta below the take off of the subclavian artery**).
- Continuous wave Doppler interrogation of the transaortic valvular flow should also be obtained using the pedoff transducer.

## Specific Comments on Imaging Planes

A. Parasternal long axis view is recorded with the transducer in the third or fourth intercostal space immediately to the left of the sternum. The transducer should be angled so that the aortic valve, mitral valve and left ventricle are in their long axis.

### IMAGING TIP 1: PARASTERNAL LONG AXIS VIEW

It is important that the parasternal long axis view displays the true long axis of the ventricle with the left ventricle lying horizontally on the image. If it is impossible to obtain a single view which optimally displays the long axis of the aortic valve and aortic root as well as the long axis of the left ventricle, record 2 separate views. It is unacceptable to record an off-axis view in which the apex "points up" on the screen. If this type of image is obtained try moving the transducer up an intercostal space or 2 or having the patient take a breath in. Sometimes having the patient move to a more lateral decubitus position will help as well.

### IMAGING TIP 2: PARASTERNAL LONG AXIS VIEW

Measurement of the left ventricular outflow tract and aortic annulus is a key component of the registry. In pre-device imaging, it is important to note that the largest annulus may not be in a plane with valve opening centered in the aorta.

B. Parasternal short axis view is obtained by angling the probe 90° with respect to the parasternal long axis of the LV. The goal of this view is to obtain information about the aortic valve as well as the LV.

### IMAGING TIP 3: PARASTERNAL SHORT AXIS VIEW

This is an essential view post-op to completely assess aortic regurgitation. This may be the only view in which prosthetic valve medial or lateral aortic regurgitant jets are imaged. Imaging at the level of as well as just below the leaflets may allow you to better image these jets.

C. Apical four-chamber view provides considerable information including the relative sizes of the right and the left ventricles and the regional function of the LV. The four chamber view is defined as a view which maximizes the LV long axis and the tricuspid and mitral annular dimensions. In this view, the full excursion of the mitral and tricuspid valves should be seen. The complete endocardial border of the LV will be traced for chamber volume assessment (method of discs) so all aspects including the apex should be visualized. In the apical four chamber view, colour Doppler of mitral and tricuspid regurgitation should be recorded. The four chamber view should visualize the lateral, septal and apical walls.

**D. Apical two-chamber view** should be obtained for the goal of assessment of LV size and function. The complete endocardial border of the LV will be traced for chamber volume assessment (method of discs) so all aspects including the apex should be visualized. The degree of MR by colour Doppler will also be assessed. The two chamber view should visualize the anterior, inferior and apical walls.

**IMAGING TIP 4: APICAL 4 and 2 CHAMBER VIEWS**

Because we will measure volumes from the apical views as an important end-point of the registry, please try to avoid apical foreshortening. If the view appears to be foreshortened, please bring the transducer down one intercostals space and have the patient take a breath in (particularly for the apical two-chamber view). Sometimes this will bring out a better (not foreshortened) view.

**E. Apical 5 chamber and 3 chamber views** are obtained to provide detailed information about the aortic valve colour, spectral and continuous wave Doppler.

**IMAGING TIP 5: APICAL 5 and 3 CHAMBER VIEWS**

Both these views are essential in imaging post-device aortic regurgitant jets. Because we will be measuring jet vena contracta and jet length, a Res/Zoom view which includes imaging of the entire jet would be helpful. In addition, the 3Ch view may be used in the biplane Simpson's calculation of LV volume when the 2Ch view is inadequate thus careful attention to endocardial definition is important.

**XI. Abbreviations**

2D – Two-dimensional	LV – Left Ventricle
AI – Aortic Insufficiency	LVED – Left ventricular end diastolic volume
AVA – Aortic valve area	LVEF – Left ventricular ejection fraction
AR – Aortic Regurgitation	LVES – Left ventricular end systolic volume
AV – Aortic Valve	LVOT – Left ventricular outflow tract
BSA – Body Surface Area	MR – Mitral Regurgitation
ED – End diastole	MV – Mitral Valve
CO – Cardiac Output	PI – Performance Index
CSA – Cross sectional area	PW – Pulse wave
EF – Ejection fraction	SV – Stroke Volume
ES – End systole	TR – Tricuspid Regurgitation
HR – Heart rate	TVI or VTI – Time Velocity Integral
LA – Left atrium	