The SPACER Trial – Repair of Tricuspid Valve Regurgitation using the Edwards FORMA TricuSPid TrAnsCatheter REpaiR System

CLINICAL PROTOCOL

(Clinical Investigational Plan)

Study Number: 2015-09
Version: C
Effective Date: December 16, 2016

CONFIDENTIAL

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

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SYNOPSIS

Study Number:	2015-09
Title:	The SPACER Trial - Repair of Tricuspid Valve Regurgitation using the Edwards FORMA Tricu**SP**id Tr**A**ns**C**atheter R**E**pai**R** System
Study Sponsor Contacts:	[redacted]
Principal Investigators:	[redacted]

	[redacted]
Study Objective:	The purpose of the study is to assess the safety and device performance of the Edwards FORMA Tricuspid Transcatheter Repair System in patients with clinically significant, symptomatic, tricuspid regurgitation who are at high surgical risk for standard tricuspid repair/replacement.
Study Devices:	The Edwards FORMA Tricuspid Transcatheter Repair System: • Edwards FORMA Tricuspid Spacer System, [redacted] • Edwards FORMA Tricuspid Introducer Sheath , [redacted] • Edwards FORMA Tricuspid Railing Delivery System, [redacted] • Edwards FORMA Tricuspid Retrieval System , [redacted]
Intended Use:	The Edwards FORMA Tricuspid Transcatheter Repair System is intended for treatment of subjects with tricuspid regurgitation who are at high surgical risk for standard tricuspid repair/replacement due to operative risks, long recovery time, and/or significant co-morbidities.
Study Design:	This is a multi-center (≤12), international, prospective, single arm, safety study. 78 subjects will be enrolled in the study. All enrolled study subjects will be assessed for clinical follow-up at the following intervals: 1 month, 6 months, 1 year and annually for 3 years post implant procedure.
Study Duration:	[redacted]

Study Population:	Adult subjects with clinically significant, symptomatic, tricuspid regurgitation who are at high surgical risk for standard tricuspid repair or replacement as assessed by the Heart Team.
Enrollment Criteria (Inclusion):	1. Signed and dated EC approved study consent form prior to study related procedures 2. Eighteen years of age or older 3. Clinically significant, symptomatic (NYHA Functional Class II or greater), tricuspid regurgitation (Stage D per 2014 AHA/ACC guidelines) requiring tricuspid valve repair or replacement as assessed by the Heart Team 4. Functional tricuspid regurgitation (e.g., EROA ≥ 0.4 cm^2 or equivalent guideline directed value) as the primary etiology 5. NYHA Functional Class II or greater or signs of persistent right heart failure, despite optimal medical therapy 6. Determined by the 'HEART Team' (a minimum of one Cardiologist, and one Cardiac Surgeon) to be at high surgical risk for tricuspid valve repair or replacement and the benefit-risk analysis supports utilization of the investigational device 7. Willing to attend study follow-up assessments for up to 3 years
Enrollment Criteria (Exclusion):	1. Tricuspid valve/right heart anatomy not suitable for the study device: a. Native tricuspid annulus area < 2.14 cm^2 (9 mm device), < 2.63 cm^2 (12 mm device) or < 3.27cm^2 (15 mm device) as measured by transthoracic echocardiography or computed tomography b. Sub-valvular structures/anatomy that would preclude from proper anchor or Spacer placement, positioning and retrieval c. Access pathway vessel diameter less than 7.1 mm (9, 12 and 15 mm devices) 2. Moderate or greater tricuspid valve stenosis 3. Untreated clinically significant coronary artery disease requiring immediate revascularization 4. Any therapeutic invasive cardiac procedure performed within 30 days of the scheduled implant procedure 5. Patients not already receiving dialysis with renal insufficiency (eGFR < 25) per lab test ≤ 48 hours prior to scheduled implant procedure 6. Myocardial infarction within 30 days of scheduled implant procedure 7. Hemodynamic instability within 30 days of scheduled implant procedure 8. Patient requiring surgery under general anesthesia for any reason within 30 days of scheduled implant procedure 9. Severe left ventricular dysfunction with ejection fraction < 25% within 90 days of scheduled implant procedure

	10. Patients with pulmonary artery systolic pressure > 70 mmHg via transthoracic echocardiography or alternative standard modality (e.g., direct pressure measurement) within 90 days 11. Concomitant clinically significant valve (aortic, mitral, or pulmonic) disease requiring immediate (± 30 days of study procedure) repair or replacement 12. Active endocarditis or infection within 3 months of scheduled implant procedure 13. Cerebrovascular accident within 3 months of scheduled implant procedure 14. Non-cardiac disease limiting life expectancy to be less than 12 months at baseline evaluation 15. Documented history of bleeding diathesis, coagulopathy or gastrointestinal bleeding within 3 months of scheduled implant procedure 16. Evidence of right sided intracardiac mass, thrombus, or vegetation 17. Prior venous stent placed within the access route (e.g., sub-clavian vein) that could negatively react with device 18. Previously treated tricuspid valve which included implantation of a bioprosthetic valve or mechanical valve 19. Known hypersensitivity to cobalt chromium, nitinol or titanium 20. Known hypersensitivity to anticoagulation therapy or contrast agent, which cannot be adequately medicated 21. Patient is a current intravenous drug user 22. Female of child-bearing potential is pregnant or lactating 23. Patient is currently participating or has participated in another investigational drug or device clinical study within 30 days of study screening activity 24. Patient requires emergent/emergency treatment for tricuspid insufficiency 25. Patient is under guardianship
Primary Endpoint:	The primary endpoint for the study will assess the all-cause mortality of the as treated cohort at 30 days compared to a literature derived Performance Goal based on high-risk surgical outcomes for tricuspid repair/replacement.
Secondary Endpoints and Clinical Outcomes:	The following secondary endpoints and clinical outcomes will also be assessed: **Technical Success (at exit from procedure room):** • Alive, with • Successful access, delivery and removal of the delivery systems, and • Deployment and correct positioning of the intended device, and • No need for additional emergency surgery or re-intervention related to the device or access procedure

	Device Success (at 1 month, 6 months & Annually):
	• Alive, with
	• Original intended device in place, and
	• No additional surgical or interventional procedures related to the device, and
	• TR reduction (assessment made by change in EROA) compared to baseline and TV gradient ≤ 5mmHg
	
	Procedural Success (at 1 month):
	• Device Success, and
	• None of the following device or procedure related SAEs:
	  • Life threatening bleeding
	  • Major vascular or cardiac structural complications requiring intervention
	  • Pericardial effusion requiring drainage or surgery (includes tamponade)
	  • Stage 2 or 3 acute kidney injury (includes new dialysis).
	  • Severe heart failure or hypotension requiring IV inotrope, ultrafiltration or mechanical circulatory support
	  • Prolonged intubation > 48 hours
	
	Clinical Outcomes (at 1 month, 6 months & Annually)
	• Re-hospitalization rates for the underlying condition (heart failure)
	• Re-intervention rates for the underlying condition (tricuspid regurgitation)
	• Change in Tricuspid Regurgitation (assessment made by change in EROA) from baseline
	• Change in peripheral edema as assessed by subject weight loss (kilograms) from baseline
	• Change in NYHA Class from baseline
	• Change in 6 minute walk test distance (meters) from baseline
	• Change in Quality of Life as assessed by the SF-12 and KCCQ questionnaires from baseline

Study Committee:	Independent Data Monitoring Committee (DMC) The DMC will consist of a minimum of 3 members, all members being physicians; one cardiothoracic surgeon, one interventional cardiologist and one cardiologist
Echocardiography Core Laboratory:	[redacted]

1 INTRODUCTION

1.1 CLINICAL BACKGROUND

1.1.1 DISEASE PROCESS

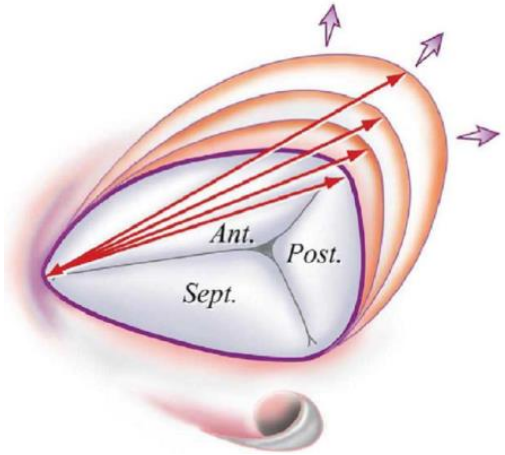
Tricuspid Regurgitation (TR), tricuspid insufficiency or tricuspid incompetence describes a condition in which blood flow through the tricuspid valve flows in the incorrect direction during part of the cardiac cycle. Normally, during diastole, the tricuspid valve opens as a result of atrial pressure from the right atrium, allowing blood to flow through the tricuspid valve, into the right ventricle. Diastole ends with atrial contraction and the tricuspid valve closing to prevent a reversal of blood flow. However, in patients with TR, the tricuspid valve is unable to form a tight seal at diastole end (when it should be closed), allowing blood to flow back into the right atrium.

Although TR often accompanies mitral or aortic valve disease, it is usually asymptomatic, traditionally considered less clinically significant, and left untreated. This scenario where the tricuspid valve is left untreated has resulted in the tricuspid valve being commonly referred to as the "forgotten" valve. While trace to mild levels of TR are commonly found in a large number of patients without clinical consequence, moderate and severe levels can have detrimental effects on a patients quality of life [1]. Patients with severe TR usually present with signs or symptoms of right heart failure (HF), including peripheral edema and ascites [2].

1.1.2 ETIOLOGY

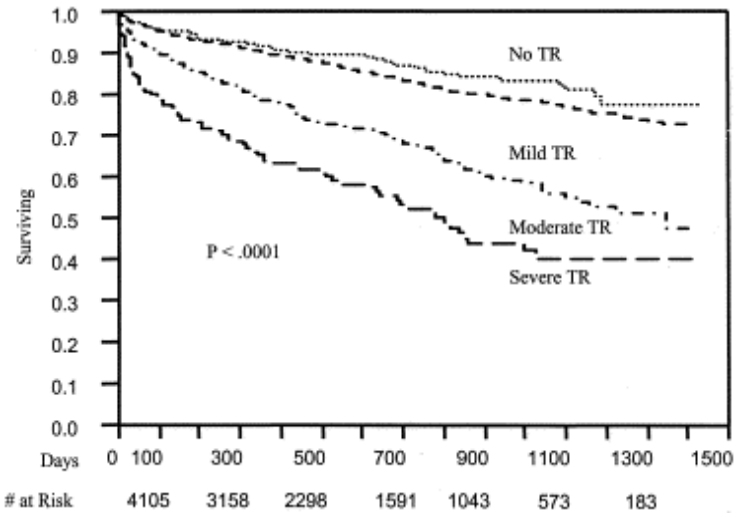
TR can have many underlying etiologies, but the majority of these can be divided into two major categories: degenerative and functional TR. Degenerative (primary, organic or structural) TR refers to regurgitation resulting from disease processes affecting the integrity of the tricuspid valve leaflets and/or valve apparatus, such as in rheumatic heart disease, tricuspid valve prolapse or endocarditis. In contrast, functional (secondary or non-structural) TR refers to regurgitation occurring in the absence of significant structural disease of the tricuspid valve and/or apparatus. Functional TR occurs in approximately 80% of cases of significant TR [2], resulting from annular dilation and right ventricular enlargement, which is often secondary to left heart failure from myocardial or valvular causes, right ventricular volume and pressure overload, and dilation of cardiac chambers. Significant TR may be clinically silent for a prolonged period, during which time progressive right ventricle (RV) dilatation and dysfunction may develop, similar to changes that can occur with asymptomatic mitral regurgitation (MR) and its' effect on LV function.

Figure 1: Dilation of the Tricuspid Annulus – Dreyfus et al.[3]



Tricuspid regurgitation is a common echocardiographic finding that is often considered benign unless associated with significant pulmonary hypertension or RV or LV dysfunction. It has been shown that increasing TR severity is associated with worse survival regardless of LVEF or pulmonary artery pressure [1]. Severe TR is associated with a poor prognosis, independent of age, biventricular systolic function, RV size, and IVC dilation [1].

Figure 2: Kaplan-Meier survival curves for all patients with tricuspid regurgitation (TR). [1]



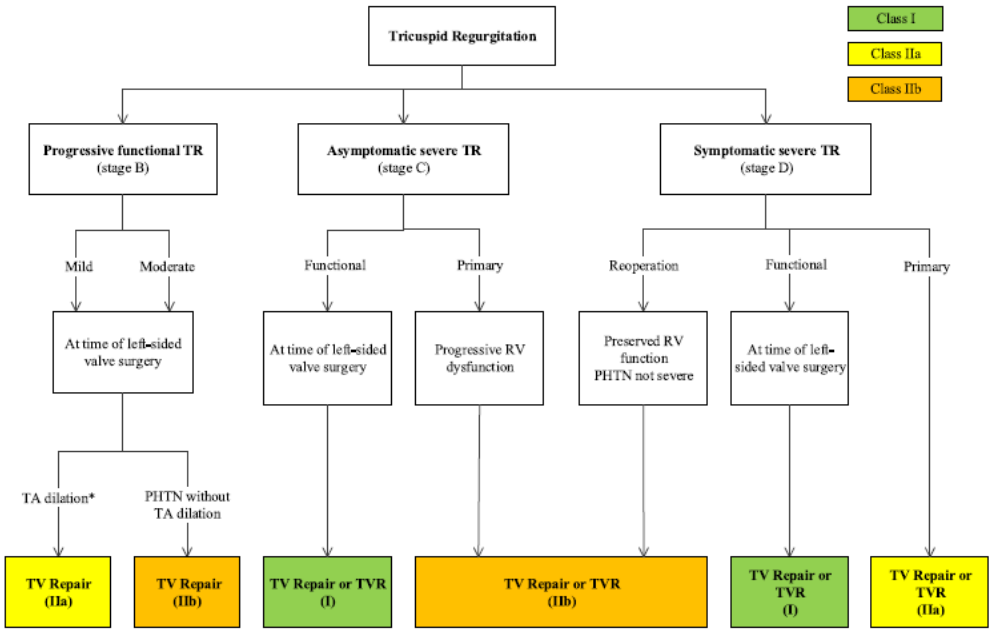
1.2 ALTERNATIVE TREATMENT/THERAPIES

1.2.1 SURGICAL TRICUSPID VALVE INTERVENTION

The decision to treat TR has been controversial over the years, but has recently become recommended in symptomatic patients and in some cases asymptotic patients as

prophylactic treatment at the time of MR surgery [4]. The decision as to whether repair or replacement is recommended is demonstrated in the diagram below.

Figure 3: 2014 AHA/ACC Indications for Tricuspid Surgery [2]



Several techniques are available to correct functional tricuspid regurgitation. These include the stitch annuloplasty, such as semicircular (classical De Vega repair) or simple lateral annuloplasty (Kay), novel techniques such as edge-to-edge or clover technique and suture bicuspidization technique, use of flexible and rigid prosthetic rings or 3D rings, flexible prosthetic bands, and use of artificial chordae with polytetrafluoroethylene sutures for anterior and septal tricuspid leaflet pathology. Whereas the short-term outcomes of these techniques are satisfactory, the majority are limited in the mid- and long term by unacceptably high rates of residual and/or recurrent regurgitation [5].

While repair, specifically annuloplasty is considered the procedure of choice, if repair is not feasible or unsuccessful, replacement may be considered [6]. For replacement both bioprosthetic as well as mechanical valves provide viable options.

1.2.2 Medical Therapy

TR patients may be managed with diuretics for symptoms and only considered for surgery after advanced RV dysfunction, liver dysfunction or cirrhosis have developed. Additionally, medical therapies may be used to reduce elevated pulmonary artery pressures and/or pulmonary resistance [2].

For the patient population that would benefit from surgical intervention, but are characterized as high-risk or non-surgical, medical management is likely to only provide temporary symptom relief. The lack of benefit from medical therapies has prompted the search for alternative repair or replacement therapies.

1.2.3 PERCUTANEOUS TRICUSPID VALVE REPAIR

Percutaneous tricuspid valve repair therapies have considerable interest due to the minimally invasive nature of the procedures, particularly since surgery in functional patients is only indicated when they are undergoing concomitant valve surgery [2, 7].

Percutaneous devices are being investigated which mimic surgical repair techniques. These devices are targeted for patients which are at high operative risk for surgery. These devices aim to approximate the leaflets by anchoring in the annulus and pulling the anterior leaflet towards the posterior leaflet, simulating a bicuspidization. Another emerging technology is a device which uses pledgets in the annulus to reduce the size of the annulus.

1.2.4 TRANSCATHETER TRICUSPID VALVE REPLACEMENT

Transcatheter valve replacement with the Edwards Sapien or Medtronic Melody valve has been described in the published literature on only single case studies or limited retrospective clinical series but primarily for valve-in-valve patients or patients with rheumatic disease. This is not the patient population that the Edwards FORMA Tricuspid Transcatheter Repair system is intended for as the Edwards' device is intended for functional tricuspid regurgitation.

Additionally, percutaneous bicaval valve implantation has been used to treat tricuspid regurgitation by placing a valve in both the inferior vena cava and the superior vena cava. While this does not directly correct the TR it prevents back flow beyond the right atrium with the goal of reducing symptoms, normalizing liver function, and improving physical capacity.

1.3 IN-HOSPITAL/30-DAY MORTALITY

The most prevalent treatment options for tricuspid regurgitation are surgical repair or replacement. Typically, these procedures are done in conjunction with other cardiac surgical procedures (AVR, MVR, CABG,) while interventions performed in an isolated tricuspid regurgitation setting are quite rare. When performed, there are multiple factors that determine the success of the surgical intervention. The literature suggest that the most successful surgical interventions occur when tricuspid repair or replacement is performed as an elective procedure in conjunction with other cardiac procedures in a patient population that has a modest history of prior cardiac surgery. For example, McCarthy et al [8], reported an 8% in-hospital mortality when a large patient population with functional tricuspid regurgitation was treated using an annuloplasty approach. This

patient population will most likely represent a lower risk population than what is proposed in the SPACER Trial due to their more favorable disposition for cardiac surgery. An additional observation that cannot be overlooked, is the mortality rate in patients requiring reoperation. This article reports an alarming in-hospital mortality rate for reoperation patients of 37%. This is not an uncommon finding as Bernal et al [9] reported a 35% in-hospital mortality rate for a similar population of reoperation patients.

Ratnatunga et al [10] reported on a large patient population and concluded that for patients undergoing tricuspid regurgitation repair "a high mortality rate is universal." Specifically, they suggest an approximate 18% operative mortality rate in a patient population with a higher NHYA functional classification distribution than McCarthy [8] as well as a blend of isolated TR surgery and TR surgery in conjunction with other cardiac surgery procedures. These results are in line with what Filsoufi et. al. [11] and Moraca et. al. [12] reported for a similar patient population (22% and 18%, respectively). In summary, operative mortality (also described as 30-day or in-hospital mortality) is very high for patients undergoing tricuspid regurgitation intervention. The most significant predictors of a higher mortality rate are previous cardiac surgery, previous tricuspid intervention and high New York Heart Association Classification (NYHA) functional class, all of which are inclusion criteria for the SPACER Trial. This literature review, summarized in Table 1 below, was the basis for determining the performance goal to which the safety of the Edwards Transcatheter Tricuspid Repair Device will be compared (reference Section 13 of this investigational plan).

Table 1 – Tricuspid Regurgitation Mortality Literature Review

Author	In-Hospital Mortality Rate	Patient Population (N)	Reference
McCarthy	6% (8% Hospital), 37% Re-Op	790	J Thorac Cariovasc Surg 2004; 127:674-85
Bernal	35.1% Re-Op	74	J Thorac Cardiovasc Surg 2005;130:498-503
Ratnatunga	15.6%-18.8%	425	Ann Thorac Surg 1998; 66:1940-7
Filsoufi	22%	81	Ann Thorac Surg 2005; 80:845-50
Moraca	18% (repair), 13% (replacement)	136	Ann Thorac Surg 2009; 87:83-9
Pfannmuller	14.6%	82	J Thorac Cariovasc Surg 2013; 146:841-7

2 STUDY PURPOSE

The study of the Edwards FORMA Tricuspid Transcatheter Repair System is a multi-center, international, prospective, single arm, safety study to assess the safety and device performance of the Edwards FORMA Tricuspid Transcatheter Repair System in patients with clinically significant, symptomatic tricuspid regurgitation who are at high surgical risk for standard tricuspid repair/replacement.

Data collected in this clinical study will include safety and device performance of the investigational system as well as up to 3 year clinical outcomes. In addition, the data shall be used to obtain regulatory approval.

2.1 INTENDED USE

The Edwards FORMA Tricuspid Transcatheter Repair System is intended for treatment of subjects with tricuspid regurgitation who are at high surgical risk for standard tricuspid repair/replacement due to operative risks, long recovery time, and/or significant co-morbidities.

2.2 PRIOR TESTING

A Report of Priors (Clinical Investigator's Brochure (CIB)) has been prepared for the Edwards FORMA Tricuspid Transcatheter Repair System. This document provides the prior testing conducted on the system components.

2.3 PRIOR CLINICAL STUDIES

[redacted]

[redacted]

2.4 STUDY DEVICE

2.4.1 GENERAL DEVICE DESCRIPTION AND COMPONENTS

The Edwards FORMA Tricuspid Transcatheter Repair System (herein after referred to as the FORMA System) is comprised of four (4) different sub-systems as listed below (Table 3). A general device description is provided for all components of the FORMA System. Further detailed information such as materials, manufacturing, testing, etc. however, will be provided in the Clinical Investigator's Brochure (CIB). The FORMA System is not currently commercially available.

The following table includes the device names and model numbers of the components that make up the FORMA System**.**

Table 3 – Device Names and Model Numbers

Product Name	Models
Edwards FORMA Tricuspid Transcatheter Spacer System	[redacted]
Edwards FORMA Tricuspid Transcatheter Introducer Sheath Set	[redacted]
Edwards FORMA Tricuspid Transcatheter Railing Delivery System	[redacted]
Edwards FORMA Tricuspid Transcatheter Retrieval System	[redacted]

2.4.2 EDWARDS FORMA TRICUSPID TRANSCATHETER SPACER SYSTEM:

[redacted]

2.4.2.1 Spacer Device

[redacted]

[redacted]

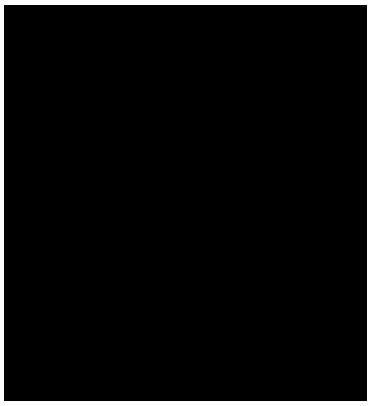
2.4.2.2 Railing System

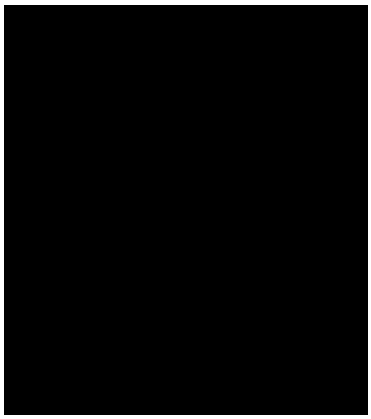
[redacted]

2.4.2.3 Locking Mechanisms

[redacted]

[redacted]





2.4.3 EDWARDS FORMA TRICUSPID TRANSCATHETER INTRODUCER SHEATH SET

[redacted]

[redacted]

2.4.4 EDWARDS FORMA TRICUSPID TRANSCATHETER RAILING DELIVERY SYSTEM

[redacted]

[redacted]

[redacted]

[redacted]

2.4.5 EDWARDS FORMA TRICUSPID TRANSCATHETER RETRIEVAL SYSTEM

[redacted]

[redacted]

3 RISK ANALYSIS

A risk analysis has been conducted, in accordance with ISO 14971: "Application of risk management to medical devices". The risks associated with this investigational device have been identified by performing Failure Mode and Effect Analysis (FMEA)/Risk Analysis. Risks have been proven minimized through appropriate design control, confirmed by bench testing, pre-clinical animal testing and clinical surveillance presented in the Clinical Investigator's Brochure.

During the conduct of the clinical study, the existing risk control measures shall be reviewed to identify if other hazards have been introduced. If any new hazards were introduced by any risk control measures, the associated risk(s) shall be re-assessed and addressed.

3.1 POTENTIAL RISKS

The potential risks of use of the FORMA System are similar to those encountered with standard cardiac catheterization and use of anesthesia and have been listed in two categories below. First, there are the potential complications associated with the overall procedure including standard cardiac catheterization and the use of anesthesia. Second, there are the additional potential risks associated with the use of the FORMA System.

Estimated occurrence rankings of the potential risks are provided in the Sample Informed Consent Form in Appendix A.

Risks related to the overall procedure including standard cardiac catheterization and the use of anesthesia may include, but may not be limited to, the following:

- abnormal lab values;
- access site AV fistula or pseudoaneurysm;
- allergic reaction to anesthesia or to contrast media;
- anemia;
- angina;
- arrhythmia;
- bleeding;
- cardiovascular or vascular injury including perforation, obstruction, or dissection of valvular structures that may require intervention, including access sites;
- conduction system injury (defect) which may require replacement or implantation of a pacemaker (temporary or permanent);
- death;
- dyspnea (e.g., orthopnea);
- electrolyte imbalance;
- embolization including air, particulate, calcific material, or thrombus;
- exercise intolerance or weakness;
- fever;
- heart failure;
- heart murmur;
- hematoma;
- hemorrhage requiring transfusion or intervention;
- leaflet damage;
- hypertension/hypotension;
- infection, including septicemia and endocarditis;
- inflammation;
- myocardial infarction;
- pain or changes at the access site;
- paralysis;
- pericardial effusion/cardiac tamponade;
- permanent disability;
- pleural effusion;
- pulmonary edema;
- renal failure;
- renal insufficiency;
- reoperation;

- restenosis;
- retroperitoneal bleed;
- syncope;
- systemic peripheral ischemia/nerve injury;
- thromboembolic events, stroke, transient ischemic attack, clusters, or neurological changes;
- wound dehiscence, delayed or incomplete healing.

In addition to the risks listed above, additional potential risks associated with the use of the FORMA System may include, but may not be limited to, the following:

- cardiac arrest;
- cardiac dysrhythmias requiring replacement or implantation of a pacemaker (temporary or permanent);
- cardiac failure/low cardiac output;
- cardiogenic shock;
- chordal damage, rupture;
- deterioration of native valve (leaflet tear/tearing, leaflet retraction, leaflet thickening, leaflet stenosis, or other);
- device degeneration;
- device explants;
- device migration, malposition or embolization potentially requiring intervention;
- device thrombosis requiring intervention;
- emergency cardiac surgery;
- hemolysis;
- leakage around device;
- non-emergent reoperation;
- nonstructural implant dysfunction;
- papillary muscle damage;
- pneumothorax;
- pulmonary artery outflow tract obstruction;
- skin burn;
- structural deterioration (wear, fracture, calcification, shaft creep, or other);
- thromboembolism (permanent or transient pulmonary and/or neurological events);
- transvalvular flow disturbances;
- valvular regurgitation;
- ventricular or atrial wall damage, abrasion, or perforation;
- worsening of heart failure;
- worsening of valvular insufficiency.

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

3.2 RISK MANAGEMENT

All efforts will be made to minimize the identified risks by selecting Investigators, team members and study sites who meet the following criteria:

- Interventional Cardiologist - must be board certified (or equivalent), experienced with performing transcatheter heart valve repair and replacement, and skilled in percutaneous coronary interventions and structural heart interventions.
- Access Management Physician - must be board certified (or equivalent), experienced with access management (subclavian/axillary vein access) and right heart interventions.

There will be strong interdepartmental collaboration between interventional cardiology and cardiovasculary surgery operators and a designated team of nurses, technicians and colleagues from supporting medical disciplines (e.g., anesthesiologist, echo-cardiographer, radiologist).

The procedural location is to be an operating room, catheterization lab or hybrid operating room with fluoroscopic and echocardiographic imaging capabilities.

All adverse events will be thoroughly reviewed by the Study Sponsor and Data Monitoring Committee. The Study Stopping Rules are outlined in Section 16.

3.3 BENEFITS

The clinical benefits of using the FORMA System for the treatment of tricuspid regurgitation are not known at the present time. There are no guaranteed benefits from participation in this clinical study and being treated with the investigational FORMA System.

Tricuspid valve repair with the FORMA System may result in one or more of the following benefits for subjects typically considered high risk for tricuspid repair or replacement: decrease in tricuspid regurgitation, acute alleviation of symptoms related to tricuspid insufficiency, and/or improved morbidity and mortality.

Information gained from the conduct of this study may be of benefit to other people with the same medical condition in the future as the indication for the system is expanded.

3.4 JUSTIFICATION

This study, is designed as a multi-center, international, prospective, single arm, safety study. This study is designed to assess the safety and device performance of the FORMA System in a controlled human population.

The treatments currently available for this patient population include palliative medical therapy and high-risk surgical replacement or repair of the tricuspid valve. Treatment with the FORMA System may enable patients with tricuspid regurgitation, to undergo tricuspid valve repair via a minimally invasive approach.

4 STUDY OBJECTIVES

The objective of this study is to assess the safety and device performance of the Edwards FORMA Tricuspid Transcatheter Repair System in patients with clinically significant, symptomatic tricuspid regurgitation who are at high surgical risk for standard tricuspid repair/replacement.

5 STUDY ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary endpoint for the study will assess the all-cause mortality of the as treated cohort at 30 days compared to a literature derived Performance Goal based on high-risk surgical outcomes for tricuspid repair/replacement.

5.2 SECONDARY ENDPOINTS & CLINICAL OUTCOMES

The following secondary endpoints and clinical outcomes will also be assessed:

5.2.1 TECHNICAL SUCCESS ENDPOINT

Technical Success will be assessed at exit from procedure room and is defined as:

- Alive, with
- Successful access, delivery and removal of the delivery systems, and
- Deployment and correct positioning of the intended device, and
- No need for additional emergency surgery or re-intervention related to the device or access procedure

5.2.2 DEVICE SUCCESS ENDPOINT

Device Success will be assessed at 1 month, 6 months and annually and is defined as:

- Alive, with
- Original intended device in place, and
- No additional surgical or interventional procedures related to the device, and

- TR reduction (assessment made by change in EROA) compared to baseline and TV gradient ≤ 5mmHg

5.2.3 PROCEDURAL SUCCESS ENDPOINT

Procedural Success will be assessed at 1 month and is defined as:

- Device Success, and
- None of the following device or procedure related SAEs:
    - Life threatening bleeding
    - Major vascular or cardiac structural complications requiring intervention
    - Pericardial effusion requiring drainage or surgery (includes tamponade)
    - Stage 2 or 3 acute kidney injury (includes new dialysis)
    - Severe heart failure or hypotension requiring IV inotrope, ultrafiltration or mechanical circulatory support
    - Prolonged intubation > 48 hours

5.2.4 CLINICAL OUTCOMES

Clinical Outcomes will be assessed at 1 month, 6 months & annually and are defined as:

- Re-hospitalization rates for the underlying condition (heart failure)
- Re-intervention rates for the underlying condition (tricuspid regurgitation)
- Change in Tricuspid Regurgitation (assessment made by change in EROA) from baseline
- Change in peripheral edema as assessed by subject weight loss (kilograms) from baseline
- Change in NYHA Class from baseline
- Change in 6 minute walk test distance (meters) from baseline
- Change in Quality of Life as assessed by the SF-12 and KCCQ questionnaires from baseline

6 STUDY DESIGN

This is a multi-center (≤12), international, prospective, single arm, safety study designed to assess the safety and device performance of the FORMA System.

A total of seventy-eight (78) subjects will be enrolled in the study. All enrolled study subjects will be assessed for clinical follow-up at the following intervals: 1 month, 6 months, 1 year and annually for 3 years post implant procedure. Centers that do not have experience with the investigational device will be allowed a single "roll-in" subject to become familiar with the study device and procedure.

A description of each study visit and required study procedures are included in Section 8.0, Procedures and Methods. In addition, a summary of required procedures is listed in Table 10.

7 SUBJECT POPULATION

7.1 DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

This clinical study is for adult subjects with clinically significant, symptomatic, tricuspid regurgitation who are at high surgical risk for standard tricuspid repair or replacement as assessed by the Heart Team.

All subjects who meet the initial study eligibility requirements will be evaluated for study participation.

Candidates for this study must meet all of the following inclusion criteria and none of the exclusion criteria:

7.2 INCLUSION CRITERIA

The Investigator has the responsibility of screening potential subjects to determine if the patients meet all the inclusion criteria. The following are requirements for entry into the study:

1. Signed and dated EC approved study consent form prior to study related procedures
2. Eighteen years of age or older
3. Clinically significant, symptomatic (NYHA Functional Class II or greater), tricuspid regurgitation (Stage D per 2014 AHA/ACC guidelines) requiring tricuspid valve repair or replacement as assessed by the Heart Team
4. Functional tricuspid regurgitation (e.g., EROA ≥ 0.4 cm2 or equivalent guideline directed value) as the primary etiology
5. NYHA Functional Class II or greater or signs of persistent right heart failure despite optimal medical therapy
6. Determined by the 'HEART Team' (a minimum of one Cardiologist, and one Cardiac Surgeon) to be at high surgical risk for tricuspid valve repair or replacement and the benefit-risk analysis supports utilization of the investigational device
7. Willing to attend study follow-up assessments for up to 3 years

7.3 EXCLUSION CRITERIA

The Investigator at the study site must exclude subjects if any of the exclusion criteria are present. The following are the criteria for exclusion from participating in the clinical study:

1. Tricuspid valve/right heart anatomy not suitable for the study device:
   a. Native tricuspid annulus area < 2.14 cm^2 (9 mm device), < 2.63 cm^2 (12 mm device) or< 3.27cm^2 (15 mm device) as measured by transthoracic echocardiography or computed tomography
   b. Sub-valvular structures/anatomy that would preclude from proper anchor or Spacer placement, positioning and retrieval
2. Access pathway vessel diameter less than 7.1 mm (9, 12 and 15 mm devices) Moderate or greater tricuspid valve stenosis
3. Untreated clinically significant coronary artery disease requiring immediate revascularization
4. Any therapeutic invasive cardiac procedure performed within 30 days of the scheduled implant procedure
5. Patients not already receiving dialysis with renal insufficiency (eGFR < 25) per lab test ≤ 48 hours prior to scheduled implant procedure
6. Myocardial infarction within 30 days of scheduled implant procedure
7. Hemodynamic instability within 30 days of scheduled implant procedure
8. Patient requiring surgery under general anesthesia for any reason within 30 days of scheduled implant procedure
9. Severe left ventricular dysfunction with ejection fraction < 25% within 90 days of scheduled implant procedure
10. Patients with pulmonary artery systolic pressure >70 mmHg via transthoracic echocardiography or alternative standard modality (e.g., direct pressure measurement) within 90 days
11. Concomitant clinically significant valve (aortic, mitral, or pulmonic) disease requiring immediate (± 30 days of study procedure) repair or replacement
12. Active endocarditis or infection within 3 months of scheduled implant procedure
13. Cerebrovascular accident within 3 months of scheduled implant procedure
14. Non-cardiac disease limiting life expectancy to be less than 12 months at baseline evaluation
15. Documented history of bleeding diathesis, coagulopathy or gastrointestinal bleeding within 3 months of scheduled implant procedure
16. Evidence of right sided intracardiac mass, thrombus, or vegetation
17. Prior venous stent placed within the access route (e.g., sub-clavian vein) that could negatively react with device
18. Previously treated tricuspid valve which included implantation of a bioprosthetic valve or mechanical valve
19. Known hypersensitivity to cobalt chromium, nitinol or titanium
20. Known hypersensitivity to anticoagulation therapy or contrast agent, which cannot be adequately medicated

21. Patient is a current intravenous drug user
22. Female of child-bearing potential is pregnant or lactating
23. Patient is currently participating or has participated in another investigational drug or device clinical study within 30 days of study screening activity
24. Patient requires emergent/emergency treatment for tricuspid insufficiency
25. Patient is under guardianship

8 PROCEDURES AND METHODS

8.1 INFORMED CONSENT

As the study Sponsor, Edwards Lifesciences must approve any modifications to the Informed Consent Form prior to submission to the regional ethics investigational review board (REB), independent ethics committee (EC) and/or Competent Authority (as required). A sample Informed Consent Form is provided in Appendix A – Sample Informed Consent Form.

Once the patient's physician has determined the patient's eligibility for the study, the background of the proposed study, and the benefits and risks of the procedures and study will be explained to the patient. The patient must sign the institution's approved Informed Consent Form prior to participation. Failure to provide informed consent renders the patient ineligible for the study.

The consent form will be written in the native language of the patient and administered only by the Investigator or EC approved personnel who speak the native language of the patient. The Principal Investigator or delegated person administering the consent must sign and date the Informed Consent Form to indicate that the purpose, risks and benefits of the study were explained to the patient and that their signature was witnessed.

The Investigator will retain the original consent form, a copy will be filed in the patient's medical record, and a copy of the Informed Consent Form will be provided to the patient.

Informed consent MUST be obtained prior to any study related procedures. A patient will be considered a "subject" and "enrolled" when they have signed the informed consent form agreeing to participate in the study and have been deemed eligible for study participation by meeting the study criteria (Sections 7.2-7.3). Subjects who are consented to participate in the study but do not fulfill enrollment criteria, will be considered "screen failures" as described below (Section 8.2). Signed informed consent forms must be retained by the study site for verification during on-site monitoring visits.

8.2 SUBJECT ENROLLMENT

A Screening/Enrollment Log provided by the Sponsor, will be maintained at the study site to document the screening and enrollment of all subjects assessed for study participation. The screening of subjects qualifying for this study should be carried out in a sequential, prospective manner, such that all patients are offered the possibility of participating in

the study and are therefore, evaluated according to the selection criteria defined in this protocol (see Figure 16). If a subject assessed for study participation does NOT enter the study, the reason in form of a "screen failure" code will be recorded on the log to ensure that a subject selection bias has not been introduced in the study. These reasons may include but not limited to:

- Qualifying patient is not offered an opportunity to participate by Investigator
- Qualifying subject refuses to participate
- Potential subject fails the screening criteria

All subjects assessed for study participation that have signed the informed consent form will be at the point of provisional enrollment and entered on the screening log. All subjects assessed for study participation that have signed the informed consent form, deemed eligible for study participation by the Screening Committee and have met the study criteria, will be at the point of final enrollment and assigned a sequential subject ID number by the study sponsor. The subject ID number together with the subject initials (if applicable) shall be used to identify the subject on all study-related documents.

[redacted]

8.3 BASELINE EVALUATION

1. Informed consent will be obtained from all patients who have been determined to be eligible study candidates and agreed to participate in the study.
2. Medical History (includes 6-month prior heart failure hospitalization rate), Clinical Evaluation (includes vital signs, weight and height), Concomitant Medication and NYHA classification
3. Administration of Health Status Questionnaires (SF-12, KCCQ)
4. Administration of Six Minute Walk Test
5. Clinical Laboratory Tests -
    a. The following lab tests shall be done within 30 days of the scheduled implant procedure:
        i. Troponins and/or cardiac enzymes (CK-MB) - *MI within 30 days of the scheduled implant procedure is an exclusion from study participation*
    b. The following lab tests shall be done ≤ 2 weeks before implant procedure:
        i. Brain Natriuretic Peptide (BNP)
        ii. CBC and platelet count
        iii. Complete metabolic panel
        iv. Liver panel
    c. The following lab tests shall be done ≤ 48 hours before the implant procedure:
        i. Estimated Glomerular Filtration Rate (eGFR) - *eGFR result of < 25 is an exclusion from study participation for patients not already receiving dialysis*
        ii. βHCG for women who are not sterile or post-menopausal- *positive result is an exclusion from study participation.*
        iii. PTT/aPTT or PT/INR
6. Standard 12-lead Electrocardiogram (ECG)
7. Comprehensive Echocardiograms (Transthoracic [TTE] and Transesophogeal [TEE]), if required[1], (within 90 days of scheduled implant procedure) including but not limited to, annulus size, ventricular size, regurgitant assessment, jet location, mean PAP and LVEF. Analysis will be conducted by the Investigator and Sponsor to certify the subject is eligible for the study.
8. Computed Tomography (CT) (within 90[2] days of scheduled implant procedure), that captures the anatomy of the subclavian and axillary veins, superior vena cava,

[1] The primary purpose of the TEE is to confirm the ability to image the tricuspid valve and possible anchoring location during the index procedure as this is the method that is used intra-procedure. If the TTE can demonstrate that the imaging of the valve and possible anchoring location is adequate, the TEE requirement at the baseline evaluation may be waived.

[2] If a pre-existing CT within 6 months of the scheduled implant procedure captures all the required anatomy for necessary measurements and the anatomy has not changed, the baseline CT can be waived and is not required to be repeated.

tricuspid valve and sub-valvular structures/anatomy, right atrium and right ventricle. Analysis will be conducted by the Investigator and Sponsor/designee to certify the subject is eligible for the study.

9. Invasive Hemodynamic Monitoring/Right Heart Catheterization (within 45 days of scheduled implant procedure) that includes, but is not limited to, right atrial pressure (RAP) and pulmonary artery pressure (PAP) measurements.[3]

Baseline evaluation data to be collected will include but is not limited to the information listed in the following table.

Table 4 - Baseline Evaluation

General Information	Clinical Information	Laboratory Measurements
• Inclusion/exclusion evaluation • Informed consent • Age • Gender • Height • Weight	• Heart Team determination • Medical history (e.g., EuroSCORE) /prior cardiovascular interventions / surgeries • Vital signs (Blood pressure, heart rate) • Concomitant Medication • NYHA classification[1] • Echocardiographic measurements (TTE & TEE), tricuspid regurgitation & heart function • Computed Tomography (CT) • Invasive Hemodynamic Monitoring/Right Heart Catheterization including pressure measurements • ECG results • Six minute walk test (pre & post walk data & results) • KCCQ & SF-12 questionnaires	Within 30 days of procedure: • Date of blood draw • Troponin[2] and/or CK-MB[2] Within ≤ 2 weeks of procedure: • Date of blood draw • BNP • WBC • RBC • Hematocrit • Hemoglobin • Platelets • ALT/SGPT • AST/SGOT • Bilirubin • LDH • Sodium & potassium • Urea Within ≤ 48 hours of procedure: • eGFR[3] • PTT/aPTT or PT/INR • βHCG, if applicable[4]

1. *Classification of < NYHA II is an exclusion from study participation*
2. *MI within 30 days of the scheduled implant procedure is an exclusion from study participation*
3. *eGFR result of < 25 is an exclusion from study participation*
4. *A positive result is an exclusion from study participation*

[3] If the screening echo confirms the PAP meets the study criteria, the right heart catheterization/ hemodynamic assessment at the baseline evaluation may be waived.

8.4 ANTIPLATELET / ANTICOAGULATION THERAPY

All subjects will receive aspirin (at least 75 - 100 mg daily) prior to implant procedure. Subjects on warfarin will be asked to discontinue use prior to implant procedure. See Table 5.

Heparin will be administered at procedure start. During the procedure, activated clotting time (ACT) will be monitored and recorded on source documentation. Heparin will be administered during the procedure as needed to maintain the subject's ACT at ≥ 250 sec. The sheaths may be removed when ACT level is appropriate (e.g., reaches < 150 sec) after implantation of the study devices.

Implanted subjects will receive aspirin (at least 75 - 100 mg daily) post implant procedure through the 6 month follow-up visit. Additionally, patients with pre-existing atrial fibrillation will continue with their prescribed blood thinning medication (e.g., Coumadin® or Jantoven®) (INR > 2.5) post implant procedure through the 6-month follow-up visit. For patients not in atrial fibrillation, a second antiplatelet medication of the investigator's choice (e.g., Plavix) shall be prescribed post implant procedure through the 6-month follow-up visit. The antiplatelet regimen past the 6-month follow-up visit will be determined at the Investigator's discretion.

Table 5 - Summary of Recommended Concomitant Medical Therapy

Medication	Pre-Procedure	Inter-Procedure	Post-Procedure	1 Month Follow-Up	6 Month Follow-Up
IV Heparin		X	X[4]		
Aspirin 75-100 mg daily	X		X	X	X
Warfarin or alternative (AFib Patients)			X	X	X
Plavix or alternative (Non-AFib Patients)			X	X	X

NOTE: The Investigator will determine the antiplatelet/anticoagulation therapy for study subjects on an existing dual antiplatelet therapy or with known hypersensitivity to the required medications in Table 5.

[4] As needed as a bridge to warfarin where applicable

8.5 DEVICE PREPARATION

A description of device preparation and use is provided in the Instructions for Uses (IFUs), (See Clinical Investigator's Brochure). Investigators must be familiar with the information described in the IFU prior to use of the FORMA System.

An Edwards Representative that has been trained on the preparation of the FORMA System will be in attendance at all implant procedures.

8.6 IMPLANT PROCEDURE

The implant procedure shall be performed under general anesthesia with hemodynamic monitoring in an operating room, catheterization lab or hybrid operating room with fluoroscopic and echocardiographic imaging capabilities. The use of cardiopulmonary bypass is not required.

The following study procedures will occur during the implant procedure:

1. Safety Evaluation
2. Transesophageal Echocardiogram
3. Angiographic Imaging
4. Invasive Hemodynamic Monitoring/Right Heart Catheterization including right atrial pressure measurements pre and post implant
5. Heparin administration to achieve (and maintain) an ACT of ≥ 250 during the implant procedure

Subjects will be monitored in the operating room as needed with special attention to hemodynamic condition and cardiac rhythm. Subsequent monitoring of subjects will be continued in the recovery room or ICU.

The date of the implant procedure will be considered as Day 0 for the purpose of determining specified time intervals for the follow-up visit for the implanted and non-implanted cohorts.

Procedure data to be collected will include but is not limited to the information listed in the following table.

Table 6 - Procedure Information

General Information	Clinical Information	Laboratory Measurements
• Hospital admission date • Subject identification number • Names of Interventional Cardiologist & Access Management Physician • Procedure date • Access site • Timing of implant procedures • FORMA System identification & disposition	• Fluoroscopy duration & contrast volume • Heparin administration & ACT levels • TEE measurements, tricuspid regurgitation & heart function • Angiographic Imaging • Invasive Hemodynamic Monitoring/Right Heart Catheterization and pressure measurements performed • Post-implant antiplatelet / anticoagulation regimen • Adverse events • Device malfunction	Within 24 hours post implant: • Troponin[1] and/or CK-MB[1]

1. *If an elevation was noted post implant (within 24 hours), tests must be repeated three times or until not clinically significant*

8.6.1 ANTIBIOTIC PROPHYLAXIS

It is recommended that all recipients be prophylactically treated for endocarditis to minimize the possibility of infection.

8.6.2 CONTRAST MEDIA

Careful management of contrast media is required for these patients. Accurate measurement of the dye used during the implant procedure shall be captured in the appropriate case report form.

8.6.3 DISCHARGE

The following procedures will be performed prior to discharge from the hospital/unit:

1. Clinical Evaluation and Concomitant Medication
2. Safety Evaluation
2. Clinical Laboratory Tests
    a. BNP
    b. CBC and platelet count
    c. Complete metabolic panel

d. Liver panel
e. PTT/aPTT or PT/INR
f. eGFR
g. Troponins and/or cardiac enzymes (CK-MB), only required if an elevation was noted post implant (within 24 hours)

3. Standard 12-lead ECG
4. Comprehensive Transthoracic Echocardiogram, including but not limited to, annulus size, ventricular size, regurgitant assessment and jet location

Discharge data to be collected will include but is not limited to the information listed in the following table.

Table 7 - Discharge Information

General Information	Clinical Information	Laboratory Measurements
• Discharge date • Weight	• Vital signs (Blood Pressure, Heart Rate) • NYHA classification • TTE measurements, tricuspid regurgitation & heart function • ECG results • Post-implant antiplatelet / anticoagulation regimen • Adverse events	• Date of blood draw • Troponin and/or CK-MB, if applicable • BNP • WBC • RBC • Hematocrit • Hemoglobin • Platelets • ALT/SGPT • AST/SGOT • Bilirubin • LDH • Sodium & potassium • Urea • eGFR • PTT/aPTT or PT/INR

8.7 FOLLOW-UP VISITS

Follow-up visits will be conducted at 1 month, 6 months, and annually for 3 years post implant procedure intervals as illustrated in Table 9. The following procedures will be conducted during follow-up visits:

1. Clinical Evaluation, Concomitant Medication and NYHA classification
2. Administration of Health Status Questionnaires (e.g., SF-12, KCCQ)

3. Administration of Six Minute Walk Test
4. Safety Evaluation
5. Clinical Laboratory Tests :
   a. BNP
   b. CBC and platelet count
   c. Complete metabolic panel
   d. Liver panel
   e. PTT/aPTT or PT/INR
   f. eGFR
6. Standard 12-lead ECG
7. Comprehensive Transthoracic Echocardiogram, including but not limited to, annulus size, ventricular size, regurgitant assessment and jet location

Follow-up data to be collected will include but is not limited to the information listed in the following table.

Table 8 - Follow-Up Visit Information

General Information	Clinical Information	Laboratory Measurements
• Visit date • Height • Weight	• Vital signs (Blood Pressure, Heart Rate) • NYHA classification • TTE measurements, tricuspid regurgitation & heart function • ECG results • Six minute walk test (pre & post walk data & results) • KCCQ & SF-12 questionnaires • Concomitant Medication • Adverse events	• Date of blood draw • BNP • WBC • RBC • Hematocrit • Hemoglobin • Platelets • ALT/SGPT • AST/SGOT • Bilirubin • LDH • Sodium & potassium • Urea • eGFR • PTT/aPTT or PT/INR

8.7.1 FOLLOW-UP VISIT WINDOWS

Post-procedure follow-up visits will be performed on all implanted study subjects at 1 month, 6 months, and annually for 3 years post implant procedure intervals as illustrated in Table 9 below:

Table 9 - Follow-up Visit Windows

Scheduled Follow-up Interval	Follow-up Window
1 month (30 days)	± 7 days
6 months (183 days)	± 30 days
Annually (365 days) up to 3 years	± 45 days

During the follow-up visits, medical information, findings and results will be entered in the appropriate electronic case report forms.

Study subjects who have signed the Informed Consent, are deemed eligible and considered enrolled in the study but do not have the study procedure (incision) occur will be exited from the study immediately.

Study subjects who have signed the Informed Consent, are enrolled in the study, have the study procedure (incision) occur but do not receive the investigational device will be classified as "non-implanted" study subjects and exit the study at the 6 month follow-up visit. Non-implanted study subjects must complete safety evaluations but, will be exempt from all other study follow-up visit procedures.

Table 10 - Summary of Required Study Procedures

STUDY PROCEDURES	BASELINE	IMPLANT PROCEDURE[1] (Day 0)	DISCHARGE[2]	1 MONTH (30 ± 7 days)	6 MONTHS (183 ± 30 days)	ANNUAL (for 3 yrs) (365 ± 45 days)
Informed Consent	X					
Medical History	X					
Clinical Evaluation	X		X	X	X	X
NYHA Class Assessment	X			X	X	X
Health Status Questionnaires	X			X	X	X
Six Minute Walk Test	X			X	X	X
Safety Evaluation		X	X	X	X	X
Brain Natriuretic Peptide (BNP)	X		X	X	X	X
CBC and Platelet Count	X		X	X	X	X
Complete Metabolic Panel	X		X	X	X	X
Liver Panel	X		X	X	X	X
PTT/aPTT or PT/INR	X		X	X	X	X
βHCG	X[3]					
eGFR	X[4]		X	X	X	X
Troponins and CK-MB	X	X[5]	X[6]			
ECG	X		X	X	X	X
Transesophageal Echocardiogram	X[7]	X				
Transthoracic Echocardiogram	X		X	X	X	X
Pre-Implant Computed Tomography	X					
Angiographic Imaging		X				
Invasive Hemodynamic Monitoring/Rt Heart Cath.	X[8]	X				

[1] Implant procedure must be scheduled within 90 days of the baseline transthoracic echocardiogram and 90 days of the pre-implant procedure computed tomography (CT). If a pre-existing CT within 6 months of the scheduled implant captures all the required anatomy for necessary measurements & the anatomy has not changed, the baseline CT can be waived & is not required to be repeated.
[2] Discharge from hospital/unit post implant procedure
[3] βHCG for women who are not sterile or post-menopausal
[4] *eGFR result of < 25* is an exclusion from study participation
[5] Test will be taken post-implant (within 24 hours). If an elevation is noted, test must be repeated three times or until not clinically significant.
[6] If an elevation was noted post implant (within 24 hours), test must be repeated three times or until not clinically significant
[7] The primary purpose of the TEE is to confirm the ability to image the tricuspid valve during the index procedure as this is the method that is used intra-procedure. If the TTE can demonstrate that the imaging of the valve is adequate, the TEE requirement at the baseline evaluation may be waived.
[8] If the screening echo confirms the PAP meets the study criteria, the right heart catheterization/hemodynamic assessment at the baseline evaluation may be waived.

8.8 MISSED SUBJECT VISITS

The Investigator shall inform study subjects of the importance of returning for scheduled follow-up visits and reporting any address or telephone number changes. The Investigator shall make every attempt to follow the study subjects.

The Investigator shall keep a separate log of the subjects' names and current contact information to facilitate their record keeping and ability to contact the subjects for future follow-up. If a subject cannot be reached for a follow-up assessment, the Investigator will document the missed visit and effort made to contact that subject, the subject's primary health care provider, and/or hospital records on the appropriate Case Report Form. Subjects who miss a visit will not be considered withdrawn, and an effort to contact them at the next follow-up visit interval will be made by the Investigator.

8.9 WITHDRAWAL CRITERIA AND PROCEDURES

The Investigator will make every attempt to follow the subjects at each of the required assessment periods. The reason for the withdrawal will be documented on the appropriate case report forms and in the medical records for each subject who has withdrawn.

Subjects may be withdrawn from the study for any of the following reasons:

- Subject Withdrawal

  The subject may voluntarily withdraw from the clinical study at any time, without penalty or loss of benefits to which they are otherwise entitled.

- Physician Withdrawal

  The Principal Investigator also has the right to withdraw a subject if they feel it is in the best interest of the subject to do so.

- Lost to Follow-up

  If a subject cannot be reached for a follow-up visit, the Investigator will document the contact efforts made to the subject and/or effort to obtain hospital records in the appropriate electronic case report form. If the subject cannot be reached in any way, or misses a visit, the subject will be considered "unable to contact" for that time interval. After three (3) documented unsuccessful attempts to make contact prove unsuccessful, a certified letter will be sent to the subject's residence. If there is no response after the certified letter is sent, the subject will be considered "lost to follow-up."

In all cases of withdrawal (as described above), withdrawn subjects will not undergo further study follow-up procedures after the time of study exit. A study subject that has been withdrawn from the study will not be replaced.

8.10 SUBJECT STUDY COMPLETION

Study subjects complete and exit the study when no additional follow-up visits, procedures, or data collection are required. Patients will then continue to be followed by their primary health care provider as required.

A subject will also be exited from the study in the following instances:

- Subject signs informed consent form, is deemed eligible and considered enrolled but does not undergo the study procedure
- Subject undergoes study procedure and does not receive investigational device (will continue in study for safety evaluations only and exit the study at the 6 month follow-up visit)
- Implanted subject requires the investigational device to be explanted for any reason (will continue in study for safety evaluations only and exit the study at the 6 month follow-up visit)
- Subject is lost-to-follow-up
- Subject withdraws participation from the study or is withdrawn from the study
- Subject expiration

9 TRAINING

9.1 INVESTIGATORS DEVICE TRAINING

[redacted]

9.2 TRAINING OF INVESTIGATIONAL CENTER PERSONNEL

[redacted]

[redacted]

9.3 TRAINING DOCUMENTATION

[redacted]

10 INVESTIGATIONAL DEVICE MANAGEMENT

10.1 DEVICE SHIPMENTS

Devices will be transported to the study center when the Clinical Study Agreement is in place, the study center has obtained applicable regulatory (e.g., EC, Health Canada, MOH) approvals, and a subject eligible for implant has been identified.

Devices will be provided to the study center as needed for scheduled implant procedures. All investigational devices used in this study for investigational purposes will be labeled with regional appropriate clinical investigation labeling and warnings.

10.2 DEVICE ACCOUNTABILITY

All device shipments will have inventory and shipment records. Devices may be hand carried to participating study centers by Study Sponsor personnel and will be accompanied by delivery of investigational device documentation (packing lists, transfer of investigational product form, etc.). The Investigator(s) or designee will take inventory of the product and complete the delivery documentation with receipt date and signature. Both the study center and the Study Sponsor will retain copies of these documents. The Investigator will maintain a Device Accountability Log (as provided by the Sponsor) of all investigational devices documenting their receipt, disposition and return during this clinical study. The log will be kept with the documents for the clinical study and will be available for review during Study Sponsor monitoring visits.

Upon Sponsor request or when enrollment has ended, FORMA System components must be returned to Edwards Lifesciences and the date of return must be recorded on the log.

10.3 DEVICE STORAGE

The device inventory will be stored in a locked, controlled, cool and dry area as described in the Instructions for Use (IFU) and/or presented on the device labeling. This secured area will be only accessible to the Investigators or approved designee. Only investigators trained and identified in the Delegation of Authority form on file at Edwards Lifesciences may use the investigational devices.

10.4 DEVICE RETURN

The Investigator will be notified in writing upon termination of the clinical study. All unused devices in original package and/or those in opened packages as well as those removed from the original package will be returned upon receipt of this notice. The Investigator will receive instructions from the Study Sponsor on the return process. The Investigator's copy of the Device Accountability log must document any unused devices that have been returned.

Used devices may be handled and disposed of in the same manner as hospital waste and bio-hazardous materials in accordance with local regulations. There are no special risks related to the disposal of these devices. Devices that malfunction or are related to a serious adverse event or device effects will be returned to the Study Sponsor for further investigation (when possible). All returns and dispositions of devices will be captured on the Device Accountability Log Procedure needed.

11 DATA COLLECTION AND REPORTING

11.1 DATA COLLECTION METHODS

The Study Sponsor will provide the study center with the clinical protocol, electronic case report forms, sample informed consent form, and all other necessary study-related documents. Study Sponsor's Clinical Affairs Department, or designee, will conduct all aspects of data quality control and assurance of the study center including but not limited to, data reviewing, data monitoring, and form collection.

11.2 CASE REPORT FORMS

Electronic CRFs will be used to collect all patient data during the trial. Paper copies will be available for printing on the website. An e-mail notification will be sent to Edwards Lifesciences when enrollment data is collected into the website. Electronic CRFs must be fully completed for each patient, and signed electronically by the investigator and/or designee. If for any reason the eCRFs are unavailable, or access to the electronic database is limited, paper CRF forms must be completed and submitted to study manager. The eCRFs should be completed at the first earliest opportunity.

The investigator, or an individual designated by him/her, is responsible for recording all data from the trial onto the eCRFs on a dedicated website. All data entered is subjected to data type verification and range checking. The operator is notified of errors that may occur, and depending on the data verification sub-routines, the operator might need to resolve that error before moving to the next entry field. The investigator is required to provide an electronic signature on the appropriate eCRF pages to verify that he/she has reviewed the recorded data.

Completed eCRFs will be reviewed at the investigational site and remotely by authorized Edwards Lifesciences personnel at regular intervals throughout the trial. Each data record is evaluated with extensive electronic intra-form and inter-form edit checking at regular intervals. If an error is discovered, the clinical site research Study Coordinator will be notified. Corrections to the eCRFs will be made by the research Study Coordinator, approved by the investigator or designee and verified by the sponsor.

Data submission will be monitored closely. Sites that do not complete all data entry tasks in a timely manner may be prohibited from enrollment until data submission is current.

The cycle of data editing will be ongoing until all the data are clean. The sponsor or designee will monitor the clinical site for source documentation verification. If further data entry or source documentation errors are discovered during the site visit, additional queries will be generated and will have to be addressed by the clinical site.

11.3 SOURCE DOCUMENTATION REQUIREMENTS

The Clinical Research Coordinator (CRC) designated by the Investigator, and documented on the Delegation of Authority log, will perform primary data collection drawn from source documentation review (subject's medical record). All data that is entered in the eCRFs must have source documentation available in the subject medical records. Data to be collected for the study purposes must not be entered directly onto eCRFs. Protocol deviation information can be recorded directly on the protocol deviation eCRF. The data must be recorded from original source documents and available for review by the study monitor. Regulations require that Investigators maintain information in the study subject's medical records that corroborate data collected on the eCRFs. The source documentation may consist of but is not limited to: operative or procedure reports, progress notes, discharge summaries, laboratory reports, radiographic reports, medication logs, and worksheets. Source Documents may be in electronic form and/or hard (paper) copies.

11.4 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

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

All clinical sites will be audited periodically by a study monitor employed by Edwards for protocol adherence, accuracy of eCRFs, and compliance to applicable regulations. Evident patterns of non-compliance with respect to these standards will be cause for the site to be put on probation for a period of one month. If corrective actions are not subsequently undertaken, the clinical site will be asked to withdraw.

Operational data is hosted for full security and availability internally by Edwards. Edwards data management provides the highest standards of availability and security:

- Hosting facility is a multi-level protected environment.
- Access is severely restricted with high-end user recognition technology.
- Multi-points backup of critical data is standard.
- Firewalls and other undisclosed technologies provide strong data security.
- Availability all year-round 24 hours a day.

Passwords will be issued to appropriate data management personnel to ensure confidentiality and protection of the data by allowing variable levels of access to the computer system.

12 REPORTABLE EVENTS / EFFECTS

12.1 REPORTING PROCEDURE

Study subjects will be carefully monitored during the clinical study for any possible adverse event. All adverse events will be fully investigated by the Investigator. Appropriate treatment for the subject will be initiated while the study follow-up continues. Adverse events will be followed until they are adequately resolved or explained.

The Investigator will attempt to assess the involvement of the investigational device and / or study procedure in the adverse event according to five different levels of causality (See Section 19, Definitions, for causality definitions). All observations and clinical findings, including the nature or the severity, will be documented on the appropriate case report form.

The Investigator will report any serious adverse event, anticipated or unanticipated, to the Study Sponsor within 24 hours after first knowledge of the event. Notification to the Study Sponsor will be made as follows:

[redacted]

In addition, the Investigator will report all adverse events to their Ethics Committee Institutional Review Board in accordance with their requirements. Adverse events will be reported to the National Regulatory Agency in accordance with the applicable requirements, for example as described in the "SAE Documentation, Evaluation and Reporting Procedure to the Competent Authorities" document for Germany.

12.2 DEFINITIONS

12.2.1 ADVERSE EVENT

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 finding) in subjects, users or other persons, whether or not related to the investigational medical device.

Note: anticipated adverse events are adverse events that have been identified as possible adverse events related to the investigational medical device or the study procedure. The anticipated events of this clinical study are outlined in Section 3.1, Potential Risks

12.2.2 ADVERSE DEVICE EFFECT

An adverse device effect (ADE) 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 abnormal use of the investigational medical device.

12.2.3 SERIOUS ADVERSE EVENT

A serious adverse event (SAE) is defined in ISO 14155:2011 as an adverse event that:

1. led to death
2. led to serious deterioration in the health of the subject that either resulted in:
   a. a life-threatening illness or injury, or
   b. a permanent impairment of a body structure or a body function, or
   c. in-patient or prolonged hospitalization, or
   d. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
3. led to fetal distress, fetal death or a congenital abnormality or birth defect (not anticipated in this study as pregnant women are excluded from the study).

12.2.4 SERIOUS ADVERSE DEVICE EFFECT

A serious adverse device effect (SADE) is defined in ISO 14155:2011 as an adverse device effect that resulted in any of the consequences characteristics 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.

12.2.5 UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT

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

12.2.6 DEVICE DEFICIENCY AND MALFUNCTION

Device deficiency is defined in ISO 14155:2011 as an inadequacy of a medical device with respects to its identity, quality, durability, reliability, safety or performance.

Device deficiencies include malfunctions, use errors and inadequacy in the information supplied by the manufacturer.

Device malfunction is defined in ISO 14155:2011 as a failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the Instructions for Use.

Device embolization is defined in ISO 5840-3 as dislodgement from the intended and documented original position to an unintended and non-therapeutic location.

Device detachment is defined as separation, under the action of applied stress or strain, of any part of the investigational device that was previously intact.

Device migration is defined in ISO 5840-3 as detectable movement or displacement of the device from its original position within the implant site, without embolization.

Structural component failure is defined as degradation of structural integrity of the support structure (e.g., railing) that results in the functional performance of the implant no longer being acceptable and/or that results in adverse events.

Device deficiencies and malfunctions will be reported to the sponsor.

12.3 DEATHS AND EXPLANTS

12.3.1 SUBJECT DEATHS

In the event of subject death, every effort should be made to obtain a copy of the autopsy report and/or death summary. Information on the cause of death and its relationship to the investigational device or study procedure will be determined by the Investigator. Copies of an autopsy report, if available, and/or a death summary are to be forwarded to the Study Sponsor.

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

12.3.2 DEVICE EXPLANTS

In the event the study devices are explanted, in the intra-operative or early post-operative period a copy of the explant procedure report must be provided to the Study Sponsor. Information on the cause of explant and its relationship to the study devices will be determined by the Investigator. Explanted study devices during this period must be returned to Study Sponsor for analysis.

In the event the study device is explanted, in the late post-operative period, every effort should be made to obtain a copy of the explant procedure report, as applicable. Information on the cause of explant and its relationship to the study device will be determined by the Investigator. Copies of an explant report, if available, are to be sent to the Study Sponsor. Explanted study devices during this period should be returned to Study Sponsor for analysis. Investigational devices shall be returned to the Study Sponsor as described in Section 10.4.

13 STATISTICAL ANALYSIS

13.1 SAMPLE SIZE

The primary endpoint is all-cause mortality at 30-days. Survival probabilities and standard errors will be estimated using the Kaplan Meier method and Greenwood formula respectively.

A performance goal of 18% was pre-specified for the 30-day rate of all-cause mortality in TVR (Tricuspid Valve Regurgitation) subjects treated with the Edwards FORMA Tricuspid Transcatheter Repair System, which was based on review of literature and early clinical studies (reference Section 1.3). The hypothesis for the primary endpoint is as follows:

- H0: $\pi \geq 18\%$
- HA: $\pi < 18\%$

Where π represents the all-cause mortality rate at 30 days.

The study is powered to detect a clinically significant difference between the expected mortality of the treatment group and the 18% Performance Goal. Based on the initial experience of the device (with some additional uncertainty assumptions), the estimated true rate was established to be 7.5% or less. Targeting a clinically significant difference of 10.5% (absolute reduction of greater than 50%), a sample size of 63 subjects will yield

at least 80% power to detect this difference at a significant level of 0.05. With a proportion of up to 9 investigational centers utilizing a roll-in subject and with a potential dropout rate of approximately 10%, an enrollment target of 78 subjects will ensure a sample size of 63 is available for analysis.

[redacted]

13.2 TIMING

Subjects will be assessed for clinical follow-up at the following intervals: 1 month, 6 months, one year and annually thereafter until 3 years after the implant procedure.

13.3 ANALYSIS POPULATION

The analysis population will be grouped into four analysis cohorts that in total comprise all subjects enrolled in this study. The analysis cohorts are defined below:

- Enrolled Cohort: all subjects enrolled in the study
- As Treated (AT) Cohort: all subjects who are enrolled and undergo the study procedure (chest incision)
- Implanted Cohort: all subjects who undergo the study procedure (chest incision), receive and retain the investigational device upon leaving the procedure room
- Roll-In Cohort: first subject enrolled and treated at a center that does not have previous device or procedure experience and is classified as a "roll-in" subject

The primary endpoint will be reported based on the AT cohort. For the secondary endpoints and clinical outcomes, technical success analysis will be performed for the AT cohort, while device success, procedure success and clinical outcomes analyses will be performed for the implanted cohort. Roll-In subjects will be analyzed separately. Subject listings for adverse events, deaths will include all enrolled subjects.

For subjects with major protocol violations, which include but are not limited to study criteria and informed consent violations, a secondary analysis will be conducted in which those subjects will be excluded from the implanted cohort analyses.

Further analysis plans will be outlined in the statistical analysis plan.

13.4 PRIMARY ENDPOINT ANALYSIS

The primary endpoint for this clinical study is all-cause mortality at 30 days post-implant procedure in the as treated (AT) cohort population. A one-sided 95% confidence interval for 30 day mortality will be computed using the Kaplan-Meier algorithm with the standard errors being computed using Greenwood's formula. The null hypothesis shall be rejected at alpha = 0.05 if the upper confidence limit is less than 0.18.

13.5 ADDITIONAL ENDPOINT ANALYSIS

All statistical analyses will be performed by Edwards Lifesciences. Subject data listings and tabular presentations of results will be provided. All clinically relevant baseline and follow-up variables will be tabulated. Descriptive statistics will be used for continuous variables (e.g., mean, standard deviation, sample size, minimum, and maximum) and frequency tables or proportions for discrete variables.

Kaplan Meier estimates will be performed at the pre-specified follow-up times to project the estimates for time-related safety endpoints. The rate of freedom from all-cause mortality at 6 month, 1 year, 2 years, and 3 years will be estimated in addition to the primary endpoint which is established at 30 days post procedure.

Echocardiographic data will be analyzed by a core laboratory. The improvement from baseline items will be presented as shift from baseline for each of the pre-specified follow-up periods. Subjects that are missing a baseline or follow-up values will be excluded from the analysis.

Subjects that undergo any type of repair or replacement procedure for the tricuspid valve will be excluded from the implant cohort analyses at the time of the re-intervention.

13.6 MISSING DATA

All possible steps will be taken to minimize missing data in the study, including monitoring of data forms for completeness and efforts to track and maintain contact with study subjects during the follow-up period.

All statistical analyses will be performed using available data. No missing value imputation will be performed.

13.7 ANALYSIS SOFTWARE

[redacted]

14 MONITORING

14.1 MONITORING METHODS

A study monitor will be assigned to monitor the progress of the study by the Study Sponsor. The study monitor may be either the Study Sponsor or contracted. The study monitor will remain in close contact with the study center throughout the duration of the study to provide any needed materials, (i.e. study forms, etc.) answer any questions and ensure that proper staffing levels are being maintained by the Investigator. The study monitor will be responsible for verifying that subjects have signed the informed consent as required by regulations, reviewing the data recorded on the eCRFs and visiting the study center periodically to observe study progress and compliance with the study protocol and regulations applicable to this clinical study.

Monitoring visits will be scheduled throughout the duration of the clinical study between the monitor and the Investigator at a mutually convenient and available time. These visits will assure that the facilities are still acceptable, the study protocol is being followed, the EC and regulatory authority have been notified of approved protocol changes as required, complete records are being maintained, appropriate timely reports have been made to the Study Sponsor and the EC, device and device inventory are controlled and the Investigator is carrying out all agreed activities. Any personnel changes must be reported to the study monitor immediately and a training program scheduled and documented.

14.2 MONITORING PLAN

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

1. EC and applicable regulatory body approvals have been obtained and documented,
2. The Investigator(s) and study personnel are appropriately trained and clearly understand the study,
3. The Investigator(s) and study personnel accept the obligations incurred in undertaking this clinical study,
4. The Delegation of Authority form has been completed properly.

Periodic monitoring visits will be made at the enrolling study center in accordance with center enrollment rates. The study center should be visited a minimum of twice per year by the study monitor.

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

14.3 PROTOCOL DEVIATION

A protocol deviation is defined as an event where the Investigator or a study personnel did not conduct the study according to the clinical protocol or the Clinical Study Agreement. Investigators shall be required to obtain proper approval from the Study Sponsor before initiating deviations from the study protocol, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval shall be documented in writing and maintained in study files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, (e.g. subject did not attend scheduled follow-up visit, etc.) however the event is still considered a deviation.

Deviations shall be reported to the Study Sponsor regardless of whether medically justifiable, pre-approved by the Sponsor, or taken to protect the subject in an emergency. Subject specific and non-subject specific deviations, (e.g. unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a physician who is not listed in the Clinical Study Agreement etc.) will be reported. Subject specific deviation information can be recorded directly on the Protocol Deviation eCRF and non-subject specific deviations will be recorded in writing. Investigators will also adhere to procedures for reporting study deviations to their EC in accordance with their specific reporting policies and procedures.

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

1. Major deviation:
    a. Any deviation from subject inclusion and exclusion criteria;
    b. Any deviation from subject informed consent procedures;
    c. Unauthorized use of an investigational device outside the study;
    d. Unauthorized use of an investigational device by a physician who is not listed in the Clinical Study Agreement

2. Minor deviation:
    a. Deviation from a protocol requirement such as incomplete/inadequate subject testing procedures;
    b. Follow-up performed outside specified time windows.

14.4 COMMUNICATION PROCEDURES

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

15 DATA MONITORING COMMITTEE

The Study Sponsor with an independent Data Monitoring Committee (DMC) will monitor all serious adverse events. The DMC will consist of a minimum of 3 members, all members being physicians; one cardiothoracic surgeon, one interventional cardiologist and one cardiologist.

[redacted]

16 STUDY STOPPING RULES

[redacted]

17 ETHICAL AND REGULATORY CONSIDERATIONS

17.1 APPLICABLE REGULATIONS AND GUIDELINES

The regulations listed in Table 11 must be observed to comply with the Study Sponsor policy for conduct and of clinical studies; they also represent sound research practice. It is the responsibilities of the Investigator(s) to comply with the requirements set forth in their country specific regulations.

Table 11 - Applicable Regulations and Guidelines

Region	Regulation / Guideline
United States	- 93/42/EEC European Medical Device Directive (MDD) - EN ISO 13485:2012 Medical Devices - Quality Management Systems - Requirements for Regulatory Purposes - ISO 14155:2011 (E) (Clinical Investigation of Medical Devices for Human Subjects - ISO 14971:2012 (Application of risk management to medical devices)

Furthermore, the Investigator(s) must comply with the requirements of the Declaration of Helsinki (2008) and with of ICH E6 GCP or with laws of the foreign country, whichever will afford greater protection to the subject screened for participation in the clinical study and subjects who participate in the study.

17.2 DATA PROTECTION AND SUBJECT CONFIDENTIALITY

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

17.3 INVESTIGATOR RESPONSIBILITIES

17.3.1 GENERAL DUTIES

The Investigator shall ensure that all work and services described herein, or incidental to those described herein, shall be conducted in accordance with the highest standards of

medical and clinical research practice and the applicable regulations. The Investigator shall be responsible for the day to day conduct of the clinical study and for the safety and well-being of subjects enrolled. The Investigator will provide copies of the current study protocol to all staff responsible for study conduct.

The Investigator is responsible for obtaining and maintaining EC approval for the study at his/her study center.

If there is a change or addition of an Investigator, an amended Clinical Study Agreement must be completed promptly.

17.3.2 INVESTIGATOR RECORDS

The Investigator will maintain the accurate, complete, and current records relating to participation in this clinical study. Study records including CRFs and supporting data, signed Clinical Study Agreement, protocols and protocol amendments, signed informed consents, device tracking logs, EC approval letters, EC submissions, correspondence, including required reports, and other documents pertaining to the conduct of the study must be kept on file by the Investigator. If the Investigator wishes to assign the responsibility of maintaining the study files to someone else or move them to another location, he/she should consult with the Study Sponsor in writing regarding the change. Upon Study completion, the study files must be maintained in a known location for a period in accordance with local regulatory requirements.

17.3.3 INVESTIGATOR REPORTS

[redacted]

17.4 SPONSOR RESPONSIBILITIES

17.4.1 GENERAL DUTIES

As the Study Sponsor of this clinical study, Edwards Lifesciences has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the pertinent regulatory agencies.

In addition, the Study Sponsor declares that no employee/affiliate of the Sponsor or Investigator will be included or encouraged to participate in this investigational study.

The Study Sponsor will inform the Investigator of any new information about the study that may affect the health, safety or welfare of the subjects or which may influence patient's decision to continue participating in the study.

Additionally, interruptions in the study or recruitment due to significant amendments will also be reported to the applicable regulatory authorities.

17.5 SELECTION OF INVESTIGATORS

[redacted]

17.5.1 MONITORING THE STUDY

The Study Sponsor will ensure compliance with the signed clinical agreement, the protocol (investigational plan), the requirements of applicable regulations and guidelines (see section 17.1) and any conditions of study approval by the EC and regulatory bodies. Edwards will conduct an immediate investigation of any unanticipated adverse device effects (UADE) and if an event is found to present an unreasonable risk to study subjects, the Study Sponsor will inform Investigators, ECs, and regulatory bodies as required.

17.5.2 SPONSOR RECORDS

The Study Sponsor will maintain accurate, complete, and current records relating to this clinical study. Study records include CRFs, signed Clinical Study Agreement, signed financial disclosure, protocols and protocol amendments, informed consent, device use, EC approval letters, submissions, correspondence, including required reports, and other documents. The Study Sponsor will maintain study documentation during the study and for a period in accordance with local regulatory requirements after the study is terminated or completed, or the study records are no longer required to support a regulatory submission. Storage of the study records may be designated to a third party.

17.5.3 SPONSOR REPORTS

[redacted]

17.6 STUDY CHANGES

Changes in the protocol may be made only by written amendment agreed upon by the Study Sponsor, the regulatory agency and EC. As appropriate, the Study Sponsor will submit protocol amendments to the pertinent regulatory agencies and Investigators to obtain EC approval prior to implementation.

17.7 STUDY COMPLETION OR TERMINATION AND CLOSE-OUT

The Investigator will be notified in writing upon termination/conclusion of the study. Edwards Lifesciences retains the right to suspend or terminate this clinical study at any time.

Safety and review committees associated with the study may recommend termination should safety concerns warrant such action as described in Section 16.

All study subjects enrolled up to the point of study termination, will continue to be followed as per protocol requirements.

17.8 AUDITS AND INSPECTIONS

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

17.9 PUBLICATION POLICY

[redacted]

18 REFERENCES

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11. Filsoufi, et al., *Long-term outcomes of tricuspid valve replacement in the current era.* Ann Thorac Surg, 2005. **80**: p. 845-50
12. Moraca, et al., *Outcomes of tricuspid valve repair and replacement: a propensity analysis.* Ann Thorac Surg, 2009. **87**: p. 83-9
13. Pfannmuller, et al., *Isolated tricuspid valve surgery in patients with previous cardiac surgery.* J Thorac Cariovasc Surg, 2013. **146**: p. 841-7

19 DEFINITIONS

Access Site	Access site defined as any location (venous) traversed by a guidewire, a catheter or a sheath (including the subclavian or axillary vein)
ACT	Activated clotting time
Acute Kidney Injury (AKI)	Refer to VARC-2 definition
Adverse Device Effect (ADE)	Refer to ISO 14155 definition
Adverse Event (AE)	Refer to ISO 14155 definition

Adverse Event Causality	Not related: Relationship to the device or procedures can be excluded when: • The event is not a known side effect of the product category the device belongs to or of similar devices and procedures • The event has no temporal relationship with the use of the investigational device or the procedures • The serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible • The discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event • The event involves a body-site or an organ not expected to be affected by the device or procedure • The serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors) • Harms to the subject are not clearly due to use error • In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event Unlikely: The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained. Possible: The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible. Probable: The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be

	explained by another cause, but additional information may be obtained. Causal Relationship: The serious event is associated with the investigational device or with procedures beyond reasonable doubt when: • The event is a known side effect of the product category the device belongs to or of similar devices and procedures • The event has a temporal relationship with investigational device use/application or procedures • The event involves a body-site or organ that the investigational device or procedures are applied to or have an effect on • The serious event follows a known response pattern to the medical device (if the response pattern is previously known) • The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible) • Other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out • Harm to the subject is due to error in use • In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event

Cardiac Tamponade	Pressure on the heart that occurs when blood or fluid builds up in the space between the heart muscle (myocardium) and the outer covering sac of the heart (pericardium).
Cardiovascular Mortality	Refer to VARC-2 definition
Cerebrovascular Accident (CVA)	See “Stroke”

Clinical Outcomes	Clinical Outcomes (at 1 month, 6 months & Annually) • Re-hospitalization rates for the underlying condition (heart failure) • Re-intervention rates for the underlying condition (tricuspid regurgitation) • Change in Tricuspid Regurgitation (assessment made by change in EROA) from baseline • Change in peripheral edema as assessed by subject weight loss (kilograms) from baseline • Change in NYHA Class from baseline • Change in 6 minute walk test distance (meters) from baseline • Change in Quality of Life as assessed by the SF-12 and KCCQ questionnaires from baseline
Death	All cause mortality
Device Deficiency	Refer to ISO 14155 definition
Device Detachment	Separation, under the action of applied stress or strain, of any part of the investigational device that was previously intact.
Device Embolization	Refer to ISO 5840-3 definition
Device Malfunction	Refer to ISO 14155 definition
Device Migration	Refer to ISO 5840-3 definition
Device Success	Device Success (at 1 month, 6-months and annually): • Alive, with • Original intended device in place, and • No additional surgical or interventional procedures related to the device, and • TR reduction (assessment made by change in EROA) compared to baseline and TV gradient ≤ 5mmHg
Embolism	Free flowing blood clot or lesion material that is located in the systemic or pulmonary circulation. A peripheral embolic event is an operative, autopsy or clinically documented embolus that produces symptoms from complete or partial obstruction or a peripheral (noncerebral) artery.

Emergency Surgery	Emergent Salvage: The patient is undergoing CPR en route to the operating room or prior to anesthesia induction Emergent: All of the following conditions are met: • Not elective status • Not emergent salvage status • Procedure required before procedure room exit in order to minimize chance of further clinical deterioration • Any surgical procedure on the previously implanted study device (repair, alteration or replacement) or study procedure access site post-implant procedure Elective: The patient's cardiac function has been stable in the days or weeks prior to the operation. The procedure can be deferred without increased risk of compromised cardiac outcome.
Endocarditis	An inflammation of the inside lining of the heart chambers and heart valves (endocardium). Endocarditis can involve the heart muscle, heart valves, or lining of the heart.
Enrollment	Subject enrollment in this clinical study is established when a subject has signed the informed consent form agreeing to participate in the study and has been deemed eligible for study participation by meeting the study criteria.
Explant	Removal of the study device after completion of the implant procedure for any reason.
Heart Failure	Heart Failure - A progressive condition that involves loss of pumping ability by the heart (heart muscle weakens and gradually loses its ability to pump enough blood through the body), generally accompanied by fluid accumulation in body tissues, especially the lungs. Heart Failure Hospitalization - An unplanned hospitalization that results in at least one overnight stay (i.e., where the admission date and the discharge date are different) that includes increased signs and/or symptoms of worsening heart failure and requires the administration or augmentation of existing heart failure therapy. Severe Heart Failure – See NYHA Class IV
HEART Team	The 'HEART Team', for the purpose of this study, must include a minimum of one Cardiologist, and one Cardiac Surgeon.

Hemolysis (Device Hemolysis)	Rupturing of red blood cells (erythrocytes) and the release of their contents (cytoplasm) into surrounding fluids. Device hemolysis is defined as hemolysis in or near the investigational device that interferes with the function of the device. Device hemolysis related thrombus may be confirmed by operation, autopsy, or diagnostically by such methods as echocardiography, angiography, or magnetic resonance imaging.
Implant procedure	Placement of the investigational device in the tricuspid valve regurgitant orifice.
Infection	Known infection requiring intravenous antibiotics for other than prophylaxis, and/or extended hospitalization.
INR	International normalized ratio
IVC	Inferior vena cava
KCCQ	Kansas City Cardiomyopathy Questionnaire is a health-related quality-of-life measure for patients with congestive heart failure.
LVEF	Left ventricular ejection fraction
Malfunction	Refer to ISO 14155 definition
Myocardial Infarction	Refer to VARC-2 definition
New York Heart Association Classification (NYHA Class)	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 anginal 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 anginal 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 anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.
Nonstructural Dysfunction	Abnormality extrinsic to the repair device that results in valve dysfunction (stenosis, regurgitation or both)
Patient	A person with the disease (tricuspid regurgitation) being screened to participate in the clinical study.

Peripheral Thromboembolic Event	See "Embolism"
Pre-Existing Condition	A pre-existing condition is one that is present at the start of study treatment.
Primary Endpoint	The primary endpoint for the study will assess the all-cause mortality of the as treated cohort at 30 days compared to a literature derived Performance Goal based on high-risk surgical outcomes for tricuspid repair/replacement.

Procedural Success	Procedural Success (at 1 month):
	• Device Success, and
	• None of the following device or procedure related SAEs:
	  • Life threatening bleeding
	  • Major vascular or cardiac structural complications requiring intervention
	  • Pericardial effusion requiring drainage or surgery (includes tamponade)
	  • Stage 2 or 3 acute kidney injury (includes new dialysis).
	  • Severe heart failure or hypotension requiring IV inotrope, ultrafiltration or mechanical circulatory support
	  • Prolonged intubation > 48 hours

Prosthesis	An artificial substitute
QoL	Quality of Life
Reintervention	Any intervention on the previously implanted study device (repair, alteration or replacement) or study procedure access site post-implant procedure.
Renal Failure	See "Acute Kidney Injury (AKI)"
Screen Failure	A patient who has signed the consent but, does not meet the inclusion criteria or who meets at least one of the exclusion criteria.
Serious Adverse Device Effect (SADE)	Refer to ISO 14155 definition
Serious Adverse Event (SAE)	Refer to ISO 14155 definition
SF-12	A short survey with 12 questions that results in two scales of mental and physical functioning and overall health related quality of life.
Six (6) MWT	Six minute walk test
Stroke/TIA	Refer to VARC-2 definition
Subject	Refer to ISO 14155 definition

Subject Withdrawal	A subject who decides not to participate in the study after signing an informed consent form and being enrolled.
Technical Success	Technical Success (at exit from procedure room): • Alive, with • Successful access, delivery and removal of the delivery systems, and • Deployment and correct positioning of the intended device, and • No need for additional emergency surgery or re-intervention related to the device or access procedure
Thromboembolic Event	See "embolism"
Thrombus (Device Thrombosis)	An aggregation of platelet, fibrin, clotting factors, and other cellular elements exclusive of infection. Device thrombosis is defined as any thrombus in the absence of infection attached to or near the investigational device that interferes with function of the device. An investigational device related thrombus may be confirmed by operation, autopsy, or diagnostically by such methods as echocardiography, angiocardiography, or magnetic resonance imaging.
Tricuspid Regurgitation	Tricuspid Regurgitation (TR), tricuspid insufficiency or tricuspid incompetence describes a condition in which blood flow through the tricuspid valve flows in the incorrect direction during part of the cardiac cycle.
Unanticipated Serious Adverse Device Effect (USADE)	Refer to ISO 14155 definition
Valvular Leak **(See Also "Nonstructural Dysfunction")**	Any evidence of leakage of blood through the native valve leaflets and around the investigational device. Diagnosis of valvular leak may be obtained from echo; however definitive diagnosis is obtained at reoperation, explant, or autopsy.
Withdrawal by Investigator	A subject who consents to participate in the study and is enrolled but is withdrawn by the Investigator.

20 APPENDIX A - SAMPLE INFORMED CONSENT FORM

21 APPENDIX B - CT ACQUISITION PROTOCOL

22 APPENDIX C - ECHO PROTOCOL

23 APPENDIX D – SCREENING COMMITTEE CHARTER