Edwards

Early Feasibility Study of the Edwards FORMA Tricuspid Transcatheter Repair System

CLINICAL PROTOCOL

(Clinical Investigational Plan)

Study Number: 2014-04
Version: K
Effective Date: February 8, 2018

CONFIDENTIAL

Study Sponsor:
Edwards Lifesciences LLC
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Irvine, CA 92614 USA

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SYNOPSIS

Study Number:	2014-04
Title:	Early Feasibility Study of the Edwards FORMA Tricuspid Transcatheter Repair System
Study Sponsor Contacts:	[redacted]
Study Principal Investigator:	[redacted]
Study Objective:	The objectives of this early feasibility study are to: • Evaluate the safety and function of the Edwards FORMA Tricuspid Transcatheter Repair System • Provide guidance for future clinical study designs utilizing the Edwards FORMA Tricuspid Transcatheter Repair System • Provide guidance for future Edwards FORMA Tricuspid Transcatheter Repair System development efforts
Study Devices:	The Edwards FORMA Tricuspid Transcatheter Repair System: • Edwards FORMA Tricuspid Transcatheter Spacer System, Model 9900SSA • Edwards FORMA Tricuspid Transcatheter Guide Sheath, Model 9900GSA20 • Edwards FORMA Tricuspid Transcatheter Introducer Sheath, Model 9900IS20 • Edwards FORMA Tricuspid Transcatheter Railing Delivery System, Model 9900DSA • Edwards FORMA Tricuspid Transcatheter Retrieval System, Model 9900RSA

Intended Use:	The Edwards FORMA Tricuspid Transcatheter Repair System is intended for patients with tricuspid regurgitation who are deemed to be candidates for transcatheter tricuspid valve repair with the Edwards FORMA Tricuspid Transcatheter Repair System by the local Heart Team (a minimum of one cardiologist and one cardiac surgeon).
Study Design:	This is a multi-site, prospective, early feasibility study. 60 patients will be enrolled in the study. All enrolled study patients 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:	Estimated Study Enrollment Start Date: December 2015 Estimated Study Enrollment End Date: December 2018 Estimated Study Follow Up Completion: January 2022
Study Population:	Adult patients with clinically significant, symptomatic, functional, tricuspid regurgitation who are deemed to be candidates for transcatheter tricuspid valve repair by the local Heart Team (a minimum of one cardiologist and one cardiac surgeon).
Enrollment Criteria (Inclusion):	1. Signed and dated IRB approved study consent form prior to study related procedures 2. ≥ eighteen (18) and ≤ eighty five (85) years old 3. Symptomatic severe (Stage D) functional, tricuspid regurgitation (per applicable guidelines) requiring transcatheter tricuspid valve repair as assessed by the local Heart Team (a minimum of one cardiologist and one cardiac surgeon) 4. Signs or symptoms of persistent right heart failure despite optimal medical therapy 5. 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 < 2.63 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 proper anchor or Spacer placement, positioning and retrieval c. Access pathway vessel diameter < 7.1 mm (Introducer Sheath) or < 8.0 mm (Guide Sheath) 2. Moderate or greater tricuspid valve stenosis 3. Tricuspid effective regurgitant orifce area (EROA) EROA ≥ 1.0 cm^2 by PISA or ≥ 2.0 cm^2 by 3D measurement 4. Severe right ventricular (RV) dysfunction as evidenced by TAPSE < 13 mm 5. Any RV lead that was implanted within the last 180 days, or that precludes proper placement of the device, or may interfere with the device, or presence of two or more RV leads 6. RV lead with pacemaker dependency

	7. Untreated clinically significant coronary artery disease requiring immediate revascularization 8. Any therapeutic invasive cardiac procedure performed within 30 days of the scheduled implant procedure 9. Patients on chronic dialysis 10. Patients with renal insufficiency (estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2) 11. Patients with chronic anemia (Hb <9 g/L) 12. Patients with thrombocytopenia (platelet count <100,000/mm^3) 13. Patients with significant pericardial effusion 14. Significant stenosis of the left subclavian vein that may preclude safe introduction of the delivery catheter 15. Myocardial infarction or unstable angina within 30 days of scheduled implant procedure 16. Hemodynamic instability or on IV inotropes within 30 days of scheduled implant procedure 17. Patient requiring surgery under general anesthesia for any reason within 30 days of scheduled implant procedure 18. Severe left ventricular dysfunction with ejection fraction < 30% within 90 days of scheduled implant procedure 19. Patients with systolic pulmonary artery pressure > 60 mmHg via transthoracic echocardiography or right heart catheterization within 90 days of scheduled implant procedure 20. Patients with uncontrolled hypertension defined as systolic blood pressure (SBP) ≥ 180 mmHg or diastolic blood pressure (DBP) ≥ 110 mmHg 21. Aortic, and/or pulmonic valve stenosis and/or regurgitation graded as moderate or greater 22. Mitral stenosis or regurgitation graded as severe 23. Active endocarditis or infection within 90 days of scheduled implant procedure 24. Cerebrovascular accident within 90 days of scheduled implant procedure 25. Six-minute walk test (6MWT) < 150 meters and > 400 meters within 90 days of scheduled implant procedure 26. Significant frailty (i.e. Katz Index of Independence in Activities of Daily Living (ADL) ≤ 2) within 90 days of scheduled implant procedure 27. Chronic liver disease with a MELD score of 12 or greater 28. Recurrent (>2 per 12 months) hospitalizations or ER visit for COPD exacerbation or continuous use of home oxygen or use of outpatient oral corticosteroids 29. Non-cardiac disease limiting life expectancy to be less than 12 months at baseline evaluation 30. Documented history of bleeding diathesis, coagulopathy or gastrointestinal bleeding within 90 days of scheduled implant procedure

	31. Evidence of left or right sided intracardiac mass, thrombus, or vegetation 32. Prior venous stent placed within the access route (e.g., sub-clavian vein) that could negatively react with device 33. Previous implantation of a bioprosthetic or mechanical tricuspid valve or a leaflet repair device 34. Known hypersensitivity to cobalt chromium, nitinol or titanium 35. Known hypersensitivity to anticoagulation therapy or contrast agent, which cannot be adequately medicated 36. Patient is a current intravenous drug user 37. Female of child-bearing potential is pregnant or lactating 38. Patient is currently participating in another drug or device clinical study 39. Patient requires emergent/emergency treatment for tricuspid insufficiency 40. Patient is under guardianship
Feasibility Endpoints:	<u>Safety</u>: Composite of major adverse events (MAE) defined as cardiovascular mortality, myocardial infarction, new need for renal replacement therapy, severe bleeding and re-intervention for study device related complications at 30 days. <u>Performance</u>: • Device success: device is deployed as intended and the delivery system is successfully retrieved as intended at the time of the patient's exit from the cardiac catheterization laboratory. • Procedural success: device success with evidence of tricuspid regurgitation (TR) reduction as evidenced by a relative reduction in EROA of ≥ 30% from baseline to discharge and without the need for a surgical or percutaneous intervention prior to hospital discharge. • Clinical success: procedural success without MAEs at 30 days. (MAEs: cardiovascular mortality, myocardial infarction, new need for renal replacement therapy, severe bleeding and re-intervention for study device related complications)
Study Committees:	<u>Independent Data Monitoring Committee (</u>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

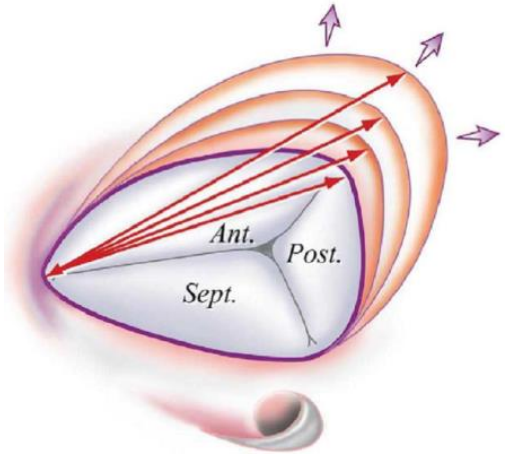
Tricuspid Regurgitation (TR), tricuspid insufficiency or tricuspid incompetence describes a condition in which blood flow through the tricuspid valve flows in the incorrect direction during part of the cardiac cycle. Normally, during diastole, the tricuspid valve opens as a result of atrial pressure 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

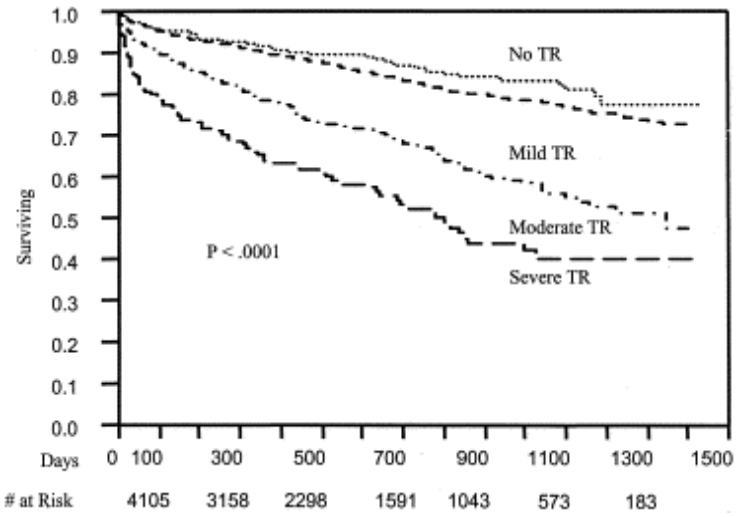
TR can have many underlying etiologies, but the majority of these can be divided into two major categories: degenerative and functional TR. Degenerative (primary, organic or structural) TR refers to regurgitation resulting from disease processes affecting the integrity of the tricuspid valve leaflets 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 left ventricular ejection fraction (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]

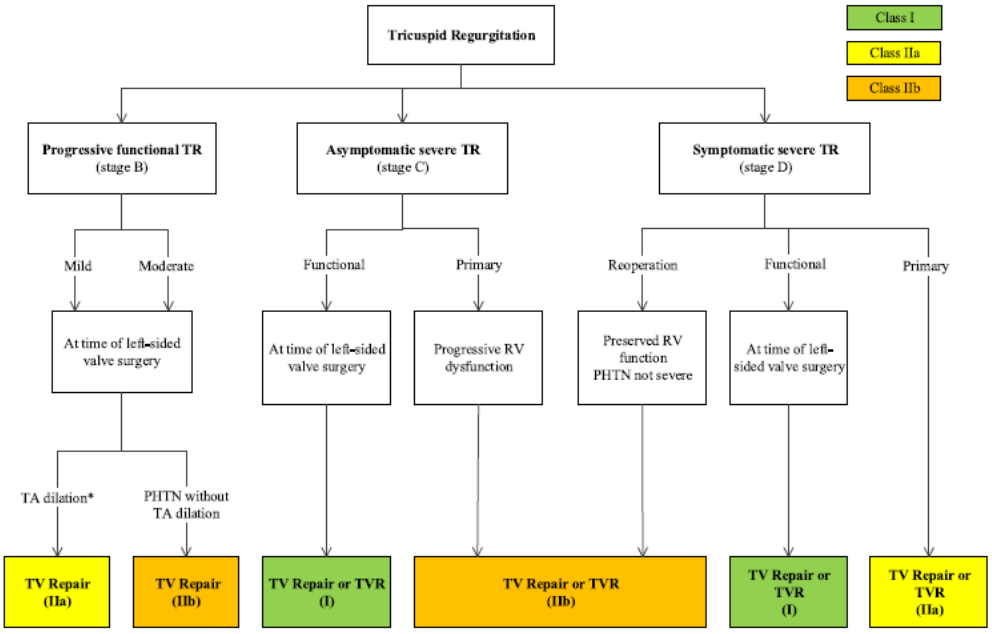


1.2 ALTERNATIVE TREATMENT/THERAPIES

1.2.1 SURGICAL TRICUSPID VALVE INTERVENTION

The decision as to treat TR has been controversial over the years, but has recently become recommended in symptomatic patients and in some cases asymptomatic 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 is 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 concominate valve surgery[2, 7].

Percutaneous devices are being investigated which mimic surgical repair techniques. These devices are targeted for patients who 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.

2 STUDY PURPOSE

The early feasibility study of the Edwards FORMA Tricuspid Transcatheter Repair System is a multi-site, prospective, early feasibility study to evaluate the safety and function of the Edwards FORMA Tricuspid Transcatheter Repair System.

Data collected in this clinical study will include safety and function of the investigational system as well as up to 3 year clinical outcomes.

2.1 INTENDED USE

The Edwards FORMA Tricuspid Transcatheter Repair System is intended for treatment of patients with tricuspid regurgitation who are deemed to be candidates for transcatheter tricuspid valve repair with the Edwards FORMA Tricuspid Transcatheter Repair System by a local team comprised of a minimum of one Cardiologist, and one Cardiac Surgeon (herein after referred to as the local Heart Team).

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 CLINICAL EXPERIENCE

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

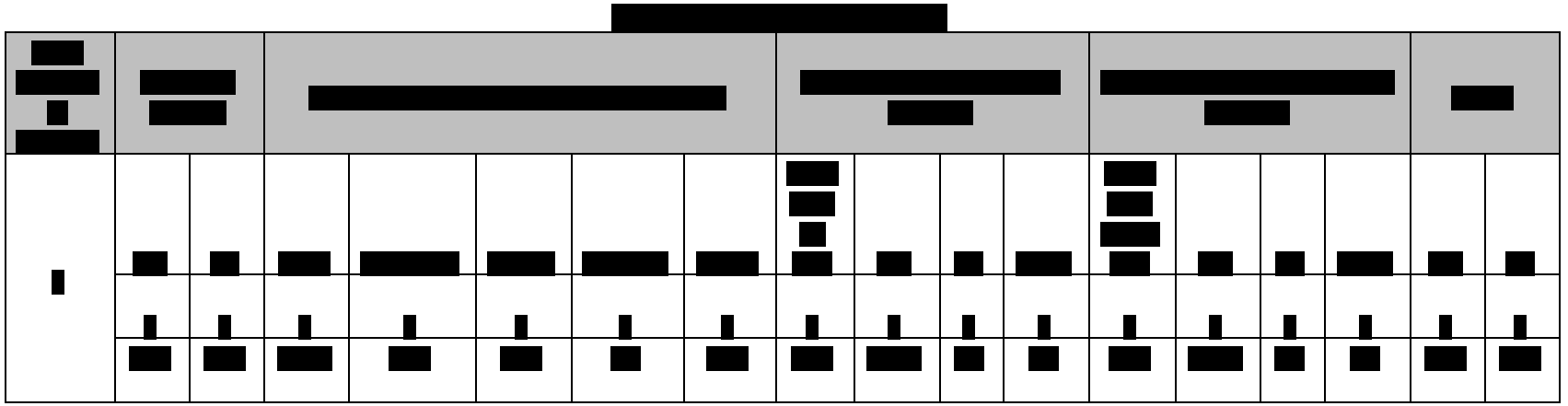
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



[redacted]

[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 five (5) different sub-systems as listed below (Table 5). A general device description will be provided for all components of the Edwards FORMA System. Further detailed information such as materials, manufacturing, testing, etc. however, will be provided in the Report of Priors (Clinical Investigator's Brochure (CIB)).

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

Table 5 – Device Names and Model Numbers

Product Name	Models
Edwards FORMA Tricuspid Transcatheter Spacer System	[redacted]
Edwards FORMA Tricuspid Transcatheter Guide Sheath	[redacted]
Edwards FORMA Tricuspid Transcatheter Introducer Sheath	[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]

[redacted]

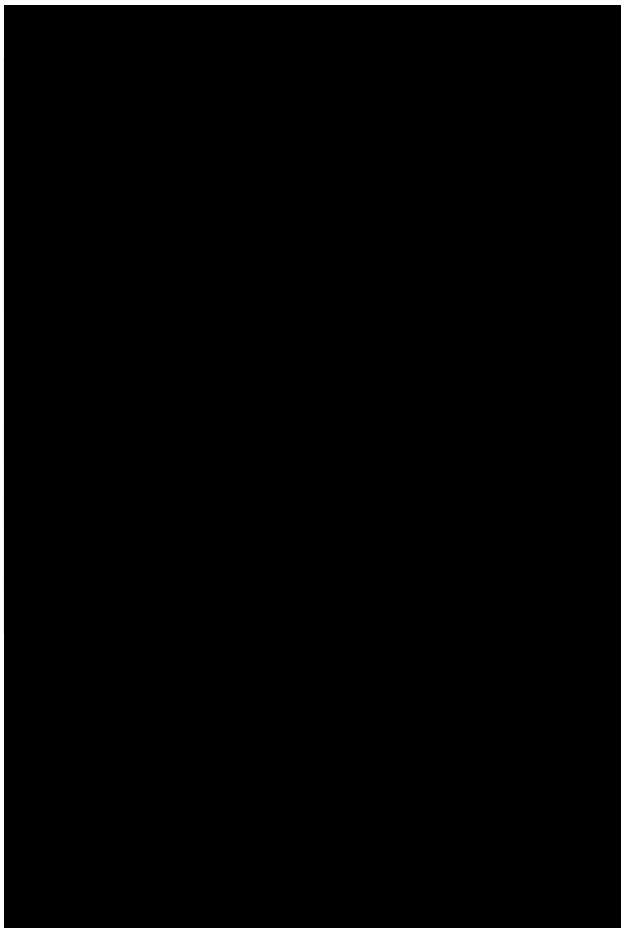
[redacted]

[redacted]

2.4.2.2 Railing System

[redacted]

[redacted]



2.4.2.3 Locking Mechanisms

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.4.3 ACCESS SHEATHS

[redacted]

2.4.3.1 Edwards FORMA Tricuspid Transcatheter Guide Sheath

[redacted]

[redacted]

[redacted]

2.4.3.2 Edwards FORMA Tricuspid Transcatheter Introducer Sheath

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.4.4 EDWARDS FORMA TRICUSPID TRANSCATHETER RAILING DELIVERY SYSTEM

[redacted]

2.4.5 EDWARDS FORMA TRICUSPID TRANSCATHETER RETRIEVAL SYSTEM

[redacted]

[redacted]

[redacted]

[redacted]

3 RISK ANALYSIS

A risk analysis has been conducted, in accordance with ISO 14971:2012 "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 (permanent or temporary);
- 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;
- skin burn;
- 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;
- damage to or interference with function of pacemaker or implantable cardioverter-defibrillator (ICD);
- deterioration of native valve (leaflet tear/tearing, leaflet retraction, leaflet thickening, leaflet stenosis, or other);
- device degeneration;
- device explants;
- device migration, malposition or embolization 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;
- 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 patients.

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, heart failure specialist, echo-cardiographer, radiologist).

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

Adverse events will be reviewed by the Study Sponsor, Data Safety Monitoring Board and Clinical Events Committee as defined in the respective charters..

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 patients 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, the first with the FORMA System, is designed as a multi-site, prospective, early feasibility study. This study is designed to confirm that the safety and function observed in non-clinical testing is also observed in a limited 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 objectives of this early feasibility study are to:

- Evaluate the safety and function of the FORMA System
- Provide guidance for future clinical study designs utilizing the FORMA System
- Provide guidance for future FORMA System development efforts

5 STUDY ENDPOINTS

5.1 FEASIBILITY ENDPOINTS

5.1.1 SAFETY ENDPOINT

Composite of major adverse events (MAE) defined as cardiovascular mortality, myocardial infarction, new need for renal replacement therapy, severe bleeding and re-intervention for study device related complications at 30 days.

5.1.2 PERFORMANCE ENDPOINT

5.1.2.1 Device Success

Device is deployed as intended and the delivery system is successfully retrieved as intended at the time of the patient's exit from the cardiac catheterization laboratory.

5.1.2.2 Procedural Success

Device success with evidence of TR reduction as evidenced by a relative reduction in EROA of ≥ 30% from baseline to discharge and without the need for a surgical or percutaneous intervention prior to hospital discharge.

5.1.2.3 Clinical Success

Procedural success without MAEs at 30 days. (MAEs: cardiovascular mortality, myocardial infarction, new need for renal replacement therapy, severe bleeding and re-intervention for study device related complications)

6 STUDY DESIGN

This is a multi-site, prospective, early feasibility study designed to evaluate the safety and function of the FORMA System.

A total of sixty patients will be enrolled in the study. All enrolled study patients 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.

A description of each study visit and required study procedures is included in Section 8.0, Procedures and Methods. In addition, a summary of required procedures is listed in Table 12.

7 PATIENT POPULATION

7.1 DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

This clinical study is for adult patients with clinically significant, symptomatic, functional, tricuspid regurgitation who are deemed to be candidates for transcatheter tricuspid valve repair by the local Heart Team.

All patients 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 patients to determine if the patients meet all the inclusion criteria. The following are requirements for entry into the study:

1. Signed and dated IRB approved study consent form prior to study related procedures
2. ≥ eighteen (18) and ≤ eighty five (85) years old
3. Symptomatic severe (Stage D) functional, tricuspid regurgitation (per applicable guidelines) requiring transcatheter tricuspid valve repair as assessed by the local Heart Team (a minimum of one cardiologist and one cardiac surgeon)
4. Signs or symptoms of persistent right heart failure despite optimal medical therapy
5. Willing to attend study follow-up assessments for up to 3 years

7.3 EXCLUSION CRITERIA

The Investigator at the study site must exclude patients 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 < 2.63 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 proper anchor or Spacer placement, positioning and retrieval
   c. Access pathway vessel diameter < 7.1 mm (Introducer Sheath) or < 8.0 mm (Guide Sheath)
2. Moderate or greater tricuspid valve stenosis
3. EROA ≥ 1.0 cm^2 by PISA or ≥ 2.0 cm^2 by 3D measurement
4. Severe RV dysfunction as evidenced by TAPSE < 13 mm
5. Any RV lead that was implanted within the last 180 days, or that precludes proper placement of the device, or may interfere with the device, or presence of two or more RV leads
6. RV lead with pacemaker dependency
7. Untreated clinically significant coronary artery disease requiring immediate revascularization
8. Any therapeutic invasive cardiac procedure performed within 30 days of the scheduled implant procedure
9. Patient on chronic dialysis
10. Patients with renal insufficiency (eGFR < 30 mL/min/1.73 m^2)
11. Patients with chronic anemia (Hb <9 g/L)
12. Patients with thrombocytopenia (platelet count <100,000/mm^3)
13. Patients with significant pericardial effusion
14. Significant stenosis of the left subclavian vein that may preclude safe introduction of the delivery catheter
15. Myocardial infarction or unstable angina within 30 days of scheduled implant procedure
16. Hemodynamic instability or on IV inotropes within 30 days of scheduled implant procedure
17. Patient requiring surgery under general anesthesia for any reason within 30 days of scheduled implant procedure
18. Severe left ventricular dysfunction with ejection fraction < 30% within 90 days of scheduled implant procedure

19. Patients with systolic pulmonary artery pressure > 60 mmHg via transthoracic echocardiography or right heart catheterization within 90 days of scheduled implant procedure
20. Patients with uncontrolled hypertension defined as SBP ≥ 180 mmHg or DBP≥ 110 mmHg
21. Aortic, and/or pulmonic valve stenosis and/or regurgitation graded as moderate or greater
22. Mitral stenosis or regurgitation graded as severe
23. Active endocarditis or infection within 90 days of scheduled implant procedure
24. Cerebrovascular accident within 90 days of scheduled implant procedure
25. Six-minute walk test (6MWT) < 150 meters and > 400 meters within 90 days of scheduled implant procedure
26. Significant frailty (i.e. Katz Index of Independence in Activities of Daily Living (ADL) ≤ 2) within 90 days of scheduled implant procedure
27. Chronic liver disease with a MELD score of 12 or greater
28. Recurrent (>2 per 12 months) hospitalizations or ER visit for COPD exacerbation or continuous use of home oxygen or use of outpatient oral corticosteroids
29. Non-cardiac disease limiting life expectancy to be less than 12 months at baseline evaluation
30. Documented history of bleeding diathesis, coagulopathy or gastrointestinal bleeding within 90 days of scheduled implant procedure
31. Evidence of left or right sided intracardiac mass, thrombus, or vegetation
32. Prior venous stent placed within the access route (e.g., sub-clavian vein) that could negatively react with device
33. Previous implantation of a bioprosthetic or mechanical tricuspid valve or a leaflet repair device
34. Known hypersensitivity to cobalt chromium, nitinol or titanium
35. Known hypersensitivity to anticoagulation therapy or contrast agent, which cannot be adequately medicated
36. Patient is a current intravenous drug user
37. Female of child-bearing potential is pregnant or lactating
38. Patient is currently participating in another drug or device clinical study
39. Patient requires emergent/emergency treatment for tricuspid insufficiency
40. 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 institutional review board (IRB), and/or FDA (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 should be explained to the patient. The patient (or the patient's legal representative) 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 IRB 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. Signed informed consent forms must be retained by the study site for verification during on-site monitoring visits.

8.2 PATIENT ENROLLMENT

A Screening/Enrollment Log, provided by the Sponsor, will be maintained at the study site to document the screening and enrollment of all patients assessed for study participation. The screening of patients 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. Patients who are consented to participate in the study but do not fulfill enrollment criteria, will be considered "screen failures" and will not count towards the overall enrollment cap. The reason for "screen failure" will be recorded on the screen failure log. Reasons for screen failure may include but are not limited to:

- Qualifying patient is not offered an opportunity to participate by Investigator
- Qualifying patient refuses to participate
- Investigator opts for alternative therapy for qualifying patient
- Potential patient fails the screening criteria

All patients assessed for study participation that have signed the informed consent form will be entered on the screening log. These patients will be assigned a sequential patient

ID number by the study Sponsor. The patient ID number together with the patient initials shall be used to identify the patient on all study-related documents.

Patient will be considered "provisionally 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). A patient will be considered "enrolled" at the time of skin incision to introduce the FORMA System into the body.

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 12 months prior hospitalizations including emergency department (ED) visits, paracentesis), Clinical Evaluation (includes vital signs, concomitant medical treatments, edema grading, weight and height) and NYHA classification
3. Administration of Health Status Questionnaires (e.g., SF-12, KCCQ)
4. Administration of Six Minute Walk Test (6MWT)
5. Administration of Katz Index of Independence in Activities of Daily Living (ADL)
6. Calculation of MELD score for liver disease prognosis
7. Clinical Laboratory Tests
    a. The following lab tests shall be done within 30 days of the scheduled implant procedure:
        i. Troponins and 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. NT-pro Brain Natriuretic Peptide (BNP), and if not available BNP
        ii. CBC and platelet count
        iii. Complete metabolic panel
        iv. Liver panel including gamma-glutamyl transferase (GGT)
        v. Serum Creatinine and eGFR
    c. The following lab tests shall be done ≤ 48 hours before the implant procedure:
        i. βHCG for women who are not sterile or post-menopausal- *positive result is an exclusion from study participation.*
        ii. INR and PTT/aPTT
8. Standard 12-lead Electrocardiogram (ECG)
9. Comprehensive Transthoracic Echocardiogram (TTE), (within 90 days of scheduled implant procedure) including but not limited to, annulus size, ventricular size, regurgitant assessment, jet location, mean pulmonary artery pressure (PAP), LVEF,

and pulmonary vascular resistance (PVR) [10]. Analysis will be conducted by the Investigator and Sponsor to certify the patient is eligible for the study[5].

10. Transesophageal Echocardiogram (TEE), (within 90 days of scheduled implant procedure) including but not limited to transgastric views.
11. All candidates must have pre-implant procedure imaging, (within 90 days of scheduled implant procedure), that captures the anatomy of the subclavian and axillary veins, superior vena cava, tricuspid valve and sub-valvular structures/anatomy, right atrium and right ventricle. Analysis will be conducted by the Investigator and Sponsor to certify the patient is eligible for the study.
    If a pre-existing Computed Tomography (CT) within 180 days of the scheduled implant procedure captures all the required anatomy for necessary measurements, and a new CT is not clinically indicated (e.g. no recent cardiac events that would alter the anatomy or no cardiac procedures performed since prior CT), the baseline CT can be waived and is not required to be repeated.
12. Invasive Hemodynamic Monitoring/Right Heart Catheterization (within 90 days of scheduled implant procedure) that should include, but is not limited to, right atrial pressure (RAP), PAP, right ventricle pressure (RVP), cardiac output (CO), and PVR measurements.[6]
13. Candidates with cardiac leads may also have a venogram (subclavian and axillary veins) as part of pre-implant procedure imaging (within 90 days of scheduled implant procedure), if venous patency cannot be determined by pre-procedure CT.
14. Candidates with pacemaker leads must have interrogation of their device within 180 days of the scheduled implant procedure to determine pacing stability and pacing dependency. Pacemaker dependency is defined as continuous ventricular stimulation without any pacemaker inhibition by spontaneous cardiac activity determined during the last interrogation within 180 days.
15. Coronary angiogram within 1 year of the scheduled implant procedure

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

[5] If candidate had new cardiac procedure since baseline TTE and TEE that were submitted for screening, the TTE and TEE should be repeated and resubmitted.

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

Table 6 - Baseline Evaluation

General Information	Clinical Information	Laboratory Measurements
• Inclusion/exclusion evaluation • Informed consent • Age • Gender • Height • Weight	• Local Heart Team determination • Medical history (e.g., EuroSCORE, STS Score) /prior cardiovascular interventions / surgeries / 12-month prior hospitalizations and paracentesis • Vital signs (Blood pressure, heart rate) • Edema grading • Concomitant Medications and doses • NYHA classification • Echocardiographic measurements (TTE & TEE), tricuspid regurgitation & heart function within 90 days of scheduled implant procedure • Computed Tomography (CT) • Coronary angiogram within 1 year • Venogram (in patients with cardiac leads) if required • Interrogation of pacemaker leads within 180 days • Invasive Hemodynamic Monitoring/Right Heart Catheterization including pressure measurements • ECG results • Six minute walk test • Katz Index (ADL) test • MELD score • KCCQ & SF-12 questionnaires	Within 30 days of procedure: • Date of blood draw • Troponin[1] and CK-MB[1] Within ≤ 2 weeks of procedure: • Date of blood draw • NT-pro BNP (preferred) or BNP • Serum Creatinine & eGFR • WBC • RBC • Hematocrit • Hemoglobin • Platelets • ALT/SGPT • AST/SGOT • Bilirubin • LDH • GGT • ALP • Albumin • Sodium & potassium • Urea Within ≤ 48 hours of procedure: • INR & PTT/aPTT • βHCG, if applicable[3]

1. *MI within 30 days of the scheduled implant procedure is an exclusion from study participation*
2. *A positive result is an exclusion from study participation*

8.4 ANTIPLATELET / ANTICOAGULATION THERAPY

Recommendations for antiplatelet/anticoagulation therapy are detailed below and in Table 7. Alternative anticoagulation/antiplatelet regimens may be considered according to the needs of individual patients or a hospital's standard practice; these will not constitute a protocol deviation. For study patients on an existing dual antiplatelet therapy or with known hypersensitivity to the required medications, the investigator will determine the antiplatelet/anticoagulation therapy.

Patients on anticoagulation (e.g. Warfarin or Apixaban) will discontinue use prior to implant procedure. Patients not on anticoagulation prior to the procedure should receive Aspirin (at least 75 – 100 mg daily) and Plavix (300 mg or per investigator's preference) prior to implant procedure.

Heparin will be administered at procedure start, before introduction of any catheter into the vasculature. During the procedure, ACT will be monitored and recorded on source documentation. Heparin will be administered during the procedure as needed to maintain the patient'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.

Post procedure, patients on Aspirin and Plavix should continue receiving dual anti-platelet therapy 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.

Patients on anticoagulation (e.g. Warfarin or Apixaban) will continue with their prescribed anticoagulation medications post implant procedure through the 6-month follow-up visit. See Table 7.

Table 7 – Summary of Recommended Concomitant Medical Therapy

Visit	Patients on anticoagulant* prior to implant procedure	Patients **Not** on anticoagulant* prior to implant procedure
Pre Procedure	Discontinue anticoagulant	Start Aspirin and Plavix
Intra-Procedure	IV Heparin	IV Heparin
Post-Procedure through Month 6	Resume anticoagulant	Continue Aspirin and Plavix

*Anticoagulant: e.g., Warfarin or Apixaban

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8.5 DEVICE PREPARATION

A description of device preparation and use is provided in the IFUs, (See Report of Priors/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. Ventriculogram 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 sec during the implant procedure

Patients will be monitored in the operating room as needed with special attention to hemodynamic condition and cardiac rhythm. Subsequent monitoring of patients 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 8 – Procedure Information

General Information	Clinical Information	Laboratory Measurements
• Hospital admission date • Patient 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 • Ventriculogram Imaging • Invasive Hemodynamic Monitoring/Right Heart Catheterization and pressure measurements performed • Adverse events • Device malfunction	Within 24 -48 hours post implant: • Troponin[1] and CK-MB[1] • NT-pro BNP (preferred) or BNP • WBC • RBC • Hematocrit • Hemoglobin • Platelets • ALT/SGPT • AST/SGOT • Bilirubin • LDH • GGT • ALP • Albumin • Sodium & potassium • Urea • Serum creatinine & eGFR • PTT/aPTT & INR

1. *If an elevation was noted post implant (within 48 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 DAY 1 POST-IMPLANT

The following study procedures will be performed 24-48 hours post implant procedure:

1. Clinical Evaluation
2. Safety Evaluation
3. Clinical Laboratory Tests
    a. NT-pro BNP (preferred) or BNP
    b. CBC and platelet count
    c. Complete metabolic panel
    d. Liver panel
    e. PTT/aPTT and INR
    f. Serum creatinine and eGFR
    g. Troponins and cardiac enzymes (CK-MB)
4. Standard 12-lead ECG

8.6.4 DISCHARGE

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

1. Clinical Evaluation and Concomitant Medications
2. Safety Evaluation
3. Clinical Laboratory Tests
    a. NT-pro BNP (preferred) or BNP
    b. CBC and platelet count
    c. Complete metabolic panel
    d. Liver panel
    e. INR and PTT/aPTT
    f. Serum creatinine and eGFR
    g. Troponins and cardiac enzymes (CK-MB), only required if an elevation was noted post implant (within 48 hours)
4. Standard 12-lead ECG
5. 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 9 – Discharge Information

General Information	Clinical Information	Laboratory Measurements
• Discharge date & location discharged to (e.g., home) • Weight	• Clinical evaluation (mobility, edema, ascites, access site) • Vital signs (Blood Pressure, Heart Rate) • TTE measurements, tricuspid regurgitation & heart function • ECG results • Concomitant medications and doses • Adverse events	• Date of blood draw • Troponin and CK-MB, if applicable • NT-pro BNP (preffered) or BNP • WBC • RBC • Hematocrit • Hemoglobin • Platelets • ALT/SGPT • AST/SGOT • Bilirubin • LDH • GGT • ALP • Albumin • Sodium & potassium • Urea • Serum creatinine & eGFR • INR & PTT/aPTT

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 11. The following procedures will be conducted during follow up visits:

1. Clinical Evaluation Hospitalizations and/or Clinic Visits and Paracentesis, Concomitant Medications and doses, Edema Grading 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. NT-pro BNP (preferred) or BNP
    b. CBC and platelet count
    c. Complete metabolic panel
    d. Liver panel

e. INR and PTT/aPTT
f. Serum creatinine and eGFR

6. Calculation of MELD score for liver status
7. Standard 12-lead ECG
8. 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 10 – Follow-Up Visit Information

General Information	Clinical Information[7]	Laboratory Measurements
• Visit date • Height • Weight	• Clinical evaluation (mobility, edema grading, ascites, access site) • Vital signs (Blood Pressure, Heart Rate) • Hospitalizations &/or clinic visits & paracentesis • NYHA classification • TTE measurements, tricuspid regurgitation & heart function • ECG results • Six minute walk test (pre & post walk data & results) • KCCQ & SF-12 questionnaires • MELD score • Concomitant Medications and doses • Adverse events	• Date of blood draw • NT-pro BNP (preferred) or BNP • WBC • RBC • Hematocrit • Hemoglobin • Platelets • ALT/SGPT • AST/SGOT • Bilirubin • LDH • GGT • ALP • Albumin • Sodium & potassium • Urea • Serum creatinine and eGFR • INR & PTT/aPTT

8.7.1 Follow Up Visit Windows

Post-procedure follow up visits will be performed on all implanted study patients at 1 month, 6 months, and annually for 3 years post implant procedure intervals as illustrated in Table 11 below:

[7] To be documented in the medical records or chart.

Table 11 – 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 patients who have signed the Informed Consent, have met all eligibility criteria, and have the study procedure attempted (at least skin incision to introduce the FORMA system) are considered enrolled in the study.

Patients who enter the procedure room but who do not have the study procedure attempted (at least skin incision to introduce the FORMA system) will be classified as "non-implanted" and will be followed 30 days for safety. These patients will be exempt from all other study follow up visit procedures.

Table 12 – Summary of Required Study Procedures

STUDY PROCEDURES	BASELINE	IMPLANT PROCEDURE[1] (Day 0)	DAY 1 (24-48 hrs)	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/Concomitant Medications	X		X	X	X	X	X
Hospitalizations &/or clinic visits & paracentesis	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
Katz Index (ADL) test	X						
MELD score	X				X	X	X
Safety Evaluation		X	X	X	X	X	X
Pacemaker interrogation (pacemaker patients)	X						
Coronary angiogram (within 1 year of procedure)	X						
Complete Metabolic Panel and Liver Panel	X		X	X	X	X	X
NT-pro BNP/ BNP and CBC and Platelet Count	X		X	X	X	X	X
INR & PTT/aPTT	X		X	X	X	X	X
βHCG	X[3]						
Serum creatinine and eGFR	X		X	X	X	X	X
Troponins and CK-MB	X		X	X[4]			
ECG	X		X	X	X	X	X
Transesophageal Echocardiogram	X	X					
Transthoracic Echocardiogram	X			X	X	X	X
Pre-Implant Procedure Imaging (CT/ Angiographic Imaging & venogram for cardiac lead patients, if required)	X						
Ventriculogram Imaging		X					
Invasive Hemodynamic Monitoring	X[5]	X					

[1] Implant procedure must be scheduled within 90 days of baseline TTE and TEE and pre-implant procedure imaging (CT and/or angiographic imaging). If a pre-existing CT within 180 days 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] Only required if an elevation was noted post implant (within 48 hrs)
[5] 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 PATIENT VISITS

The Investigator shall inform study patients 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 patients.

The Investigator shall keep a separate log of the patients' names and current contact information to facilitate their record keeping and ability to contact the patients for future follow-up. If a patient cannot be reached for a follow-up assessment, the Investigator will document the missed visit and effort made to contact that patient, the patient's primary health care provider, and/or hospital records on the appropriate Case Report Form. Patients 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 patients 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 patient who has withdrawn.

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

- Patient Withdrawal

  The patient 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 patient if s/he feels it is in the best interest of the patient to do so.

- Lost to Follow-up

  If a patient cannot be reached for a follow-up visit, the Investigator will document the contact efforts made to the patient and/or effort to obtain hospital records in the appropriate electronic case report form. If the patient cannot be reached in any way, or misses a visit, the patient 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 patient's residence. If there is no response after the certified letter is sent, the patient will be considered "lost to follow-up."

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

8.10 PATIENT STUDY COMPLETION

Study patients 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 patient will also be exited from the study in the following instances:

- Patient signs informed consent form, is deemed eligible but does not undergo the study procedure
- Patient has study procedure attempted (at least skin incision to introduce the FORMA System) and does not have the investigational device implanted (will exit study at the 1 month follow up visit)
- If the study device is explanted, the patient will be followed for 30 days after the explant procedure for safety evaluations only, and will be exited from the study at that point. If one or more ongoing adverse event(s) related to the explant procedure is unresolved 30 days after the explant, the patient will remain in the study until the adverse event(s) have been resolved, or 180 days post explant, whichever comes first
- Patient is lost-to-follow-up
- Patient withdraws participation from the study or is withdrawn from the study
- Patient expiration

9 TRAINING

9.1 INVESTIGATORS DEVICE TRAINING

[redacted]

9.2 TRAINING OF INVESTIGATIONAL SITE PERSONNEL

[redacted]cific

[redacted]

9.3 TRAINING DOCUMENTATION

[redacted]

10 INVESTIGATIONAL DEVICE MANAGEMENT

10.1 DEVICE SHIPMENTS

Devices will be transported to the study site when the Clinical Study Agreement is in place, the study site has obtained applicable regulatory (e.g., IRB, FDA) approvals, and a patient eligible for implant has been identified.

Devices will be provided to the study site as needed for scheduled implant procedures. All investigational devices used in this study for investigational purposes will be labeled "Caution: Investigational Device, Limited by Federal (USA) law to investigational use".

10.2 DEVICE ACCOUNTABILITY

All device shipments will have inventory and shipment records. Devices may be hand carried to participating study sites 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 site 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 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. 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 site 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 site 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 study. 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 study 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 study. 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 (patient's medical record). All data that is entered in the eCRFs must have source documentation available in the patient medical records. Protocol deviation information can be recorded directly on the protocol deviation eCRF. Data to be collected for the study purposes must not be entered directly onto eCRFs. 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 patient'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 patient 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 DEFINITIONS

12.1.1 ADVERSE EVENT

An 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

12.1.2 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 misuse of the investigational medical device.

12.1.3 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).

12.1.4 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.

12.1.5 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.

12.1.6 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 inadequate labeling.

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.

All suspected device deficiencies, malfunctions or failures for the study device will be documented on the appropriate eCRF. In the event of a suspected device deficiency or other device issue, the device shall be returned to the Sponsor to the extent possible for analysis. Investigational devices shall be returned to the Study Sponsor as described in Section 10.4.

12.2 REPORTING PROCEDURE

Study patients 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 patient 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. All observations and clinical findings, including the nature or the seriousness, will be documented on the appropriate case report form (CRF). The investigator will classify the adverse events (AEs) based on the definitions in section 12.3

Adverse events will be assessed by the Investigator for causality to the investigational device or index procedure as defined in MEDDEV 2.7/3 revision 3:

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

The Investigator will report any serious adverse event, anticipated or unanticipated, to the Study Sponsor within three (3) calendar days after first knowledge of the event. Unanticipated Adverse Device Effects (UADE) should be reported to the Sponsor within three (3) calendar days. Notification to the Study Sponsor preferentially be made via the adverse event form in the electronic database (EDC).

In the event that the EDC system is not accessible, the Sponsor may be notified initially by emai[redacted] At the time of initial notification, the following minimal information should be provided:

- Study site number
- Patient ID
- Date of event
- Aware date
- Adverse event description
- Causal relationship to device and implant procedure

The AE eCRF should be completed as soon as possible thereafter.

The Investigator (or designee) shall provide source documents related to reported adverse event as requested by Sponsor or their designee.

The Sponsor will evaluate all adverse events for reportability as an UADE in accordance with 21 CFR part 812.46(b). The Investigator and Sponsor will comply with reporting requirements per 21 CFR part 812.150. A Sponsor who conducts an evaluation of an UADE under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating Investigators within 10 business days after the Sponsor first receives notice of the event. Thereafter the Sponsor shall submit such additional reports concerning the event as FDA requests.

In addition, the Investigator will report all adverse events to their Institutional Review Board and / or National Regulatory Agency in accordance with the applicable requirements.

Finally, the Investigator should follow all unresolved adverse events until the events are resolved or otherwise explained, or the patient is lost to follow-up or has withdrawn consent.

12.3 FINDINGS EXPECTED TO OCCUR WITH TREATMENT OF TRICUSPID REGURGITATION AND/OR INTERVENTIONAL CARDIAC PROCEDURES THAT DO NOT REQUIRE REPORTING TO THE SPONSOR

For purposes of this study, the following findings are not considered adverse events requiring reporting to the Sponsor. These findings are normally expected to occur in association with treatment of tricuspid regurgitation, and/or are associated with customary, standard care of patients undergoing interventional cardiovascular interventions:

- Post-procedure pain (within 48 hour of procedure) not requiring treatment or treated with non-opioids
- Emesis, nausea, or headache (within 48 hours of procedure) associated with anesthesia
- Out of range (outside the standard laboratory normal value) or "abnormal" lab values (including electrolyte imbalance) that are not clinically significant and do not require correction.

  Note: Abnormal lab values that roll up to a diagnosis should not be reported as separate AEs (e.g. elevated BNP in patient with heart failure; increased K+ in patient with renal insufficiency; elevated white blood count without signs or symptoms of infection)
- Low grade temperature increase without signs and symptoms of infection
- Minor, localized tenderness, swelling, induration, oozing, etc. at access site(s)
- Sinus bradycardia or tachycardia that does not require treatment or intervention
- Systolic or diastolic blood pressure changes that do not require treatment or intervention
- The need for insulin in a diabetic patient in the post op period

This listing of events is intended to provide guidance to the investigational sites for the purpose of adverse event reporting. The Investigator should utilize his/her clinical judgment in evaluating adverse experiences, and may decide that the above events should be reported as adverse events.

12.4 DEATHS AND EXPLANTS

12.4.1 PATIENT DEATHS

Patient death occurring during the study should be reported to the Sponsor or designee within one (1) business day of Investigator's knowledge of the death. The Adverse Event that resulted in death should be entered in the database on the Adverse Event form within one (1) business day and include a brief description of the relevant clinical information leading to the death of the patient. In the event of patient 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. In addition, patient death must be reported to the IRB in accordance with IRB requirements.

12.4.2 DEVICE EXPLANTS

If the study device is 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.

If 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

This clinical study will enroll 60 patients. This sample size was established based on typical sample sizes for early feasibility studies and no statistical justification was utilized.

13.2 ANALYSIS POPULATION

The analysis population will be grouped into three analysis cohorts that in total comprise all patients in whom the study procedure has been attempted (vascular access obtained) in this study. The analysis cohorts are defined below:

- **Intent-to-treat population**
  The intention-to-treat (ITT) population includes all patients who signed informed consent, met eligibility criteria, and in whom the study procedure has been attempted (i.e. at least skin incision to introduce the FORMA System).

- **As-treated population**
  The as-treated population is a subset of ITT population and includes all patients in whom the study device is implanted and remains in position at the time of the patient's exit from the procedure room.

- **Per-protocol population**
  The per-protocol (PP) population is a subset of as-treated (implanted) population in whom there are no major protocol deviations.

The as-treated population will be the primary analysis population for performance and safety assessment. The ITT population will be used for device success, and additional safety analysis. Additional analyses of performance and safety data using the PP population will also be performed.

13.3 DEVICE SUCCESS ENDPOINT ANALYSIS

The device success endpoint will be summarized by counts and percentages for the ITT and as-treated cohort. The endpoint will be assessed at the 1 month, 6-month, 1 year, 2-year and 3-year follow-up intervals.

In addition to the device success analysis, hemodynamic performance data will be obtained at the following time points: baseline, 1 month, 6 months and annually up to 3 years. Descriptive statistics such as mean, standard deviation will be calculated for the continuous echo variables as well as the change from baseline for each variable.

13.4 PROCEDURE SUCCESS ENDPOINT ANALYSIS

The procedure success endpoint will be summarized by counts and percentages for the as-treated cohort. The endpoint will be assessed at the index procedure hospital discharge.

13.5 CLINICAL SUCCESS ENDPOINT ANALYSIS

The clinical success endpoint will be summarized by counts and percentages for the as-treated cohort. The endpoint will be assessed at the 1 month follow-up interval.

Patient specific functional status (NYHA Class), exercise capacity (6MWT), blood test parameters, and quality of life (SF-12 and KCCQ) metrics will be assessed at baseline, 1 month, 6 months and annually up to 3 years. The distribution (numbers of patients and percentages) in the various NYHA classes will be tabulated at baseline, 1 month, 6 months and annually up to 3 years. Patients that are missing a baseline or follow up values will be excluded from the analysis. Patients that undergo any type of repair or replacement procedure for the tricuspid valve will be excluded from these analyses at the time of the reintervention and summarized in a table.

Rehosptilization rates will be assessed at 1 month, 6 months and annually up to 3 years.

13.6 ADDITIONAL SAFETY ANALYSIS

In addition to the above endpoints, a listing of all the AEs and SAEs for the entire study population will be provided.

13.7 MISSING DATA

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

Unless otherwise specified, all statistical analyses for the endpoints will be performed using available data. No missing value imputation will be performed.

13.8 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 will remain in close contact with the study site 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 patients have signed the informed consent as required by regulations, reviewing the data recorded on the eCRFs and visiting the study site 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 IRB and FDA 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 IRB, 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 patient enrollment, an initiation visit will be completed at the study site to ensure the following:

1. IRB 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 site in accordance with site enrollment rates. The study site 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 patient 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. patient 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 patient in an emergency. Patient specific and non-patient 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 in writing. Patient specific deviation information can be recorded directly on the Protocol Deviation eCRF and non-patient specific deviations will be recorded in writing. Investigators will also adhere to procedures for reporting study deviations to their IRB 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 patient inclusion and exclusion criteria;
    b. Any deviation from patient 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 indentified in the Delegation of Authority Log

2. Minor deviation:
   a. Deviation from a protocol requirement such as incomplete/inadequate patient 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 safety data. The DMC will consist of a minimum of 3 members, all members being physicians; one cardiothoracic surgeon, one interventional cardiologist and one cardiologist.

DMC activities, including stopping rules, will be defined in DMC Charter.

16 APPLICABLE REGULATIONS AND GUIDELINES

The regulations listed in Table 13 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 13 – Applicable Regulations and Guidelines

Region	Regulation / Guideline
United States	- 21 CFR 50 – Protection of Human Patients - 21 CFR 56 – Institutional Review Boards - 21 CFR 54 – Financial Disclosure by Clinical Investigators - 21 CFR 58 – Good Laboratory Practice for Nonclinical Laboratory Studies - 21 CFR 812: Investigational Device Exemptions - 21 CFR 820 – Quality System Regulation - EN ISO 13485:2012 Medical Devices – Quality Management Systems – Requirements for Regulatory Purposes - ISO 14155:2011 I (Clinical Investigation of Medical Devices for Human Patients - 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 patient screened for participation in the clinical study and patients who participate in the study.

16.1 DATA PROTECTION AND PATIENT CONFIDENTIALITY

The Study Sponsor is dedicated to maintaining the confidentiality and privacy of patients 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 patient identifiers will be obliterated from all photocopies of source documents that have been removed from the study site. Patient identifiers include, but are not limited to: patient's name, social security number or equivalent, and medical / hospital number. All study documents for the clinical study will identify the patient by a patient study identification number assigned by the Sponsor and the patient's initials.

16.2 INVESTIGATOR RESPONSIBILITIES

16.2.1 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 patients 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 IRB approval for the study at his/her study site.

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

16.2.2 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, IRB approval letters, IRB 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.

16.2.3 INVESTIGATOR REPORTS

[redacted]

16.3 SPONSOR RESPONSIBILITIES

16.3.1 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 patients or which may influence patient's decision to continue participating in the study.

16.4 SELECTION OF INVESTIGATORS

[redacted]

16.4.1 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 16.1) and any conditions of study approval by the IRB 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 patients, the Study Sponsor will inform Investigators, IRBs, and regulatory bodies as required.

16.4.2 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, IRB 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.

16.4.3 SPONSOR REPORTS

[redacted]

- [redacted]

16.5 STUDY CHANGES

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

16.6 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 15.

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

16.7 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.

16.8 PUBLICATION POLICY

[redacted]

17 REFERENCES

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18 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
Bleeding (VARC-2)	<u>Life Threatening or Disabling Bleeding</u> • Fatal bleeding (BARC type 5) OR • Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) OR • Bleeding causing hypovolaemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) OR • Overt source of bleeding with drop in haemoglobin >5 g/dL or whole blood or packed red blood cells (RBCs) transfusion >4 units* (BARC type 3b) <u>Major Bleeding</u> • Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dl or requiring transfusion of two or three units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND • Does not meet criteria of life-threatening or disabling bleeding <u>Minor Bleeding</u> Any bleeding worthy of clinical mention (e.g. access site hematoma) that does not qualify as life-threatening, disabling, or major
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 Success	Clinical success: procedural success without MAEs at 30 days.
Death	See "Cardiovascular 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: device is deployed as intended and the delivery system is successfully retrieved as intended at the time of the patient's exit from the cardiac catheterization laboratory.
eGFR	Estimated glomerular filtration rate
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 Cardiac Surgery	Emergent Salvage: The patient is undergoing CPR en route to the operating room or prior to anesthesia induction Emergent: The patient's clinical status includes any of the following: 1. Ischemic dysfunction of any of the following: a. ongoing ischemia including rest angina despite maximal medical therapy (medical and/or IABP); b. Acute Evolving Myocardial Infarction within 24 hours before surgery or c. pulmonary edema requiring intubation 2. Mechanical dysfunction (either of the following): a. shock with circulatory support; or b. shock without circulatory support. Urgent: All of the following conditions are met: • Not elective status • Not emergent status • Procedure required during same hospitalization in order to minimize chance of further clinical deterioration • Worsening, sudden chest pain, CHF, acute myocardial infarction (AMI), anatomy, IABP, unstable angina with intravenous (IV) nitroglycerin (NTG) or rest angina may be included. 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	Patient enrollment in this clinical study is established when a patient has signed the informed consent form agreeing to participate in the study and has been deemed eligible for study participation by meeting the study eligibility 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 (local)	The local '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
KCCQ	Kansas City Cardiomyopathy Questionnaire is a health-related quality-of-life measure for patients with congestive heart failure.
LVEF	Left ventricular ejection fraction
MAE	Major adverse event defined as cardiovascular mortality, myocardial infarction, new need for renal replacement therapy, severe bleeding and re-intervention for study device related complications
Malfunction	Refer to ISO 14155 definition
Mortality	See "Cardiovascular Mortality"
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)
Pacemaker Dependency	Continuous ventricular stimulation without any pacemaker inhibition by spontaneous cardiac activity determined during the last interrogation within 180 days.
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.
Procedural Success	Procedural success: device success with evidence of TR reduction as evidenced by a relative reduction in EROA of ≥ 30% from baseline to discharge and without the need for a surgical or percutaneous intervention prior to hospital discharge.
Prosthesis	An artificial substitute
QoL	Quality of Life
Reintervention	Any intervention (surgical or transcatheter) 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
Severe Bleeding	Severe bleeding is a major, life-threatening/disabling or fatal bleeding, as defined by VARC-2.
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
Patient	Refer to ISO 14155 definition
Patient Withdrawal	A patient who decides not to participate in the study after signing an informed consent form and being enrolled.
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 patient who consents to participate in the study and is enrolled but is withdrawn by the Investigator.

19 APPENDIX A - SAMPLE INFORMED CONSENT FORM