Edwards

Early Feasibility Study of the Edwards FORMA Tricuspid Transcatheter Repair System

CLINICAL PROTOCOL

(Clinical Investigational Plan)

Study Number: 2014-04
Version: M
Effective Date: February 4, 2019

CONFIDENTIAL

Study Sponsor:

[redacted]

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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 9900GSA • Edwards FORMA Tricuspid Transcatheter Introducer Sheath, Model 9900IS • 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 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. Age ≥ 18 years old 2. Symptomatic severe (Stage D) functional, tricuspid regurgitation (per applicable guidelines) 3. Symptomatic despite medical therapy; patient must be on diuretic therapy. 4. The local site Heart Team determines that the patient is appropriate for transcatheter tricuspid repair 5. Patient is willing and able to comply with all specified study evaluations and provides written informed consent.
Enrollment Criteria (Exclusion):	1. Echocardiographic/CT parameters (any of the following): a. Vessel access or right heart anatomy precluding proper device introduction, deployment and function b. LVEF < 30% c. Severe right ventricular dysfunction as assessed by the core lab d. Patients with systolic pulmonary artery pressure > 60 mmHg 2. Primary tricuspid disease (e.g. rheumatic, myxomatous degeneration, tricuspid valve prolapse, tricuspid stenosis) 3. Previous tricuspid leaflet repair or tricuspid valve replacement 4. Presence of two or more trans-tricuspid leads or any single trans-tricuspid lead: a. Precluding proper placement of or interferes with device b. Implanted within the last 180 days c. With pacemaker dependency 5. Severe aortic, mitral and/or pulmonic valve stenosis and/or regurgitation 6. Active endocarditis within 90 days of the scheduled implant 7. Significant pericardial effusion 8. Intra-cardiac mass, thrombus, or vegetation

	9. Untreated clinically significant coronary artery disease requiring revascularization 10. Recurrent (>2 per 12 months) hospitalizations or ER visit for COPD exacerbation 11. MI or known unstable angina within 30 days prior to the index procedure 12. Any therapeutic invasive cardiac procedure within 30 days prior to the index procedure, or any dual anti-platelet therapy (DAPT) requirement which cannot be interrupted for 7 days 13. Any cardiac surgery, within 3 months prior to procedure 14. Hemodynamic instability or on IV inotropes within 30 days of the scheduled implant 15. Severe uncontrolled hypertension (SBP ≥ 180 mmHg and/or DBP ≥ 110 mm Hg) 16. Cerebrovascular Accident (CVA) or TIA within the past 30 days 17. Kidney dysfunction with estimated Glomerular Filtration Rate (eGFR) $\leq$ 30 ml/min/1.73 m^2 or patient is on chronic dialysis 18. Any physical impairment which limits the patient's capacity to complete functional testing due to other medical conditions independent of their TR (e.g. orthopedic condition) 19. Significant frailty (i.e. Katz Index of Independence in Activities of Daily Living (ADL) ≤ 2) within 90 days of scheduled implant procedure 20. Continuous home oxygen for primary severe COPD 21. Chronic anemia (Hgb < 9 g/dL) not corrected by transfusion 22. Thrombocytopenia (Platelet count< 100,000/mm^3) or thrombocytosis (Platelet count > 750,000/mm^3) 23. Bleeding disorders or hypercoagulable state 24. Active peptic ulcer or active gastrointestinal (GI) bleeding within 90 days of the scheduled implant 25. Cardiac cachexia 26. Contraindication to anticoagulants or antiplatelet agents 27. Currently or history of IV drug use 28. Pregnant or lactating; or female of childbearing potential with a positive pregnancy test 24 hours before any study-related radiation exposure 29. Patients in whom transesophageal echocardiography is contraindicated 30. Known allergy to cobalt chromium, nitinol, titanium or contrast agents that cannot be adequately pre-medicated.

	31. Known hypersensitivity or contraindication to procedural medications which cannot be adequately managed medically 32. Impaired judgment and/or is undergoing emergent or urgent treatment for tricuspid insufficiency 33. Currently participating in another investigational drug or device study that has not completed the primary endpoint or that clinically interferes with the endpoints of this study 34. Co-morbid condition(s) that, in the opinion of the Investigator, limit life expectancy to < 12 months 35. Co-morbid condition(s) that, in the opinion of the investigator, could limit the patient's ability to participate in the study, including compliance with follow-up requirements, or that could impact the scientific integrity of the study 36. Patient is under guardianship
Feasibility Endpoints:	Safety: Composite of major adverse events (MAE) defined as cardiovascular mortality, myocardial infarction, new need for renal replacement therapy, severe bleeding, re-intervention and major access site and vascular complications at 30 days. Performance: • 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, re-intervention and major access site and vascular complications)

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

1 INTRODUCTION

1.1 CLINICAL BACKGROUND

1.1.1 DISEASE PROCESS

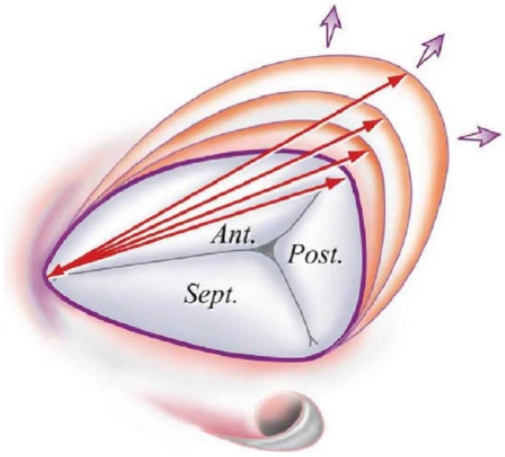
Tricuspid Regurgitation (TR), tricuspid insufficiency or tricuspid incompetence describes a condition in which blood flow through the tricuspid valve flows in the incorrect direction during part of the cardiac cycle. Normally, during diastole, the tricuspid valve opens as a result of atrial pressure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

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

1.1.2 ETIOLOGY

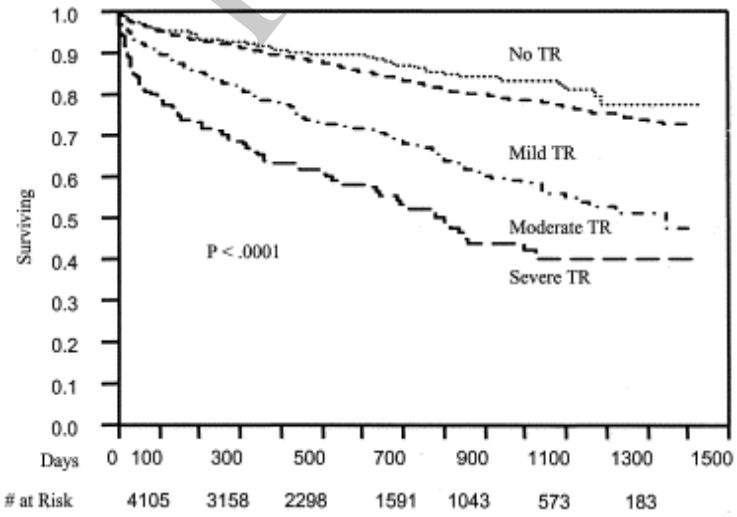
TR can have many underlying etiologies, but the majority of these can be divided into two major categories: degenerative and functional TR. Degenerative (primary, organic or structural) TR refers to regurgitation resulting from disease processes affecting the integrity of the tricuspid valve leaflets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

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



Tricuspid regurgitation is a common echocardiographic finding that is often considered benign unless associated with significant pulmonary hypertension or RV or LV dysfunction. It has been shown that increasing TR severity is associated with worse survival regardless of 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]

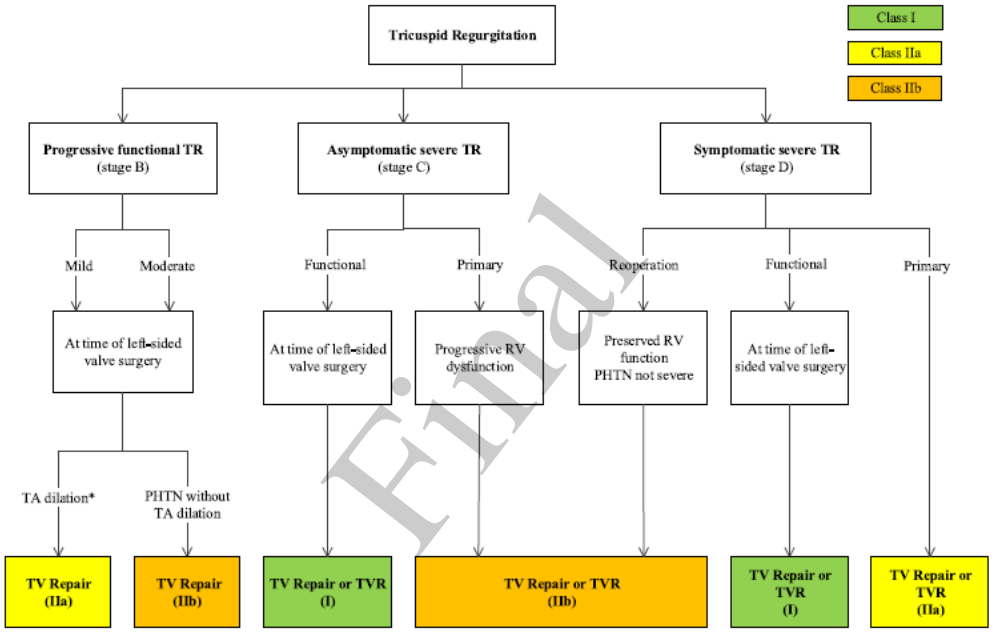


1.2 ALTERNATIVE TREATMENT/THERAPIES

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 concomitant 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. Edwards is also currently exploring annular reconstruction devices and edge to edge repair techniques. However all of the devices mentioned are in the investigational phase and are not commercially available.

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.

Percutaneous devices are being investigated for tricuspid valve replacement. 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).

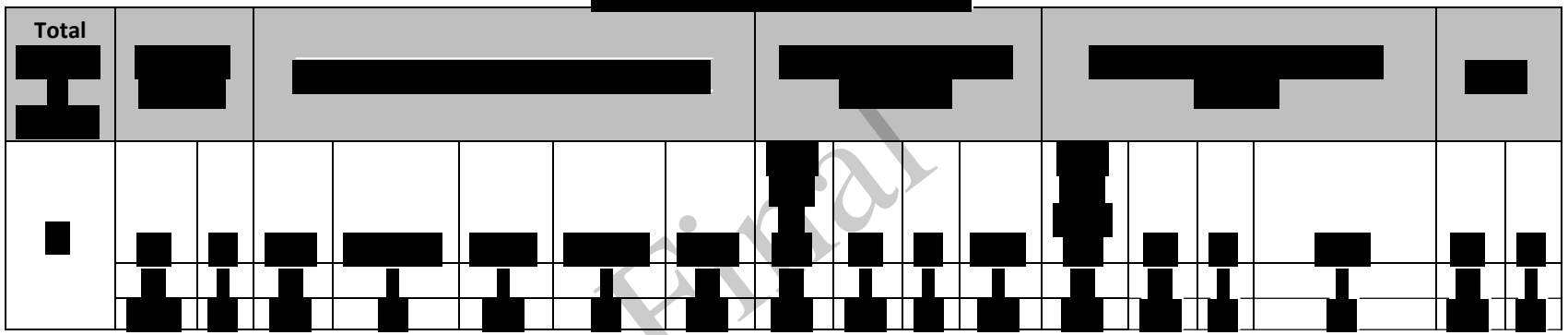
2.2 PRIOR TESTING

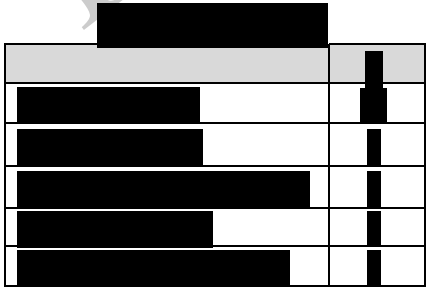
A Report of Priors (Clinical Investigator's Brochure (CIB)) has been prepared for the Edwards FORMA Tricuspid Transcatheter Repair System. This document provides the prior testing conducted on the system components.

2.3 CLINICAL EXPERIENCE

[redacted]

[redacted]





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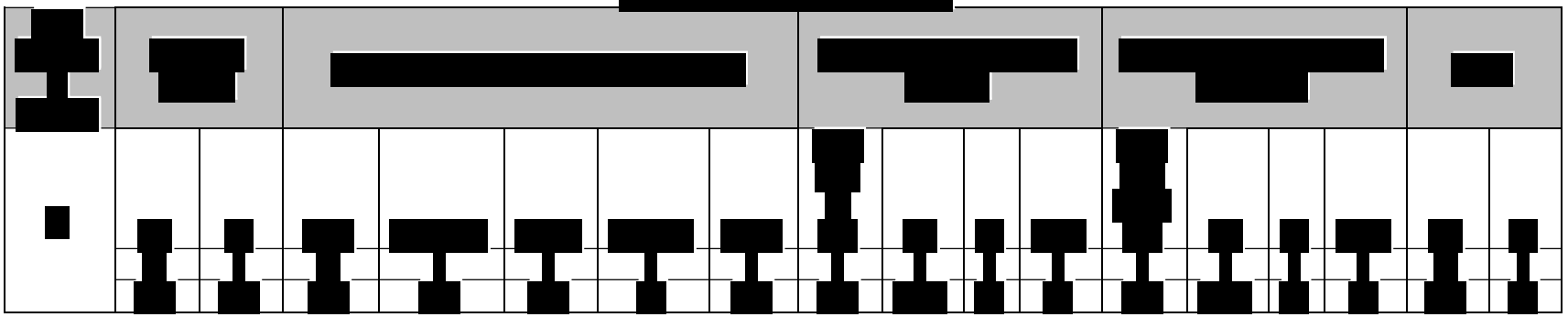

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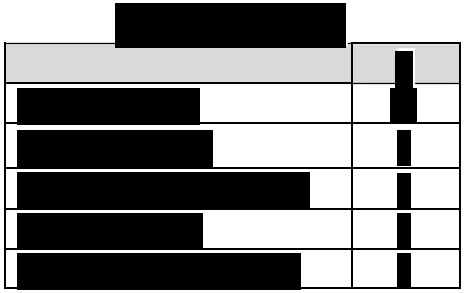

[redacted]

[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]

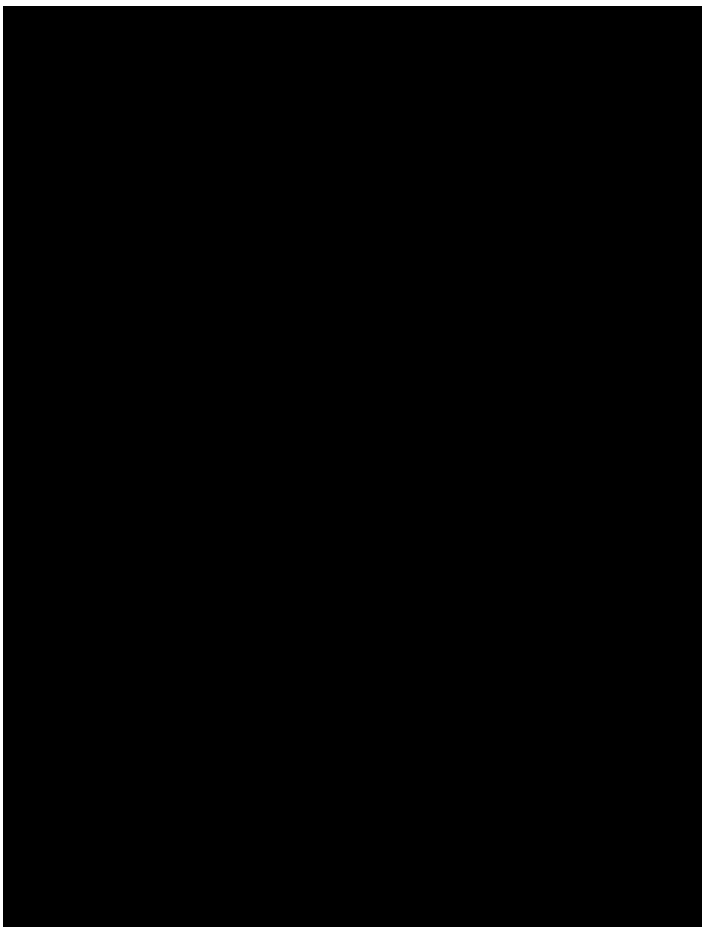

Figure 11: Edwards FORMA Tricuspid Transcatheter Guide Sheath, Model 9900GSA

[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.

[redacted]

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;
- hypertension/hypotension;
- infection, including septicemia and endocarditis;
- inflammation;
- leaflet damage;
- 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 cardiovascular 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, re-intervention and major access site and vascular 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, re-intervention and major access site and vascular complications)

5.1.3 OTHER ENDPOINTS

5.1.3.1 Echocardiographic parameters

A. Reduction in TR severity (assessed by TR grade and quantitative measures) as assessed by TEE pre- and post-implant in the procedure room.

Additional echocardiographic parameters will be compared to baseline:

B. TTE parameters assessed at baseline, discharge, 30 days, 6 months, 1 year and annually until 3 years post procedure.
    1. TR grade- qualitative assessment
    2. Vena Contracta (2D)
    3. EROA (PISA/2D or 3D/3D color doppler)
    4. Regurgitant volume
    5. Tricuspid annular diameter (end-diastolic – S-L)
    6. Tricuspid annular area (2D/3D mid-diastolic)
    7. Tenting area and distance
    8. Forward stroke volume
    9. RV dimensions
    10. Right atria volume
    11. Left ventricular Ejection Fraction
    12. Inferior Vena Cava dimensions/respiratory variations
    13. Hepatic vein flow reversal
    14. Pulmonary artery pressure (peak)
    15. Right ventricular function

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 13.

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. Age ≥ 18 years old
2. Symptomatic severe (Stage D) functional, tricuspid regurgitation (per applicable guidelines)
3. Symptomatic despite medical therapy; patient must be on diuretic therapy.
4. The local site Heart Team determines that the patient is appropriate for transcatheter tricuspid repair
5. Patient is willing and able to comply with all specified study evaluations and provides written informed consent.

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. Echocardiographic/CT parameters (any of the following):
    a. Vessel access or right heart anatomy precluding proper device introduction, deployment and function
    b. LVEF < 30%
    c. Severe right ventricular dysfunction as assessed by the core lab
    d. Patients with systolic pulmonary artery pressure > 60 mmHg
2. Primary tricuspid disease (e.g. rheumatic, myxomatous degeneration, tricuspid valve prolapse, tricuspid stenosis)
3. Previous tricuspid leaflet repair or tricuspid valve replacement
4. Presence of two or more trans-tricuspid leads or any single trans-tricuspid lead:

   a. Precluding proper placement of or interferes with device
   b. Implanted within the last 180 days
   c. With pacemaker dependency
5. Severe aortic, mitral and/or pulmonic valve stenosis and/or regurgitation
6. Active endocarditis within 90 days of the scheduled implant
7. Significant pericardial effusion
8. Intra-cardiac mass, thrombus, or vegetation
9. Untreated clinically significant coronary artery disease requiring revascularization
10. Recurrent (>2 per 12 months) hospitalizations or ER visit for COPD exacerbation
11. MI or known unstable angina within 30 days prior to the index procedure
12. Any therapeutic invasive cardiac procedure within 30 days prior to the index procedure, or any dual anti-platelet therapy (DAPT) requirement which cannot be interrupted for 7 days
13. Any cardiac surgery, within 3 months prior to procedure
14. Hemodynamic instability or on IV inotropes within 30 days of the scheduled implant
15. Severe uncontrolled hypertension (SBP ≥ 180 mmHg and/or DBP ≥ 110 mm Hg)
16. Cerebrovascular Accident (CVA) or TIA within the past 30 days
17. Kidney dysfunction with estimated Glomerular Filtration Rate (eGFR) < 30 ml/min/1.73 m2 or patient is on chronic dialysis
18. Any physical impairment which limits the patient's capacity to complete functional testing due to other medical conditions independent of their TR (e.g. orthopedic condition)
19. Significant frailty (i.e. Katz Index of Independence in Activities of Daily Living (ADL) ≤ 2) within 90 days of scheduled implant procedure
20. Continuous home oxygen for primary severe COPD
21. Chronic anemia (Hgb < 9 g/dL) not corrected by transfusion
22. Thrombocytopenia (Platelet count< 100,000/mm3) or thrombocytosis (Platelet count > 750,000/mm3)
23. Bleeding disorders or hypercoagulable state
24. Active peptic ulcer or active gastrointestinal (GI) bleeding within 90 days of the scheduled implant
25. Cardiac cachexia
26. Contraindication to anticoagulants or antiplatelet agents
27. Currently or history of IV drug use
28. Pregnant or lactating; or female of childbearing potential with a positive pregnancy test 24 hours before any study-related radiation exposure

29. Patients in whom transesophageal echocardiography is contraindicated
30. Known allergy to cobalt chromium, nitinol, titanium or contrast agents that cannot be adequately pre-medicated.
31. Known hypersensitivity or contraindication to procedural medications which cannot be adequately managed medically
32. Impaired judgment and/or is undergoing emergent or urgent treatment for tricuspid insufficiency
33. Currently participating in another investigational drug or device study that has not completed the primary endpoint or that clinically interferes with the endpoints of this study
34. Co-morbid condition(s) that, in the opinion of the Investigator, limit life expectancy to < 12 months
35. Co-morbid condition(s) that, in the opinion of the investigator, could limit the patient's ability to participate in the study, including compliance with follow-up requirements, or that could impact the scientific integrity of the study
36. 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

All patients enrolled under this Revision L of the Clinical Protocol will be consented, treated and followed according to the requirements described herein. Patients enrolled under previous versions of the Clinical Protocol will not be required to reconsent under Revision L and will be followed according to the requirements of the protocol version to which they were consented.

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. Patient demographics and medical history (includes 12 months prior hospitalizations including emergency department (ED) visits, paracentesis)
3. Clinical Evaluation (includes vital signs, concomitant medical treatments, edema grading, ankle circumference measurements, weight and height) and NYHA classification
4. Administration of Health Status Questionnaires (e.g., SF-12, KCCQ)
5. Administration of Six Minute Walk Test (6MWT)
6. Administration of Katz Index of Independence in Activities of Daily Living (ADL)
7. Administration of Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale©

8. Administration of Patient Edema Questionnaire
9. Administration of Patient Preference Survey
10. Modified Rankin score (mRS) *
11. 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. CBC and platelet count
        ii. Complete metabolic panel
        iii. Liver panel including gamma-glutamyl transferase (GGT)
        iv. 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
12. Standard 12-lead Electrocardiogram (ECG)
13. Comprehensive Transthoracic Echocardiogram (TTE must be collected per Echocardiography Acquisition Protocol) [6].
14. Transesophageal Echocardiogram (TEE), including but not limited to transgastric views.
15. All candidates must have pre-implant procedure imaging (e. g., Computed Tomography (CT) Angiogram), 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.
16. Invasive Hemodynamic Monitoring/Right Heart Catheterization that should include, but is not limited to, right atrial pressure (RAP), PAP, right ventricle pressure (RVP), cardiac output (CO), and PVR measurements.[7]
17. Candidates with cardiac leads may also have a venogram (subclavian and axillary veins) as part of pre-implant procedure imaging, if venous patency cannot be determined by pre-procedure CT.
18. Candidates with pacemaker leads must have interrogation of their device to determine pacing stability and pacing dependency. Pacemaker dependency is defined as continuous ventricular stimulation without any pacemaker inhibition by

[6] 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.

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

spontaneous cardiac activity determined during the last interrogation within 180 days.

19. Coronary angiogram

*mRS will be conducted at baseline for all patients with a history of stroke. For patients who experience a stroke during the study, mRS will be conducted closest to 90 days post event. It is recognized that an assessment of stroke is incomplete without an appropriate measurement of the disability resulting from the stroke, hence, mRS closest to 90 days post event will be used to assess clinical disability. Every effort should be made to have a neurologist or neurology fellow perform the neurological assessments, or alternatively, a trained research team member certified in stroke assessment. mRS can be obtained by a certified research team member via phone interview with the patient or caregiver member if the patient is unable to visit the research office.

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

Table 6 - Baseline Evaluation

General Information	Clinical Information	Laboratory Measurements
• Inclusion/exclusion evaluation • Informed consent • Age • Gender • Height • Weight	• Local Heart Team determination • Patient demographics 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 & ankle circumference measurements • Concomitant Medications and doses • NYHA classification • Echocardiographic measurements (TTE & TEE), tricuspid regurgitation & heart function • CT • Coronary angiogram • Venogram (in patients with cardiac leads) if required	Within 30 days of procedure: • Date of blood draw • Troponin[1] and CK-MB[1] Within ≤ 2 weeks of procedure: • Date of blood draw • 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[2]

General Information	Clinical Information	Laboratory Measurements
	• Interrogation of pacemaker leads • Invasive Hemodynamic Monitoring/Right Heart Catheterization including pressure measurements • ECG results • Six minute walk test • Katz Index (ADL) test • CSHA Frailty scale • KCCQ & SF-12 questionnaires • Edema Questionnaire • Preference Survey • mRS (if applicable)	

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

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, angiographic 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] • 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. CBC and platelet count
    b. Complete metabolic panel
    c. Liver panel
    d. PTT/aPTT and INR
    e. Serum creatinine and eGFR
    f. 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. CBC and platelet count
    b. Complete metabolic panel
    c. Liver panel
    d. INR and PTT/aPTT
    e. Serum creatinine and eGFR
    f. Troponins and cardiac enzymes (CK-MB), only required if an elevation was noted post implant (within 48 hours)
4. Standard 12-lead ECG
5. Administration of Patient Edema Questionnaire
6. Comprehensive Transthoracic Echocardiogram per echo core lab acquisition protocol

7. Modified Rankin score (mRS) mRS will be conducted for all patients who had a stroke since their last assessment. It is recognized that an assessment of stroke is incomplete without an appropriate measurement of the disability resulting from the stroke, hence, mRS closest to 90 days post event will be used to assess clinical disability. Every effort should be made to have a neurologist or neurology fellow perform the neurological assessments, or alternatively, a by a trained research team member certified in stroke assessment. mRS can be obtained by a certified research team member via phone interview with the patient or caregiver member if the patient is unable to visit the research office.

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 grading & ankle circumference measurements, ascites, access site) • Vital signs (Blood Pressure, Heart Rate) • TTE measurements, tricuspid regurgitation & heart function • ECG results • Concomitant medications and doses[1] • Edema Questionnaire • Adverse events • mRS (if applicable)	• Date of blood draw • Troponin and CK-MB, if applicable • WBC • RBC • Hematocrit • Hemoglobin • Platelets • ALT/SGPT • AST/SGOT • Bilirubin • LDH • GGT • ALP • Albumin • Sodium & potassium • Urea • Serum creatinine & eGFR • INR & PTT/aPTT

1. *No changes in diuretics are allowed for at least 3 months post procedure unless patient presents with severe hypotension.*

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, ankle circumference measurements, and NYHA classification
2. Administration of Health Status Questionnaires (e.g., SF-12, KCCQ)
3. Administration of Six Minute Walk Test
4. Administration of Patient Edema Questionnaire
5. Safety Evaluation
6. Clinical Laboratory Tests :
    a. CBC and platelet count
    b. Complete metabolic panel
    c. Liver panel
    d. INR and PTT/aPTT
    e. Serum creatinine and eGFR
7. Standard 12-lead ECG
8. Comprehensive Transthoracic Echocardiogram (TTE) per echo core lab acquisition protocol
9. Modified Rankin Scale (mRS): mRS will be conducted for all patients who had a stroke since their last assessment. It is recognized that an assessment of stroke is incomplete without an appropriate measurement of the disability resulting from the stroke, hence, mRS closest to 90 days post event will be used to assess clinical disability. Every effort should be made to have a neurologist or neurology fellow perform the neurological assessments, or alternatively, a by a trained research team member certified in stroke assessment. mRS can be obtained by a certified research team member via phone interview with the patient or caregiver member if the patient is unable to visit the research office.

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	Laboratory Measurements
• Visit date • Height • Weight	• Clinical evaluation (mobility, edema grading, ankle circumference measurements, 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 • Edema Questionnaire • Concomitant Medications and doses[1] • Adverse events • mRS (if applicable)	• Date of blood draw • WBC • RBC • Hematocrit • Hemoglobin • Platelets • ALT/SGPT • AST/SGOT • Bilirubin • LDH • GGT • ALP • Albumin • Sodium & potassium • Urea • Serum creatinine and eGFR • INR & PTT/aPTT

1. *No changes in diuretics are allowed for at least 3 months post procedure unless patient presents with severe hypotension.*

8.7.1 VISIT & ASSESSMENT 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:

Table 11 – Follow-up Visit Windows

Scheduled Follow-up Interval	Follow-up Window
1 month (30 days)	± 7 days
6 months (180 days)	± 30 days
Annually (365 days) up to 3 years	± 45 days

Table 12: Screening/Baseline Assessment Windows

Assessment	Window
TTE*	Within 60 days of submission to Sponsor
TEE**	Within 90 days of submission to Sponsor
Hemodynamic Monitoring	Within 90 days of scheduled implant procedure[7]
Venogram (pacemaker lead patients)	Within 90 days of scheduled implant procedure if venous patency cannot be determined by CT
CT Angiogram**	Within 180 days of submission to Sponsor
Coronary Angiogram	Within 180 days of scheduled implant procedure
Pacemaker interrogation	Within 180 days of scheduled implant procedure

* TTE must be conducted after informed consent and must be collected according to echo core lab acquisition protocol.

**pre-existing TEE/CT image of adequate quality capturing required anatomy for assessment can be used.

Note: For all imaging (TTE, TEE, CT angiogram, coronary angiogram), if imaging is deemed incomplete or inadequate for assessment, repeat imaging may be required.

Note: Procedure should be scheduled within 90 days of consent.

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

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

"non-implanted" and will be followed 30 days for safety. These patients will be exempt from all other study follow up visit procedures.

Table 13 – 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 (180 ± 30 days)	ANNUAL (for 3 yrs) (365 ± 45 days)
Informed Consent	X						
Patient Demographics & Medical History	X						
Clinical Evaluation/Concomitant Medications[3]	X		X	X	X	X	X
Edema grading, ankle circumference measurements & Patient Edema Questionnaire	X			X	X	X	X
Hospitalizations &/or clinic visits & paracentesis	X				X	X	X
NYHA Class Assessment	X				X	X	X
Health Status Questionnaires KCCQ, SF-12	X				X	X	X
Six Minute Walk Test	X				X	X	X
Katz Index (ADL), Clinical Frailty Score©	X						
Patient Preference Survey	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
CBC and Platelet Count	X		X	X	X	X	X
INR & PTT/aPTT	X		X	X	X	X	X
βHCG	X[4]						
Serum creatinine and eGFR	X		X	X	X	X	X
Troponins and CK-MB	X		X	X[5]			
ECG	X		X	X	X	X	X
Transesophageal Echocardiogram	X	X					

[1] Implant procedure should be scheduled within 90 days of consent. 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.

[2] Discharge from hospital/unit post implant procedure.

[3] No changes in diuretics are allowed for at least 3 months post procedure unless patient presents with severe hypotension.

[4] βHCG for women who are not sterile or post-menopausal.

[5] Only required if an elevation was noted post implant (within 48 hours).

[6] mRS will be conducted at baseline for all patients with a history of stroke. For patients who experience a stroke during the study, mRS will be conducted closest to 90 days post event. It is recognized that an assessment of stroke is incomplete without an appropriate measurement of the disability resulting from the stroke, hence, mRS closest to 90 days post event will be used to assess clinical disability. Everey effort should be made to have a neurologist or neurology fellow perform the neurological assessments, or alternatively, a trained research team member certified in stroke assessment. mRS can be obtained by a certified research team member via phone interview with the patient or caregiver member if the patient is unable to visit the research office.

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	X					
Modified Rankin Scale	X[6]			X[6]	X[6]	X[6]	X[6]

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 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]

[redacted]

9.2 TRAINING OF INVESTIGATIONAL SITE PERSONNEL

[redacted]ific

[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

[redacted]

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.

[redacted]

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

[redacted]

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 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 deficiencies include malfunctions, use errors and inadequate labeling.

All suspected device deficiencies, malfunctions or fractures of 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 (starting from the signing of inform consent) 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 [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. 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.

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

Analysis populations 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 inclusion/exclusion criteria-related 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, if there is a clinically meaningful difference in sample size from the as-treated population.

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

[redacted]

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]

[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. 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. If an Investigator or designee contacts a Clinical Affairs representative to obtain prior approval for a change to the clinical study requirements, the approval or disapproval will be documented in writing. A copy of the approval or disapproval will be forwarded to the Investigator and a copy will be maintained in the 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 Delegation of Authority Log etc.) will be reported to the Sponsor. Patient specific deviation information must 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.

A major protocol deviation or noncompliance is one that may have a significant impact on subject safety, well-being, the subject's willingness to participate in the study, or that may compromise the integrity of the study data and analysis, including:

a) Subject implanted/treated with study device not having met eligibility criteria at the time of implant/treatment.

b) Informed Consent not signed or signed after the initiation of non-standard of care, research related assessments.

c) UADE not reported to IRB/EC/Sponsor within the required timeframe

d) Unauthorized use/implant of an investigational device

A minor protocol deviation or noncompliance is unlikely to have a significant impact on subject safety, wellbeing, or is unlikely to compromise the integrity of the study data and analysis. All protocol deviations or noncompliance will be reported to the IRB/EC, as required.

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.

With regards to Safety oversight committee, in case of inconsistency between the protocol and the Safety oversight committee's charter (e.g. DMC), the charter will be the final determining document.

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 - ISO 13485:2016 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]

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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]

[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]

- [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]

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18 DEFINITIONS

Access Site (VARC-1)	Any location (arterial or venous) traversed by a guidewire, a catheter or a sheath (including the subclavian or axillary vein)
Access Site and Vascular Complications (MVARC)	I. **Vascular complications** **A. Major access site vascular complications, including:** i. Aortic dissection or aortic rupture, or ii. Access site-related† arterial or venous injury (dissection, stenosis, ischemia, arterial, or venous thrombosis including pulmonary emboli, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, retroperitoneal hematoma, atrial septal defect‡), irreversible nerve injury, or compartment syndrome resulting in death; hemodynamic compromise; life-threatening, extensive, or major bleeding (MVARC bleeding scale); visceral ischemia; or neurological impairment, or iii. Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage, or iv. Unplanned endovascular or surgical interventions resulting in death; life-threatening, extensive, or major bleeding (MVARC bleeding scale); visceral ischemia; or neurological impairment **B. Minor access site vascular complications, including:** i. Access site arterial or venous injury (dissection, stenosis, arterial, or venous thrombosis including pulmonary emboli, ischemia, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, retroperitoneal hematoma, atrial septal defect‡) not resulting in death; life-threatening, extensive, or major bleeding (MVARC scale); visceral ischemia; or neurological impairment, or ii. Distal embolization treated with embolectomy and/or thrombectomy not resulting in amputation or irreversible end-organ damage, or iii. Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication, or iv. Vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)

	II. Cardiac structural complications due to access-related issues **A. Major cardiac structural complications, including:** i. Cardiac perforation* or pseudoaneurysm resulting in death, life-threatening bleeding, hemodynamic compromise, or tamponade, or requiring unplanned surgical or percutaneous intervention **B. Minor cardiac structural complications, including:** i. Cardiac perforation or pseudoaneurysm not meeting major criteria *Including the right ventricle, right atrium, coronary sinus, right atrium, and right ventricle. †May arise from the access procedure per se or complications from vascular closure devices. ‡Meeting pre-specified criteria for a hemodynamically significant shunt, or requiring unplanned percutaneous or surgical closure.
Access Site and Vascular Complications Requiring Intervention	Complications (i.e. dissection, perforation, arteriovenous fistula, pseudoaneurysm formation, retroperitoneal hemorrhage, thromboembolism) requiring intervention (percutaneous or surgical).
ACT	Activated clotting time

[redacted]

Acute Kidney Injury (AKI) (MVARC)	**Maximal change in serum Creatinine (sCR) from baseline to 7 days post-procedure** **Stage 1:** Increase in sCr to 150%–199% (1.50–1.99 x increase vs. baseline), increase of ≥0.3 mg/dl (≥26.4 mmol/l) within 48 h, or urine output <0.5 ml/kg/h for ≥6 h but <12 h **Stage 2:** Increase in sCr to 200%–299% (2.00–2.99 x increase vs. baseline) or urine output <0.5 ml/kg/h for ≥12 h but <24 h **Stage 3:** Increase in sCr to ≥300% (>3.0 x increase vs. baseline), sCr of ≥4.0 mg/dl (≥354 mmol/l) with an acute increase of ≥0.5 mg/dl (44 mmol/l), urine output <0.3 ml/kg/h for ≥24 h, or anuria for ≥12 h; patients receiving renal replacement therapy are considered stage 3 irrespective of other criteria.
Adverse Device Effect (ADE)	Refer to ISO 14155 definition
Adverse Event (AE) (ISO 14155:2011)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device
Anchor Detachment	Anchor has detached from original implanted position and is not attached to any structure, Spacer is still within the tricuspid valve (therapeutic)
Anchor Detachment with Spacer Migration	Anchor has detached from original implant position and is not attached to any structure, Spacer is no longer within the tricuspid valve (non-therapeutic)
Anchor Migration	Anchor has migrated and attached to a different structure/location than original implanted position, Spacer is still within the tricuspid valve (therapeutic)
Anchor Migration with Spacer Migration	Anchor has migrated and attached to a different structure/location than original implanted position, Spacer is no longer within the tricuspid valve (non-therapeutic)
Bleeding (MVARC)	*Endpoint is severe bleeding, defined as major, extensive, life-threatening or fatal bleeding.* *All bleeding events will be classified as:*

	I. Minor *Any overt*, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that meets ≥1 of the following: requiring nonsurgical medical intervention by a health care professional; leading to hospitalization or increased level of care; prompting evaluation; or requires 1 or 2 U of whole blood or packed RBC transfusion and otherwise does not meet criteria for major, extensive, or life threatening bleeding.* ***II. Major*** *Overt bleeding either associated with a drop in the hemoglobin of ≥3.0 g/dl or requiring transfusion of ≥3 U of whole blood or packed RBCs AND does not meet criteria of life-threatening or extensive bleeding.* ***III. Extensive*** *Overt source of bleeding with drop in hemoglobin of ≥4 g/dl or whole blood or packed RBC transfusion ≥4 U within any 24-h period, or bleeding with drop in hemoglobin of ≥6 g/dl or whole blood or packed RBC transfusion ≥4 U (BARC type 3b) within 30 days of the procedure.* ***IV. Life-threatening*** *Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating surgery or intervention, or intramuscular with compartment syndrome OR bleeding causing hypovolemic shock or hypotension (systolic blood pressure <90 mm Hg lasting >30 min and not responding to volume resuscitation) or requiring significant doses of vasopressors or surgery.* ***V. Fatal*** *Bleeding adjudicated as being a proximate cause of death. Severe bleeding adjudicated as being a major contributing cause of a subsequent fatal complication, such as MI or cardiac arrest, is also considered fatal bleeding.* *"Overt" bleeding is defined as clinically obvious (visible bleeding and bleeding identified by imaging only). Examples of overt bleeding include:

	○ Pseudoaneurysm ○ Retroperitoneal hematoma seen on CAT scan ○ Visible access site hematoma ○ Gross hematuria ○ Hematemesis and hematochezia Procedural bleeding has to be an overt bleeding from vascular system either at or remote from the access/surgical site. With respect to blood transfusions, it is critical to acknowledge that a bleeding complication has to be the result of overt bleeding and cannot be adjudicated based on blood transfusions alone. Prophylactic transfusion given for reasons other than due to the overt bleeding will not be considered as a bleeding event. If the reason for Hgb drop was other than due to the overt bleeding i.e. due to hemodilution, chronic iron deficiency anemia, this will not be considered as a bleeding event. For purposes of calculating the drop in hemoglobin during the index hospitalization, the Hgb value identified closest to the beginning of the index procedure, before the occurrence of bleeding event, will be used as the baseline value. If the bleeding event occurs after discharge from index procedure, the Hgb value just prior to the occurrence of bleeding event will be the baseline value for calculating the drop in Hgb. Timing of a bleeding event that meets MVARC criteria is based on the time and date of transfusion or the first Hgb drop, whichever occurs first. To calculate the total number of transfusions given, consider only units given to treat the bleeding event itself. Transfusions given before the procedure should not be combined with the units given for the bleeding event

Cardiac Tamponade	Pressure on the heart that occurs when blood or fluid builds up in the space between the heart muscle (myocardium) and the outer covering sac of the heart (pericardium).
Cardiovascular Mortality	see "Death"
Cerebrovascular Accident (CVA)	See "Stroke"
Clinical Success	Clinical success: procedural success without MAEs at 30 days.
Clinical Frailty Scale©	A 9 point single question administered to measure frailty. Developed by the Canadian Study of Health and Aging (CSHA).

Death (MVARC)	**Cardiovascular (CV) Death** The primary cause of CV death will be categorized using the following choices: ○ Arrhythmia and/or conduction system disturbance ○ Cardiovascular infection and sepsis (e.g. Endocarditis) ○ Device failure ○ Heart failure ○ Major bleeding ○ Myocardial Infarction ○ Stroke ○ Sudden, unexpected death / unknown ○ Tamponade ○ Thromboembolism ○ Other CV cause If death was due to a heart failure, it will be sub classified into: ○ LV dysfunction ○ RV dysfunction ○ Biventricular dysfunction **Non-Cardiovascular (CV) Death** A diagnosis of non-CV death requires the primary cause to be clearly related to another condition due primarily to an identifiable non-CV cause or etiology. Specific diagnoses may include respiratory failure, pneumonia, trauma, suicide, or any other non-cardiovascular defined causes (e.g., liver disease, malignancies etc.) not included in the previous categories. ***Primary cause of non-CV death*** *The primary cause of non-CV death will be categorized using the following choices:* ○ *Adverse drug reaction or overdose* ○ *Cancer* ○ *Gastrointestinal*

	○ *Liver failure* ○ *Non-cardiovascular infection and sepsis (e.g. pneumonia)* ○ *Pancreatic* ○ *Renal failure* ○ *Respiratory Failure* ○ *Trauma* ○ *Other non-CV cause*
Device Deficiency (ISO 14155:2011)	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 Fracture	Break or other structural defect in anchor, railing, or spacer with or without embolization
Device Malfunction	Device malfunction is defined in 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. See "Device Deficiency"
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 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. A patient will be considered "enrolled" at the time of skin incision to introduce the FORMA System into the body.
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.

Hospitalization/ Rehospitalization	Hospitalization is defined as any unplanned admission to the hospital (including an emergency department visit) for either a diagnostic or therapeutic purpose following discharge from the index hospitalization. All hospitalizations will be classified to determine whether the hospitalization was related to: ○ **CHF (Congestive Heart Failure) hospitalization:** a hospital stay for ≥ 24 hours with signs and/or laboratory evidence of worsening heart AND administration of intravenous or mechanical heart failure therapies. An ER stay for ≥ 24 hours would qualify as a CHF hospitalization endpoint, even absent formal hospital admission, as such a prolonged stay represents a severe episode of heart failure. ○ **Other CV hospitalization:** hospitalization due for coronary artery disease, acute myocardial infarction, hypertension, cardiac arrhythmias, cardiomegaly, pericardial effusion, atherosclerosis, stroke, or peripheral vascular disease without qualifying heart failure. ○ **Non-CV hospitalization:** hospitalization that is not due to heart failure or other cardiovascular causes, as defined above Patients hospitalized with heart failure meeting these criteria should further be subclassified into: ○ **Primary (cardiac related) heart failure**: this may be due to any cardiac cause, including primary LV dysfunction with or without medication or dietary noncompliance, acute MI, arrhythmias, and worsening valve dysfunction ○ **Secondary (non-cardiac related) heart failure**: when a non-cardiac primary condition is present such as pneumonia, urinary tract infection, or renal failure, which results in fluid overload or myocardial failure. Note: only primary heart failure should be considered a valid criterion for heart failure hospitalization
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, re-intervention and major access site and vascular complications
Malfunction	Refer to ISO 14155 definition
Mortality	See “Death”

Myocardial Infarction (MVARC)	○ **Periprocedural MI (≤48 hours after index procedure procedure)*†:** **A. In patients with normal baseline CK-MB (or cTn):** ○ The peak CK-MB measured within 48 h of the procedure rises to ≥10x the local laboratory ULN (Upper Limit of Normal) **PLUS** new ST-segment elevation or depression of ≥1 mm in ≥2 contiguous leads (measured 80 ms after the J-point) ○ The peak CK-MB measured within 48 h of the procedure rises to ≥5x ULN with new pathological Q waves in ≥2 contiguous leads or new persistent LBBB ○ In the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the PCI rises to ≥70x the local laboratory ULN **PLUS** new ST-segment elevation or depression of ≥1 mm in ≥2 contiguous leads (measured 80 ms after the J-point) ○ The peak CK-MB measured within 48 h of the procedure rises to ≥35x ULN with new pathological Q waves in ≥2 contiguous leads or new persistent LBBB. **B. In patients with elevated baseline CK-MB (or cTn):** The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level plus, new ECG changes as described. ○ **Spontaneous MI (>48 hours after index procedure procedure):** Detection of rise and/or fall of cardiac biomarkers (preferably cTn) with at least 1 value above the 99th percentile URL (or ULN in the absence of URL) together with at least 1 of the following: ☐ Symptoms of ischemia ☐ ECG changes indicative of new ischemia (new ST-segment or T-wave changes or new LBBB) or new pathological Q waves in ≥2 contiguous leads ☐ Imaging evidence of a new loss of viable myocardium or new wall motion abnormality

	○ **MI associated with sudden, unexpected cardiac death‡:** Sudden cardiac death or cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST-segment elevation or new LBBB and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurs before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood ○ **Pathological findings of an acute myocardial infarction‡** **Note:** The use of high sensitivity (hs)-troponins is recommended for diagnosis of Type II (spontaneous) MI, but has not been studied for assessment of periprocedural MI. Standard troponin assays are therefore recommended for evaluation of Type I MI Situations where MI is suspected must be carefully evaluated by taking into consideration past medical history, procedural specifics, renal function etc. It is known that cardiac procedures are associated with multiple confounding factors that contribute to myocardial damage *Periprocedural biomarker elevation >ULN not meeting the criteria for MI should be categorized as “myonecrosis not meeting MI criteria.” †Adapted from Moussa et al.

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 or participating in this clinical study.
Peripheral Thromboembolic Event	See "Embolism"
Pre-Existing Condition	A pre-existing condition is one that was present prior to clinical study screening.
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).
Renal Failure	See "Acute Kidney Injury (AKI)"
Screen Failure	A patient who has signed the consent but, does not fulfill enrollment criteria: 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) (ISO 14155:2011)	Adverse event that: 1. led to death 2. led to serious deterioration in the health of the patient 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 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)
Severe Bleeding (MVARC)	Severe bleeding is a major, extensive, life-threatening or fatal bleeding.
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
Spacer Migration	Anchor has not migrated from original implanted position, Spacer is no longer within the tricuspid valve (non-therapeutic)

Stroke/TIA (MVARC)	**Stroke** 1. Acute episode of a focal or global neurological deficit with at least one of the following: • Change in level of consciousness • Hemiplegia • Hemiparesis • Numbness • Sensory loss affecting one side of the body • Dysphasia or aphasia • Hemianopia • Amaurosis fugax • Other neurological signs or symptoms consistent with stroke 2. Duration of symptoms: • A focal or global neurological deficit ≥ 24 hours • A focal or global neurological deficit < 24 hours if available neuroimaging indicates a new intracranial or subarachnoid hemorrhage (hemorrhagic stroke) or central nervous system infarction (ischemic stroke) • The neurological deficit results in death 3. No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences) to be determined by or in conjunction with designated neurologist.* 4. Confirmation of the diagnosis by at least one of the following: o Neurologist or neurosurgical specialist, or o Neuroimaging procedure (CT scan or brain MRI) o Non-neurologist physician (if neurologist is not available) o Clinical presentation alone **Stroke etiology** will be classified as:

	• **Ischemic:** an acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of the central nervous system tissue • **Hemorrhagic**: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage • **Undetermined:** if there is insufficient information to allow categorization as ischemic or hemorrhagic **Stroke severity** • **Disabling:** mRS score of ≥ 2 at 90 days (or the last available clinical visit with evaluable data) AND an increase in ≥ 1 mRS category from an individual's pre-stroke baseline • **Non-disabling:** mRS score of < 2 at 90 days (or the last available clinical visit with evaluable data) or doesn't result in an increase in ≥ 1 mRS category from pre-stroke baseline It is recognized that an assessment of stroke is incomplete without an appropriate measurement of the disability resulting from the stroke, hence, mRS closest to 90 days post event** will be used to assess clinical disability using the following scale: 0 - No symptoms at all 1 - No significant disability despite symptoms (able to carry out all usual duties and activities) 2 - Slight disability (unable to carry out all previous activities but able to look after own affairs without assistance 3 - Moderate disability (requiring some help, but able to walk without assistance) 4 - Moderately severe disability (unable to walk without assistance and unable to attend to own bodily needs without assistance) 5 - Severe disability (bedridden, incontinent, and requiring constant nursing care and attention) 6 - Dead

	CEC adjudicator will indicate if there was an increase of mRS since pre-stroke baseline, how much the mRS has increased, and the mRS total score closest to 90 days post Stroke. **TIA** Acute episode of a focal or global neurological deficit fulfilling the following criteria: 1. Resulting in at least one of the following • Change in level of consciousness • Hemiplegia • Hemiparesis • Numbness • Sensory loss affecting one side of the body • Dysphasia or aphasia • Hemianopia • Amaurosis fugax • Other neurological signs or symptoms consistent with stroke 2. Duration of deficit could be one of the following: • A focal or global neurological deficit < 24 hours • Any available neuroimaging does not demonstrate a new hemorrhage or infarct 3. No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences) to be determined by or in conjunction with designated neurologist.* **Notes:** • If neurological event does not meet the definition of Stroke or TIA, the CEC adjudication will indicate that accordingly on the form. • *Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies.

	• **Evaluation of stroke between 30 and 90 days is acceptable if 90-day follow-up not available #If a stroke is reported without evidence of confirmation of the diagnosis by one of these methods, the event may still be considered a stroke on the basis of the clinical presentation alone.
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.
Transient Ischemic Attack (TIA) (MVARC)	See "Stroke/TIA"
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 Adverse Device Effect (UADE) (FDA)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problems associated with a device that relates to the rights, safety, or welfare of patients.
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