Edwards EVOQUE Tricuspid valve Replacement: Investigation of Safety and Clinical Efficacy after replacemeNt of tricuspid valve with transcatheter Device

Short Title: TRISCEND Study

Clinical Protocol
(Clinical Investigation Plan)

Study Number: 2019-06
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Edwards Lifesciences LLC
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Protocol Synopsis

Study Number	2019-06
Study Version	[redacted]
Title	Edwards EVOQUE Tricuspid valve Replacement: Investigation of Safety and Clinical Efficacy after replacemeNt of tricuspid valve with transcatheter Device
Short Title	TRISCEND Study
Device Name	Edwards EVOQUE tricuspid valve replacement system (hereinafter referred to as the EVOQUE system).
Intended Use	The EVOQUE system is intended for the treatment of patients with at least moderate tricuspid regurgitation (TR) or prior heart failure hospitalization for TR.
Study Objectives	The objectives of this study are to: • Evaluate the safety and performance of the EVOQUE system • Provide guidance for future clinical study designs utilizing the EVOQUE system • Provide guidance for future EVOQUE system development efforts
Study Design	Prospective, single-arm, multi-center study to evaluate the safety and performance of the EVOQUE system in the treatment of patients with at least moderate TR, signs of TR, symptoms from TR, or prior heart failure hospitalizations for TR. Up to 200 patients (upon FDA approval) will be enrolled in this study at up to 30 investigational sites (upon FDA approval) in the US. All enrolled study patients will be assessed at the following intervals: Screening/baseline, Procedure, Discharge, 30 days, 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years post-procedure.
Enrollment Criteria (Inclusion)	Patients enrolled must meet **ALL** of the following criteria: 1. Age ≥ 18 years old 2. Despite medical therapy (OMT) per the Local Heart Team, patient has signs of TR (peripheral edema or ascites), symptoms from TR, or prior heart failure hospitalization from TR • Note: Medical therapy is at investigator discretion and includes diuretic medications in stable doses, unless patient has documented history of intolerance. With the exception of prehabilitation, it is recommended no new diuretics be introduced and current diuretic doses be stable (i.e. no decrease of more than ½ or increase of 2x) unless medically required (e.g., severe hypotension or signs and symptoms of hypervolemia) for 30 days prior to the procedure. 3. Functional and/or degenerative TR graded as at least moderate on a transthoracic echocardiogram (assessed by the echo core lab using a 5-grade classification)[a] 4. The Local Heart Team determines that the patient is appropriate for transcatheter tricuspid valve replacement 5. Patient is willing and able to comply with all specified study evaluations and provides written informed consent.

[a] The TR grading scale used to determine patient eligibility is based on the scale proposed by Hahn and Zamorano (scale: none/trace, mild, moderate, severe, massive, torrential).

Enrollment Criteria (Exclusion)	Potential patients will be excluded if **ANY** of the following criteria apply: 1. Tricuspid valve anatomy precluding proper device deployment and function, evaluated by echo core lab and by CT 2. Echocardiographic parameters (any of the following, assessed by echo core lab): a. LVEF < 25% b. Echocardiographic evidence of severe right ventricular dysfunction c. Pulmonary arterial systolic pressure (PASP) > 70 mmHg by echo Doppler or R heart catheterization OR PASP > 2/3 systemic BP with PVR > 5 Wood units after vasodilator challenge, in the absence of symptomatic hypotension or systolic BP < 90 mmHg 3. Previous tricuspid intervention that could interfere with placement of the EVOQUE System 4. Presence of trans-tricuspid pacemaker or defibrillator lead with any of the following: a. Implanted in the RV within the last 3 months b. Patient is pacemaker dependent[1] on trans-tricuspid lead without alternative pacing option c. Which has delivered appropriate ICD therapy 5. Severe aortic, mitral and/or pulmonic valve stenosis and/or regurgitation • Note: patients with concomitant mitral or aortic or pulmonic and tricuspid valve disease will have the option of getting their respective valve treated, and wait 60 days post-transcatheter or 90 days after surgical treatment prior to being reassessed for the study 6. Active endocarditis within 3 months or infection requiring antibiotic therapy (oral or intravenous) within 2 weeks of the scheduled implant 7. Hemodynamically significant pericardial effusion 8. Intra-cardiac mass, thrombus, or vegetation. Chronic scarred LV apical or LAA thrombi can be considered. 9. Clinically significant, untreated coronary artery disease requiring revascularization, evidence of acute coronary syndrome, recent myocardial infarction[2] within 30 days prior to the index procedure 10. Any percutaneous coronary, intracardiac (e.g., left atrial appendage occlusion, ASD closure, atrial fibrillation [AF] ablation, etc.), carotid, endovascular intervention, carotid surgery, within 30 days or cardiac surgery within 90 days prior to the index procedure 11. Need for emergent or urgent surgery for any reason or any planned cardiac surgery within the next 12 months 12. Hemodynamic instability defined as systolic pressure < 90 mmHg with or without afterload reduction, cardiogenic shock or the need for inotropic support or intra-aortic balloon pump or other hemodynamic support device within 30 days of index procedure 13. Resting systolic blood pressure < 90 or > 160 mmHg after repeated measurements 14. Patient with refractory heart failure requiring advanced intervention (i.e. left ventricular assist device, transplantation) (ACC/AHA/ESC/EACTS Stage D heart failure) 15. History of deep vein thrombosis (DVT) or pulmonary embolism (PE) or DVT/PE in the past 6 months prior to index procedure 16. Presence of an occluded or thrombosed IVC filter that would interfere with the delivery catheter 17. Stroke within 90 days prior to the index procedure 18. Modified Rankin Scale ≥ 4 disability

	19. Severe renal insufficiency with estimated glomerular filtration rate (eGFR) ≤ 25 mL/min/1.73m^2 or requiring chronic renal replacement therapy at the time of screening committee approval 20. Patients with hepatic insufficiency or cirrhosis with Child-Pugh score Class C[b] 21. 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) 22. Continuous home oxygen for primary severe COPD 23. Chronic anemia with transfusion dependency or Hgb < 9 g/dL not corrected by transfusion at time of screening committee approval 24. Thrombocytopenia (Platelet count < 75,000/mm^3) or thrombocytosis (Platelet count > 750,000/mm3) at the time of screening committee approval 25. Known bleeding or clotting disorders or patient refuses blood transfusion 26. Active gastrointestinal (GI) bleeding within 3 months of the scheduled implant 27. Current or history of illicit drug use 28. Pregnant or lactating; or female of childbearing potential with a positive pregnancy test within 14 days prior to intervention 29. Patients in whom transesophageal echocardiography is contraindicated or cannot be completed. 30. In the opinion of the investigator, access to the femoral vein with a guide sheath is deemed not feasible (e.g., occluded IVC filter, active DVT, occluded femoral veins). 31. Untreatable hypersensitivity or contraindication to any of the following: all antiplatelets, all anticoagulants, nitinol alloys (nickel and titanium), bovine tissue, glutaraldehyde, or contrast media. • Note: Patient must be able to tolerate at least one antiplatelet medication AND one anticoagulant medication 32. Currently participating in another investigational biologic, drug or device study in which the patient has not reached a primary endpoint. 33. Co-morbid condition(s) that, in the opinion of the Investigator, limit life expectancy to < 12 months. 34. Presence of significant congenital heart disease including but not limited to hemodynamically significant atrial septal defect, RV dysplasia, and arrhythmogenic RV. 35. Presence of significant iatrogenic interatrial shunt (Qp/Qs > 1.5), or persistent/pancyclic (or respirophasic) right-to-left shunt, or right-to-left shunt with resting desaturation (SpO2 < 90%). 36. Any condition, in the opinion of the investigator, making it unlikely the patient will be able to complete all protocol procedures and follow-ups 37. Other medical, social, or psychological conditions that preclude appropriate consent and follow-up, including patients under guardianship 38. Any patient considered to be part of a vulnerable population
Safety Endpoint	Safety will be analyzed as a composite endpoint of Major Adverse Events (MAEs) at 30 days post-enrollment which includes: • Cardiovascular mortality • Myocardial infarction (MI) • Stroke • Renal complications requiring unplanned dialysis or renal replacement therapy • Severe bleeding (includes fatal, life-threatening, extensive, or major bleeding, as defined by MVARC[3])

[b] See Appendix E for Child-Pugh scoring system

	• Non-elective tricuspid valve re-intervention, percutaneous or surgical • Major access site and vascular complications • Major cardiac structural complications • Device-related pulmonary embolism
Performance Endpoints	**Device Success** at exit from OR/Cath Lab • 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** at Discharge • Device success without clinically significant paravalvular leak (PVL)[4-6] on a transthoracic echocardiogram (assessed by the echo core lab). **Clinical Success** at 30 days • Procedural success without MAEs at 30 days.
Echocardiographic Endpoint	Reduction in TR grade: screening/baseline TTE compared to discharge TTE (assessed by the echo core lab using a 5-grade classification)
Echocardiographic Parameters	TTE parameters assessed at screening/baseline, discharge, all 30 days, 6 months, 1 year, and annually until 5 years post-procedure (by the echo core lab) 1. TR grade 2. Paravalvular leak severity 3. Regurgitant volume 4. TV inflow gradient 5. Cardiac output 6. Right atrium volume 7. Left Ventricular Ejection Fraction 8. Inferior Vena Cava dimensions/respiratory variations 9. Hepatic vein flow reversal 10. Pulmonary artery pressure (mean) 11. Right ventricular function
Clinical and Functional Endpoints	The following endpoints assessed at 12 months and annually until 5 years post-procedure: A. All-cause mortality B. Heart failure hospitalizations C. Non-elective tricuspid valve re-intervention, percutaneous or surgical The following endpoints assessed at baseline, 30 days, 6 months, 12 months, and annually until 5 years post-procedure: D. Volume overload assessed by serial measurements of: 1. Body weight 2. Edema assessment (1+ to 4+) 3. Ankle circumference measurement 4. Patient edema questionnaire E. Functional Class, functional status, and Quality of Life assessed by: 1. NYHA Classification 2. 6-Minute Walk Test (6MWT)[7] 3. Kansas City Cardiomyopathy Questionnaire (KCCQ) 4. Short Form Health Survey (SF-36), version 2
Clinical and Functional Parameters	The following parameters assessed at baseline: A. Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale B. Katz Index of Independence in Activities of Daily Living (Katz ADL) C. Patient Preference Survey

	The following assessed at discharge, 30 days, 6 months, 12 months, and annually until 5 years post-procedure D. General Clinical and Laboratory Parameters: 1. Complete Blood Count (CBC; including platelet count) 2. Comprehensive Metabolic Panel (CMP; including Albumin, Bilirubin, ALP, ALT, AST, creatinine, BUN) 3. Coagulation Panel (PT or PTT; INR for patients on vitamin K antagonist [VKA]) 4. BNP or NT-proBNP 5. GGT 6. Uric acid and eGFR
Exploratory Computed Tomography (CT) Parameters	The following parameters will be assessed at 30 days and 12 months (where data is available): A. Cardiac remodeling (e.g., RV dimensions and volume) B. EVOQUE frame dimensions C. EVOQUE leaflet assessment D. EVOQUE positioning
Electronic Diary and Activity Monitoring Sub-study (up to 10 sites, 45 patients, upon FDA approval)	At up to 10 sites and up to 45 patients (upon FDA approval) with data through 12 months. A. Electronic Diary (eDiary)[c]: To measure quality of life improvement in greater detail, electronic patient reported outcomes will be collected via a handheld device. The following assessments will be used to measure quality of life throughout the sub-study period: 1. KCCQ 2. EQ-5D-5L 3. SF-12 4. Mood questionnaire 5. Symptom burden A daily assessment will be administered from baseline (for a minimum of 14 days before the index procedure) and then from post discharge through the 12-month follow-up visit. B. Activity Monitoring: To measure the improvement in functional status, an activity monitor (wristwatch) will be worn by patients. The monitor is worn from baseline (for a minimum of 14 days before index procedure), paused at time of admission for index procedure, and resumed post-discharge and worn through the 12-month follow-up visit.
Sponsor	[redacted]
Sponsor Contact	[redacted]

[c] eDiary and Activity Monitoring to be implemented at system launch. Patients enrolled prior to system launch will not be required to participate in these assessments.

Data Safety Monitoring Board (DSMB)	The Data Safety Monitoring Board (DSMB) will be comprised of independent, non-investigator physicians, who will be responsible for reviewing aggregate safety data reported during the study and assessing whether the overall safety of the trial remains acceptable. DSMB activities, including roles and responsibilities, operating procedures, and monitoring criteria will be defined in the DSMB Charter.
Clinical Events Committee (CEC)	The Clinical Events Committee (CEC) will be comprised of independent, non-investigator physicians, and will be responsible for reviewing and adjudicating specified individual adverse events (AEs) over the course of the study. CEC activities, including roles and responsibilities, operating procedures, specific events to be adjudicated and definitions to be used by the CEC during adjudication will be defined in the CEC Charter.
Cardiac Imaging Core Lab	An independent echocardiographic imaging core laboratory will be utilized for assessment of echocardiograms. Echocardiogram image acquisition shall be performed in accordance with the core laboratory's recommended manual, which is provided to the sites. [redacted] [redacted]

1. Introduction

1.1. Clinical Background on Tricuspid Regurgitation

1.1.1. Disease Process

Tricuspid Regurgitation (TR), tricuspid insufficiency or tricuspid incompetence describe a condition in which blood flow through the tricuspid valve (TV) flows in the incorrect direction during part of the cardiac cycle. Normally, during diastole, the tricuspid valve opens due to right ventricular relaxation and the base of the heart descending; this results in a gradient of pressure from the right atrium (RA) to the right ventricle (RV), allowing blood to flow through the tricuspid valve and into the RV. Diastole ends with atrial contraction. During early systole, the tricuspid valve closes thereby preventing a reversal of blood flow. However, in patients with TR, the closed tricuspid valve is unable to form a tight seal in systole and allows blood to flow back into the right atrium.

While TR often accompanies mitral or aortic valve disease, it is initially asymptomatic, traditionally considered less clinically significant, and usually left untreated. The tricuspid valve is commonly referred to as the "forgotten" valve. Moderate to severe TR affects up to 1.6 million patients in the U.S, of whom only 8,000 annually undergo tricuspid surgery.[8] 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 patient's quality of life and is associated with higher mortality.[9] Patients with severe TR usually present with signs or symptoms of right heart failure (HF), including peripheral edema and ascites.[10]

1.1.2. Etiology

TR can have many underlying etiologies, but the majority of these can be divided into two major categories: primary TR and secondary TR.

Primary (degenerative, 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, secondary (functional or non-structural) TR refers to regurgitation occurring in the absence of significant structural disease of the tricuspid valve and/or apparatus. Functional TR is present in approximately 80% of cases of significant TR[10] and results from annular dilation and/or right ventricular enlargement that are 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 RV dilatation and dysfunction may develop, similar to changes that can occur with asymptomatic mitral regurgitation (MR) and its effect on left ventricle (LV) function.

1.1.3. Anatomy and Pathophysiology of Tricuspid Regurgitation

The tricuspid valve orifice is semilunar and consists of three leaflets (anterior, posterior and septal) inserted into a fibrous annulus. Each leaflet is typically connected to one papillary muscle (as opposed to the redundancy found in the mitral valve apparatus). Being the largest valve orifice in the heart, the normal diameter is typically 30-35 mm. Annular dilatation is limited to the free wall due to fixation of the annulus at the septal portion and occurs from the antero-septal junction as shown in **Figure 1**.[11]

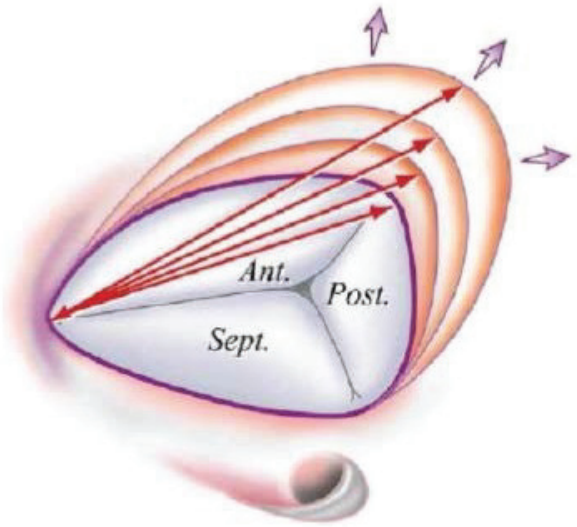


Figure 1: Dilatation of the Tricuspid Annulus

1.1.4. Prognosis of Tricuspid Regurgitation

Tricuspid regurgitation is a common echocardiographic finding that is often considered benign unless associated with significant pulmonary hypertension, RV dysfunction, 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 (**Figure 2**).[9] Severe TR is associated with a poor prognosis and is independent of age, biventricular systolic function, RV size, and inferior vena cava (IVC) dilation. [9]

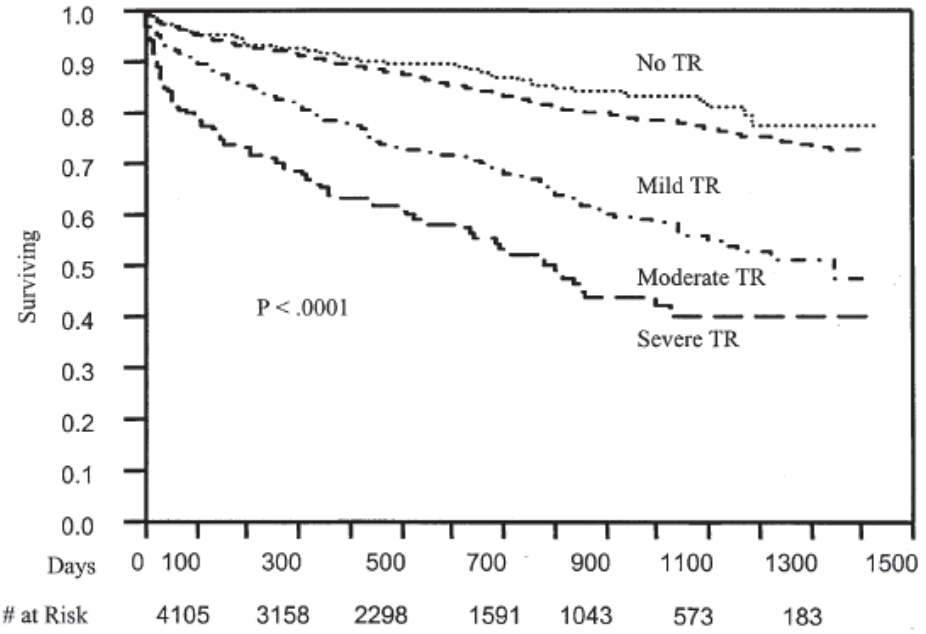


Figure 2: Kaplan-Meier Survival Curves for All Patients with Severe TR (Nath et al., JACC 2004)

1.1.5. Diagnostic Assessments for Tricuspid Regurgitation

Tricuspid regurgitation can present without symptoms and may be a chance finding during echocardiography. The holosystolic murmur typical of TR increases during inspiration and can be auscultated on the lower left sternal border.[12] When TR is severe it is typically associated with right heart failure and symptoms usually include neck palpitations, lower limb edema, ascites, fatigue, and dyspnea.

Transthoracic echocardiography (TTE) is currently the gold standard for diagnosis of TR and for assessing its severity.[10] Transesophageal echocardiography (TEE) can be considered when TTE images are suboptimal or in specific cases such as endocarditis or presence of pacemaker leads.[10] Better valve assessment and quantification may be achieved by real-time 3D echocardiography.[13] Cardiovascular magnetic resonance (CMR) imaging, although not widely available, can provide more accurate regurgitation assessment and RV function measurements. Computed tomography (CT) is useful for

measurements of the annulus and depicting surrounding structures, and is increasingly used to properly plan transcatheter interventions.[14]

The current American Society of Echocardiography parameters for grading the severity of chronic TR are presented in **Table 1**.[15] The grading system incorporates qualitative, semiquantitative, and quantitative echocardiography parameters. Signs that have an inherently high positive predictive value for TR severity are highlighted in bold font.

Table 1: Grading the Severity of Chronic TR by Echocardiography (Zoghbi et al., JASE 2017[15])

Parameters	Mild	Moderate	Severe
Structural			
TV morphology	**Normal or mildly abnormal leaflets**	Moderately abnormal leaflets	**Severe valve lesions** (e.g., flail leaflet, severe retraction, large perforation)
RV and RA size	Usually normal	Normal or mild dilatation	Usually dilated*
Inferior vena cava diameter	Normal < 2 cm	Normal or mildly dilated 2.1-2.5 cm	Dilated > 2.5 cm
Qualitative Doppler			
Color flow jet area†	**Small, narrow, central**	Moderate central	**Large central jet** or eccentric wall-impinging jet of variable size
Flow convergence zone	**Not visible, transient or small**	Intermediate in size and duration	**Large throughout systole**
CWD jet	**Faint/partial**/parabolic	Dense, parabolic or triangular	Dense, often triangular
Semiquantitative			
Color flow jet area (cm^2) †	Not defined	Not defined	**>10**
VCW (cm)†	<0.3	0.3-0.69	**≥0.7**
PISA radius (cm)‡	≤0.5	0.6-0.9	**>0.9**
Hepatic vein flow§	Systolic dominance	Systolic blunting	**Systolic flow reversal**
Tricuspid inflow§	**A-wave dominant**	Variable	E-wave >1.0 m/sec
Quantitative			
EROA (cm^2)	<0.20	0.20-0.39‖	**≥0.40**
RVol (2D PISA) (mL)	<30	30-44‖	≥45

* RV and RA size can be within the "normal" range in patients with acute severe TR.
† With Nyquist limit >50-70 cm/sec.
‡ With baseline Nyquist limit shift of 28 cm/sec.
§ Signs are nonspecific and are influenced by many other factors (RV diastolic function, atrial fibrillation, RA pressure).
‖ There are little data to support further separation of these values.

To better characterize the variability of TR seen in patients with transcatheter devices, an expanded grading scale for assessing TR severity was proposed by Hahn & Zamorano and is presented in **Table 2**.[16] The scale further expands the "severe" grade to include "massive" and "torrential" grades.

Table 2: Expanded 5-grade Scale for Determining Severity of TR[16]

Variable	Mild	Moderate	Severe	Massive	Torrential
Vena contracta (VC; biplane)	<3 mm	3-6.9 mm	7-13 mm	14-20 mm	≥21 mm
Effective regurgitant orifice area (EROA) (PISA)	<20 mm^2	20-39 mm^2	40-59 mm^2	60-79 mm^2	≥80 mm^2
3D vena contracta area (VCA) or quantitative EROA*	-	-	75-94 mm^2	95-114 mm^2	≥115 mm^2

*3D VCA and quantitative Doppler EROA cut-offs may be larger than PISA EROA.

1.2. Treatments and Therapies for Tricuspid Regurgitation

1.2.1. Medical Treatment

Medical TR treatment, mainly diuretics (Class IIa recommendation), is intended to manage volume overload. Medical therapies to reduce elevated pulmonary artery pressures and/or pulmonary vascular resistance might be considered in patients with severe functional TR (Class IIb). Treatment for conditions elevating left sided filling pressures is also recommended.[10,17] TR patients are managed medically for symptoms and typically only considered for surgery after advanced RV dysfunction, liver dysfunction and/or cirrhosis have developed.

1.2.2. Surgical Intervention of the Tricuspid Valve

The decision to surgically treat TR has been controversial over the years, and is currently recommended for symptomatic patients and in some cases for asymptomatic patients as prophylactic treatment at the time of left-sided valve surgery.[18] The decision as to whether to repair or replace depends on disease stage and etiology as depicted in **Figure 3**. Surgical treatment of functional TR is only recommended in patients with severe TR at the time of left-sided valve surgery (Class I). TV repair can also be beneficial for patients with less severe TR who are undergoing left-sided surgery and in the presence of annular dilatation (Class IIa) or prior evidence of HF (Class IIa).

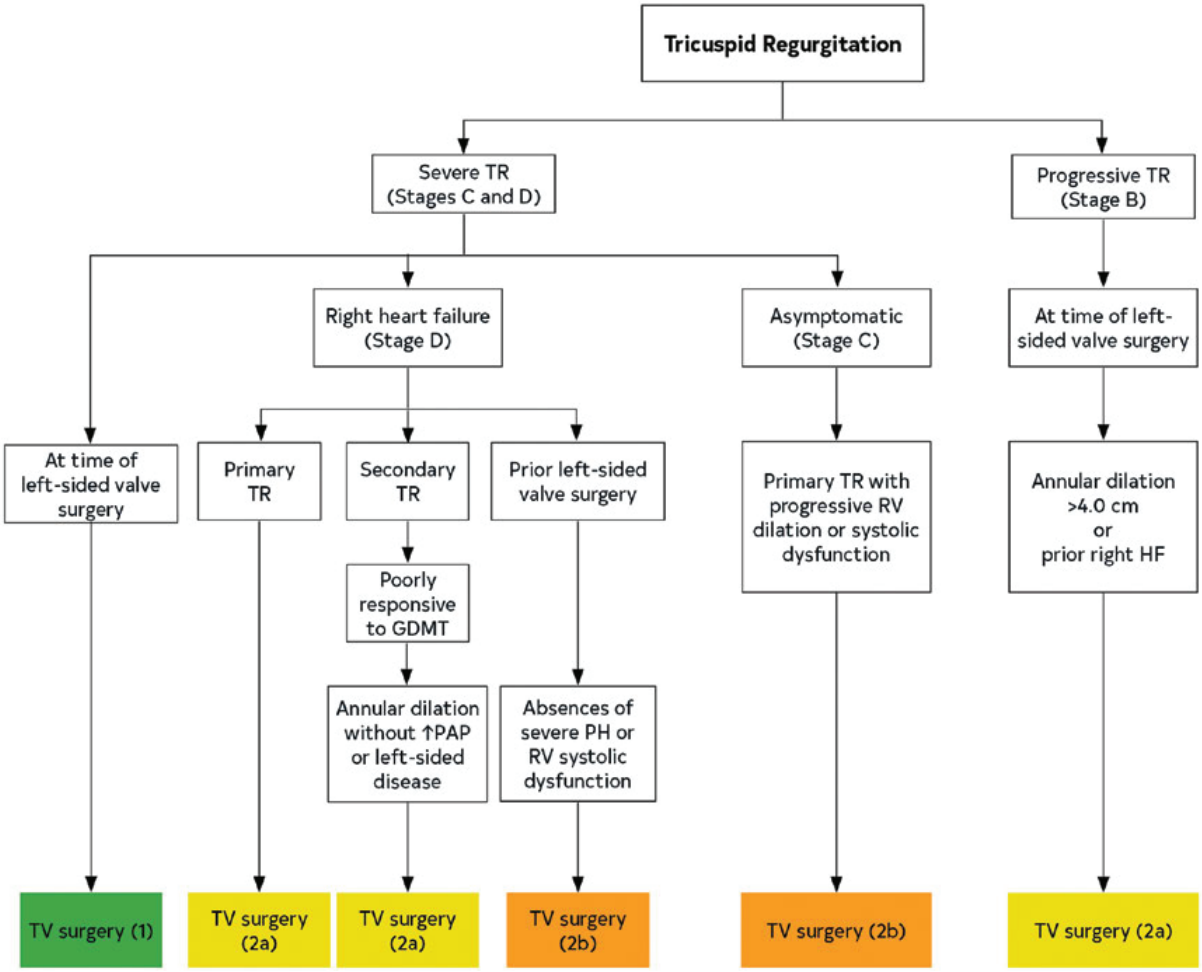


Figure 3: Indication for Surgery According to the 2020 ACC/AHA VHD Guidelines

Surgical treatment of moderate TR at the time of left-sided valve surgery in the presence tricuspid annular dilation (tricuspid annulus end diastolic diameter >4.0 cm) or prior signs and symptoms of right-sided heart failure was assigned as a class IIa indication in the 2020 ACC/AHA guidelines.[19] The 2017 ESC/EACTS Guidelines for the management of valvular heart disease provide a class I (level of evidence: C) recommendation for tricuspid valve surgery in patients with severe functional TR undergoing left-sided valve surgery. The ESC guidelines also include as class IIa patients with severe functional TR not undergoing left sided surgery who have symptoms or progressive RV dilation/dysfunction.[10,17]

The timing of surgical intervention remains controversial, mostly due to the limited data available and their heterogeneous nature (see indications for tricuspid valve surgery in **Figure 4**). Surgery should be carried out sufficiently early to avoid irreversible RV dysfunction.

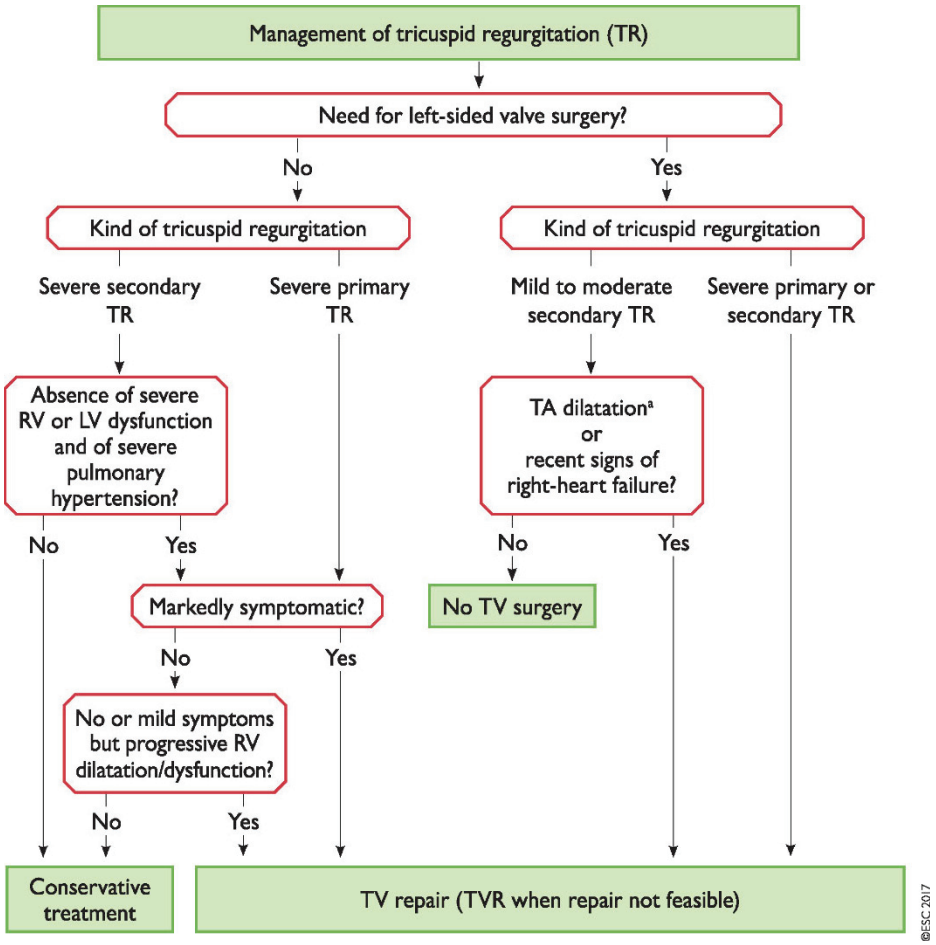
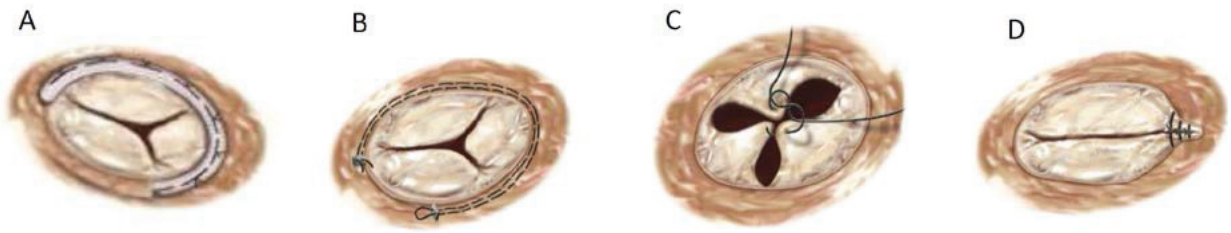


Figure 4: Recommendations for surgery in tricuspid regurgitation 2017 ESC/EACTS Guidelines

Although the guidelines have expanded the indications for invasive TR treatment, surgical repair/replacement is uncommonly performed probably due to high morbidity and mortality related to TV surgery, especially in patients who already had previous cardiac surgery. Most surgeons prefer to repair the TV rather than replace it, especially in functional TR.[17,20]

There are four main surgical TV repair techniques[21]: Kay repair, De Vega technique, Clover repair (degenerative) and annuloplasty with a tissue-based or synthetic ring (**Figure 5**).

- The Kay repair is a simple and validated solution in which a bicuspidization of the TV is accomplished by placating the annulus along the posterior leaflet. The sutures are tied, obliterating the posterior leaflet and thus creating a bicuspid valve. [22]
- The De Vega technique used to be one of the most common procedures for TV repair, where a single "purse-ring" suture is placed around the tricuspid annulus, avoiding the area of the atrioventricular node. The suture is tied, completing the annuloplasty.[23]
    - The 'Clover' repair is a technique in which the central part of the free edges of the tricuspid leaflets are stitched together, producing a 'clover'-shaped valve. This technique is reserved mainly for degenerative TR with valve prolapse.



A. Annuloplasty Ring, B. De-Vega technique, C. Clover repair, D. Kay repair

Figure 5. Tricuspid Surgical Repair Techniques

1.2.3. Transcatheter Treatment Methods

Medical management for the treatment of tricuspid regurgitation is likely to provide only temporary symptom relief for most patients. This lack of sustained benefit from medical therapies and the low prevalence of surgery has prompted the search for and development of alternative transcatheter repair and replacement therapies.[24,25]

1.2.3.1 Transcatheter Tricuspid Valve Repair (TTVr)

In the past decade, transcatheter aortic valve replacement (TAVR) has been used successfully in increasing numbers in patients suffering from severe aortic stenosis and is considered a treatment option even for moderate risk patients.[26] The success of TAVR led to attempts at transcatheter mitral valve repair (TMVr) for percutaneous treatment of mitral regurgitation (MR). While the technology has been proven to be far more complex than TAVR, there are several approved TMVr devices: The MitraClip System (Abbott Vascular, Santa Clara, CA) is approved for use in the EU (2008) and the U.S. (2013) for the treatment of mitral regurgitation; the PASCAL System (Edwards Lifesciences) was recently approved in EU (2019) for treatment of mitral regurgitation; the Cardioband Mitral System (Edwards Lifesciences (formerly Valtech Cardio LTD, Or Yehuda, Israel) was also approved in the EU (2015).[27] There are additional transcatheter mitral valve replacement and repair devices under development; the field of percutaneous intervention for the mitral valve is expected to continue to grow in the coming years.

It is a clear expectation that the next step in percutaneous structural heart disease treatments will focus on the “forgotten” tricuspid valve. Several transcatheter repair devices are being investigated for the treatment of TR and can be classified according to their therapeutic approaches.[24,25]

- annuloplasty/annular reconstruction devices
- coaptation devices
- caval valve implantation (CAVI)
- leaflet devices

Annuloplasty/Annular Reconstruction Devices

The first commercially available transcatheter therapy for the treatment of TR was the Cardioband Tricuspid Valve Reconstruction System (Edwards Lifesciences, formerly Valtech Cardio LTD, Or Yehuda, Israel); it received CE mark in April 2018. Data from the TRI-REPAIR study showed that annular reduction from the Cardioband system provided significant reduction in EROA and this result was sustained 6 months post-procedure. The study also observed clinically and statistically significant improvements in functional status (NYHA Class and peripheral edema), quality of life (KCCQ Score), and exercise capacity (6MWD) at 6 months after the Cardioband implant procedure.[28]

Other tricuspid valve annuloplasty devices under investigation include: the Trialign System (Mitralign, Tewksbury, MA), the TriCinch System (4Tech Cardio Ltd., Galway, Ireland), TRAIPTA device (NIH, Bethesda, MD), Millipede IRIS Transcatheter Annuloplasty Ring (Millipede, Santa Rosa, CA), and the MIA annuloplasty implant:

- The Trialign System mimics the surgical Kay procedure and reduces TR by plicating the annulus, resulting in bicuspidization. Published 30-day follow-up results from the SCOUT trial (NCT02574650) showed the Trialign device was safe, successfully reduced annular area and regurgitant orifice, and improved left ventricular forward stroke volume.[29]
- The TriCinch device is comprised of a corkscrew anchor that is anchored in the anteroposterior annulus and then retracted into the inferior vena cava by a Dacron band that connects the anchor to a self-expanding Nitinol stent. Data from the PREVENT trial (NCT02098200) showed an implant success rate of 75% (18/24) and four (17%) late anchor detachments during the 12-month follow-up period. A new generation of the device has been developed and is under evaluation in the PROTECT feasibility study (NCT03294200).[24]
- The TRAIPTA device is an experimental epicardial Nitinol loop placed around the atrioventricular groove providing an external annuloplasty.[30] Currently, a new TRAIPTA device for human testing is under development.[24]
- The Millipede IRIS Transcatheter Annuloplasty Ring is a complete semi-rigid annuloplasty ring that is placed in the supra-annular position. It has been used for mitral valve repair and is under investigation.[24]
- The MIA is a device comprised of ultra-low mass proprietary compliant PolyCor™ anchors and MyoLast™ implantable elastomer that allow bicuspidization of the tricuspid valve. It is currently under investigation.[24]

Coaptation Devices

The FORMA Tricuspid Transcatheter Repair System (Edwards Lifesciences, Irvine, CA) involves a spacer placed in the center of the valve orifice for the purposes of improving leaflet coaptation and reducing TR. One-year follow-up data of patients in Canada and Switzerland under special access/compassionate use setting showed that use of the FORMA System was feasible and safe in high-risk patients with severe TR.[24,31] In addition, follow-up data at 24-36 months showed considerable and

sustained TR reduction accompanied by significant functional improvement.[32] In the FORMA Early Feasibility Study (EFS; NCT02471807), significant TR reduction was observed and sustained at one year. Clinically significant and sustained improvements in NYHA functional class, 6MWD, and KCCQ scores at one year were observed, as well.[33] The US EFS and outside the United States (OUS) CE Mark studies have since been stopped, with visits of all enrolled patients continuing through the 3-year follow-up.

Caval Valve Implantation

Implantation of a prosthesis in the caval space has been performed as a last-resort approach for treatment with TR with refractory right HF as it aims to reduce the negative effects of venous congestion leading to reduced symptoms of right HF. 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. Lauten et al. reported the successful implantation of a self-expandable valve tailored to the dimensions of the inferior vena cava with significant reductions in IVC pressures.[34,35] Similarly, the ongoing HOVER trial is assessing heterotopic implantation of the Edwards-SAPIEN XT valve in the inferior vena cava (NCT02339974).[36] Of note, such an intervention may lead to ventricularization of the RV and cause severe deterioration in patients with severe RV heart failure.

Leaflet Devices

The MitraClip System (Abbott Vascular, Santa Clara, CA) is approved for use in the EU (2008) and the U.S. (2013) for the treatment of mitral regurgitation and the TriClip System (Abbott Vascular, Santa Clara, CA) is approved for the treatment of tricuspid regurgitation in the EU (2020). Edge-to-edge tricuspid valve repair with single or multiple MitraClip System (Abbott Vascular, Santa Clara, CA) devices has been successfully used for the treatment of TR in selected high-risk patients with malcoaptation of the tricuspid valve.[37-40] In retrospective analysis of 42 cases treated at a single center in Germany, successful edge-to-edge repair was achieved in 83% (35/42) patients.[38] In another report of 50 patients with right-sided HF and severe TR treated at 2 centers in Germany, persistent reduction of at least one TR grade was achieved in 90% of patients at 6 months and the NYHA class improved in 79% of patients.[40] Several case reports and series have been published on the use of the MitraClip System in the treatment of TR. The TriClip device is being evaluated in the TRILUMINATE study (NCT03227757) and the TRILUMINATE Pivotal Trial (NCT03904147).

The Edwards PASCAL System, recently approved in EU for treatment of mitral (2019) and tricuspid (2020) regurgitation, percutaneously delivers a leaflet reconstruction device, which brings the leaflets together around an intravalvular spacer using independently actuating clasps. Use of the PASCAL System in treating patients with mitral regurgitation has been shown to be safe and feasible with a high rate of technical success.[41,42] Evaluation of the PASCAL System in treating patients with TR is warranted and clinical cases have been performed under a compassionate use setting. Additionally, a multi-center, prospective, single-arm early feasibility trial assessing the PASCAL system for TR is enrolling and more studies are planned.

1.2.3.2 Transcatheter Tricuspid Valve Replacement (TTVR)

Transcatheter valve replacement with the Edwards SAPIEN or Medtronic Melody valve has been described in the published literature on single case studies and limited retrospective clinical series, primarily for valve-in-valve patients[43-45] and patients with rheumatic heart disease.[46] The distinctive anatomy of the tricuspid valve has precluded expanded use of these devices for TTVR in native valves.[47]

Several companies have developed TTVR specific systems and are in varying stages of development: the GATE Tricuspid Valved Stent (NaviGate Cardiac Structures, Lake Forest, CA), the LUX-Valve (Jenscare Biotechnology, Ningbo, China), TriSol (Trisol Medical Ltd., Inc., Yokneam, Israel), the TRiCares system (TRiCares GmbH, München, Germany).

With the exception of NaviGate Cardiac Structures, the TTVR systems described below have yet to publish clinical trial data, though limited pre-clinical data, clinical data, and device descriptions have been published for some:

- The NaviGate Cardiac Structures GATE Tricuspid Valved Stent is a self-expanding, conical-shaped, nitinol device with three pericardial leaflets derived from equine pericardial tissue. The device has been implanted into patients either via the transatrial or transjugular approach under compassionate use and is currently under investigation.[24]
  Of 27 reported successful first-in-human GATE implantations in patients with severe/torrential TR, 78% (21/27) patients had none/trivial TR post-procedure and 100% patients (27/27) had TR ≤2+ post-procedure.[48] Similar findings were observed in single-site compassionate use experience: 5 patients with symptomatic massive or torrential TR were observed to have significant reductions of their TR of ≤2+ post-implant. In 3-to-6 month post-procedure follow-up visits by 4 of the 5 subjects, evidence of RV remodeling, increased cardiac output, and reduction in NYHA functional class was observed.[49]
- The INTREPID™ system is a self-expanding, tri-leaflet bovine pericardial prosthesis housed within a nitinol frame.[50] A First-in-Man Case Experience was recently presented on the use of the INTREPID valve for severe TR.[51]
- The LUX-Valve is a self-expanding nitinol device with bovine pericardial leaflets and a skirt designed to minimize paravalvular leak; it is intended to be deployed transatrially via thoracotomy.[47]
- The TriSol valve is a self-expanding device comprised of an elastic nitinol frame with a porcine pericardial ventricular skirt, atrial polyester skirt, and bileaflet valve made from bovine pericardial tissue. The outside skirt is designed to seal the valve and prevent paravalvular leak.[48]
- The TriCares valve is a self-expanding device comprised of bovine pericardial tissue on a nitinol stent.[48]

1.3. Intended Use of the Device

The EVOQUE system is intended for treatment of patients with at least moderate TR or prior heart failure hospitalizations for TR.

1.4. Prior Testing

[redacted]

1.4.1. Bench Testing

[redacted]

1.4.2. Biocompatibility Testing

[redacted]

1.4.3. Sterilization Validation

[redacted]

1.4.4. Acute Cadaver Testing

[redacted]

1.4.5. Chronic Study Results

[redacted]

1.4.6. Existing Clinical Data

Between May 2019 and June 2020, 27 patients were treated for symptomatic TR with the EVOQUE system. Due to the nature of compassionate use cases, limited follow-up data is available.[52]

[redacted]

2. Study Device

2.1. General System Description and Components

The EVOQUE system is intended for the treatment of patients with at least moderate TR, signs of TR, symptoms from TR, or prior heart failure hospitalization for TR. [redacted]

[redacted]

Table 3: EVOQUE System Components – Name and Model Number

[redacted]

Refer to the Edwards EVOQUE System's Instructions for Use (IFU) and corresponding Investigator's Brochure for complete information regarding its use. Lot numbers and serial numbers are assigned, as applicable, to each of the required and optional components for traceability purposes.

[redacted]

2.1.1. Edwards EVOQUE Valve

[redacted]

2.1.2. Edwards EVOQUE Tricuspid Delivery System

Figure 7: The EVOQUE Tricuspid Delivery System

2.1.3. Edwards EVOQUE Dilator Kit

Figure 8: Edwards EVOQUE Dilator Kit

2.1.4. Edwards EVOQUE Loading System

Figure 9: Edwards EVOQUE Loading System Components

2.1.5. Edwards EVOQUE Accessories (Stabilizer, Base, Plate)

Figure 10: Edwards EVOQUE Stabilizer, Base, and Plate

2.2. Method of Operation for the EVOQUE System

[redacted]

3. Risks and Benefits

3.1. Summary

A risk management process has been implemented that is compliant with EN/ISO 14971:2019; in addition, a risk management plan was developed, and a risk analysis conducted.

The risk analysis confirmed that the residual risks associated with the transcatheter tricuspid valve replacement (TTVR) System are similar to the clinical risks associated with any catheter-based (transcatheter) valve replacement system and have been mitigated to an acceptable level. The anticipated clinical risks to patients participating in the clinical investigation of the Edwards EVOQUE Tricuspid Valve Replacement System are identified in **Section 3.3**.

The risks of participation are offset by the significant potential in clinical and functional benefits to patients with TR that comes through improving tricuspid valve function.

3.2. Potential Benefits

[redacted]

3.3. Potential Risks

Adverse events (AEs) that are anticipated in this clinical study are believed to be consistent with those associated with other minimally invasive surgical and catheter-based interventional cardiac/ structural heart procedures (**Table 4**). Complications may occur at any time during the procedure, post-procedure or follow-up period.

These events may be associated with the EVOQUE System, transcatheter procedure, diagnostic cardiac tests (e.g., TEE, TTE, MSCT scan, etc.), use of anesthesia, ancillary procedures or may occur in the heart failure population over time.

Table 4: Anticipated or Potential Adverse Events

• Abnormal Lab Values • Allergic reaction to anesthesia, contrast media, anti-coagulation medication or device materials • Anaphylactic Shock • Anemia or decreased Hgb, may require transfusion • Aneurysm or Pseudoaneurysm • Angina or Chest pain	• Injury to the tricuspid apparatus including chordal damage, rupture, papillary muscle damage • Leaflet Tearing • Local and Systemic Infection • Mesenteric Ischemia or Bowel Infarction • Multi-System Organ Failure • Myocardial Infarction

• Arrhythmia – atrial (i.e. AF, SVT) • Arrhythmias – ventricular (i.e. VT, VF) • Arterio-venous Fistula • Bleeding • Cardiac (heart) Failure • Cardiac Arrest • Cardiac injury, including perforation • Cardiac tamponade / Pericardial effusion • Cardiogenic Shock • Chordal entanglement or rupture that may require intervention • Coagulopathy, coagulation disorder, bleeding diathesis • Conduction System Injury, which may require implantation of a pacemaker (temporary or permanent) • Conversion to open heart surgery • Coronary artery occlusion • Damage to or interference with function of pacemaker or implantable cardioverter defibrillator (ICD) • Death • Edema • Electrolyte Imbalance • Embolization including air, particulate, calcific material, or thrombus • Emergent Cardiac Surgery • Endocarditis • Esophageal Irritation • Esophageal Perforation or Stricture • EVOQUE system component(s) embolization • Failure to retrieve any EVOQUE system components • Fever • Frame Strut Fracture • Gastrointestinal Bleeding • Hematoma • Hemodynamic Compromise • Hemolysis / Hemolytic Anemia • Hemorrhage requiring transfusion/surgery • Hypertension • Hypotension • Inflammation	• Nausea and/or vomiting • Nerve Injury • Neurological symptoms, including dyskinesia, without diagnosis of TIA or stroke • Non-emergent reoperation • Pain • Pannus Formation • Paralysis • Percutaneous Valve Intervention • Peripheral Ischemia • Permanent Disability • Pleural Effusion • Pneumonia • Pulmonary Edema • Pulmonary Embolism • Reaction to anti-platelet or anticoagulation agents • Rehospitalization • Renal Failure, • Respiratory failure, atelectasis – may require prolonged intubation • Retroperitoneal Bleed • RVOT Obstruction • Septicemia, sepsis • Skin burn, injury or tissue changes due to exposure to ionizing radiation • Stroke • Structural Deterioration • Thromboembolism • Transient ischemic attack (TIA) • Valve Dislodgement/Embolization • Valve Endocarditis • Valve Explant • Valve Leaflet Entrapment • Valve Malposition • Valve Migration • Valve Paravalvular Leak (PVL) • Valve Regurgitation (new or worsening tricuspid, aortic, mitral, pulmonary) • Valve Stenosis • Valve Thrombosis • Vessel Spasm • Wound Dehiscence, delayed or incomplete healing

There may also be other risks that are unknown at this time. Adverse events will be collected and reviewed throughout the duration of the 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.

3.4. Minimization of Risk

All efforts will be made to minimize the identified risks by taking the following measures:

- Selection of investigators in this study: Interventional Cardiologist or Cardiothoracic Surgeon 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 as well as access site management.
- Investigators will be trained in proper procedure performance and device operation prior to patient treatments. Training will include didactic and hands-on training with the EVOQUE System.
- Well-defined clinical study protocol, including specific inclusion/exclusion criteria to enroll appropriate patients in the study.
- A Screening Committee ensures final eligibility of patients for participation in the study.
- 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.
- Close patient monitoring during the implant procedure and follow-up period.
- Ongoing monitoring of study data and results, including the use of independent Clinical Events Committee (CEC) and Data Safety Monitoring Board (DSMB).

3.5. Justification for Clinical Study

This is a prospective, single-arm, multi-center study to evaluate the safety and performance of the EVOQUE system in the treatment of patients with at least moderate TR, signs of TR, symptoms from TR, or prior heart failure hospitalizations for TR.

The currently available treatments for this patient population are palliative medical therapy and high-risk surgical replacement or repair of the tricuspid valve. Treatment with the EVOQUE system may enable patients with tricuspid regurgitation to have a complete tricuspid valve replacement with a minimally invasive approach.

The Sponsor and clinical Investigators believe the potential benefits outweigh the potential risks.

4. Study Objectives

The objectives of this feasibility study are to:

- Evaluate the safety and performance of the EVOQUE system
- Provide guidance for future clinical study designs utilizing the EVOQUE system
- Provide guidance for future EVOQUE system development efforts

Data collected in this clinical study will include safety and performance of the investigational system, as well as up to 5-year clinical outcomes. Analyses of the primary and secondary endpoints are discussed in more detail in **Section 12**.

5. Endpoints

5.1. Safety Endpoint

Safety will be analyzed as a composite endpoint of Major Adverse Events (MAEs) at 30 days post-enrollment which includes:

- Cardiovascular mortality
- Myocardial infarction (MI)
- Stroke
- Renal complications requiring unplanned dialysis or renal replacement therapy
- Severe bleeding (includes fatal, life-threatening, extensive, or major bleeding, as defined by MVARC)[3]
- Non-elective tricuspid valve re-intervention, percutaneous or surgical
- Major access site and vascular complications
- Major cardiac structural complications
- Device-related pulmonary embolism

5.2. Performance Endpoints

5.2.1. Device Success

Device success is achieved if the study 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. This endpoint will have a per device analysis performed.

5.2.2. Procedural Success

Procedural success is "device success" without clinically significant paravalvular leak (PVL)[4-6] on a transthoracic echocardiogram (assessed by the echo core lab) at time of discharge. This endpoint will have a per patient analysis performed.

5.2.3. Clinical Success

Clinical success is "procedural success" without any MAEs at 30 days. This endpoint will have a per patient analysis performed.

5.3. Echocardiographic Endpoint and Parameters

5.3.1. Echocardiographic Endpoint

The echocardiographic endpoint is reduction in TR grade, measured by comparing the screening/baseline TTE to the discharge TTE. This endpoint will be assessed by the echo core lab using a 5-grade classification system (**Table 2**).

5.3.2. Echocardiographic Parameters

TTE parameters assessed at screening/baseline, discharge, 30 days, 6 months, 1 year, and annually until 5 years post-procedure (assessed by the echo core lab)

1. TR grade
2. Paravalvular leak severity
3. Regurgitant volume
4. TV inflow gradient
5. Cardiac output
6. Right atrium volume
7. Left Ventricular Ejection Fraction
8. Inferior Vena Cava dimensions/respiratory variations
9. Hepatic vein flow reversal
10. Pulmonary artery pressure (mean)
11. Right ventricular function

5.4. Clinical and Functional Endpoints and Parameters

5.4.1. Clinical and Functional Endpoints

The following endpoints will be assessed at 12 months and annually until 5 years post-procedure:

A. All-cause mortality
B. Heart failure hospitalizations
C. Non-elective tricuspid valve re-intervention, percutaneous or surgical

The following endpoints assessed at baseline, 30 days, 6 months, 12 months, and annually until 5 years post-procedure:

D. Volume overload assessed by serial measurements of:
    1. Body weight
    2. Edema assessment (1+ to 4+)
    3. Ankle circumference measurement
    4. Patient edema questionnaire

E. Functional class, functional status and Quality of life assessed by:
   1. NYHA Classification
   2. 6-Minute Walk Test (6MWT)
   3. KCCQ
   4. Short Form Health Survey (SF-36v2)

5.4.2. Clinical and Functional Parameters

The following parameters will be assessed at baseline:

A. Baseline Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale
B. Baseline Katz Index of Independence in Activities of Daily Living (Katz ADL)
C. Baseline Patient Preference Survey (see Appendix B)

The following general Clinical and Laboratory Parameters assessed at discharge, 30 days, 6 months, 12 months, and annually until 5 years post-procedure:

A. Complete Blood Count (CBC)
B. Comprehensive Metabolic Panel (CMP)
C. Coagulation Panel (PT or PTT; INR for patients on vitamin K antagonist
D. BNP or NT-proBNP
E. GGT
F. Uric acid and eGFR

5.5. Additional Safety Listings

A listing of all AEs and SAEs for the entire study population will be provided.

5.6. Exploratory Computed Tomography (CT) Parameters

The following parameters will be assessed at 30 days and 12 months (where data is available):

A. Cardiac remodeling (e.g., RV dimensions and volume)
B. EVOQUE frame dimensions
C. EVOQUE leaflet assessment
D. EVOQUE positioning

5.7. Electronic Diary and Activity Monitoring Sub-study

A sub study of up to 10 sites and up to 45 patients (upon FDA approval) with data through 12 months will be conducted as follows:

A. **Electronic Diary (eDiary)**: To measure quality of life improvement in greater detail, electronic patient reported outcomes will be collected via a handheld device. The following assessments will be used to measure quality of life throughout the sub-study period:
   1. KCCQ
   2. EQ-5D-5L
   3. SF-12
   4. Mood questionnaire
   5. Symptom burden

A daily assessment will be administered from baseline (for a minimum of 14 days before the index procedure) and then from post discharge through the 12-month follow-up visit.

B. **Activity Monitoring**: To measure the improvement in functional status, an activity monitor (wristwatch) will be worn by patients. The monitor is worn from baseline (for a minimum of 14 days before index procedure), paused at time of admission for index procedure, and resumed post discharge and worn through the 12-month follow-up visit.

6. Study Design

This is a prospective, single-arm, multi-center study to evaluate the safety and performance of the EVOQUE system in the treatment of patients with at least moderate TR and signs of, symptoms from, or prior heart failure hospitalizations for TR.

6.1. Number of Planned Patients

Up to 200 patients (upon FDA approval) are planned to be enrolled in this study.

6.2. Number of Planned Clinical Study Sites

Up to 200 patients (upon FDA approval) will be enrolled in this study at up to 30 investigational sites (upon FDA approval) in the US.

6.3. Expected Duration of Patient Participation

All implanted study patients will be assessed for clinical follow-up at the following intervals: discharge, 30 days, 6 months, 12 months and annually thereafter for 5 years post-procedure.

Study enrollment is expected to last approximately 18-24 months followed by 5 years of follow-up.

7. Patient Population

7.1. Demographic and Clinical Characteristics

This clinical study is for adult patients with at least moderate TR and signs of TR, symptoms from TR, or prior heart failure hospitalizations for TR.

Patients who appear to the Local Heart Team (which may include one Cardiologist, one Cardiac Surgeon, one Heart Failure specialist, and one Echocardiographer) to meet the initial study eligibility requirements will be evaluated for study participation by the Clinical Screening Committee. Candidates for this study must meet all of the following inclusion criteria and none of the exclusion criteria.

This study is expected to enroll patients with similar baseline characteristics to previously studied populations of percutaneous TR interventions. The mean age of the first-in-human compassionate use experience with the Edwards EVOQUE device in the treatment of patients with severe TR was 78 years, and we expect that this trial will enroll patients with similar baseline characteristics. Therefore, we

expect that participants will qualify for Medicare coverage through the age criteria and we anticipate that the results of this study will be generalizable to the Medicare population.

7.2. Inclusion Criteria

Patients enrolled must meet **ALL** of the following criteria in **Table 5**:

Table 5: Inclusion Criteria

Inclusion Criteria #	Criteria
1	Age ≥ 18 years old
2	Despite medical therapy (OMT) per the Local Heart Team, patient has signs of TR (peripheral edema or ascites), symptoms from TR, or prior heart failure hospitalization from TR *Note: Medical therapy is at investigator discretion and includes diuretic medications in stable doses, unless patient has documented history of intolerance. In With the exception of prehabilitation, it is recommended no new diuretics be introduced and current diuretic doses be stable (i.e. no decrease of more than ½ or increase of 2x) unless medically required (e.g., severe hypotension or signs and symptoms of hypervolemia) for 30 days prior to the procedure.*
3	Functional and/or degenerative TR graded as at least moderate on a transthoracic echocardiogram (assessed by the echo core lab using a 5-grade classification[16])
4	The Local Heart Team determines that the patient is appropriate for transcatheter tricuspid valve replacement
5	Patient is willing and able to comply with all specified study evaluations and provides written informed consent.

7.3. Exclusion Criteria

Potential patients will be excluded if **ANY** of the following criteria apply in **Table 6**:

Table 6: Exclusion Criteria

Exclusion Criteria #	Criteria
1	Tricuspid valve anatomy precluding proper device deployment and function, evaluated by echo core lab and by CT
2	Echocardiographic parameters (any of the following, assessed by echo core lab): a. LVEF < 25% b. Echocardiographic evidence of severe right ventricular dysfunction c. Pulmonary arterial systolic pressure (PASP) > 70 mmHg by echo Doppler or R heart catheterization OR PASP > 2/3 systemic BP with PVR > 5 Wood units after vasodilator challenge, in the absence of symptomatic hypotension or systolic BP < 90 mmHg
3	Previous tricuspid intervention that could interfere with placement of the EVOQUE System
4	Presence of trans-tricuspid pacemaker or defibrillator lead with any of the following: a. Implanted in the RV within the last 3 months b. Patient is pacemaker dependent[1] on trans-tricuspid lead without alternative pacing option c. Which has delivered appropriate ICD therapy

Exclusion Criteria #	Criteria
5	Severe aortic, mitral and/or pulmonic valve stenosis and/or regurgitation *Note: patients with concomitant mitral or aortic or pulmonic and tricuspid valve disease will have the option of getting their respective valve treated, and wait 60 days post-transcatheter or 90 days after surgical treatment prior to being reassessed for the study*
6	Active endocarditis within 3 months or infection requiring antibiotic therapy (oral or intravenous) within 2 weeks of the scheduled implant
7	Hemodynamically significant pericardial effusion
8	Intra-cardiac mass, thrombus, or vegetation. Chronic scarred LV apical or LAA thrombi can be considered.
9	Clinically significant, untreated coronary artery disease requiring revascularization, evidence of acute coronary syndrome, recent myocardial infarction[2] within 30 days prior to the index procedure
10	Any percutaneous coronary, intracardiac (e.g., left atrial appendage occlusion, ASD closure, AF ablation, etc.), carotid, endovascular intervention, carotid surgery, within 30 days or cardiac surgery within 90 days prior to the index procedure
11	Need for emergent or urgent surgery for any reason or any planned cardiac surgery within the next 12 months
12	Hemodynamic instability defined as systolic pressure < 90 mmHg with or without afterload reduction, cardiogenic shock or the need for inotropic support or intra-aortic balloon pump or other hemodynamic support device within 30 days of index procedure
13	Resting systolic blood pressure < 90 or > 160 mmHg after repeated measurements
14	Patient with refractory heart failure requiring advanced intervention (i.e. left ventricular assist device, transplantation) (ACC/AHA/ESC/EACTS Stage D heart failure)
15	History of DVT or PE or DVT/PE in the past 6 months prior to index procedure
16	Presence of an occluded or thrombosed IVC filter that would interfere with the delivery catheter
17	Stroke within 90 days prior to the index procedure
18	Modified Rankin Scale ≥ 4 disability
19	Severe renal insufficiency with estimated glomerular filtration rate (eGFR) ≤ 25 mL/min/1.73m^2 or requiring chronic renal replacement therapy at the time of screening committee approval
20	Patients with hepatic insufficiency or cirrhosis with Child-Pugh score Class C
21	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)
22	Continuous home oxygen for primary severe COPD
23	Chronic anemia with transfusion dependency or Hgb < 9 g/dL not corrected by transfusion at time of screening committee approval
24	Thrombocytopenia (Platelet count < 75,000/mm3) or thrombocytosis (Platelet count > 750,000/mm3) at the time of screening committee approval
25	Known bleeding or clotting disorders or patient refuses blood transfusion
26	Active GI bleeding within 3 months of the scheduled implant
27	Current or history of illicit drug use
28	Pregnant or lactating; or female of childbearing potential with a positive pregnancy test within 14 days prior to intervention

Exclusion Criteria #	Criteria
29	Patients in whom transesophageal echocardiography is contraindicated or cannot be completed.
30	In the opinion of the investigator, access to the femoral vein with a guide sheath is deemed not feasible (e.g., occluded IVC filter, active DVT, occluded femoral veins).
31	Untreatable hypersensitivity or contraindication to any of the following: all antiplatelets, all anticoagulants, nitinol alloys (nickel and titanium), bovine tissue, glutaraldehyde, or contrast media. *Note: Patient must be able to tolerate at least one antiplatelet medication AND one anticoagulant medication*
32	Currently participating in another investigational biologic, drug or device study in which the patient has not reached a primary endpoint.
33	Co-morbid condition(s) that, in the opinion of the Investigator, limit life expectancy to < 12 months.
34	Presence of significant congenital heart disease including but not limited to hemodynamically significant atrial septal defect, RV dysplasia, and arrhythmogenic RV.
35	Presence of significant iatrogenic interatrial shunt (Qp/Qs > 1.5), or persistent/pancyclic (or respirophasic) right-to-left shunt, or right-to-left shunt with resting desaturation (SpO_2 < 90%).
36	Any condition, in the opinion of the investigator, making it unlikely the patient will be able to complete all protocol procedures and follow-ups
37	Other medical, social, or psychological conditions that preclude appropriate consent and follow-up, including patients under guardianship
38	Any patient considered to be part of a vulnerable population

To further clarify exclusion criterion #4, pacemaker dependency is the risk of serious injury or death from sudden pacemaker failure. For exclusion #20, refer to Appendix E for Child-Pugh scoring details. For exclusion criterion #38, the definition of a "vulnerable population" is in **Section 15.1.**

8. Procedures and Methods

8.1. Site Personnel Training

[redacted]

[redacted]

8.2. Device and Procedure Training

[redacted]

8.3. Informed Consent Procedure

Patient participation in this study is voluntary.

Informed consent shall be obtained in writing from the patient or their legally authorized representative and the process shall be documented before any procedure specific to the clinical study is applied to the patient. The Investigator is responsible for ensuring that patient informed consent is obtained.

The obtaining and documentation of patient informed consent must be in accordance with 21 CFR Part 50, the principles of the Declaration of Helsinki, relevant part of ICH/GCP, ISO 14155, and the local IRB.

The ICF must be approved by the study site's IRB.

If, during the course of the study baseline/screening assessments, a patient is found not to be eligible for inclusion in the study, the patient or their representative should be notified and the reason for ineligibility documented on the screening log/form, and the patient will be exited from the study.

The general process for obtaining informed consent is as follows:

- Study investigator(s) and/or delegated study personnel will approach patients with TR who meet general requirements to assess their interest in participating in the study
- Ensure that the principal investigator or his/her authorized designee conducts the informed consent process;
- Include all aspects of the clinical study that are relevant to the patient's decision to participate throughout the clinical study;
- Avoid any coercion or undue improper influence on, or inducement of, the patient to participate;
- Not waive or appear to waive the patient's legal rights;
- Use native non-technical language that is understandable to the patient;
- Provide ample time for the patient to read and understand the informed consent form and to consider participation in the clinical study;
- Include personally dated signatures of the patient and the principal investigator, or an authorized designee responsible for conducting the informed consent process;
- Provide the patient with a copy of the informed consent form and any other written information; and,
- Ensure important new information is provided to new and existing patients throughout the clinical study.

For the purpose of the study, and based on the local requirements at the site, the patients can initially agree to the transfer of their images to the Sponsor for their evaluation. Upon full review and confirmation of suitability of the patient for both the EVOQUE Tricuspid valve replacement procedure and the study eligibility, the full ICF can then be signed. This process is providing that no study specific exams are being carried out as part of the screening process

The Sponsor must approve any modifications to the ICF prior to submission to the IRB and/or FDA (as required).

Once the Investigator has determined the patient's eligibility, the patient must sign the institution's IRB-approved ICF prior to any study-specific procedures being performed. Failure to provide informed consent renders the patient ineligible for the study.

The ICF will be written in a language understandable to the patient (or authorized representative) and administered only by the Investigator or IRB-approved personnel who speaks a language understandable to the patient (or authorized representative). The Investigator or delegated person administering the consent must sign and date the ICF to indicate that the purpose, risks and benefits of the study were explained to the patient and that their signature was witnessed.

The signed ICF must be retained by the study site for verification during on-site monitoring visits. The Investigator will retain the original consent form, a copy will be filed in the patient's medical record, and a copy will be provided to the patient.

8.4. Case Review

Patients who are considered for participation will be reviewed by the Cardiac Imaging Core Lab and Clinical Screening Committee (CSC). Before a case is submitted for review, the site Principal Investigator and Heart Team will screen the patient for fundamental enrollment criteria. Once fully screened and deemed an appropriate candidate, the site will submit the case for review and approval consideration by the CSC.

8.5. Patient Enrollment

A Screening/Enrollment Log will be maintained to document the screening and enrollment of all patients assessed for study participation. All patients who consent to the study will be entered into the Electronic Data Capture (EDC) system, including screen failures.

8.5.1. Screened Failures

Screening is conducted as follows: all patients considered to qualify for the study are offered the possibility of participating and are thereafter evaluated according to the selection criteria defined in this protocol.

Patients who consent to participate in the study but do not fulfill enrollment criteria will be classified as “screen failures” and will not count towards the overall enrollment. The screen failure reason(s) will be documented.

8.5.2. Provisionally Enrolled

Patients are considered “provisionally enrolled” when they have signed the ICF agreeing to participate in the study and have been deemed eligible for study.

8.5.3. Enrolled Patients

A patient will be considered “enrolled” at the time of skin incision to introduce the EVOQUE System into the body. Enrolled patients will be assigned a unique identification 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.

A study procedure should be scheduled within 90 days of a patient signing an informed consent.

8.6. Study Exit Criteria and Procedures

All patients that sign an informed consent document for this study will have the study exit reason documented in the medical record and on the appropriate eCRF. Patients may exit the study for any of the following reasons:

- **Screen Failure**: Patients who are consented to participate in the study, but do not fulfill enrollment criteria.

- **Study Device Attempted but Not Implanted:** Enrolled patient for whom the implant procedure was prematurely aborted will be followed either for 30 days (for only safety evaluations) OR until resolution, stabilization, or is adequate explanation of any implant-related AEs and then exited from the study. Examples include:
    - Procedure attempted (i.e. skin incision to introduce the EVOQUE System) but patient did not receive a study device
- **Study Device Re-intervention/Explant:** Patient who has a surgical re-intervention for study device explant will be followed for 30 days after the re-intervention for safety evaluations only or until resolution of any AEs related to the re-intervention and then exited from the study. Note: a patient who has a percutaneous re-intervention where the study device remains in place will continue to be followed for the duration of the study.
- **Withdrawal**
    - **Patient Withdrawal**: A 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**: An 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.
- **Patient death**
- **Lost to Follow-up**
    - If a patient cannot be reached for a follow-up visit, the Investigator will document contact efforts and/or efforts to obtain hospital records in the appropriate eCRF. If a patient cannot be reached in any way, or misses a visit, the patient will be considered "unable to contact" for that time interval.
    - After 3 documented unsuccessful attempts to make contact, a certified letter will be sent to the patient's residence. If there is no response after a certified letter is sent, the patient will be classified as "lost to follow-up".
- **Completion Per Protocol**

Withdrawn patients will not have any study follow-up visits or procedures after the time of study exit. All data collected up until the time of withdrawal, including imaging studies such as echocardiography scans, will be analyzed.

For patients lost to follow-up or withdrawn early, the Sponsor may request the site to search the Social Security Death Index and/or other death registries and, if applicable, request the site to obtain a death certificate.

Withdrawn or lost to follow-up patients will not be replaced.

8.7. Imaging Assessments

Imaging assessments (TTE, TEE, and CT) shall be performed according to the current version of the acquisition manual/guide. For screening and baseline examinations, pre-existing TTE and TEE examinations obtained through standard of care treatment and within trial specified windows (Table 8, "Screening/baseline assessment windows") may be used if they provide the required images/views to qualify anatomical inclusion/exclusion criteria and TR grade. For chest CT scan, a standard of care assessment of adequate quality capturing required anatomy for assessment can be used as the screening/baseline assessment, provided it is within 1 year prior to consent.

8.8. Screening/Baseline Examinations and Windows

If local IRB approval is obtained, a screening consent form may be implemented to enable the collection of standard assessments for this population (e.g., TEE and TTE). Data collected from screening assessments may be used to simultaneously assess the patient's anatomic eligibility for this Study or other Edwards Clinical Studies using a transcatheter tricuspid repair or replacement study device. If local IRBs do not allow the use of a screening consent form, all screening assessments will be described under the applicable standard study ICF.

Table 7 identifies the procedures and measurements that will be performed during baseline/screening. Data available in the patient's medical record may be utilized to fulfill requirements and do not need to be repeated if completed within 30 days prior to informed consent, unless otherwise noted in **Table 8** (screening and Baseline Windows). If not previously completed, the following tests and procedures must be performed after informed consent and prior to submission to the Central Screening Committee. Additional repeat clinical information or laboratory measurements may be required prior to CSC case review or device implantation.

Table 7: Screening and Baseline Procedures

General Information	• Informed consent§ • Demographics • Inclusion/exclusion and other screening evaluation
Clinical Information	• Medical history (e.g., co-morbidities, EuroSCORE II, STS score (MV Repair and MVR), prior cardiovascular interventions / surgeries, paracentesis procedures) • Clinical Evaluation/Prior Recent Hospitalizations • Targeted physical exam, lower limb edema grading (+1-+4), and ankle circumference measurements • Concomitant Medications (including diuretic dose/s) • Modified Rankin Scale (mRS)† • Patient Edema Questionnaire • NYHA Classification • 12-lead ECG • 6MWT results • Health outcome questionnaires - KCCQ, SF-36v2 • Patient preference survey • Katz Index of Independence in Activities of Daily Living (Katz ADL) • Canadian Study of Health and Aging Survey Clinical Frailty Scale • Transthoracic echocardiogram (TTE) ‡, § • Transesophageal echocardiogram (TEE) ‡, § • Chest CT Scan § • Pulmonary function test, for patients with chronic lung disease (e.g., COPD) §

Laboratory Measurements ¶	• βHCG, for females of childbearing potential only§ • BNP or NT-proBNP • Coagulation panel (PT or PTT; INR for patients on vitamin-K antagonist) • Complete blood count (CBC; including platelets) • Comprehensive metabolic panel (CMP; including Albumin, Bilirubin, ALP, ALT, AST, creatinine, BUN) • GGT • Troponin or CK/CK-MB • Uric acid and eGFR
Sub-study Only§	**Initiated at baseline, a minimum of 2 weeks prior to index procedure:** • eDiary collection • Activity monitoring

§ See Table 8 for associated assessment window

† 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.[53,54]

‡ All TTE and TEE imaging deemed incomplete or inadequate for assessment may require repeat imaging. If multiple echo (TTE or TEE) examinations are performed during the screening/baseline period, the most recent baseline echo (TTE or TEE) examination should be used to determine study eligibility.

¶ Repeated peri-procedurally per local institutional standard of care. Blood samples will be analyzed by local institution and any remaining blood sample will be discarded according to institutions regulations.

Table 8 provides the screening/baseline assessments windows if a patient has a pre-existing assessment. If a patient does not have an in-window assessment, the assessment should be collected after collection of ICF and prior to CSC case review.

Table 8: Screening/Baseline Assessment Windows

General Information	Window
Informed consent	Index procedure should be scheduled within 90 days of signing
TTE	A pre-existing TTE of adequate quality capturing required anatomy for assessment can be used as the screening/baseline assessment, provided it is within 60 days of submission to the study-specific image transfer system
TEE	A pre-existing TEE of adequate quality capturing required anatomy for assessment can be used as the screening/baseline assessment, provided it is within 180 days of submission to the study–specific image transfer system
Chest CT Scan	Standard of care assessment of adequate quality capturing required anatomy for assessment can be used as the screening/baseline assessment, provided it is within 1 year prior to consent
Pulmonary function test *(for patients with chronic lung disease, e.g., COPD)*	Standard of care assessment within 1 year prior to consent is acceptable

General Information	Window
βHCG, for females of childbearing potential	To be assessed via blood or urine test within 14 days prior to intervention in female patients of childbearing potential.
Sub-study: eDiary assessment*	Initiated at baseline; A minimum of 2 weeks prior to index procedure
Sub-study: Activity Monitoring Initiation*	Initiated at baseline; A minimum of 2 weeks prior to index procedure

* Applies to all patients participating in sub-study

8.9. Prior to Index Procedure

8.9.1. Pre-Procedure Therapy

Device Preparation

A description of device preparation and use is provided in the IFU. Investigators must be familiar with the information described in the IFU prior to use of the EVOQUE System. Edwards representative(s) that have been trained on the preparation of the EVOQUE System will be in attendance at all implant procedures.

Antibiotic Prophylaxis

All recipients will be prophylactically treated for endocarditis per institution's standard of care to minimize the possibility of infection.

Pre-Procedure Medical Therapy

Medical therapy in the 30 days prior to the procedure includes diuretic medications in stable doses, unless patient has documented history of intolerance. No new diuretics should be introduced and current diuretic doses should be stable (i.e. no decrease of more than ½ or increase of 2x) unless medically required (e.g., severe hypotension or signs and symptoms of hypervolemia).

8.10. Procedure

8.10.1. 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.

8.10.2. Implantation Procedure

Refer to the current IFU version for detailed information on the use of the EVOQUE System.

The date of the implant procedure will be considered as Day 0 for the purpose of determining specified time intervals for the study's follow up visits.

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 following study procedures/data collection will be performed (**Table 9**):

Table 9: Procedural Information

General Information	• Date of study procedure • Patient identification number • Name of implanting physicians • Access site • Timing of implant procedures • Study device identification & disposition
Clinical Information	• Pre-procedure 12-lead ECG* • Pre-implant right heart pressure measurements (mean): RA, RV, PA, and PCW using invasive hemodynamic monitoring and PASP (mean) measurements via echo • Post-implant pressure measurements for RA via appropriate catheter and PASP (mean) measurements via echo • TEE measurements pre-and immediately post-procedure** • Procedural fluoroscopic imaging • Fluoroscopy duration & contrast volume • Safety Evaluation and Adverse Events Assessments • Device malfunction/deficiency, if applicable *Note: In-hospital telemetry for a minimum of 24 hours to begin post-procedure (as identified in Table 10)*
Laboratory Measurements	• Heparin administration to achieve (and maintain) an Activated Clotting Time (ACT) ≥ 250 sec during the implantation procedure
Sub-study only	• eDiary collection will be paused at time of admission. The patient must arrive to the index procedure admission with the eDiary. • Activity monitoring will be paused at time of admission. The patient must arrive to the index procedure admission wearing the activity monitor.

* Must be performed within 24 hours prior to the procedure.
** Optional adjunct imaging (e.g., ICE) during the procedure may be performed.

8.11. Recommended Pre- and Post-Procedure Antiplatelet/Anticoagulation Therapy

Prior to enrollment in the study and during every study assessment period, the risk of bleeding and thrombosis formation will be assessed. Anticoagulation and antiplatelet therapy will be recorded at baseline.

Post-procedural surveillance of the implanted device may be administered as described in **Figure 11**. Patients with other indications for oral anticoagulant therapy (OAC) for AF, PE, DVT, etc. will be treated at the Investigator's discretion.

Changes in anticoagulation and antiplatelet therapy will be recorded at every visit. Patient must be able to tolerate at least one antiplatelet medication AND one anticoagulant medication for eligibility.

8.11.1. Known Thrombosis and Bleeding Risk Factors

Known baseline thrombosis risk factors include: previously identified aspirin/clopidogrel resistance; prior history of TIA, stroke or venous thrombosis; spontaneous echo contrast ("smoke") noted

preoperatively in the left atrium or left atrial appendage or post-implant in the left atrium or left ventricle; low ejection fraction or stroke volume, arrhythmia (e.g., AF), large left atrium, infection or inflammation, INR post-valve implantation below the target range of 2.5-3.5.

Known baseline bleeding risk factors include: history of uncontrolled hypertension (> 160 mmHg systolic); renal disease (dialysis, transplant, Cr > 2.6 mg/dL or > 200 µmol/L); liver disease (cirrhosis or bilirubin > 2x normal or AST/ALT/AP > 3x normal); stroke history; prior major bleeding or predisposition to bleeding; labile INR (unstable/high INR, time in therapeutic range < 60%); age > 65; medication usage predisposing to bleeding (antiplatelet agents, NSAIDS), alcohol or drug use history (> 8 drinks/week).

8.11.2. Pre-Procedure Therapy

Patients on warfarin or DOACs at baseline may be asked to discontinue use prior to implant procedure as deemed appropriate by the treating physician.

8.11.3. Intraprocedural Therapy

Heparin will be administered at procedure start.

During the procedure, ACTs 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 seconds. The sheaths may be removed using closure devices and/or figure-of-eight sutures, or when ACT level is appropriate (e.g., reaches < 200 seconds) after implantation of the study devices.

Use of protamine to reverse heparin therapy may be used at the investigator's discretion with due consideration given to the relative risk of thrombosis formation.

8.11.4. Post-Procedure Therapy

8.11.4.1 Post-Implant Up to 6 Months

Recommendation for all patients: warfarin (target INR range 2.5-3.5) or other appropriate anticoagulant + acetylsalicylic acid (ASA, 75-100 mg) for up to the 6-month follow-up visit.

Post-implant for patients on warfarin therapy, the use of heparin as a bridging agent to warfarin therapy may be used until the INR stabilizes at 2.5 or greater. The use of home INR monitoring devices in addition to frequent assessment of INR by the treating physicians is recommended.

8.11.4.2 Beyond 6 Months Post-Implant

While long-term anticoagulation regimen is recommended, the anticoagulant and antiplatelet regimen past the 6-month follow up visit will be determined at the Investigator's discretion. However, it is recommended that before and after warfarin (or other appropriate anticoagulant) discontinuation, patients should be assessed by transthoracic echocardiography to ensure an absence of valve thrombosis (**Figure 11**).

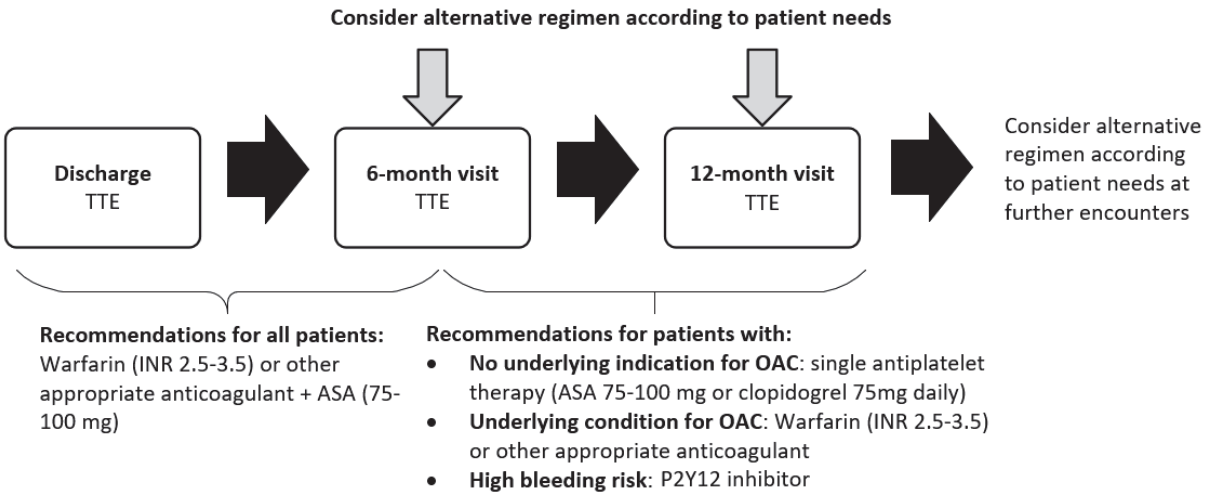


Figure 11: Anticoagulant/Antiplatelet Therapy and Surveillance Recommendations

Following the 6-month visit, alternative anticoagulation/antiplatelet regimens may be considered according to the needs of individual patients or a hospital's standard practice.

In the **absence** of underlying indication for oral anticoagulation, the following is recommended:

- Single antiplatelet therapy (aspirin 75-100 mg or clopidogrel 75 mg once daily).
- Aspirin and clopidogrel should be prescribed for an overall duration of 6-12 months in case of coronary stenting in the setting of TTVR.

In the **presence** of underlying indication for oral anticoagulation, the following is recommended:

- Warfarin or other appropriate oral anticoagulation (OAC) alone without concomitant antiplatelet treatment.
- For patients on warfarin or other appropriate OAC who also have an indication for anti-platelet therapy, an OAC and a single anti-platelet (either ASA or P2Y12 inhibitor) may be used.
- In case of high bleeding risk, P2Y12 inhibitor may be prescribed.

The precise long-term antithrombotic regimen should be dictated by patient-specific comorbidities relating to both thromboembolic and bleeding risk. However, there is a growing body of literature[55] suggesting better safety profiles of direct oral anticoagulants (DOACs) in head-to-head trials against warfarin for non-valvular atrial fibrillation. DOACs could be considered, based on investigators assessment.

8.12. Recommended Post-Procedure Diuretic Therapy

While post procedure OMT is per investigator discretion, it is recommended that patients be maintained on their pre-procedure diuretic regimen for 3 months post-implant.

8.13. Post-Procedure Cardiac Rhythm Monitoring

All study patients will have ECGs performed:

- within 24 hours prior to the procedure (Section 8.10.2 "Implantation Procedure")
- 12-24 hours post procedure (Section 8.14.1 "Post-Procedure Study Procedures/Data Collection")
- at discharge (Section 8.15 "Discharge Evaluation/Data Collection")
- as needed per physician discretion (e.g., if new ECG changes are noted).

All study patients will be monitored on telemetry in-hospital for at least 24 hours post-procedure.

All study patients will be monitored by an ambulatory cardiac monitor for at least 2 weeks immediately following discharge (except those with pre-existing or newly implanted functional permanent pacemaker (PPM), implantable cardioverter defibrillator (ICD), cardiac resynchronization therapy (CRT) devices, or implantable cardiac monitor (ICM) with real-time monitoring service).

Use of the Sponsor provided ambulatory cardiac monitoring device is preferred. Investigator may select an alternative commercially available monitoring device, per local routine practice, if deemed medically necessary.

Patients will be treated per institutional standard of care if ECG changes are identified. Newly identified clinically significant ECG changes will be reported as adverse events.

8.14. Post-Procedure/Pre-Discharge

8.14.1. Post-Procedure Study Procedures/Data Collection

The following study procedures/data collection will be performed 12-24 hours post-implant procedure (**Table 10**).

Table 10: Post-Procedure and Pre-Discharge

General Information	• N/A
Clinical Information	• Targeted physical examination • Clinical evaluation / prior or recent hospitalization • In-hospital telemetry monitoring (minimum 24 hours)* • 12-lead ECG** • Concomitant Medication • Safety Evaluation and AE/Device Deficiency (DD) Assessments
Laboratory Measurements†	• BNP or NT-proBNP • Complete Blood Count (CBC; including platelets) • Comprehensive metabolic panel (including Albumin, Bilirubin, ALP, ALT, AST, creatinine, BUN) • Coagulation Panel (PT or PTT; INR for patients on vitamin-K antagonist) • GGT • Uric acid and eGFR • Troponin or CK/CK-MB (according to site standard practice)

* In-hospital telemetry (minimum of 24 hours) should start as soon as possible post procedure.

**All study patients will undergo ECGs 12-24 hours post procedure, at discharge, and as needed per physician discretion if new ECG changes are noted.
†Within 12-24 hours post-implant. Blood samples will be analyzed by local institution and any remaining blood sample will be discarded according to institutions regulations.

8.15. Discharge Evaluation/Data Collection

The following study procedures/data collection will be performed at discharge or at 7 days post-procedure, whichever comes first (**Table 11**):

Table 11: Discharge / 7 Days Post-Procedure

General Information	• Discharge date
Clinical Information	• Targeted physical exam • Clinical evaluation / prior or recent hospitalization • Concomitant Medication including diuretic dose/s • Safety Evaluation and AE/DD assessments • Modified Rankin Scale* • TTE • 12-lead ECG • Ambulatory cardiac monitoring**
Laboratory Measurements†	• BNP or NT-proBNP • Complete Blood Count (CBC; including platelets) • Comprehensive metabolic panel (including Albumin, Bilirubin, ALP, ALT, AST, creatinine, BUN) • Coagulation Panel (PT or PTT; INR for patients on vitamin-K antagonist) • GGT • Uric acid and eGFR • Troponin or CK/CK-MB (according to site standard practice)
Sub-study only	• eDiary collection (including KCCQ, EQ-5D-5L, SF-12, mood questionnaire, and symptom burden) will resume for 1 year after discharge. Starting post discharge, question(s) will be administered daily until the 12-month follow-up visit. • Activity Monitoring will resume at discharge daily until the 12-month follow-up visit. The patient will be discharged wearing the activity monitoring device.

* 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.[53,54]
** All study patients will be monitored by an ambulatory cardiac monitor for at least 2 weeks immediately following discharge (except those with pre-existing or newly implanted functional PPM, ICD, CRT devices, or implantable cardiac monitor with real-time monitoring service).
†Blood samples will be analyzed by local institution and any remaining blood sample will be discarded according to institutions regulations.

8.16. Follow-up Visit Evaluations/Data Collection and Windows

Follow-up visits will be conducted at 30 days, 6 months, 1 year and annually thereafter for 5 years. **Table 12** lists the procedures to be conducted during the follow up visits and **Table 13** lists the follow-up visit windows.

Post-implant chest CT scans (ECG gated MSCT scan) should be collected at the 30 day and 12 month follow-up visits according to the current version of the acquisition guide unless medically contraindicated or patient refuses. Chest CT scan collected as standard of care may be used if available.

Table 12: Follow-up Evaluations

General Information	• N/A
Clinical Information	• Medical history since last visit • Clinical Evaluation/Prior Recent Hospitalizations • Targeted physical examination, lower limb edema grading (+1-+4), ankle circumference measurements • Concomitant Medications (including diuretic dose/s) • Safety Evaluation and AE/DD assessments • Modified Rankin Scale* • Patient Edema Questionnaire • NYHA Classification • TTE • 12-lead ECG • 6MWT • KCCQ, SF-36v2 • Chest CT Scan (ECG Gated MSCT Scan)**
Laboratory Measurements†	• BNP or NT-proBNP • Complete Blood Count (CBC; including platelets) • Comprehensive metabolic panel (including Albumin, Bilirubin, ALP, ALT, AST, creatinine, BUN) • Coagulation Panel (PT or PTT; INR for patients on vitamin-K antagonist) • GGT • Uric acid and eGFR
Sub-study only	• eDiary collection (including KCCQ, EQ-5D-5L, SF-12, mood questionnaire, and symptom burden) will resume for 1 year after discharge. Starting post discharge, question(s) will be administered daily until the 12-month follow-up visit. • Activity Monitoring will resume at discharge daily until the 12-month follow-up visit. The patient will be discharged wearing the activity monitoring device.

*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.[53,54]

** Should be collected at the 30 day and 12 month follow-up visits according to the current version of the acquisition guide unless medically contraindicated or patient refuses.

†Blood samples will be analyzed by local institution and any remaining blood sample will be discarded according to institutions regulations.

Table 13: Follow-up Visit Windows

Scheduled Follow-up Interval	Follow-Up Window
Discharge or Day 7 (whichever comes first)	± 0 days
1 month (30 days)	± 7 days
6 months (180 days)	-90/+30 days (90 to 210 days)
Annually (365 days) up to 5 years	± 45 days

8.17. Unscheduled Follow-Up

An unscheduled follow-up is defined as a visit occurring outside of protocol-defined visit intervals but is relevant/related to the conduct of the study. Sites must document all unscheduled visits during which protocol-defined assessments and/or observations occurred.

8.18. Description of Data to Be Collected

Sites are required to collect and report in the electronic data capture (EDC) all data and supporting documentation including, but not limited to, the assessments and evaluations detailed above.

8.19. Study Patient Completion

Patients complete and exit the study when no additional follow-up visits, procedures, or data collection as described in **section 8.6** are required. Patients will continue to be followed by their primary health care provider as required.

8.20. Study Termination and Close-Out

The Investigator will be notified in writing upon termination or conclusion of the study. The Sponsor 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.

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

8.21. Schedule of Assessments

Study patients must adhere to the activities in **Table 14**. Study-specific activities with patients must commence only after a signed IRB-approved informed consent form is obtained. Screening activities are performed to determine patient eligibility.

Table 14: Schedule of Assessments

	Screening / Baseline[A]	Index Procedure[B] Day 0	Post-Procedure 12-24 hours	Discharge or day 7 whichever is earlier	30 Day Visit ± 7 days	6 Month Visit -90/+30 days	1 Year Visit ± 45 days	2, 3, 4, 5 Year Visit ± 45 days
Study Visit Number	1/2	3	4	5	6	7	8	9-12
General Assessments								
Informed Consent	X							
Demographics and Medical History	X							
Clinical Evaluation/Prior or Recent Hospitalizations	X		X	X	X	X	X	X
Targeted Physical Exam	X		X	X	X	X	X	X
Medications (including diuretic doses)	X		X	X	X	X	X	X
Safety Evaluation and AEs/DD		X	X	X	X	X	X	X
Tests/Assessments								
Ankle circumference measurements	X				X	X	X	X
Chest CT Scan	X				X[C]		X[C]	
Clinical Frailty Scale (CSHA)	X							
EuroSCORE II/STS Score	X							
Fluoroscopic Imaging		X						
Katz Index of Independence in Activities of Daily Living (ADL)[D]	X							
Lower limb edema grading (+1-+4)	X				X	X	X	X
Modified Rankin Scale[E]	X[E] (only for patients with hx of stroke)			X[E]	X[E]	X[E]	X[E]	X[E]
NYHA Class Assessment	X				X	X	X	X
PASP (mean) measurements pre/post-implant via echo		X						
Pulmonary function test	X (only for patients with hx of chronic lung disease)							
Right heart pressure measurements[F]		X (pre procedure and at completion of implant procedure)						
Six Minute Walk Test[G]	X				X	X	X	X
Standard 12-Lead ECG	X	X[H]	X[H]	X[H]	X	X	X	X
In-hospital Telemetry Monitoring[I]			X[I]					
Ambulatory Cardiac Monitoring[J]				X[J]				
Transesophageal Echocardiogram (TEE)[K]	X	X						
Transthoracic Echocardiogram (TTE)	X			X	X	X	X	X

	Screening / Baseline[A]	Index Procedure[B] Day 0	Post-Procedure 12-24 hours	Discharge or day 7 whichever is earlier	30 Day Visit ± 7 days	6 Month Visit -90/+30 days	1 Year Visit ± 45 days	2, 3, 4, 5 Year Visit ± 45 days
Study Visit Number	1/2	3	4	5	6	7	8	9-12
Questionnaires (Patient completed)								
Kansas City Cardiomyopathy Questionnaire (KCCQ)	X				X	X	X	X
Patient Edema Questionnaire[L]	X				X	X	X	X
Patient Preference Survey[M]	X							
SF-36v2	X				X	X	X	X
Bloodwork[N]								
βHCG (if applicable)[O]	X							
BNP or NT-proBNP	X		X	X	X	X	X	X
Coagulation Panel (PT or PTT; INR for patients on vitamin-K antagonist)	X		X	X	X	X	X	X
Complete Blood Count (CBC; including platelets)	X		X	X	X	X	X	X
Complete Metabolic Panel (CMP; including Albumin, Bilirubin, ALP, ALT, AST, creatinine, BUN)	X		X	X	X	X	X	X
GGT	X		X	X	X	X	X	X
Uric Acid and eGFR	X		X	X	X	X	X	X
Troponin or CK-MB	X		X	X				
Electronic Diary and Activity Monitoring Sub study - Up to 45 patients (upon FDA approval) at up to 10 sites								
eDiary Assessment (KCCQ, EQ-5D-5L, SF-12, mood questionnaire, and symptom burden)[P]	X (daily)				X (daily)			
Activity Monitoring[Q]	X (daily)				X (daily)			

A. Refer to Table 7 for assessment windows
B. 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 Edwards EVOQUE 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.
C. Should be collected at the 30 day and 12-month follow-up visits according to the current version of the acquisition guide unless medically contraindicated or patient refuses.
D. See Appendix C for Katz Index of Independence in Activities of Daily Living
E. 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.
F. Pre-implant right heart pressure measurements (mean): RA, RV, PA, and PCW using invasive hemodynamic monitoring and PASP using echo; Post-implant right heart pressure measurements (mean): RA via appropriate catheter and PASP using echo.
G. See Appendix D for instructions for 6-Minute Walk Test and American Thoracic Society Statement on the Guidelines for the Six-Minute Walk Test[7]
H. All study patients will undergo ECGs at pre procedure (within 24 hours prior to the procedure), 12-24 hours post procedure, at discharge, and as needed per physician discretion if new ECG changes are noted.
I. In-hospital telemetry monitoring for at least 24 hours post-procedure (Should start as soon as possible post procedure).
J. All study patients will be monitored by an ambulatory cardiac monitor for at least 2 weeks immediately following discharge (except those with pre-existing or newly implanted functional PPM, ICD, CRT devices, or implantable cardiac monitor with real-time monitoring service).
K. Optional adjunct imaging (e.g., ICE) during the procedure may be performed

L. See Appendix F for Patient Edema Questionnaire Template
M. See Appendix B for Patient Preference Survey Template
N. Blood samples will be analyzed by local institution and any remaining blood sample will be discarded according to institutions regulations
O. To be conducted within 14 days prior to intervention for females of childbearing potential. Repeated peri-procedurally per local institutional standard of care as needed.
P. eDiary collection via a handheld device: A daily assessment will be administered for a minimum of 14 days before the index procedure and then from post discharge through the 12-month follow-up visit.
Q. Activity monitoring (via a wearable monitor): An activity monitor is worn for a minimum of 14 days before index procedure, then paused at time of admission for index procedure, resumed post discharge and worn through the 12-month follow-up visit.

9. Device Management

9.1. Device Shipment

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

Devices will be provided to study sites on an as needed basis 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.”

9.2. Inventory and Accountability Records

All device shipments will have inventory and shipment records. Devices may be hand carried to study sites by Study Sponsor personnel; will have delivery of investigational device documentation (e.g., packing lists, transfer of investigational product form, etc.).

The Investigator(s) or designee will take inventory of the product and complete delivery documentation with receipt date and signature. Both the study site and Sponsor will retain copies of these documents. The Investigator or designee will maintain a Device Accountability Log (as provided by the Sponsor) for all investigational devices that document their receipt, disposition, and return. The log will be kept with the documents for the clinical study and will be available for review during Sponsor monitoring visits. Only investigators trained and identified in the Delegation of Authority form on file at Edwards Lifesciences may use the investigational devices.

Use of the investigational devices and accessories provided for use in this study is prohibited outside of this study protocol.

9.3. 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 only be accessible to the Investigators or approved designees.

9.4. Device Return

All device returns and dispositions must be captured on the Device Accountability Log.

The Investigator will receive instructions from the Sponsor on the return process, when applicable (e.g., Sponsor request, study is terminated, or product expiration, etc.).

All unused investigational devices (in original packaging, in opened packages, or removed from the original packaging) will be returned to the Sponsor, upon request.

Study devices suspected to have a device malfunction or deficiency should be returned to the Sponsor (see **Section 11.8 and 11.9** for more details).

9.5. Patient Implant Card

An implant card will be supplied to each patient implanted with the EVOQUE valve.

10. Data Collection and Reporting

The Sponsor will provide the study site with the clinical protocol, electronic case report forms, sample ICF(s), and all other necessary study-related documents. The Sponsor's Clinical Affairs Department, or designee, will conduct quality control and assurance of the study site, including but not limited to, data reviewing, data monitoring, and form collection. Every reasonable effort should be made to complete data entry in a timely manner.

10.1. Data Management

Sponsor will provide data management through a secure, password protected Electronic Data Capture (EDC) system accessible via the internet.

10.2. Electronic Case Report Forms (eCRFs)

Electronic case report forms (eCRFs) will be used to collect patient data during the study. The Investigator, or individual(s) designated by the Investigator, is responsible for entering all data from the study onto the eCRFs hosted on a dedicated website. Electronic CRFs must be fully completed for each patient and signed electronically by the investigator and/or designee. The eCRFs should be completed at the first earliest opportunity.

Data entered into the eCRFs may be subject to system validation checks (e.g., format range checks). System checks are automatic (i.e. generated at the time of data entry) and ensure the validity of submitted data. A query will be generated when a discrepancy requiring review has been identified. Discrepancies will remain open until a resolution is reached.

The site Investigator or designee must ensure the accuracy and completeness of the recorded data and then provide an electronic signature on the appropriate eCRFs. Changes to data previously submitted to the Sponsor will require a new electronic signature to acknowledge/approve the changes.

The Sponsor will conduct ongoing reviews of eCRF data. Sites that do not complete all data entry tasks in a timely manner may be prohibited from enrollment until data submission is current.

10.3. Source Documentation Requirements

All data that is entered in the eCRFs must have source documentation available in the patient medical records. 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. Data recorded directly on CRFs such as patient-reported questionnaires or other data are deemed acceptable for collection outside of the EDC.

Protocol deviation information can be recorded directly on the protocol deviation eCRF.

10.4. 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 or contracted by the Sponsor 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.

The Sponsor will provide data management through a secure, password protected EDC system accessible via the Internet. 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.

11. Adverse Event Reporting and Assessments

Adverse events will be captured for all study patients from the time of enrollment until the patient's participation has ended (i.e., completion of study, lost to follow-up, withdrawal of consent, or patient has died).

11.1. Definitions

11.1.1. Adverse Event

An Adverse Event (AE; MDR 2017) is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device.

11.1.2. Serious Adverse Event

A serious adverse event (SAE; MDR 2017) is any AE that led to any of the following:

a) death,
b) serious deterioration in health of the patient, that resulted in any of the following:
   - life-threatening illness or injury,
   - permanent impairment of a body structure or a body function,
   - hospitalization or prolongation of patient hospitalization,
   - medical or surgical intervention to prevent life threatening illness,
   - injury or permanent impairment to a body structure or a body function,
   - chronic disease
c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

Note: A planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a SAE.

11.1.3. Anticipated Adverse Events

Anticipated adverse events are AEs that have been identified in the CIP, IFU, and informed consent as possible adverse events.

11.1.4. Unanticipated Adverse Device Effect

Unanticipated adverse device effect (UADE, 21 CFR Part 812) is 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 problem associated with a device that relates to the rights, safety, or welfare of patients.

11.1.5. Device Deficiency

A device deficiency (DD, MDR 2017) is any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

11.1.6. Device Malfunction

A device malfunction (ISO 14155) is a failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the IFU

11.2. General Adverse Event Reporting Requirements

The Investigator or designee or designee will report all AEs and DDs to the Sponsor as soon as possible, but no later than 10 calendar days after the Investigator or designee or designee first learns of the event.

Each AE must be reported on a separate AE CRF. In the event that the EDC system is not in service or otherwise not accessible, the Sponsor must be notified by email [redacted]. The AE CRF should be completed as soon as possible thereafter.

Completion of the AE form should not be delayed due to missing information. At the time of initial notification, the following minimal information should be provided:

- Study site number
- Patient ID number
- Date of event
- Site's awareness date
- AE description
- Seriousness
- Causal relationship to device and implant procedure

The site will provide the Sponsor copies of relevant supporting source documentation requested (e.g., Implant procedure report, discharge summary, medication administration record (MAR), echocardiogram and laboratory results) for any of the following reasons: AEs requiring CEC adjudication (at a minimum, safety endpoints), events determined by the Sponsor to require additional investigation, and to determine patient care.

Adverse events must be followed until resolution, the patient is lost to follow-up, the patient has withdrawn consent, or the AE is otherwise explained.

The Investigator will inform the respective entities (IRB or FDA) of AEs in accordance with the relevant local and regional regulatory requirements.

11.3. Findings That Do Not Require Reporting to the Sponsor

For purposes of this study, the following findings are not considered adverse events, because of their nature, do not require 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 transcatheter, cardiovascular procedures.

- Post-procedure pain (within 48 hour of procedure) not requiring treatment or treated with non-opioids
- Abnormal or out of range lab values (e.g., electrolyte imbalance) that are not clinically significant and do not require correction or treatment
  Note: Abnormal lab values that roll up to a diagnosis should not be reported as separate AEs (e.g., elevated BNP in patient with heart failure; increased K+ in patient with renal insufficiency; elevated white blood count in a patient with a diagnosed 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 list of findings is intended to provide guidance to the study sites for the purpose of AE reporting. The Investigator should utilize his/her own clinical judgment in evaluating adverse experiences and may decide that the above findings should be reported as adverse events.

11.4. Pre-Existing Conditions

Pre-existing medical conditions or symptoms should not be reported as an AE. In the event there is a clinically significant worsening in the pre-existing medical condition or symptoms, then an AE must be recorded.

11.5. Investigator AE Causality Assessment

Adverse events will be assessed by the Investigator for causality to the study device and index procedure. The relationship between the use of the study device and study/implant procedure and the occurrence of each AE will be assessed and categorized.

During causality assessment, clinical judgement shall be used and the relevant study documents (i.e. CIP, ICF, IFU and/or CIB) shall be consulted for the listing of foreseeable AEs/potential risks. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illnesses or risk factors shall also be considered.

- **Not related:** There is no relationship between the event and the device or implant procedure.
- **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 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 where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
- **Probable:** The relationship with the use of the device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.
- **Related (Causal relationship):** The event is related to the device and/or procedure beyond a reasonable doubt.

*Reference **Appendix A Study Definitions** for the full causality definitions.

An AE can be related to both the study procedure and the study device. Complications of procedures are considered not related if the said procedures would have been applied to the patients in the absence of study device use/application.

In certain cases, the event may not be able to be adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The Sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations.

11.6. Patient Deaths

Every effort should be made to provide a copy of the death summary, and autopsy report as applicable, to the Sponsor. The Sponsor may also request additional information to support the cause of death (e.g., last available medical consult, echo report). All source documents should be de-identified.

11.7. Sponsor Assessment and Reporting

The Sponsor is responsible for the classification, assessment, and reporting of AEs and device deficiencies and ongoing safety evaluation of the clinical investigation in accordance with 21 CFR 812.

A summary of adverse events will be reported to the FDA annually in the Annual Progress Report (APR).

The Sponsor will also report any confirmed UADEs to the investigators, FDA, and IRBs as soon as possible, but no later than 10 working days after first receiving notice of the effect or in compliance with local regulatory requirements.

11.8. Investigational Device Observations and Deficiencies

All suspected device observations and deficiencies (i.e. malfunctions, use errors resulting in device malfunction, inadequate labelling) will be documented on an individual device observation and deficiency form or equivalent.

In the event of a suspected deficiency or other device issue, the device shall be returned to the Sponsor, to the extent possible, for analysis. Instructions for returning the investigational device will be provided by the Sponsor.

11.9. Investigational Device Explants

An Edwards' study device that is explanted at any time during the study should be returned to the Sponsor for evaluation.

Once the study device is explanted, the patient is followed for 30 days after the explant, unless there is an ongoing related adverse event and its outcome is not deemed resolved by the Investigator. Return kits for explanted devices will be provided upon request by the clinical monitor or study team.

12. Statistical Analysis

12.1. Sample Size

This is a multi-center, prospective, and single-arm study. Up to 200 patients (upon FDA approval) will be enrolled in this study at up to 30 investigational sites (upon FDA approval) in the US. This sample size is adequate to evaluate the safety and performance of the EVOQUE System.

12.2. Analysis Populations

Analysis will be performed for the Enrolled, As-Treated (AT), Per-Protocol (PP) populations defined below:

- **Enrolled Population**: all patients enrolled in the study, defined as patients who sign informed consent and have had the study procedure attempted (attempted defined as skin incision for study device). Enrolled population will be used for the safety analyses.
- **As-Treated Population**: is a subset of the enrolled population who have had the study device implanted at the exit of procedure room. The AT population will be the analysis population for performance and functional endpoint analysis.
- **Per-Protocol Population**: is a subset of the AT population who had no protocol deviations relating to inclusion and exclusion criteria for the trial.

Additional analyses of performance and safety data using the PP population will be performed if there is/are a clinically meaningful difference(s) from the enrolled and the as-treated populations.

The safety analysis will be performed for enrolled population with due consideration given to the respective required follow-up intervals and the performance analysis including device success, procedural success and clinical success will be performed for implanted population.

The echocardiographic and functional analyses will be a summarization of measures of hemodynamic performance including reduction of tricuspid regurgitation, NYHA Functional Class, 6-minute walk test, and Quality of Life based on the implanted population. Patients that undergo any type of repair or replacement procedure for the tricuspid valve will be excluded from the echocardiographic analysis at the time of the reintervention and summarized in a table.

Clinical endpoints including all-cause mortality, heart failure hospitalizations, and non-elective re-intervention related to the device will be analyzed based on implanted population.

For patients participating in the sub-study, a separate data analysis plan will be developed to analyze the actigraphy data collected from the activity monitor and electronic patient reported outcome data collected from the eDiary.

12.3. General Approach

For continuous variables, results will be summarized with the number of observations, mean, standard deviation, median, minimum, maximum, and 90% confidence interval (CI) by normal approximation. For categorical variables, results will be summarized with patient count, percentage, and 90% CI by normal approximation, where appropriate.

Survival analysis techniques will be used to analyze time-to-event variables. Patients without events will be censored at their participation date in the study. For patients who did not have an event but remain in the study, they will be censored at the database extract date. Time to first event curves will be constructed using Kaplan-Meier estimates.

Descriptive statistics will be presented at each assessment, including change from baseline to subsequent time point for selected endpoints. For the determination of event rates, the number of all patients in the patient population will be used as the denominator. For variables ascertained at follow-up visit, the denominator will be based on number of evaluable patients. Unless otherwise noted, patients with missing data will be excluded from the denominator.

When the sample size is small (e.g., <10 patients), analysis may be performed in the form of listings only.

12.4. Safety Endpoint Analysis

The safety endpoint of major adverse events (MAEs) at 30 days shall be analyzed via the Kaplan-Meier (KM) method for implanted population. In addition, the event rates of individual adverse event of MAEs will also be calculated at 30 days, 6 months, and annually by the Kaplan-Meier method:

- Cardiovascular mortality
- Myocardial infarction (MI)
- Stroke
- Renal complications requiring unplanned dialysis or renal replacement therapy
- Severe bleeding (includes fatal, life-threatening, extensive, or major bleeding, as defined by MVARC)
- Non-elective tricuspid valve re-intervention, percutaneous or surgical
- Major access site and vascular complications
- Major cardiac structural complications
- Device-related pulmonary embolism

12.5. Additional Safety Analysis

A summary of the percentage of patients who experience an early adverse event (≤ 30-day post-procedure) and late adverse event (> 30 days post-procedure) will be reported for all adverse events.

The count and percentage of patients who experience newly identified ECG changes, as identified by ambulatory cardiac monitoring, resulting in PPM, ICD, or CRT device implantation will be reported. Two-sided 90% confidence intervals will be constructed around the percentage of patients who experience newly identified ECG changes resulting in PPM, ICD, or CRT device implantation. This

analysis will only include patients who undergo ambulatory cardiac monitoring. The reported confidence intervals will be compared to the range as reported in the literature data.

The count and percentage of patients who have a change in therapy (either new pacemaker for bradycardia or new ICD/new pharmacotherapy for tachycardias) as a result of ECG changes identified by ambulatory cardiac monitoring will be reported. This analysis will only include patients who undergo ambulatory cardiac monitoring.

12.6. Performance, Functional and Other Endpoint Analysis

The device success, procedural success, and clinical success will be summarized by counts and percentages for the implanted population. NYHA performance will be assessed at baseline, 1 month, 6 months, and annually up to 5 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 5 years. Echocardiographic performance data will be obtained at the following time points: baseline, 1 month, 6 months, and annually up to 5 years. Descriptive statistics such as mean, standard deviation and range will be calculated for the continuous echo variables as well as the change from baseline for each variable.

Change in overall (general) quality of life will be measured through the use of health status questionnaires (e.g., KCCQ) and a six-minute walk test. QoL metrics will be assessed at 1 month, 6 months, and annually for 5 years from the implant procedure.

The average overall (general) quality of life changes at baseline, 1 month, 6 months, and annually for 5 years and the changes from baseline to follow up will be summarized by mean and standard deviation for the implanted cohort. Patients that are missing a baseline or follow up values will be excluded from the analysis.

12.7. Exploratory Computed Tomography (CT) Analysis

The following data will be assessed and summarized descriptively as described **Section 12.3** at 30 days and 12 months

- Cardiac remodeling (e.g., RV dimensions and volume)
- EVOQUE frame dimensions
- EVOQUE leaflet assessment
- EVOQUE positioning

12.8. Missing Data

All statistical analyses will be performed using only those patients with available data required for endpoint analysis.

12.9. Analysis Software

Unless otherwise specified, the exact form of each algorithm will be the default of SAS®, using the latest release generally available at the time of analysis. This will be version 9.4 or later.

13. Monitoring

The Sponsor, or its designee, will monitor and manage the data for the investigational study. [redacted]

[redacted]

13.1. Monitoring Methods

All clinical sites will be monitored periodically by the Sponsor or designee to ensure compliance with the protocol and the Investigator's Agreement and that all study patients have been properly consented. The monitor will ensure that the completed eCRFs match the source documents and work with the site to resolve differences through electronically generated queries or formal action items.

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 Form 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.

13.2. Monitoring Plan

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 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.

Prior to activating a site for patient screening and enrollment, the Sponsor will ensure the following:

1. An initiation visit has been conducted,
2. IRB approval have been obtained and documented,
3. The Investigator(s) and study personnel are appropriately trained and clearly understand the study,
4. The Investigator(s) and study personnel accept the obligations incurred in undertaking this clinical study,
5. The Delegation of Authority form has been completed properly

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

13.3. Protocol Deviation and Medical Emergencies

A protocol deviation is defined as an event where the Investigator or study personnel did not conduct the study according to the clinical protocol. Investigators shall be required to obtain approval from the 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 the Sponsor 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 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 documented. 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 patient safety, well-being, the patient's willingness to participate in the study, or that may compromise the integrity of the study data and analysis, including:

A. Patients 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/USADE not reported to IRB/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 patient 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, as required.

13.4. Communication Procedures

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

14. Clinical Study Boards

14.1. Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will be comprised of independent, non-investigator physicians, who will be responsible for reviewing aggregate trial data reported during the study and assessing whether the overall safety of the trial remains acceptable. DSMB activities, including roles and responsibilities, operating procedures, and monitoring criteria will be defined in the DSMB Charter.

14.2. Clinical Events Committee

The Clinical Events Committee (CEC) will be comprised of independent, non-investigator physicians, and will be responsible for reviewing and adjudicating specified individual adverse events over the course of the study. CEC activities, including roles and responsibilities, operating procedures, specific events to be adjudicated, and definitions to be used by the CEC during adjudication will be defined in the CEC Charter.

14.3. Central Screening Committee

A Central Screening Committee (CSC) is comprised of members who are participating in the study. The role of the CSC is to review submitted cases to determine if the patient is an appropriate candidate for the study, with a focus on confirming suitability for enrollment.

14.4. Echocardiography Imaging Core Laboratory

An independent echocardiographic imaging core laboratory will be utilized for assessment of echocardiograms. Echocardiogram image acquisition shall be performed in accordance with the core laboratory's manual, which is provided to the sites.

15. Ethical and Regulatory Considerations

15.1. Applicable Regulations and Guidelines

The regulations listed in **Table 15** must be observed to comply with the Sponsor policy for conduct 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 15: Applicable Regulations and Guidelines

Region	Clinical Information
United States	• 21 CFR 50 – Protection of Human Subjects • 21 CFR 56 – Institutional Review Boards • 21 CFR 54 – Financial Disclosure by Clinical Investigators • 21 CFR 58 – Good Laboratory Practice for Non-clinical Laboratory Studies • 21 CFR 812 – Investigational Device Exemptions • 21 CFR 11 – Electronic Records and Signatures • 42 CFR 11 – Clinical Trials Registration and Results Information Submission • 45 CFR 46 – Protection of Human Subjects • ISO 14155*– Clinical Investigation of Medical Devices for Human Patients – Good Clinical Practice • ISO 14971 – 2019 – Medical Devices – Application of Risk Management to Medical Devices • ISO 5840 – 2009 - Cardiovascular implants-cardiac valve prostheses • ISO 5840-3 – 2013 - Cardiovascular implants-cardiac valve prostheses – Part 3: Heart valve substitutes implanted by transcatheter techniques • Medical Device Regulation 2017/745 (MDR) • MDCG 2020-10 Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745; as applicable • Other applicable local and national regulatory requirements, as applicable
*ISO 14155:2020 will be implemented in this trial following Sponsor's revision of corporate SOPs to align with the updated edition of the ISO 14155 standard	

This study does not include any patients considered to be part of a vulnerable population, as per ISO 14155. Vulnerable populations include individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response.

Furthermore, the Investigator(s) must comply with the requirements of the Declaration of Helsinki (2008) and with 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.

15.2. Data Protection and Patient Confidentiality

The Sponsor is dedicated to maintaining the confidentiality and privacy of patients who volunteer to participate in the study. The Investigator is responsible for maintaining confidentiality throughout the clinical study.

All data used in the analysis and reporting of this evaluation will be without identifiable reference to the patient (patient identifiers include but are not limited to: patient's name/initials, social security number or equivalent, and medical/hospital number). Authorized personnel assigned by the Sponsor will have access to the confidential files and will have the right to inspect and copy all records pertinent to this study. Additionally, IRBs/ECs and/or regulatory authority bodies, acting in their official

capacities, will have direct access to original/source data and will have the right to inspect all records pertinent to this study.

With respect to data protection and patient confidentiality, Sponsor, Institution and all Study Personnel will comply with applicable requirements, including providing Notice and obtaining patient Consent regarding the processing of their personal data.

15.3. Institutional Review Board

This protocol, the proposed ICF, other written patient information and any proposed advertising material must be submitted to the IRB for written approval. A copy of the written IRB approval of the protocol and ICF must be received by the Sponsor before recruitment of patients into the study and shipment of investigational product.

The Investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the ICF.

The Investigator is responsible for obtaining annual IRB approval and renewal throughout the duration of the study. Copies of the Investigator's reports and the IRB continuance of approval must be sent to the Sponsor.

15.4. Informed Consent

Sponsor will provide a sample ICF to the Investigator to prepare for use at his/her site. The site-specific ICF, and any subsequent modifications, must be in agreement with current regulations and guidelines and must be approved by Sponsor prior to submission to the IRB. The reviewing IRB must approve the ICF before use at the site.

Before participating in the clinical study, each patient must give written informed consent after the context of the study has been fully explained in a language that is easily understood by the patient. The patient must also be given the opportunity to ask questions and have those questions answered to his/her satisfaction.

A copy of each patient's signed and dated ICF must be maintained by each Investigator in a designated clinical study administrative file. A signed copy of the consent form must be given to each patient. The consent process must be documented in the patient's medical chart; the documentation should include minimally that consent was obtained prior to participation in the research study, date consent was obtained, and confirmation that a copy of the consent was given to the patient.

15.5. Investigator Responsibilities

15.5.1. General Duties

The Investigator shall ensure that all work and services described herein, or incidental to those described herein, shall be conducted in accordance with the highest standards of medical and clinical research practice and the applicable regulations. The Investigator shall be responsible for the day to day conduct of the clinical 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 center.

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

15.5.2. Investigator Records

The Principal Investigator (or designee) must maintain the following records for each patient enrolled in the study:

- Signed patient consent form(s)
- Copy of final completed eCRFs
- All lab and testing results
- Record of any complications, adverse events, device deficiencies and/or malfunctions, with supporting documentation
- Procedure reports, progress notes, physician and/or nursing notes, and patient office files
- Records pertaining to patient deaths throughout the course of the study (including death records, death certificate and autopsy report, if performed)
- Any other records that FDA/regulatory authority or ISO 14155 requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

15.5.3. Investigator Reports

The Investigator will prepare and submit the following accurate and complete reports to the Study Sponsor and IRB in a timely manner:

- Anticipated and unanticipated serious adverse device effects occurring during the study will be reported as described in **Section 11**, Adverse Event Reporting and Assessments.
- Withdrawal of IRB approval will be reported to the Sponsor within 5 business days.
- Annual progress reports will be submitted to the IRB.
- Deviation from the clinical study protocol. Deviations to protect the patient's life or physical well-being in an emergency will be reported to the Study Sponsor within 5 business days and to the IRB according to their reporting policy.
- Use of the study device without informed consent will be reported within 5 business days after the use occurs.
- A final written report within twelve (12) months of completion or termination of the study.

Upon request by a reviewing IRB or the pertinent regulatory agencies, the Investigator will provide current information about any aspect of the investigation.

15.5.4. Investigator Record Retention

Investigator files containing all records and reports of the investigation should be retained for a minimum of two years after the completion/ termination of the investigational study, or as required by applicable regulations. They may be discarded upon written notification by the Sponsor. To avoid error, the Principal Investigator should contact Sponsor, before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained.

In addition, in accordance with the Clinical Study Agreement, the Sponsor should be contacted if the Principal Investigator plans to leave the study site so that appropriate arrangements for file custodianship can be made.

15.5.5. Investigator's and Sponsor's Annual and Final Reports

Each year an annual summary report shall be prepared by the Investigator which provides a summary of the number of patients treated to date as well as other pertinent clinical information associated with the investigational procedure. The annual report is required to be provided to the IRB and the Sponsor or their authorized agent.

The Sponsor or their designee will be responsible for preparing a compilation of all of the participating site results for submittal as an annual progress report to the FDA/regulatory authority.

Upon completion and/or termination of the study a final report shall be prepared. This report will contain a critical evaluation of all data collected during the course of the investigation at each institution. The Sponsor or its designee is responsible for preparing this compilation to Investigators for submittal as a final report to their reviewing IRB. The Sponsor or its designee will also provide this final report to FDA/regulatory authority.

15.6. Sponsor Responsibilities

15.6.1. 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 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 the patient's decision to continue participating in the study.

15.7. Selection of Investigators

The Study Sponsor will select qualified Investigators and will provide investigational devices to participating study sites only. The Study Sponsor will obtain signed CTAs and provide the Investigators with the information and supplies necessary to conduct the clinical study.

15.7.1. 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 15.1**) and any conditions of study approval by the IRB and regulatory bodies. The Sponsor 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.

15.7.2. Sponsor Records

The Study Sponsor will maintain accurate, complete, and current records relating to this clinical study. Study records include CRFs, signed CTA, 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.

15.7.3. Sponsor Reports and Notifications

The Study Sponsor will prepare and submit the following accurate and complete reports to the IRB and the pertinent regulatory agencies as follows:

- Unanticipated adverse device effects reported by the study site will be evaluated and the participating Investigators, IRBs, and pertinent regulatory agencies will be informed of the results of the evaluation no later than 10 business days after the Sponsor first learns of the event.
- Withdrawal of IRB approval will be reported to all participating IRBs and regulatory agencies within five (5) business days of receipt of withdrawal of approval.
- Withdrawal of the pertinent regulatory agencies' approval will be reported to investigational sites and IRB within five (5) business days after receiving the notice of approval of withdrawal.
- Progress reports to the IRB at least annually and to the pertinent regulatory agencies as required.
- Instances of return, repair, or disposition of any units of a device will be sent to IRB and the pertinent regulatory agencies within 30 days after a field safety corrective action is made and should include the reason for the request.
- A final written report is to be completed and submitted to IRB and the pertinent regulatory agencies within twelve (12) months after completion or termination of the study.
- Use of the study device without informed consent will be reported to IRB and pertinent regulatory authorities within five (5) business days after notification of device use.
- Upon request by a reviewing IRB or the pertinent regulatory agencies, the Sponsor will provide current information about any aspect of the investigation.
- Temporary or any termination (planned or unplanned) of the clinical investigation will be reported to IRB and pertinent regulatory agencies within 15 days. If the study has been temporarily halted or terminated on safety grounds, notice will be given to pertinent regulatory agencies within 24 hours.

15.8. Clinical 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.

15.9. Clinical Study Site Termination

The Sponsor reserves the right to terminate a study site from the study for any of the following reasons including, but not limited to:

- Failure to obtain Informed Consent
- Failure to report Serious Adverse Events in a timely manner
- Repeated protocol violations
- Repeated failure to complete Case Report Forms
- Failure to enroll an adequate number of patients

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

15.10. Audits and Inspections

The study may be subject to a quality assurance audit by the Sponsor or a designee, as well as inspection/audit by appropriate regulatory authorities or IRBs acting in their official capacities. The Investigator must provide the auditor with all clinical investigation documents including the medical records for all enrolled patients. It is important that the Investigator and relevant study personnel are available during any audits and that sufficient time is devoted to the process. In the event of an audit by regulatory authorities, the Investigator should contact the Sponsor as soon as possible.

15.11. Publication Policy

[redacted]

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Appendix A: Study Definitions

Access Site
(VARC-1 Definition)
Any location (arterial or venous) traversed by a guidewire, catheter or sheath.

Access Site and Vascular Complications
(MVARC 2015 Definition)

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 primary 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 primary bleeding 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 left ventricle, left 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

Activity Monitoring
The continuous tracking of physical activity through the use of a patient deployed wearable actigraphy device

Bleeding
(MVARC 2015 Definition)

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 units of whole blood or packed red blood cell (RBC) transfusion and otherwise does not meet criteria for major, extensive, or life threatening.

II. Major
Overt bleeding either associated with a drop in the hemoglobin level of ≥ 3.0 g/dl or requiring transfusion of ≥3 units of whole blood or packed RBC AND does not meet the 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
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. Thresholds for reporting procedural bleeding for study index procedure >100 ml total EBL (Estimated Blood Loss) from access site.
All post-procedural overt bleeding events must be reported including hematuria, melena, hematemesis, occult gastrointestinal bleeds or drop in Hgb with overt source of bleeding detected requiring transfusions etc. If the reason for Hgb drop was other than due to the overt bleeding i.e. due to hemodilution, chronic iron deficiency anemia etc., it will not be considered as a bleeding event.

Causality Assessment

Adverse events will be assessed by the Investigator for causality to the study device and index procedure. The relationship between the use of the study device and study/implant procedure and the occurrence of each adverse event shall be assessed and categorized. During causality assessment, clinical judgement shall be used and the relevant study documents (i.e. Clinical Protocol, ICF, IFU and/or IB) shall be consulted for the listing of foreseeable adverse events/potential risks. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illnesses or risk factors shall also be considered.

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);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;
- harms to the patient 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 (Related): 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;
    - the investigational device or procedures 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 patient is due to error in use;
- the event depends on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish relatedness, not all criteria listed above must be met at the same time, depending on the type of device, procedure and the serious event.
An adverse event can be related both to the study procedure and the study device. Complications of procedures are considered not related if the said procedures would have been applied to the patients also in the absence of investigational device use/application.

In some particular cases the event may not be able to be not adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations.

Clinical Frailty Scale©
A 9 point single question administered to measure frailty. Developed by the Canadian Study of Health and Aging (CSHA).

Death
(MVARC 2015 Definition)

A. Cardiovascular Death

Cardiovascular death is defined as any of the following contributing conditions:

- Heart failure (sub-classified into left ventricular vs. right ventricular dysfunction)
- Myocardial infarction
- Major bleeding
- Thromboembolism
- Stroke
- Arrhythmia and conduction system disturbance
- Cardiovascular infection and sepsis (e.g., mediastinitis and endocarditis)
- Tamponade
- Sudden, unexpected death
- Other cardiovascular
- Device failure
- Death of unknown cause (adjudicated as cardiovascular)

B. Non-cardiovascular Death

Any death in which the primary cause of death is clearly related to another condition:

- Non-cardiovascular infection and sepsis (e.g., pneumonia)
- Renal failure
- Liver failure
- Cancer
- Trauma

• Other non-cardiovascular
Device Deficiency *(MDR 2017 definition)* A device deficiency (MDR 2017) is any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.
Device Embolization *(MVARC 2015 Definition)* Device movement during or after deployment such that it loses contact with its initial position, includes detachment leading to device embolization.
Device Malfunction *(ISO 14155 Defintion)* Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the IFU.
Electronic Diary (eDiary) The collection of electronic patient-reported outcomes (PRO) through a patient-deployed handheld device to administer quality of life assessments to the patient.
EQ-5D-5L A survey comprised of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that measures health-related quality of life.
Explant Removal of the study device after completion of the implant procedure for any reason.
Hemolysis *(MVARC 2015 / Sponsor Definition)* The presence of a paravalvular leak on transesophageal or transthoracic echocardiography plus anemia requiring transfusion plus decreased haptoglobin and/or increased LDH levels

Hospitalization/Re-hospitalization
(MVARC 2015 Definition)
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 failure 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 sub-classified as:

- **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

Local Heart Team
The 'Local Heart Team', for the purpose of this study, may include one Cardiologist, one Cardiac Surgeon, one Heart Failure specialist, and one Echocardiographer.

Kansas City Cardiomyopathy Questionnaire (KCCQ)
A health-related quality-of-life measure for patients with congestive heart failure.

Katz Index of Independence in Activities of Daily Living (Katz ADL)
Completed by the site, the Katz ADL is a 6-question assessment of functional status as a measurement of the patient's ability to perform activities of daily living

Major Adverse Event (MAE)
In this study, MAEs are defined as Cardiovascular mortality, Myocardial infarction (MI), Stroke, Renal complications requiring unplanned dialysis or renal replacement therapy, Severe bleeding (includes fatal, life-threatening, extensive, or major bleeding, as defined by MVARC[3]), Non-elective tricuspid valve re-intervention, percutaneous or surgical, Major access site and vascular complications, Major cardiac structural complications, and Device-Related Pulmonary Embolism.

Modified Rankin Scale (mRS)

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

Mood Questionnaire

A combined anxiety and depression assessment, developed by the National Institute of Health, to be administered on the eDiary for patients participating in the sub-study.

Myocardial Infarction

(MVARC Definition)

Myocardial infarction (MI) classification and criteria for diagnosis is defined as follows:

I. Periprocedural MI (≤48 hours after index 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 (left bundle branch block) 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.

II. Spontaneous MI (>48 hours after index 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:

A. Symptoms of ischemia
B. 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
C. Imaging evidence of a new loss of viable myocardium or new wall motion abnormality

III. 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

IV. 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.[56]
‡Adapted with permission from Thygesen et al.[57]

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. Patients 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

Patient Preference Survey
A survey that includes but is not limited to a patient's preference for an intervention, clinical outcome/result, or functional change

Pre-Existing Condition
A pre-existing condition is one that was present prior to clinical study screening.

Pulmonary Embolism
(Sponsor Definition)

Pulmonary embolic event is an operative, autopsy or clinically documented embolus that produces symptoms from complete or partial obstruction of a pulmonary or bronchial artery. Confirmation of pulmonary embolism is done through diagnostic testing such as TTE/TEE, ventilation/perfusion lung (VQ) scan, angiogram, MRI or CT.

Re-intervention
(Sponsor Definition)
Any surgical or percutaneous intervention that repairs, alters or adjusts, or replaces the previously implanted study device or native valve after the patient leaves the procedure room from the index procedure.
NOTE: The endpoint is "Non-elective tricuspid valve re-intervention (percutaneous or surgical)".
Elective: The procedure could be deferred without increased risk of compromised cardiac outcome.
Non-Elective: The procedure could not be deferred without increased risk of compromised cardiac outcome; includes Urgent and Emergent:

- **Urgent –** Procedure required during same hospitalization in order to minimize chance of further clinical deterioration.
- **Emergent –** An emergency operation is one in which there should be no delay in providing operative intervention.

Renal Complications
(Sponsor Definition)
Renal Complication is defined as new need for replacement therapy, including hemodialysis, renal transplant, continuous renal replacement therapy, peritonal dialysis, etc.

Severe Bleeding
(Sponsor Definition)
Severe bleeding is a fatal, life-threatening, extensive, or major bleeding, as defined by MVARC.

SF-36v2
A survey with 36 questions that results in two scales of mental and physical functioning and overall health related quality of life.
SF-12v2: A 12 question abridged and validated version of the SF-36v2

Stroke/TIA (Transient Ischemic Attack)
(MVARC 2015 Definition)

Stroke Diagnostic Criteria:

I. Acute episode of a focal or global neurological deficit with at least one of the following:
   A. Change in level of consciousness
   B. Hemiplegia, hemiparesis, numbness, sensory loss affecting one side of the body
   C. Dysphasia or aphasia, hemianopia, amaurosis fugax, other neurological signs or symptoms consistent with stroke

II. 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 a neurologist.*

The neurological event type classification

I. Stroke:
   Duration of symptoms:
   - A focal or global neurological deficit ≥ 24 hours or
   - 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) or
   - The neurological deficit results in death

II. TIA: duration of a focal or global neurological deficit < 24 hours and neuroimaging does not demonstrate a new hemorrhage or infarct

Confirmation of the diagnosis by at least one of the following:

I. Neurologist or neurosurgical specialist, or
II. Neuroimaging procedure (CT scan or brain MRI)
III. Non-neurologist physician (if neurologist is not available)
IV. Clinical presentation alone***

Stroke types will be adjudicated as:

I. Ischemic: an acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of the central nervous system tissue
II. Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage
III. Undetermined: if there is insufficient information to allow categorization as ischemic or hemorrhagic

Stroke severity

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.

I. **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
II. **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

TIA

Acute episode of a focal or global neurological deficit fulfilling the following criteria:

I. 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
II. 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
III. 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 a neurologist.*

Notes: **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.*
6-Minute Walk Test (6MWT) A submaximal exercise test used to assess aerobic capacity and endurance that entails measurement of distance walked over a span of 6 minutes.

Appendix B: Patient Preference Survey Template

Edwards

Patient Preference Survey – Screening/Baseline

Page **1** of **4**

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Edwards

Patient Preference Survey – Screening/Baseline

Edwards

Patient Preference Survey – Screening/Baseline

Edwards

Patient Preference Survey – Screening/Baseline

[redacted]

Appendix C: Katz Index of Independence in Activities of Daily Living

Katz Index of Independence in Activities of Daily Living

[redacted]

Appendix D: Instructions for 6-Minute Walk Test

[redacted]

Appendix E: Child-Pugh Score

Appendix F: Patient Edema Questionnaire Template

Edwards

Edema Grading – Ankle Measurements – Patient Edema Questionnaire

Page **1** of **2**

[redacted]

Note: Patient Edema Questionnaire on next page.

Edwards

Edema Grading – Ankle Measurements – Patient Edema Questionnaire

[redacted]

Appendix G: Abbreviations

Below is a list of commonly used abbreviations in Transcatheter Tricuspid Clinical Studies

Abbreviation / Acronym	Definition
6MWT	6-Minute Walk Test
6MWD	6-Minute Walk Distance
ACC	American College of Cardiology
ACT	Activated Clotting Time
ADL	Activities of daily living
AE	Adverse Event
AF	Atrial Fibrillation
AHA	American Heart Association
AKI	Acute Kidney Injury
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ASA	Acetylsalicylic acid
ASD	Atrial septal defect
AST	Aspartate aminotransferase
AT	As-Treated
BNP	B-type natriuretic peptide
BP	Blood pressure
BUN	Blood urea nitrogen
CABG	Coronary Artery Bypass Graft
CAVI	Caval valve implantation
CBC	Complete blood count
CE	Conformitè Europëenne
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CI	Confidence interval
CIB	Clinical Investigator's Brochure
CIP	Clinical Investigational Plan
CK	Creatine kinase
CMP	Comprehensive metabolic panel
CMR	Cardiovascular Magnetic Resonance
COPD	Chronic obstructive pulmonary disease
CRF	Case Report Form
CRT	Cardiac resynchronization therapy
CSC	Clinical Screening Committee
CSHA	Canadian Study of Health and Aging (Clinical Frailty Scale)
CT	Computed Tomography

Abbreviation / Acronym	Definition
CTA	Clinical Trial Agreement
CV	Cardiovascular
CWD	Continuous Wave Doppler
DAPT	Dual anti-platelet therapy
DD	Device Deficiency
DOAC	Direct oral anticoagulant
DSMB	Data Safety Monitoring Board
DVT	Deep vein thrombosis
EACTS	European Association for Cardio-Thoracic Surgery
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EF	Ejection Fraction
EFS	Early Feasibility Study
eGFR	Estimated glomerular filtration rate
EROA	Effective regurgitant orifice area
ESC	European Society of Cardiology
FDA	Food and Drug Administration
Fr	French
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
HF	Heart Failure
Hgb	Hemoglobin
hx	History
ICD	Implantable cardioverter-defibrillator
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICM	Implantable cardiac monitor
ICU	Intensive care unit
IFU	Instructions for Use
INR	International normalized ratio
IRB	Institutional Review Board
IVC	Inferior vena cava
ISO	International Standardization Organization
IVC	Inferior vena cava
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAA	Left atrial appendage
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MAE	Major Adverse Event

Abbreviation / Acronym	Definition
MAR	Medication administration record
MCOT	Mobile cardiac outpatient telemetry
MDR	Medical Device Regulation
MI	Myocardial Infarction
MR	Mitral Regurgitation
mRS	Modified Rankin Scale
MSAE	Major Serious Adverse Event
MSCT	Multi-slice computed tomography
MV	Mitral Valve
MVARC	Mitral Valve Academic Research Consortium
MVR	Mitral Valve Replacement
NSAIDs	Nonsteroidal anti-inflammatory drugs
NT-proBNP	N-terminal (NT)-pro hormone BNP
OAC	Oral anticoagulation
OMT	Medical Therapy
OR	Operating room
OUS	Outside the United States
NYHA	New York Heart Association
PA	Pulmonary Artery
PASP	Pulmonary Artery Systolic Pressure
PCW	Pulmonary capillary wedge
PE	Pulmonary embolism
PHTN	Pulmonary hypertension
PISA	Proximal Isovelocity Surface Area
PP	Per-protocol
PPM	Permanent pacemaker
PT	Prothrombin time
PTT	Partial thromboplastin time
PVL	Paravalvular Leak
PVR	Pulmonary vascular resistance
QOL	Quality of Life
RA	Right atrium
RV	Right ventricle
Rvol	Regurgitant volume
RVOT	Right ventricular outflow tract
SAE	Serious Adverse Event
SF-36	Short Form Health Survey
STS	Society of Thoracic Surgeons
SVT	Supraventricular tachycardia
TEE	Transesophageal echocardiography
TIA	Transient Ischemic Attack
TMVr	Transcatheter Mitral Valve Repair
TMVR	Transcatheter Mitral Valve Replacement

Abbreviation / Acronym	Definition
TR	Tricuspid Regurgitation
TTE	Transthoracic Echocardiography
TTVr	Transcatheter tricuspid valve repair
TTVR	Transcatheter tricuspid valve replacement
TV	Tricuspid valve
TVR	Tricuspid valve replacement
UADE	Unanticipated adverse device effect
US	United States
USADE	Unanticipated serious adverse device effect
VC	Vena contracta
VCA	Vena contracta area
VCW	Vena contracta width
VF	Ventricular fibrillation
VKA	Vitamin K antagonist
VT	Ventricular tachycardia