Edwards PASCAL TrAnScatheter Valve RePair System in Tricuspid Regurgitation (CLASP TR) Early Feasibility Study

Short Title: Edwards CLASP TR EFS

Clinical Protocol
(Clinical Investigational Plan)
Study Number: 2018-10
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Effective Date: 12-APR-2019

CONFIDENTIAL

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

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PROTOCOL SYNOPSIS

Study Number	2018-10
Study Version	C
Title	Edwards PASCAL TrAnScatheter Valve RePair System in Tricuspid Regurgitation (CLASP TR) Early Feasibility Study
Short Title	Edwards CLASP TR EFS
Sponsor	Edwards Lifesciences, LLC One Edwards Way Irvine, CA 92614
Sponsor Contact	TMTT Clinical Affairs Edwards Lifesciences, LLC One Edwards Way, Irvine, CA 92614 USA Email: TMTT_Clinical@edwards.com
Device Name	Edwards PASCAL Transcatheter Valve Repair System (hereinafter referred to as "the PASCAL System")
Intended Use	The Edwards PASCAL Transcatheter Valve Repair System (the PASCAL System) is intended for patients with tricuspid regurgitation deemed to be potential candidates for transcatheter tricuspid valve repair with the PASCAL System by the local Heart Team.
Study Objectives	The objectives of this early feasibility study are to: • Evaluate the safety and performance of the PASCAL System • Provide guidance for future clinical study designs utilizing the PASCAL System • Provide guidance for future PASCAL System developments
Study Design	Prospective, single arm, multi-center, early feasibility study (EFS) to evaluate the safety and performance of the PASCAL System in the treatment of symptomatic severe tricuspid regurgitation (TR). Up to 65 patients (pending FDA approval) will be enrolled in this study at up to 30 investigational sites (pending 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, and annually for 5 years post implant procedure.

Feasibility Endpoints	**Safety Endpoint:** Safety will be analyzed as a composite endpoint of Major Adverse Events (MAEs) at 30 days which includes: • Cardiovascular mortality • Myocardial infarction (MI) • Stroke • Renal complications requiring unplanned dialysis or renal replacement therapy • Severe bleeding* • Unplanned or emergency re-intervention (either percutaneous or surgical) related to the device • Major access site and vascular complications requiring intervention **Performance Endpoints:** • **Device success:** device is deployed as intended and the delivery system is successfully retrieved as intended at the time of the patient's exit from the cardiac catheterization laboratory. *Per device analysis.* • **Procedural success:** device success with evidence of a reduction in TR grade by at least one grade[i] (scale: none/trace, mild, moderate, severe, massive, torrential[ii]) at end of procedure, and without the need for a surgical or percutaneous intervention prior to hospital discharge. *Per patient analysis.* • **Clinical success:** procedural success without MAEs at 30 days. *Per patient analysis.* *Severe bleeding includes fatal, life-threatening, extensive, or major bleeding, as defined by MVARC[iii] [see also Appendix A: Study Definitions]

[i] The TR grading scale used to determine procedural success is based on the scale proposed by Hahn and Zamorano (scale: none/trace, mild, moderate, severe, massive, torrential), while patient eligibility is based on the grading scale presented in the current ASE guidelines (Zoghbi et al., JASE 2017).

[ii] Hahn RT, Zamorano JL. The need for a new tricuspid regurgitation grading scheme. *Eur Heart J Cardiovasc Imaging.* 2017;18(12):1342-1343.

[iii] Stone GW, Adams DH, Abraham WT, et al. Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions: A Consensus Document From the Mitral Valve Academic Research Consortium. *J Am Coll Cardiol.* 2015;66(3):308-321.

Echocardiographic, Clinical, and Functional Endpoints and Parameters	**Echocardiographic Endpoint and Parameters:** A. Reduction in TR severity (assessed by TR grade and quantitative measures) as assessed by TEE pre- and post-implant in the procedure room. B. TTE parameters assessed at baseline, discharge, 30 days, 6 months, 1 year, and annually until 5 years post procedure 1. TR grade 2. Vena Contracta (2D) 3. EROA (PISA/2D or 3D/3D color Doppler) 4. Regurgitant volume 5. Tricuspid annular dimensions 6. TV inflow gradient 7. Cardiac output 8. Right ventricle dimensions 9. Right atrium volume 10. Left ventricular Ejection Fraction 11. Inferior Vena Cava dimensions/respiratory variations 12. Hepatic vein flow reversal 13. Pulmonary artery pressure (mean) 14. Right ventricular function **Clinical and Functional Endpoints:** A. All-cause mortality B. Heart failure hospitalizations C. Unplanned or emergency re-intervention (either percutaneous or surgical) related to the device 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. Quality of life and functional status assessed by: 1. NYHA Classification 2. 6-Minute Walk Test (6MWT) 3. KCCQ 4. Short Form Health Survey (SF-36)

Echocardiographic, Clinical, and Functional Endpoints and Parameters (cont.)	**Clinical and Functional Parameters:** 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 D. Electronic Diary (eDiary)[iv]: Administered via a handheld device as follows: 1. Baseline: Question(s) from PROMIS Mood questionnaire, Visual Analog Scale (VAS), and KCCQ-12 will be administered daily for a minimum of 2 weeks before the index procedure and then paused at time of admission for index procedure. 2. Post discharge: Starting post discharge, question(s) will be administered daily for 7 days, every other week, to the 12-month follow-up visit. 3. 12-month follow-up visit: Starting at the 12-month follow-up visit, question(s) will be administered daily for a week, up to 7 days. E. Activity Monitoring[iv]: Administered via a wearable monitor as follows: 1. Baseline: Activity monitoring will occur for a minimum of 2 weeks before the index procedure and then paused at time of admission for index procedure 2. 30 days post discharge 3. 2 weeks at 3 months, 6 months, 9 months, and 12 months post index procedure. F. General Clinical and Laboratory Parameters assessed by: 1. Creatinine, BUN, uric acid, and eGFR 2. Liver Panel (Albumin, Bilirubin, ALP, ALT, AST, GGT) G. Diuretic medications and doses (No change in current or new addition to diuretics are allowed for at least 3 months post procedure unless medically required, i.e. severe hypotension or signs and symptoms of hypervolemia.)

[iv] 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.

Enrollment Criteria (Inclusion)	Patients enrolled must meet **ALL** of the following criteria: 1. Age ≥ 18 years old 2. Symptomatic despite optimal medical therapy per local Heart Team 3. Functional or degenerative TR graded as severe[v] as assessed by the echo core lab 4. The local site Heart Team determines that the patient is appropriate for transcatheter tricuspid valve repair 5. Patient is willing and able to comply with all specified study evaluations and provides written informed consent.
Enrollment Criteria (Exclusion)	Potential patients will be excluded if **ANY** of the following criteria apply: 1. Echocardiographic parameters (any of the following): a. Tricuspid valve anatomy precluding proper device deployment and function, including: i. Evidence of severe calcification in the annulus or subvalvular apparatus ii. Evidence of moderate to severe calcification in the grasping area iii. Excessive chordae structure in the grasping area iv. Presence of perforation in the grasping area v. Leaflet length < 8 mm vi. Septo-lateral coaptation gap > 10 mm vii. Severe leaflet tethering or immobile leaflet b. LVEF < 30% c. Severe right ventricular dysfunction as assessed by the core lab 2. Primary non-degenerative tricuspid disease (e.g. carcinoid, rheumatic, endocarditis, traumatic, pacemaker lead-induced, iatrogenic, tricuspid stenosis)

[v] The TR grading scale used to determine procedural success is based on the scale proposed by Hahn and Zamorano (scale: none/trace, mild, moderate, severe, massive, torrential), while patient eligibility is based on the current ASE guidelines; Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation: A Report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr.* 2017;30(4):303-371.

Enrollment Criteria (Exclusion) (cont.)	3. Previous tricuspid valve repair or replacement that would interfere with placement of PASCAL 4. Presence of trans-tricuspid pacemaker or defibrillator leads which: a. Would prevent proper TR reduction due to interaction of the lead with the leaflets b. Were implanted in the RV within the last 3 months 5. Severe aortic, mitral and/or pulmonic valve stenosis and/or regurgitation 6. Active endocarditis within 3 months of the scheduled implant 7. Hemodynamically significant pericardial effusion 8. Intra-cardiac mass, thrombus, or vegetation 9. Untreated clinically significant coronary artery disease requiring revascularization 10. MI or known unstable angina within 30 days prior to the index procedure 11. Any invasive cardiac procedure within 30 days prior to the index procedure 12. Any cardiac surgery within 3 months prior to procedure 13. Suspicion of pericardial adhesions that may preclude leaflet approximation (e.g. post pericarditis, constrictive pericarditis, calcifications visible on imaging) 14. Hemodynamic instability or on IV inotropes unless part of prehabilitation 15. Severe uncontrolled hypertension (SBP ≥ 180 mmHg and/or DBP ≥ 110 mmHg) 16. Pulmonary systolic pressure > 60 mmHg as assessed by echo core lab 17. Stroke or transient ischemic attack (TIA) within the past 30 days 18. Kidney dysfunction with estimated Glomerular Filtration Rate (eGFR) ≤ 30 mL/min/1.73 m^2 or patient is on chronic dialysis 19. 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) 20. Significant frailty (i.e. Katz Index of Independence in Activities of Daily Living (ADL) ≤ 2) within 3 months of scheduled implant

Enrollment Criteria (Exclusion) (cont.)	21. Continuous home oxygen for primary severe COPD 22. Chronic anemia (Hgb < 9 g/dL) not corrected by transfusion 23. Thrombocytopenia (Platelet count < 100,000/mm^3) or thrombocytosis (Platelet count > 750,000/mm^3) 24. Bleeding disorders or hypercoagulable state 25. Active peptic ulcer or active gastrointestinal (GI) bleeding within 3 months of the scheduled implant 26. Contraindication to anticoagulants or antiplatelet agents 27. Current, or history of IV drug use 28. Pregnant or lactating; or female of childbearing potential with a positive pregnancy test 24 hours before any study-related radiation exposure 29. Patients in whom transesophageal echocardiography is contraindicated. 30. In the opinion of the investigator, access to the femoral vein with a 22 FR guide is deemed not feasible (e.g. IVC filter, DVT, occluded femoral veins). 31. Untreatable hypersensitivity or contraindication to any of the following: a. Aspirin and Clopidogrel and Ticlopidine b. Heparin and Bivalirudin, or Warfarin c. Nitinol Alloys (Nickel and Titanium) d. Contrast media 32. Currently participating in another investigational biologic, drug or device study that has not completed the primary endpoint or that clinically interferes with the endpoints of this study. 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 atrial septal defect, RV dysplasia, and arrhythmogenic RV. 35. Co-morbid condition(s) that, in the opinion of the investigator, could limit the patient's ability to participate in the study, including compliance with follow-up requirements, or that could impact the scientific integrity of the study. 36. Patient is under guardianship.

Echo 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 protocol, which is provided to the sites.
Data Safety Monitoring Board (DSMB)	The DSMB is 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, procedures, and monitoring criteria will be defined in the DSMB Charter.
Clinical Events Committee (CEC)	The CEC is responsible for reviewing and adjudicating specified individual adverse events over the course of the study. CEC activities, including roles and responsibilities, procedures, and definitions will be defined in the CEC Charter.

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 as a result of right ventricular relaxation and descent of the base of the heart resulting in a gradient of pressure from the atrium to the right ventricle (RV), allowing blood to flow through the tricuspid valve, 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 tricuspid valve is unable to form a tight seal in systole (when it should be closed), allowing blood to flow back into the right atrium.

Although TR often accompanies mitral or aortic valve disease, it is initially asymptomatic, traditionally considered less clinically significant, and usually left untreated. Hence, 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.[1] 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.[2] Patients with severe TR usually present with signs or symptoms of right heart failure (HF), including peripheral edema and ascites.[3]

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 functional 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, functional (secondary or non-structural) TR refers to regurgitation occurring in the absence of significant structural disease of the tricuspid valve and/or apparatus. Functional TR is present in approximately 80% of cases of significant TR[3] 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 TV orifice is semilunar and consists of three leaflets (anterior, posterior and septal) inserted into a fibrous annulus. Each leaflet is 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.[4]

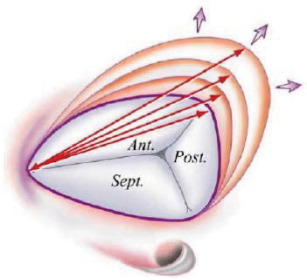


Figure 1. Dilation of the Tricuspid Annulus

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 or RV or LV dysfunction. It has been shown that increasing TR severity is associated with worse survival regardless of left ventricular ejection fraction (LVEF) or pulmonary artery pressure (Figure 2).[2] Severe TR is associated with a poor prognosis, independent of age, biventricular systolic function, RV size, and inferior vena cava (IVC) dilation.[2]

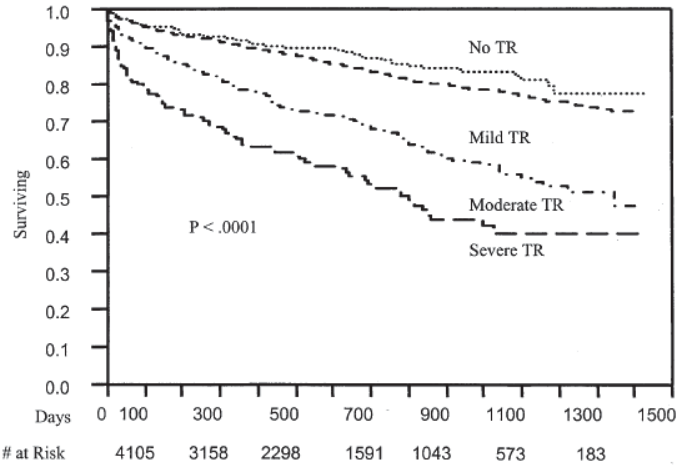


Figure 2. Kaplan-Meier Survival Curves for All Patients with Severe Tricuspid Regurgitation (Nath et al., JACC 2004)

1.1.5 Diagnostic Assessments for Tricuspid Regurgitation

As mentioned before, TR, even severe, can present without symptoms and may be a chance finding during echocardiography. The holosystolic murmur typical of TR can be auscultated on the lower left sternal border and increases during inspiration.[5] When severe, and typically associated with right heart failure, 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.[3] Transesophageal echocardiography (TEE) can be considered when TTE images are suboptimal or in specific cases such as endocarditis or presence of pacemaker leads.[3] Better valve assessment and quantification may be achieved by real-time 3D echocardiography.[6] Cardiovascular magnetic resonance (CMR), 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.[7] The various parameters for grading the severity of chronic TR by echocardiography are presented in Table 1.[8]

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

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

RA, Right atrium. Bolded signs are considered specific for their TR grade.
*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.

An expanded grading scale for determining severity of TR proposed by Hahn is presented in Table 2.[9] The scale further expands severe grade to include massive and torrential.

Table 2. Expanded 5-grade Scale for Determining Severity of TR (Hahn, Eu Heart J Cardiovasc Imag 2017)

Variable	Mild	Moderate	Severe	Massive	Torrential
VC (biplane)	<3 mm	3-6.9 mm	7-13 mm	14-20 mm	≥21 mm
EROA (PISA)	<20 mm^2	20-39 mm^2	40-59 mm^2	60-79 mm^2	≥80 mm^2
3D VCA or quantitative EROA[a]	-	-	75-94 mm^2	95-114 mm^2	≥115 mm^2

VC, vena contracta; EROA, effective regurgitant orifice area; 3D VCA, three-dimensional vena contracta area.
[a]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.[3,10] 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.[11] 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).

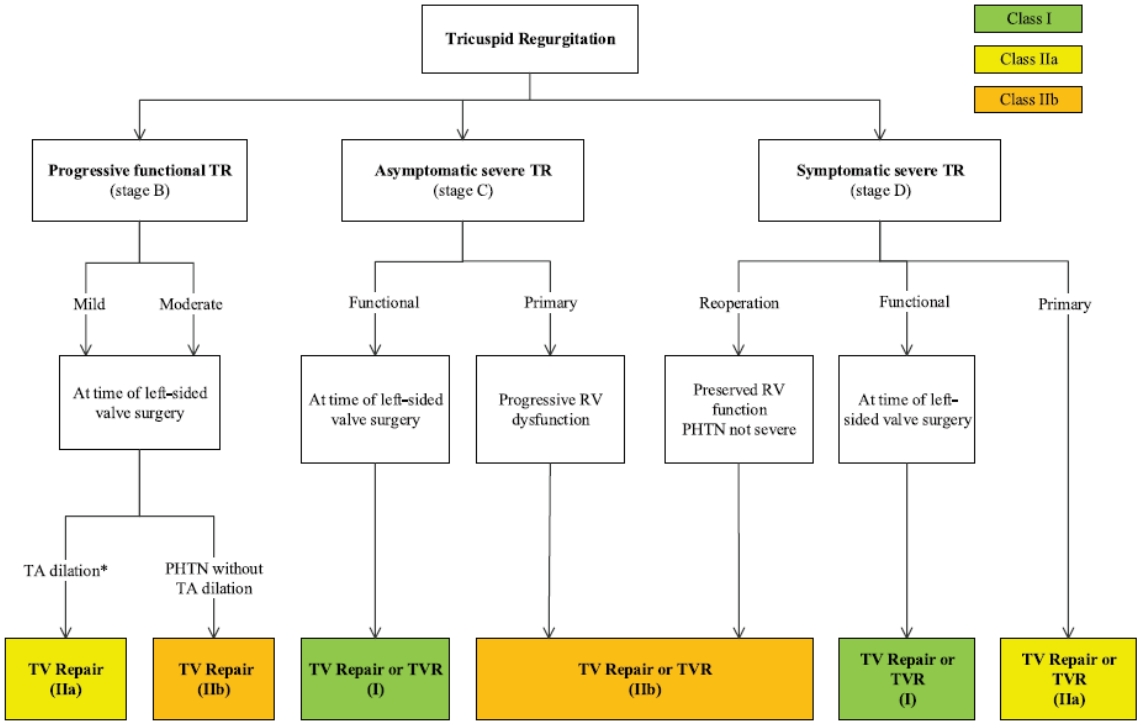
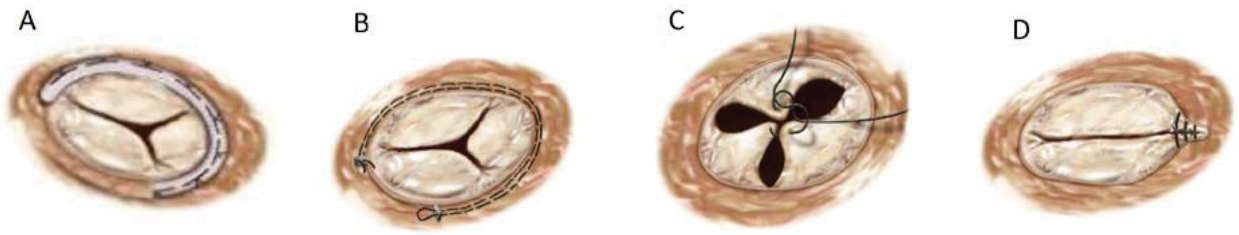


Figure 3. Indication for Surgery According to the 2014 AHA/ACC VHD Guidelines

Left-sided valve surgery and moderate functional TR in the presence of pulmonary hypertension (PHTN) was assigned as a class IIb indication in the AHA guidelines. 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.[3,10]

Although the guidelines have expanded the indications for invasive TR treatment, surgical repair/replacement is uncommonly performed[12] 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.[10,13]

There are four main surgical TV repair techniques[14]: Kay repair, De Vega technique, Clover repair (degenerative) and annuloplasty (Figure 4). The Kay repair is a simple and validated solution in which a bicuspidation 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.[15] 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.[16] 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, B. De-Vega technique, C. Clover repair, D. Kay repair

Figure 4. Tricuspid Surgical Repair Techniques

1.2.3 Transcatheter Methods of Treatment

Medical management is likely to provide only temporary symptom relief. The lack of sustained benefit from medical therapies and the low prevalence of surgery has prompted the search for alternative transcatheter repair and/or replacement therapies.[17,18]

1.2.3.1 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 or limited retrospective clinical series, primarily for valve-in-valve patients[19,20] or patients with rheumatic disease.[21] In addition, the GATE Tricuspid Valved Stent (NaviGate Cardiac Structures, Lake Forest, CA) has been performed in patients under compassionate use and is under investigation.[18]

1.2.3.2 Transcatheter Tricuspid Valve Repair (TTVr)

In the past decade, transcatheter aortic valve replacement (TAVR) has been used successfully in increasing numbers and is considered a treatment option even in moderate risk patients.[22] The success of TAVR stimulated attempts at transcatheter mitral valve replacement (TMVR) to facilitate percutaneous treatment of mitral regurgitation (MR). TMVR has been proven to be far more complex than TAVR. However, there are several transcatheter devices that are approved for transcatheter mitral valve repair (TMVr). The MitraClip System (Abbott Vascular, Santa Clara, CA) is approved for use in the EU (2008) and the U.S. (2013). 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.[23] TMVR devices are also being tested[24] and the field of transcatheter repair and replacement of the mitral valve is expected to grow further in the following years. It is clear, therefore, that the next important step in the field of percutaneous treatment of structural heart disease will focus on the "forgotten", tricuspid valve.

Several transcatheter devices are being investigated for the treatment of TR. The devices that have been developed can be divided according to the therapeutic target as follows: annuloplasty/annular reconstruction devices, coaptation devices, and caval valve implantation (CAVI), and leaflet devices.[17,18]

Annulopasty/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), which received CE mark in April 2018. Data from the TRI-REPAIR study showed that annular reduction provided significant reduction in EROA and was sustained at 6 months. Clinically and statistically significant improvements in functional status (NYHA Class and peripheral edema), quality of life (KCCQ Score) and exercise capacity (6MWD) were observed at 6 months.[25]

Other annuloplasty devices including 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 MIA annuloplasty implant are in the investigational stage.

The Trialign System is a system that mimics the surgical Kay procedure, with the aim of reducing TR by bicuspidization obtained with the plication of the anterior and posterior annulus. Published 30-day follow-up results from the SCOUT trial (NCT02574650) showed that the Trialign device was safe, successfully reduced annular area and regurgitant orifice, and improved left ventricular forward stroke volume.[26]

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).[18]

The TRAIPTA device is an experimental epicardial Nitinol loop placed around the antrioventricular groove providing an external annuloplasty.[27] Currently, a new TRAIPTA device for human testing is under development.[18]

The Millipede IRIS Transcatheter Annuloplasty Ring is a complete simi-rigid annuloplasty ring that is placed in the supra-annular position. It has been used for mitral valve repair and is under investigation.[18]

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.[18]

Coaptation Devices

The FORMA Tricuspid Transcatheter Repair System (Edwards Lifesciences, Irvine, CA) includes a Spacer that is placed in the center of the TV orifice improving leaflet coaptation, thereby aiming to reduce the large regurgitant orifice and decrease TR. One-year follow-up data on 18 patients treated 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.[28] In addition, follow-up data at 24-36 months showed considerable and sustained TR reduction accompanied by significant functional improvement.[29] In the FORMA Early Feasibility Study (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.[30]

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.[31,32] Similarly, the ongoing HOVER trial is assessing heterotopic implantation of the Edwards-Sapien XT valve in the inferior vena cava (NCT02339974).[33] 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), which has been approved for mitral repair has also been used in the tricuspid valve. Edge-to-edge tricuspid valve repair with single or multiple clip(s) has been successfully used for the treatment of TR in selected high-risk patients with malcoaptation of the tricuspid valve.[34-37] In a retrospective analysis of 42 cases treated at a single center in Germany, successful edge-to-edge repair was achieved in 83% (35/42) patients.[36] 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.[37] While several case reports and series

have been published on the use of the MitraClip System in the treatment of TR, it remains under investigation and is being evaluated in the TRILUMINATE study (NCT03227757).

The Edwards PASCAL System 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.[38,39] Evaluation of the PASCAL System in treating patients with TR is warranted and clinical cases have been performed under a compassionate use setting (summarized in section 1.5).

1.3 Intended Use of Device

The Edwards PASCAL System is intended for patients with tricuspid regurgitation deemed to be potential candidates for transcatheter tricuspid valve repair with the PASCAL System by the local Heart Team.

1.4 Prior Testing

A Report of Priors contained in the Clinical Investigator's Brochure (CIB) has been prepared for the PASCAL System. This document provides the prior testing conducted on the system components for pre-clinical testing, in-vivo testing, and biocompatibility testing.

1.5 Prior Clinical Experience With the PASCAL System

1.5.1 [redacted]

[redacted]

[redacted]

2 STUDY DEVICE

[redacted]

[redacted]

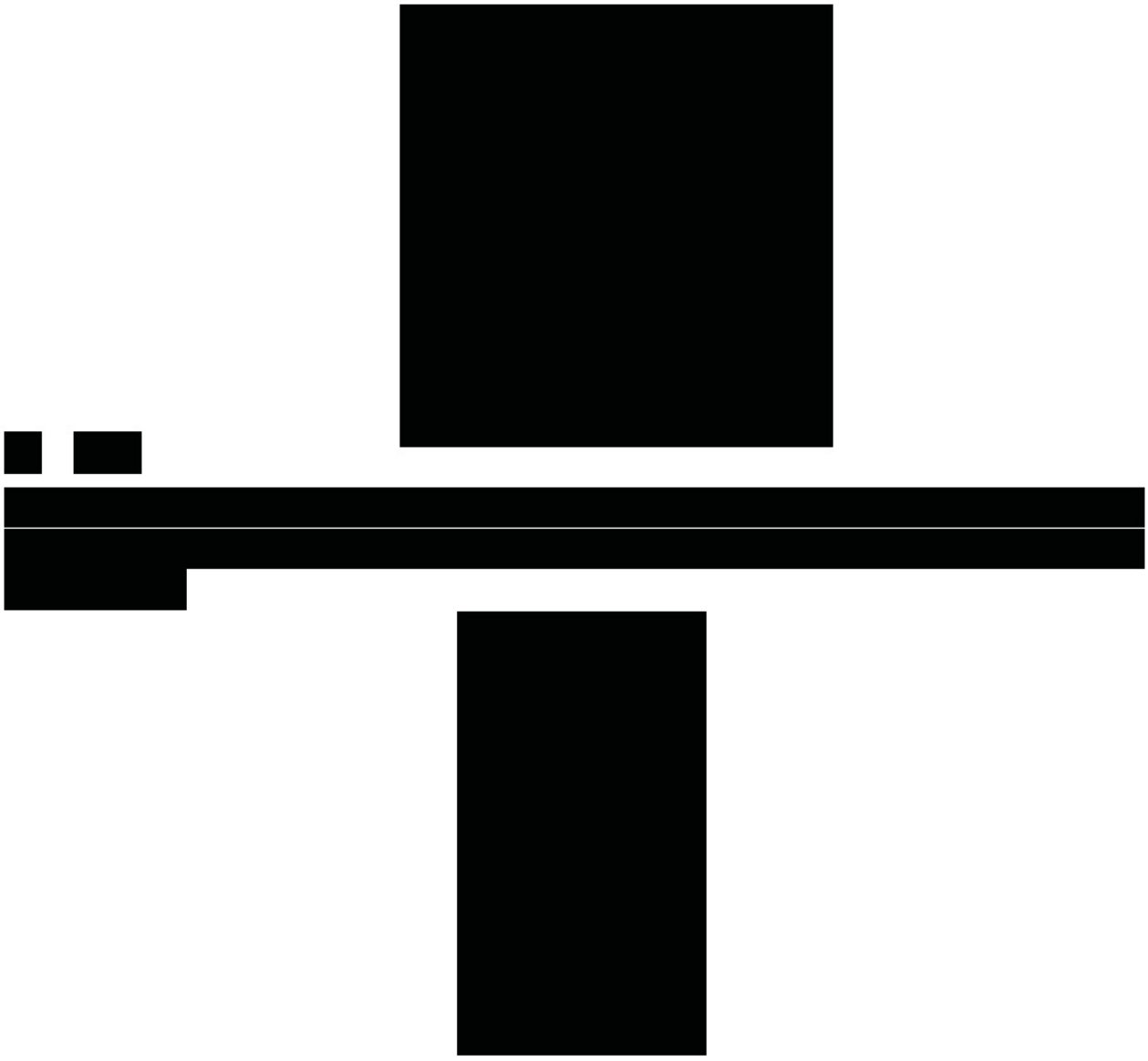
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



3 RISKS AND BENEFITS

The risks to patients receiving the PASCAL System procedure are listed in Section 3.1. The risks of participation are offset by the significant potential in clinical and functional benefits to patients with TR that comes through improving TV function.

3.1 Potential Risks

Adverse events 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 procedures. Complications may occur at any time during the procedure, post-procedure or follow-up period.

Anticipated or potential adverse events that may occur during the study are listed below. These events may be associated with the PASCAL System, transcatheter procedure, diagnostic cardiac tests (e.g. TEE, TTE, MSCT scan, exercise tolerance, etc.), ancillary procedures or may occur in the heart failure population over time. Complications associated with standard cardiac catheterization, the use of anesthesia and use of the PASCAL System could lead to the following outcomes: conversion to open heart surgery, emergent or non-emergent reoperation, explant, permanent disability, or death. There may also be other risks that are unknown at this time.

The following anticipated adverse events have been identified as possible complications of the PASCAL System and procedure:

- Abnormal lab values
- Allergic reaction to anesthetic, contrast, heparin, Nitinol
- Anemia or decreased Hgb, may require transfusion
- Aneurysm or pseudoaneurysm
- Angina or chest pain
- Anaphylactic shock
- Arrhythmias – atrial (i.e. AF, SVT)
- Arrhythmias – ventricular (i.e. VT, VF)
- Arterio-venous fistula
- Atrial septal injury requiring intervention
- Bleeding
- Cardiac arrest
- Cardiac failure
- 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 permanent pacemaker
- Deep vein thrombosis (DVT)
- Deterioration of native valve (e.g. leaflet tearing, retraction, thickening)
- Dislodgement of previously deployed implant
- Dyspnea
- Edema

- Electrolyte imbalance
- Emboli/embolization including air, particulate, calcific material, or thrombus
- Endocarditis
- Esophageal irritation
- Esophageal perforation or stricture
- Exercise intolerance or weakness
- Fever
- Failure to retrieve any PASCAL system components
- Gastrointestinal bleeding or infarct
- Heart failure
- Hematoma
- Hemodynamic compromise
- Hemolysis
- Hemorrhage requiring transfusion or intervention
- Hypertension
- Hypotension
- Implant deterioration (wear, tear, fracture, or other)
- Implant embolization
- Implant malposition or failure to deliver to intended site
- Implant migration
- Implant thrombosis
- Infection
- Inflammation
- LVOT obstruction
- Mesenteric ischemia
- Multi-system organ failure
- Myocardial infarction
- Nausea and/or vomiting
- Nerve injury
- Neurological symptoms, including dyskinesia, without diagnosis of TIA or stroke
- Non-neurological thromboembolic events
- Pain

- Papillary muscle damage
- Paralysis
- PASCAL system component(s) embolization
- Peripheral ischemia
- Pleural effusion
- Pulmonary edema
- Pulmonary embolism
- Reaction to anti-platelet or anticoagulation agents
- Renal failure
- Renal insufficiency
- Respiratory compromise, respiratory failure, atelectasis, pneumonia - may require prolonged ventilation
- Retroperitoneal bleed
- Septal damage or perforation
- Septicemia, sepsis
- Skin burn, injury or tissue changes due to exposure to ionizing radiation
- Single leaflet device attachment (SLDA)
- Syncope
- Stroke
- Transient ischemic attack (TIA)
- Tricuspid valve injury
- Tricuspid valve stenosis
- Urinary tract infection and/or bleeding
- Vascular injury or trauma, including dissection or occlusion
- Valvular regurgitation
- Vessel spasm
- Ventricular wall damage or perforation
- Wound dehiscence, delayed or incomplete healing
- Worsening of heart failure
- Worsening tricuspid regurgitation / valvular insufficiency

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

3.2 Minimization of Risks

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

- Selection of investigators in this study: Interventional Cardiologist – must be board certified (or equivalent), experienced with performing transcatheter heart valve repair and replacement, and skilled in percutaneous coronary interventions and structural heart interventions 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 PASCAL 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).

3.3 Potential Benefits

The potential benefits associated with the use of the PASCAL System are related to eliminating the need for open chest surgery and cardiopulmonary bypass associated with surgical mitral repair/replacement by using a percutaneous approach. The potential benefits to patients are expected to be similar to those of other leaflet repair transcatheter devices. The benefits may include but are not limited to, the following:

- Delay in time to first surgical tricuspid valve replacement/repair and cardiopulmonary bypass
- Elimination of need for surgical tricuspid valve replacement/repair and cardiopulmonary bypass, thus reducing incidence of:
    i. Reoperation due to cardiac complications
    ii. Myocardial infarctions
    iii. Neurological complications (i.e. TIA, stroke)
    iv. Infections
    v. Pulmonary complications (i.e. pulmonary edema) and the need for mechanical ventilation support required after the procedure
    vi. Need for blood transfusions due to bleeding
    vii. Post-procedural arrhythmias
    viii. Pain and complications (i.e. deep wound infection) associated with sternotomy or thoracotomy
    ix. Overall recovery time, including a reduction in the time spent in the intensive care unit
- The ability to reliably assess post-placement tricuspid regurgitation during the valve repair procedure (because the heart has not been arrested)
- Clinical improvement (e.g. NYHA Class, 6 minute walk test)
- Overall advancement of medical and scientific knowledge which may benefit future patients with similar conditions may be gained through this clinical study.
- There may also be other benefits that are unknown at this time

3.4 Justification For Clinical Study

This study, the first with the PASCAL System in the United States, is designed as a prospective, single arm, multi-center, early feasibility study. This study is designed to assess the safety and performance of the PASCAL System in the treatment of TR.

Treatments currently available for this patient population include medical therapy, surgical replacement or repair of the tricuspid valve, and alternative investigational transcatheter tricuspid valve repair systems (e.g. Edwards FORMA or Cardioband, Abbott MitraClip).

4 STUDY OBJECTIVES

The objectives of this early feasibility study are to:

- Evaluate the safety and performance of the PASCAL System
- Provide guidance for future clinical study designs utilizing the PASCAL System
- Provide guidance for future PASCAL System developments

Data collected in this clinical study will include safety and performance of the investigational system, as well as up to 5-year clinical outcomes.

5 FEASIBILITY ENDPOINTS

5.1 Safety Endpoint

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

- Cardiovascular mortality
- Myocardial infarction (MI)
- Stroke
- Renal complications requiring unplanned dialysis or renal replacement therapy
- Severe bleeding*
- Unplanned or emergency re-intervention (either percutaneous or surgical) related to the device
- Major access site and vascular complications requiring intervention

5.2 Performance Endpoints

5.2.1 Device Success

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

* Severe bleeding includes fatal, life-threatening, extensive, or major bleeding, as defined by MVARC [see also Appendix A: Study Definitions]

5.2.2 Procedural Success

Device success with evidence of a reduction in TR grade by at least one grade (scale: none/trace, mild, moderate, severe, massive, torrential[*9]) at end of procedure, and without the need for a surgical or percutaneous intervention prior to hospital discharge. *Per patient analysis.*

5.2.3 Clinical Success

Procedural success without MAEs at 30 days. *Per patient analysis.*

5.3 Echocardiographic, Clinical, and Functional Endpoints and Parameters

5.3.1 Echocardiographic Endpoints and Parameters

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

Additional echocardiographic parameters will be compared to baseline:

B. TTE parameters assessed at baseline, discharge, 30 days, 6 months, 1 year and annually until 5 years post procedure:

1. TR grade
2. Vena Contracta (2D)
3. EROA (PISA/2D or 3D/3D color Doppler)
4. Regurgitant volume
5. Tricuspid annular dimensions
6. TV inflow gradient
7. Cardiac output
8. Right ventricle dimensions
9. Right atrium volume
10. Left ventricular Ejection Fraction
11. Inferior Vena Cava dimensions/respiratory variations
12. Hepatic vein flow reversal
13. Pulmonary artery pressure (mean)
14. Right ventricular function

[*] The TR grading scale used to determine procedural success is based on the scale proposed by Hahn and Zamorano (scale: none/trace, mild, moderate, severe, massive, torrential), while patient eligibility is based on the grading scale presented in the current ASE guidelines (Zoghbi et al., JASE 2017).

5.3.2 Clinical and Functional Endpoints and Parameters

Clinical and Functional Endpoints – assessed at baseline and at various time points, depending on the parameter (see Table 11)

A. All-cause mortality
B. Heart failure hospitalizations
C. Unplanned or emergency re-intervention (either percutaneous or surgical) related to the device
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. Quality of life and functional status assessed by:
    1. NYHA Classification
    2. 6-Minute Walk Test (6MWT)
    3. KCCQ
    4. Short Form Health Survey (SF-36)

Clinical and Functional Parameters

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
D. Electronic Diary (eDiary)*: Administered via a handheld device as follows:
    1. Baseline: Question(s) from PROMIS Mood questionnaire, Visual Analog Scale (VAS), and KCCQ-12 will be administered daily for a minimum of 2 weeks before the index procedure and then paused at time of admission for index procedure.
    2. Post discharge: Starting post discharge, question(s) will be administered daily for 7 days, every other week, to the 12-month follow-up visit.
    3. 12-month follow-up visit: Starting at the 12-month follow-up visit, question(s) will be administered daily for a week, up to 7 days.

* 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.

E. Activity Monitoring*: Administered via a wearable monitor as follows:
    1. Baseline: Activity monitoring will occur for a minimum of 2 weeks before the index procedure and then paused at time of admission for index procedure
    2. 30 days post discharge
    3. 2 weeks at 3 months, 6 months, 9 months, and 12 months post index procedure.
F. General Clinical and Laboratory Parameters assessed by:
    1. Creatinine, BUN, uric acid, and eGFR
    2. Liver Panel (Albumin, Bilirubin, ALP, ALT, AST, GGT)
G. Diuretic medications and doses (No change in current or new addition to diuretics are allowed for at least 3 months post procedure unless medically required, i.e. severe hypotension, or signs and symptoms of hypervolemia.)

5.3.3 Additional Safety Assessments

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

6 STUDY DESIGN

This is a prospective, single arm, multi-center, early feasibility study designed to evaluate the safety and performance of the PASCAL System in the treatment of symptomatic severe tricuspid regurgitation (TR).

Up to 65 patients (pending FDA approval) will be enrolled in the study at up to 30 investigational sites (pending FDA approval) in the US. All enrolled study patients will be assessed for clinical follow-up at the following intervals: discharge, 30 days, 6 months, 1 year, and annually for 5 years post implant procedure.

A description of each study visit and required study procedures are included in Section 8, Procedures and Methods. In addition, a summary of required procedures is listed in Table 11.

7 PATIENT POPULATION

7.1 Demographic and Clinical Characterisitics

This clinical study is for adult patients with symptomatic severe tricuspid regurgitation who are deemed to be appropriate potential candidates for transcatheter tricuspid repair with the PASCAL System as assessed by the Heart Team.

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 PASCAL device in the treatment of patients with severe TR was 78 ± 5 years, and we expect that this EFS will enroll patients with the same baseline characteristics. Additionally, patients that received the Edwards Cardioband Tricuspid Valve Reconstruction System as part of the European TRI-REPAIR study were on average 75.6 ± 6 years of age. Although those patients were not treated with the Edwards PASCAL System, we expect that this EFS will enroll patients with similar baseline characteristics as those studied under the TRI-REPAIR protocol, as well. 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.

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

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

7.2 Inclusion Criteria

Patients enrolled must meet ALL of the following criteria:

1. Age ≥ 18 years old
2. Symptomatic despite optimal medical therapy per local Heart Team
3. Functional or degenerative TR graded as severe* as assessed by the echo core lab
4. The local site Heart Team determines that the patient is appropriate for transcatheter tricuspid valve repair
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:

1. Echocardiographic parameters (any of the following):
    a. Tricuspid valve anatomy precluding proper device deployment and function, including:

* The TR grading scale used to determine procedural success is based on the scale proposed by Hahn and Zamorano (scale: none/trace, mild, moderate, severe, massive, torrential), while patient eligibility is based on the grading scale presented in the current ASE guidelines (Zoghbi et al., JASE 2017).

   i. Evidence of severe calcification in the annulus or subvalvular apparatus
   ii. Evidence of moderate to severe calcification in the grasping area
   iii. Excessive chordae structure in the grasping area
   iv. Presence of perforation in the grasping area
   v. Leaflet length < 8 mm
   vi. Septo-lateral coaptation gap > 10 mm
   vii. Severe leaflet tethering or immobile leaflet
   b. LVEF < 30%
   c. Severe right ventricular dysfunction as assessed by the core lab
2. Primary non-degenerative tricuspid disease (e.g. carcinoid, rheumatic, endocarditis, traumatic, pacemaker lead-induced, iatrogenic, tricuspid stenosis)
3. Previous tricuspid valve repair or replacement that would interfere with placement of PASCAL.
4. Presence of trans-tricuspid pacemaker or defibrillator leads which:
   a. Would prevent proper TR reduction due to interaction of the lead with the leaflets
   b. Were implanted in the RV within the last 3 months
5. Severe aortic, mitral and/or pulmonic valve stenosis and/or regurgitation
6. Active endocarditis within 3 months of the scheduled implant
7. Hemodynamically significant pericardial effusion
8. Intra-cardiac mass, thrombus, or vegetation
9. Untreated clinically significant coronary artery disease requiring revascularization
10. MI or known unstable angina within 30 days prior to the index procedure
11. Any invasive cardiac procedure within 30 days prior to the index procedure
12. Any cardiac surgery within 3 months prior to procedure
13. Suspicion of pericardial adhesions that may preclude leaflet approximation (e.g. post pericarditis, constrictive pericarditis, calcifications visible on imaging)
14. Hemodynamic instability or on IV inotropes unless part of prehabilitation
15. Severe uncontrolled hypertension (SBP ≥ 180 mmHg and/or DBP ≥ 110 mmHg)
16. Pulmonary systolic pressure > 60 mmHg as assessed by echo core lab
17. Stroke or transient ischemic attack (TIA) within the past 30 days
18. Kidney dysfunction with estimated Glomerular Filtration Rate (eGFR) ≤ 30 mL/min/1.73 m^2 or patient is on chronic dialysis

19. 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)
20. Significant frailty (i.e. Katz Index of Independence in Activities of Daily Living (ADL) ≤ 2) within 3 months of scheduled implant
21. Continuous home oxygen for primary severe COPD
22. Chronic anemia (Hgb < 9 g/dL) not corrected by transfusion
23. Thrombocytopenia (Platelet count < 100,000/mm^3) or thrombocytosis (Platelet count > 750,000/mm^3)
24. Bleeding disorders or hypercoagulable state
25. Active peptic ulcer or active gastrointestinal (GI) bleeding within 3 months of the scheduled implant
26. Contraindication to anticoagulants or antiplatelet agents
27. Current, or history of, IV drug use
28. Pregnant or lactating; or female of childbearing potential with a positive pregnancy test 24 hours before any study-related radiation exposure
29. Patients in whom transesophageal echocardiography is contraindicated.
30. In the opinion of the investigator, access to the femoral vein with a 22 FR guide is deemed not feasible (e.g. IVC filter, DVT, occluded femoral veins).
31. Untreatable hypersensitivity or contraindication to any of the following:
    a. Aspirin and Clopidogrel and Ticlopidine
    b. Heparin and Bivalirudin, or Warfarin
    c. Nitinol Alloys (Nickel and Titanium)
    d. Contrast media
32. Currently participating in another investigational biologic, drug or device study that has not completed the primary endpoint or that clinically interferes with the endpoints of this study.
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 atrial septal defect, RV dysplasia, and arrhythmogenic RV.
35. Co-morbid condition(s) that, in the opinion of the investigator, could limit the patient's ability to participate in the study, including compliance with follow-up requirements, or that could impact the scientific integrity of the study.
36. Patient is under guardianship.

7.4 Study Exit Criteria and Procedures

The reason for study exit will be documented on the appropriate case report forms and in the medical records for each patient who exits the study.

Patients may exit the study for any of the following reasons:

- Screen Failure
- Study Device Attempted But Not Implanted
    - Enrolled patients for whom the implant procedure was prematurely aborted (e.g., entered procedure room and anesthesia induced, but study procedure not attempted (i.e. skin incision to introduce the PASCAL System) or TTVr procedure attempted but did not receive a study device, will be followed for 30 days for safety evaluations only or until resolution of any adverse events related to the implant procedure and then exited from the study.
- Study Device Re-intervention/Explant
    - Patients who have a surgical re-intervention where the device is explanted will be followed for 30 days post-re-intervention for safety evaluations only or until resolution of any adverse events related to the re-intervention and then exited from the study. Patients who have a percutaneous re-intervention where the study device remains in place will continue to be followed for the duration of the study.
- Completion per Protocol
- Withdrawal
    - Patient Withdrawal: The patient may voluntarily withdraw from the clinical study at any time, without penalty or loss of benefits to which they are otherwise entitled.
    - Physician Withdrawal: The 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.
- Death
- Lost to Follow-up
    - If a patient cannot be reached for a follow-up visit, the Investigator will document the contact efforts made to the patient and/or effort to obtain hospital records in the appropriate electronic case report form. If the patient cannot be reached in any way, or misses a visit, the patient will be considered "unable to contact" for that time interval. After three (3) documented unsuccessful attempts to make contact prove unsuccessful, a certified letter will

be sent to the patient's residence. If there is no response after the certified letter is sent, the patient will be considered "lost to follow-up".

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

- In all cases of withdrawal (as described above), withdrawn patients will not undergo further study follow-up procedures after the time of study exit. A study patient who has been withdrawn from the study will not be replaced.
- All data collected up until the time of withdrawal, including imaging studies such as echocardiography scans, will be analyzed in encrypted form and will be kept in encrypted form for the entire duration of the study.

8 PROCEDURES AND METHODS

8.1 Site Personnel Training

To ensure proper device usage, uniform data collection and protocol compliance training is required for relevant study site personnel in accordance with the roles outlined in the Individual Delegation of Authority Log.

At the beginning of the study, the Sponsor will provide training to site personnel. Training will include the Instructions for Use (IFU) of the device, study protocol, case review process, identification of eligible patients, instructions on data collection, standardized data collection for core laboratory analysis, methods for soliciting data from alternative sources and regulatory requirements.

Ongoing training may be provided in one of the following formats by the Sponsor or its designee: live training sessions, teleconference, WebEx, online or read and review. Retraining may be performed for sites who have demonstrated protocol or implant procedure compliance issues.

Documentation of site personnel qualifications and training should be maintained in the site's clinical study files and copies collected and forwarded to the Sponsor.

8.2 Device and Procedure Training

Investigators performing the implant procedure will receive device training, prior to patient enrollment that includes:

- Didactic session – presentations outlining the functionality of the device and all procedural steps with an in-depth discussion on the unique aspects of the system.
- Hands on session – bench-top simulator deployments providing a simulated clinical experience.

The Investigator formal training will be performed by the Study Sponsor prior to patient enrollment at the study site.

Sponsor or affiliated personnel shall be available to assist with the technical aspects of the device/procedure. Training will be documented.

8.3 Informed Consent

The 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 by providing them an overview of the study including the background, risks, benefits and study procedures. If patients are interested in participating in the study, the patient will sign the Institutional Review Board (IRB) approved informed consent form (ICF) prior to any study-specific procedures being performed.

The Sponsor must approve any modifications to the ICF prior to submission to the IRB, and/or FDA (as required). A sample ICF is provided in *Appendix D: Sample Informed Consent Form*.

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

The ICF will be written in the native language of the patient and administered only by the Investigator or IRB-approved personnel who speaks the native language of the patient. 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 Patient Enrollment

A Screening/Enrollment Log will be maintained to document the screening and enrollment of all patients assessed for study participation. The screening of patients qualifying for this study should be such that all patients are offered the possibility of participating and are therefore evaluated according to the selection criteria defined in this protocol. Patients who are consented to participate in the study, but do not fulfill enrollment criteria, will be considered "screen failures" and will not count towards the overall enrollment cap. The reason for "screen failure" will be documented.

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.

Patients will be considered "provisionally enrolled" when they have signed the ICF agreeing to participate in the study and have been deemed eligible for study participation by meeting the study criteria (Sections 7.2 and 7.3).

A patient will be considered "enrolled" at the time of skin incision to introduce the PASCAL System into the body.

8.5 Imaging Assessments

Imaging assessments (TTE, TEE) shall be performed according to the current version of the core lab echocardiographic acquisition protocol.

8.6 Screening/Baseline Assessments

The following procedures and measurements will be performed during this visit (Table 4; refer to Table 5 for assessment windows):

Table 4. Screening/Baseline

General Information	Clinical Information	Laboratory Measurements**
• Informed consent • Inclusion/exclusion and other screening evaluation • Demographics	• Medical history (e.g., co-morbidities, EuroSCORE, STS score (MV Repair), prior cardiovascular interventions / surgeries, paracentesis procedures) • Clinical Evaluation/Prior Recent Hospitalizations • Complete physical exam, lower limb edema grading (+1-+4), and ankle circumference measurements • Concomitant Medication (including diuretic dose/s) • Safety Evaluation and Adverse Events Assessments • Modified Rankin Scale* • Patient Edema Questionnaire • NYHA Classification • TTE and TEE • 12-lead ECG • 6MWT results • Health outcome questionnaires - KCCQ, SF-36 • Patient preference survey • Katz Index of Independence in Activities of Daily Living (Katz ADL) • Canadian Study of Health and Aging Survey Clinical Frailty Scale • eDiary collection®† • Activity monitoring†	• βHCG, for females of childbearing potential only • Complete blood count/ platelets • Complete metabolic panel • Coagulation panel (PT or PTT; INR for patients on vitamin-K antagonist) • Liver panel (Albumin, Bilirubin, ALP, ALT, AST, GGT) • Serum creatinine, BUN, uric acid, and eGFR • Troponin or CK/CK-MB (according to site standard practice)

* 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.[44,45]

** Repeated peri-procedurally per local institutional standard of care

† Initiation at baseline visit for a minimum of 2 weeks before the index procedure

Table 5. Screening/Baseline Assessment Windows

General Information	Window
TTE*	Within 60 days of submission to image transfer system
TEE**	Within 90 days of submission to image transfer system
eDiary Collection	A minimum of 2 weeks prior to index procedure
Activity Monitoring Initiation	A minimum of 2 weeks prior to index procedure
* TTE must be conducted after informed consent and must be collected according to echo core lab acquisition protocol. **Pre-existing TEE of adequate quality capturing required anatomy for assessment can be used. Note: For all imaging (TTE, TEE), if imaging is deemed incomplete or inadequate for assessment, repeat imaging may be required. Note: Procedure should be scheduled within 90 days of consent.	

8.7 Recommended Antiplatelet / Anticoagulation Therapy

Short-term antiplatelet (81 mg aspirin/30 days) therapy is recommended after PASCAL implantation. Anticoagulation and other medical therapy should be used as needed for other patient indications. Patients already on anticoagulants for other indications do not need the addition of antiplatelet therapy.

To avoid thrombus formation, patients should be heparinized sufficiently to maintain an Activated Clotting Time (ACT) of at least 250 seconds throughout the procedure.

8.8 Implantation Procedure

Refer to the current IFU version for detailed information on the use of the PASCAL System. Delivery of the implant should be performed under general anesthesia with hemodynamic monitoring in an operating room, catheterization lab, or hybrid operating room with fluoroscopic and echocardiographic imaging capabilities. The use of cardiopulmonary bypass is not required.

The implant procedure should be scheduled within 90 days of the informed consent being signed. The date of the implant procedure will be considered as Day 0 for the purpose of determining specified time intervals for the follow up visit.

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 6):

Table 6. Procedure Information

General Information	Clinical Information	Laboratory Measurements
• Date of study procedure • Patient identification number • Name of implanting physicians • Access site • Timing of implant procedures • Study device identification & disposition	• 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 sheath and PASP using echo • TEE measurements pre- and immediately post-procedure* • Procedural fluoroscopic imaging • Fluoroscopy duration & contrast volume • Safety Evaluation and Adverse Events Assessments • Device malfunction • 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.	• Heparin administration to achieve (and maintain) an ACT of ≥ 250 sec during the implant procedure
*Optional adjunct imaging (e.g. ICE) during the procedure may be performed.		

8.8.1 Device Preparation

A description of device preparation and use is provided in the IFU (see Report of Priors/Clinical Investigator's Brochure). Investigators must be familiar with the information described in the IFU prior to use of the PASCAL System.

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

8.8.2 Antibiotic Prophylaxis

All recipients will be prophylactically treated for endocarditis to minimize the possibility of infection.

8.8.3 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.

8.9 Post-Procedure/Pre-Discharge (12-24 Hours)

The following study procedures/data collection will be performed 12-24 hours post implant procedure (Table 7):

Table 7. Post Procedure/Pre-Discharge

General Information	Clinical Information	Laboratory Measurements**
• N/A	• Complete physical examination • 12-lead ECG • Concomitant Medication • Safety Evaluation and Adverse Events Assessments	• Complete blood count/platelets • Complete metabolic panel • Coagulation panel (PT or PTT; INR for patients on vitamin-K antagonist) • Liver panel (Albumin, Bilirubin, ALP, ALT, AST, GGT) • Serum Creatinine, BUN, uric acid, and eGFR • Troponin or CK/CK-MB (according to site standard practice)
**Within 12-24 hours post-implant		

8.10 Discharge

The following study procedures will be performed at discharge or at 7 days post-procedure, whichever comes first (Table 8):

Table 8. Discharge/7 Days Post-procedure

General Information	Clinical Information	Laboratory Measurements
• Discharge date	• Complete physical exam • Concomitant Medication including diuretic dose/s* • Safety Evaluation and Adverse Events assessments • Modified Rankin Scale** • TTE • 12-lead ECG • eDiary collection will resume for 1 year after discharge. Starting post discharge, question(s) will be administered daily for 7 days, every other week, to the 12-month follow-up visit. • Activity Monitoring will resume at discharge for a duration of 30 days. The patient will be discharged wearing the activity monitoring device.	• Complete blood count/ platelets • Complete metabolic panel • Coagulation panel (PT or PTT; INR for patients on vitamin-K antagonist) • Liver panel (Albumin, Bilirubin, ALP, ALT, AST, GGT) • Serum Creatinine, BUN, uric acid, and eGFR • Troponin or CK/CK-MB (according to site standard practice)

*No change in current or new addition to diuretics are allowed for at least 3 months post procedure unless medically required, i.e. severe hypotension, or signs and symptoms of hypervolemia.
**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.[44,45]

8.11 Follow-up Evaluations

Follow-up visits will be conducted at 30 days, 6 months, 1 year and annually thereafter for 5 years.

The following procedures will be conducted during follow up visits (Table 9):

Table 9. Follow-Up Evaluations

General Information	Clinical Information	Laboratory Measurements
• N/A	• Medical history since last visit • Clinical Evaluation/Prior Recent Hospitalizations • Complete physical examination, lower limb edema grading (+1-+4), ankle circumference measurements • Concomitant Medications (including diuretic dose/s) • Safety Evaluation and Adverse Events assessments • Modified Rankin Scale* • Patient Edema Questionnaire • NYHA Classification • TTE • 12-lead ECG • 6MWT (through 1 year) • KCCQ, SF-36 (through 1 year) • eDiary collection** • Activity Monitoring†	• Complete blood count • Complete metabolic panel • Coagulation panel (PT or PTT; INR for patients on vitamin-K antagonist) • Liver panel (Albumin, Bilirubin, ALP, ALT, AST, GGT) • Serum creatinine, BUN, uric acid, and eGFR

*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.[44,45]

** Starting post discharge, question(s) from PROMIS Mood questionnaire, Visual Analog Scale (VAS), and KCCQ-12 will be administered daily for 7 days, every other week, to the 12-month follow-up visit. Then starting at the 12-month visit, question(s) will be administered daily for a week, up to 7 days. The eDiary collection device will be returned after the 7 days.

† Activity monitoring will be administered via a wearable monitor post discharge for 30 days, and will continue for 2 weeks at 3 months, 6 months, 9 months, and 12 months post index procedure.

Table 10. 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)	± 30 days
Annually (365 days) up to 5 years	± 45 days

8.12 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.

8.13 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.

8.14 Study Patient Completion

Patients complete and exit the study when no additional follow-up visits, procedures, or data collection as described in section 7.4 are required. Patients will then continue to be followed by their primary health care provider as required.

8.15 Study Termination and Close-Out

The Investigator will be notified in writing upon termination/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 as per protocol requirements.

8.16 Schedule of Assessments

Table 11. Schedule of Assessments

Test/ Assessment	Screening/ Baseline[1]	Index Procedure[2] (Day 0)	Post- Procedure (12-24 hours)	Discharge (or day 7, whichever is earlier)	30 Day F/U (± 7 days)	6 month F/U (± 30 days)	1 Year F/U (± 45 days)	2, 3, 4, 5 Year F/U (± 45 days)
Study Visit Number	**1/2**	**3**	**4**	**5**	**6**	**7**	**8**	**9-12**
Informed Consent	X							
Demographics and Medical History	X							
Clinical Evaluation/Prior or Recent Hospitalizations	X		X	X	X	X	X	X
Medications (including diuretic doses)[3]	X		X	X	X	X	X	X
Complete Physical Exam	X		X	X	X	X	X	X
Lower limb edema grading (+1-+4)	X				X	X	X	X
Ankle circumference measurements	X				X	X	X	X
Patient Edema Questionnaire	X				X	X	X	X
Clinical Frailty Scale®, Katz ADL	X							
Patient Preference Survey	X							
eDiary Collection[4]	X	X		X	X	X	X	
Activity Monitoring[5]	X	X		X	X	X	X	
NYHA Class Assessment	X				X	X	X	X
Modified Rankin Scale[6]	X			X	X	X	X	X
Six Minute Walk Test	X				X	X	X	
KCCQ	X				X	X	X	
SF-36	X				X	X	X	
Complete Blood Count, Platelet Count	X		X	X	X	X	X	X
Serum Creatinine, BUN, Uric Acid, and eGFR	X		X	X	X	X	X	X
Complete Metabolic Panel and Liver Panel (Albumin, Bilirubin, ALP, ALT, AST, GGT)	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
Troponin or CK-MB	X		X	X				
βHCG (if applicable)	X							

Test/ Assessment	Screening/ Baseline[1]	Index Procedure[2] (Day 0)	Post- Procedure (12-24 hours)	Discharge (or day 7, whichever is earlier)	30 Day F/U (± 7 days)	6 month F/U (± 30 days)	1 Year F/U (± 45 days)	2, 3, 4, 5 Year F/U (± 45 days)
Standard 12-Lead ECG	X		X	X	X	X	X	X
Safety Evaluation and Adverse Events	X	X	X	X	X	X	X	X
Transthoracic Echocardiogram (TTE)	X			X	X	X	X	X
Transesophageal Echocardiogram (TEE)[7]	X	X (pre procedure and at completion of implant procedure)						
Fluoroscopic Imaging		X						
Right heart pressure measurements[8]		X (pre procedure and at completion of implant procedure)						

1. Refer to Table 5 for assessment windows
2. 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 PASCAL 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.
3. No change in current or new addition to diuretics are allowed for at least 3 months post procedure unless medically required, i.e. severe hypotension, or signs and symptoms of hypervolemia.
4. eDiary collection via a handheld device: Question(s) from PROMIS Mood questionnaire, Visual Analog Scale (VAS), and KCCQ-12 will be administered daily for 2 weeks before index procedure and then paused at time of admission for index procedure; Starting post discharge, question(s) will be administered daily for 7 days, every other week, to the 12-month follow-up visit. Then starting at the 12-month visit, question(s) will be administered daily for a week, up to 7 days. The eDiary collection device will be returned after the 7 days.
5. Activity monitoring will be administered via a wearable monitor for a duration of 2 weeks before index procedure and then paused at time of admission for index procedure, and will be resumed post discharge for 30 days, and will continue for 2 weeks at 3 months, 6 months, 9 months, and 12 months post index procedure.
6. mRS will be conducted at baseline for all patients with a history of stroke. For patients who experience a stroke during the study, mRS will be conducted closest to 90 days post event. It is recognized that an assessment of stroke is incomplete without an appropriate measurement of the disability resulting from the stroke, hence, mRS closest to 90 days post event will be used to assess clinical disability. 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.
7. Optional adjunct imaging (e.g. ICE) during the procedure may be performed
8. 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 sheath and PASP using echo.

9 DEVICE MANAGEMENT

9.1 Device Shipment

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

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

9.2 Inventory and Accountability Records

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

9.4 Device Return

The Investigator will receive instructions from the Sponsor on the return process (e.g. Sponsor request, study is terminated, or product expiration, etc.). All investigational devices must be returned to Edwards Lifesciences and the date of return must be recorded on the log. All unused devices in original package and/or those in opened packages as well as those removed from the

original package will be returned upon receipt of this notice. The Investigator's copy of the Device Accountability log must document any unused devices that have been returned.

Used devices may be handled and disposed of in the same manner as hospital waste and bio-hazardous materials in accordance with local regulations. There are no special risks related to the disposal of these devices. All returns and dispositions of devices will be captured on the Device Accountability Log.

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 Case Report Forms (CRFs)

Electronic case report forms (eCRFs) will be used to collect patient data during the study. The Investigator, or an individual 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 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 or withdrawal of consent).

11.1 Definitions

11.1.1 Adverse Event

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in patients, users, or other persons, whether or not related to the investigational medical device.

11.1.2 Serious Adverse Event

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

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is an important medical event which may jeopardize the patient, and may require medical or surgical intervention to prevent one of the above outcomes

A planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigation plan (CIP), without a serious deterioration in health, is not considered a serious adverse event.

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 (UADE)

Unanticipated adverse device effect (UADE) 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.

11.2 AE Reporting Requirements

The Investigator will report all adverse events to the Sponsor as soon as possible, but no later than 10 working days after the Investigator first learns of the event.

Each adverse event 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.

At the time of initial notification, the following minimal information must be provided:

- Study site number
- Patient ID number
- Site's awareness date
- AE description
- Causal relationship to device and implant procedure, if known

The site will provide the Sponsor copies of relevant supporting source documentation (e.g. admission H&P, implant procedure report, discharge summary, echocardiogram and laboratory results) for all adverse events requiring CEC adjudication (at a minimum, safety endpoints) and those events determined by the Sponsor to require additional investigation.

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

The Investigator will inform their IRB and FDA of adverse events 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 requiring reporting to the Sponsor. These findings are normally expected to occur in association with treatment of tricuspid regurgitation, and/or are associated with customary, standard care of patients undergoing 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 without signs or symptoms of infection).

- Low grade temperature increase without signs and symptoms of infection
- Minor, localized tenderness, swelling, induration, oozing, etc. at access site(s)
- Sinus bradycardia or tachycardia that does not require treatment or intervention
- Systolic or diastolic blood pressure changes that do not require treatment or intervention
- The need for insulin in a diabetic patient in the post op period

This list of findings is intended to provide guidance to the study sites for the purpose of adverse event 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 reported prior to patient enrollment will not be recorded as an AE. In the event there is a worsening in the pre-existing medical condition or symptoms due to the device, implant procedure, or study-related procedures, 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 adverse event 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 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:** 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

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 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 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 study 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.

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).

11.7 Sponsor Assessment and Reporting

The Sponsor is responsible for the classification and reporting of adverse events and ongoing safety evaluation of the clinical investigation in accordance with 21 CFR 812.

All AEs will be reviewed by the Sponsor's Clinical Safety department. Each AE will be assessed for seriousness, device and procedure relatedness, and whether it was anticipated or not anticipated (based on the list of potential risks provided in section 3.1). In case of disagreement between the Sponsor or CEC and the Investigator, the Sponsor will communicate both opinions to concerned parties, as necessary.

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 unanticipated adverse device effect (UADE) to FDA as soon as possible, but no later than 10 working days after first receiving notice of the effect.

11.8 Investigational Device Explants

An Edwards' study device that is explanted at any time with an allegation of device malfunction or deficiency, should be returned to the Sponsor for evaluation. All other explants should be discarded.

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. Patients will then be exited from the study once AE(s) resolved or 180 days post-explant, whichever comes first. Return kits for explanted devices will be provided upon request by the clinical monitor or study team.

11.9 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.

12 STATISTICAL ANALYSIS

12.1 Sample Size

This clinical study will enroll up to 65 patients (pending FDA approval). [redacted]

12.2 Analysis Populations

12.2.1 Intention-to-Treat (ITT) Population

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

The ITT population will be used for performance endpoints and safety analysis.

12.2.2 As-Treated (Implanted) Population

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

The as-treated (implanted) population will be the primary analysis population for performance and additional safety assessment.

12.2.3 Per-protocol (PP) Population

The per-protocol (PP) population is a subset of as-treated (implanted) population in whom there are no major inclusion/exclusion criteria-related deviations.

Additional analyses of performance and safety data using the PP population will be performed if there is a clinically meaningful difference from the as-treated population.

12.3 Statistical Analysis

Descriptive analyses will be performed for all study endpoints and parameters.

For continuous variables, data will be summarized using the number of observations, mean, median, standard deviation, minimum, maximum, and 95% confidence intervals (based on normal distribution). Nonparametric techniques may be used if the data does not meet the assumptions of parametric tests.

For categorical variables, data will be summarized using the number of observations, percentages, and 95% confidence intervals.

For time-to-event variables, survival analysis will be used to analyze the data. Summary data including the number of patients at risk and number of patients with the event will be provided. Patients without events will be censored at their last known event-free time point. Time to first event curves will be constructed using Kaplan-Meier estimates.

For selected variables, in addition to descriptive summary statistics at each follow-up assessment, change from baseline to subsequent time point will be summarized. Paired (i.e., patients with available data at both baseline and respective time point) and unpaired data will be presented separately for selected variables. In general, patients with missing baseline or following-up values will be excluded from the analysis unless otherwise specified.

12.4 Safety and Performance Endpoint Analysis

12.4.1 Safety Endpoints

The safety endpoint for this clinical study is a composite endpoint of Major Adverse Events (MAEs) at 30 days. No hypothesis testing will be performed for this endpoint. MAE endpoint and its components will be summarized by counts, percentage and 95% Confidence Interval (CI) of the percentage. CEC-adjudicated data will be used in the analysis.

12.4.2 Performance Endpoints

All performance endpoints will be summarized by counts and percentages.

The device success endpoint will be evaluated on a per device basis.

The procedure and clinical endpoints will be evaluated on a per patient analysis.

12.5 Analysis of Other Endpoints and Parameters

Echocardiographic data will be evaluated by a core laboratory. The change from baseline for selected TTE and TEE parameters will be summarized for each of the pre-specified follow-up time points.

All-cause mortality rates will be computed using binary proportion or Kaplan-Meier method.

Heart failure re-hospitalization rates, unplanned or emergency re-intervention (either percutaneous or surgical) rates related to the device, and composite of MAEs at pre-specified follow-up periods will be summarized with counts and percentages.

Change from baseline in NYHA Functional Classification and Edema assessment will be presented as shift from baseline for each of the pre-specified follow-up periods.

For other continuous endpoints and parameters, change from baseline at pre-specified follow-up time points will be summarized by mean and standard deviation. For other categorical endpoints and parameters, summary statistics including number of observations, percentage, and 95% confidence intervals will be provided.

12.6 Additional Safety Analysis

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

12.7 Treatment of Missing or Spurious Data

Unless otherwise specified, all analysis will be based on available data only.

12.8 Analysis Software

Unless otherwise specified, all analyses will be performed using SAS®, version 9.4 or later.

13 MONITORING

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

The clinical contact on behalf of the Sponsor will be:

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.

A study monitor will be assigned to monitor the progress of the study by the Sponsor. The study monitor will remain in close contact with the study site throughout the duration of the study to provide any needed materials, (i.e. study forms, etc.) answer any questions and ensure that proper staffing levels are being maintained by the Investigator. The study monitor will be responsible for verifying that patients have signed the ICF 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.

13.1.1 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 and applicable regulatory body approvals 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.

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

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

13.2 Protocol Deviations 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 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.

13.3 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 (DSMB)

The Data Safety Monitoring Board is responsible for reviewing aggregate safety data reported during the study and assessing whether the overall safety of the study remains acceptable. DSMB activities, including roles and responsibilities, procedures, and monitoring criteria will be defined in the DSMB Charter.

14.2 Clinical Events Committee (CEC)

The Clinical Events Committee is responsible for reviewing and adjudicating specified individual adverse events over the course of the study. CEC activities, including roles and responsibilities, procedures, and definitions 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

Study patients will receive an echocardiogram at the visits specified in section 8.16. An echocardiographic core laboratory will be established to independently review and analyze echocardiographic images. A standardized protocol for acquiring images will be developed by the core lab and be provided to the clinical sites prior to study initiation. Sites will be trained on acquiring images prior to study initiation.

15 ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Applicable Regulations and Guidelines

The regulations listed in Table 12 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 12. 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 212 – Investigational Device Exemptions • ISO 14155:2011 Clinical Investigation of Medical Devices for Human Patients – Good Clinical Practice • ISO 14971:2007 Medical Devices – Application of Risk Management to Medical Devices

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.

With respect to data protection and patient confidentiality, Sponsor, Institution and all Study Personnel will comply with applicable requirements (for example, the General Data Protection Regulation 2016/679 ("GDPR") for EU patients), including providing notice and obtaining patient consent regarding the processing of their personal data.

15.3 Institutional Review Board Approval

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 site. If there is a change or addition of an Investigator, all required documents must be updated, accordingly.

15.5.2 Investigator Records

Records to be maintained by the Investigator include, but are not limited to, the following:

- Clinical study protocol and all amendments
- Signed Clinical Trial Agreement (CTA) and any amendments
- IRB approval letters, including continuing reviews and all amendments/changes
- IRB-approved informed consent documents
- All correspondence with another Investigator, IRB, Sponsor, Monitor or FDA, including required reports
- Records of receipt, use or disposition of a device

The following records must be maintained for each patient enrolled in the study:

- Signed ICF and documentation of informed consent process
- All relevant source documentation for study visits and study-related procedures including Investigator assessment of clinically significant or non-clinically significant findings (e.g. abnormal ECG, out-of-range lab values, etc.)
- Supporting documentation of any adverse events

- 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.

Upon study completion, the study files must be maintained in a known location for a period in accordance with local regulatory requirements.

15.5.3 Investigator Reports

In addition to adverse event reporting requirements discussed in Section 11, the following reports are required:

- Withdrawal of IRB approval. Within five (5) business days, the Investigator will report a withdrawal of approval by the reviewing IRB of the Investigator's part of an investigation to the Sponsor.
- Informed Consent. If an Investigator uses a device without obtaining informed consent, the Investigator shall report such use to Sponsor and the reviewing IRB within five (5) working business days after the use occurs.
- Progress reports. The Investigator will submit progress reports on the investigation to Sponsor and the IRB at least yearly.
- Final Report. Upon completion or termination of this Study, the Investigator must submit a final written report to Sponsor and the IRB as required by the regulations. The report must be submitted within three (3) 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.

15.6 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.

15.6.2 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.

15.6.3 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.

15.6.4 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.

15.6.5 Sponsor Reports

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

- 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 the request was made and should include the reason for the device recall.
- A final written report is to be completed and submitted to IRB and the pertinent regulatory agencies within six (6) 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.

15.7 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.

15.8 Audits and Inspections

The study may be subject to a quality assurance audit by the Sponsor or a designee, as well as inspection by appropriate regulatory authorities. 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.

15.9 Publication Policy

Publication or presentation of the overall clinical study results and/or site-specific results requires prior written approval of Edwards. If Edwards approves the publication or presentation of the overall clinical study results and/or site-specific results, then Institutions and Investigators will comply with the Publications and Public Disclosure Section of the Clinical Trial Agreement. Edwards may provide statistical support for the publication process.

The study results will be made public within 24 months of the end of data collection and a full report of the outcomes.

APPENDIX A: STUDY DEFINITIONS

Endpoints identified in the CEC Charter will be adjudicated by the independent CEC. A detailed CEC Charter will further define the endpoint definitions. In case of inconsistency between the protocol and the CEC Charter, the CEC Charter will be the final determining document.

Access Site
(Sponsor Definition)

Site of insertion of study device components.

Access Site and Vascular Complications
(MVARC Definition)

I. Vascular complications

x. Major access site vascular complications, including:

i. Aortic dissection or aortic rupture, or
ii. Access site-related† arterial or venous injury (dissection, stenosis, ischemia, arterial, or venous thrombosis including pulmonary emboli, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, retroperitoneal hematoma, atrial septal defect‡), irreversible nerve injury, or compartment syndrome resulting in death; hemodynamic compromise; life-threatening, extensive, or major bleeding (MVARC bleeding scale); visceral ischemia; or neurological impairment, or
iii. Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage, or
iv. Unplanned endovascular or surgical interventions resulting in death; life-threatening, extensive, or major bleeding (MVARC bleeding scale); visceral ischemia; or neurological impairment

xi. Minor access site vascular complications, including:

i. Access site arterial or venous injury (dissection, stenosis, arterial, or venous thrombosis including pulmonary emboli, ischemia, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, retroperitoneal hematoma, atrial septal defect‡) not resulting in death; life-threatening, extensive, or major bleeding (MVARC scale); visceral ischemia; or neurological impairment, or
ii. Distal embolization treated with embolectomy and/or thrombectomy not resulting in amputation or irreversible end-organ damage, or
iii. Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication, or
iv. Vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)

II. Cardiac structural complications due to access-related issues

i. 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

ii. 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

Access Site and Vascular Complications Requiring Intervention

(Sponsor Definition)

Complications (i.e. dissection, perforation, arteriovenous fistula, pseudoaneurysm formation, retroperitoneal hemorrhage, thromboembolism) requiring intervention (percutaneous or surgical).
**refer to MVARC definition above for definition of access site and vascular complications*

Activity Monitoring

The continuous tracking of physical activity through the use of a patient deployed wearable monitoring device

Acute Kidney Injury (AKI)

(MVARC)

Defined per MVARC as maximal change in serum Creatinine (sCR) from baseline to 7 days post-procedure.

Stage 1: Increase in sCr to 150%–199% (1.50–1.99 x increase vs. baseline), increase of ≥0.3 mg/dl (≥26.4 mmol/l) within 48 h, or urine output <0.5 ml/kg/h for ≥6 h but <12 h

Stage 2: Increase in sCr to 200%–299% (2.00–2.99 x increase vs. baseline) or urine output <0.5 ml/kg/h for ≥12 h but <24 h

Stage 3: Increase in sCr to ≥300% (>3.0 x increase vs. baseline), sCr of ≥4.0 mg/dl (≥354 mmol/l) with an acute increase of ≥0.5 mg/dl (44 mmol/l), urine output <0.3 ml/kg/h for ≥24 h, or anuria for ≥12 h; patients receiving renal replacement therapy are considered stage 3 irrespective of other criteria

Adverse Device Effect

(ISO 14155:2011)

Adverse event related to the use of an investigational medical device.

NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device

Bleeding

(MVARC 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 bleeding

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

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

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.

Cardiac Tamponade

(Sponsor Definition)

Pressure on the heart that occurs when blood or fluid builds up in the space between the heart muscle (myocardium) and the outer covering sac of the heart (pericardium).

Causality Assessment

Adverse events will be assessed by the Investigator for causality to the study device and index procedure as defined in MEDDEV 2.7/3 revision 3. 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 explained by another cause, but additional information may be obtained.

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).

Clinical Success

Procedural success without MAEs at 30 days. Per patient analysis.

Death

(MVARC Definition)

All events with an outcome of death will be classified to determine whether the death was related to cardiovascular (CV) or non-cardiovascular (non-CV) cause.

Although categorizing the initiating or proximate cause of cardiovascular death may be difficult, major complications contributing to death should be identified. A diagnosis of non-cardiovascular death requires the primary cause to be clearly related to another condition (e.g., trauma, cancer, or suicide). For this study purpose, all deaths that are not unequivocally related to a non-cardiovascular condition are considered cardiovascular death.

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
- Homicide
- Suicide
- Other noncardiovascular

Device Deficiency

(ISO 14155:2011 Definition)

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error (outcome of device use was different than intended) and inadequacy in the information supplied by the manufacturer.

Device Embolization

(ISO 5840-3)

Dislodgement from the intended and documented original position to an unintended and non-therapeutic location

Device Malfunction

(FDA 21 CFR 803.3)

Failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device.

Device Migration

(ISO 5840-3)

Detectable movement or displacement of the device from its original position within the implant site, without embolization.

Device Success

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

Embolism Free flowing blood clot or lesion material that is located in the systemic or pulmonary circulation A peripheral embolic event is an operative, autopsy or clinically documented embolus that produces symptoms from complete or partial obstruction or a peripheral (noncerebral) artery.
Endocarditis An inflammation of the inside lining of the heart chambers and heart valves (endocardium). Endocarditis can involve the heart muscle, heart valves, or lining of the heart.
Enrollment Patient will be considered "provisionally enrolled" when they have signed the informed consent form agreeing to participate in the study and have been deemed eligible for study participation by meeting the study criteria (Sections 7.2-7.3). A patient will be considered "enrolled" at the time of skin incision to introduce the PASCAL System into the body.
Electronic Diary (eDiary) The collection of patient reported outcomes (PRO) through a patient deployed computer or mobile/handheld/tablet device to administer questions/questionnaires to the patient.
Explant Removal of the study device after completion of the implant procedure for any reason.
Heart Failure A progressive condition that involves a supply-demand mismatch, usually due to loss of pumping ability by the heart (heart muscle weakens and gradually loses its ability to pump enough blood through the body), generally accompanied by fluid accumulation in body tissues, especially the lungs and lower limbs. Heart Failure Hospitalization – An unplanned hospitalization that results in at least one overnight stay (i.e., where the admission date and the discharge date are different) that includes increased signs and/or symptoms of worsening heart failure and requires the administration or augmentation of existing heart failure therapy. Severe Heart Failure – See NYHA Class IV
Heart Team The 'HEART Team', for the purpose of this study, must include a minimum of one Cardiologist, one Cardiac Surgeon, one Heart Failure specialist, and one Echocardiographer.

Hemolysis (Device Hemolysis)

Rupturing of red blood cells (erythrocytes) and the release of their contents (cytoplasm) into surrounding fluids.

Device hemolysis is defined as hemolysis in or near the investigational device that interferes with the function of the device. Device hemolysis related thrombus may be confirmed by operation, autopsy, or diagnostically by such methods as echocardiography, angiography, or magnetic resonance imaging

Hospitalization/Re-hospitalization

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 subclassified into:

- **Primary (cardiac related) heart failure:** this may be due to any cardiac cause, including primary LV dysfunction with or without medication or dietary noncompliance, acute MI, arrhythmias, and worsening valve dysfunction
- **Secondary (non-cardiac related) heart failure:** when a non-cardiac primary condition is present such as pneumonia, urinary tract infection, or renal failure, which results in fluid overload or myocardial failure.

Note: only primary heart failure should be considered a valid criterion for heart failure hospitalization

Infection

Known infection requiring intravenous antibiotics for other than prophylaxis, and/or extended hospitalization.

Kansas City Cardiomyopathy Questionnaire (KCCQ)

A health-related quality-of-life measure for patients with congestive heart failure.

KCCQ-12: A 12 question abridged and validated version of the full KCCQ questionnaire

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, MI, stroke, renal complications requiring unplanned dialysis or renal replacement therapy, severe bleeding, unplanned or emergency re-intervention (either percutaneous or surgical) related to the device and major access site and vascular complications requiring intervention.

Modified Rankin Scale

0: No symptoms at all
1: No significant disability despite symptoms; able to carry out all usual duties and activities
2: Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3: Moderate disability; requiring some help, but able to walk without assistance
4: Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5: Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6: Dead

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 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.
‡Adapted with permission from Thygesen et al.

New York Heart Association Classification (NYHA Class) **Class I:** Patients with cardiac disease but without resulting limitations of physical activity. **Class II:** Patients with cardiac disease resulting in slight limitation of physical activity. Patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain. **Class III:** Patients with cardiac disease resulting in marked limitation of physical activity. 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 A person with the disease (tricuspid regurgitation) being screened to participate or participating in this clinical study
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
Peripheral Thromboembolic Event See "Embolism"
Pre-Existing Condition A pre-existing condition is one that was present prior to clinical study screening.
Procedural Success Device success with evidence of a reduction in TR grade by at least one grade (scale: none/trace, mild, moderate, severe, massive, torrential[10]) at end of procedure, and without the need for a surgical or percutaneous intervention prior to hospital discharge. Per patient analysis.
Prosthesis An artificial substitute
Re-intervention ***(Sponsor Definition)*** Any intervention on the previously implanted study device (repair, alteration or replacement)

10 Hahn RT, Zamorano JL. The need for a new tricuspid regurgitation grading scheme. *Eur Heart J Cardiovasc Imaging.* 2017;18(12):1342-1343.

Renal Complication (Long-Term) Long-term Renal Complication is defined as onset of renal replacement therapy (i.e hemodialysis, renal transplant)
New need for renal replacement therapy ***(Sponsor Definition)*** New need for renal replacement therapy (i.e hemodialysis, renal transplant)
Screen Failure A patient who has signed the consent but, does not fulfill enrollment criteria: does not meet the inclusion criteria or who meets at least one of the exclusion criteria.
Septicemia ***(Sponsor Definition)*** Systemic infection requiring hospitalization and treatment with antibiotics.
Serious Adverse Event (SAE) ***(FDA 21 CFR 812.3)*** An adverse event that • Results in death • Is life-threatening • Requires inpatient hospitalization or prolongation of existing hospitalization • Results in persistent or significant disability/incapacity   ○ Is an important medical event which may jeopardize the patient, and may require medical or surgical intervention to prevent one of the above outcomes
Severe Bleeding ***(Sponsor Definition)*** Severe bleeding is a fatal, life-threatening, extensive, or major bleeding, as defined by MVARC.
SF-36 A survey with 36 questions that results in two scales of mental and physical functioning and overall health related quality of life. **SF-12:** A 12 question abridged and validated version of the SF-36

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
- 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 h and neuroimaging does not demonstrate a new haemorrhage or infarct

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

- Neurologist or neurosurgical specialist, or
- Neuroimaging procedure (CT scan or brain MRI)
- Non-neurologist physician (if neurologist is not available)
- 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:

1. Resulting in at least one of the following
   - Change in level of consciousness
   - Hemiplegia
   - Hemiparesis
   - Numbness
   - Sensory loss affecting one side of the body
   - Dysphasia or aphasia
   - Hemianopia
   - Amaurosis fugax
   - Other neurological signs or symptoms consistent with stroke
2. Duration of deficit could be one of the following:
   - A focal or global neurological deficit < 24 hours
   - Any available neuroimaging does not demonstrate a new hemorrhage or infarct
3. No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences) to be determined by or in conjunction with 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.

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APPENDIX C: ABBREVIATIONS AND ACRONYMS

Abbreviation/Acronym	Definition
6MWT	6 Minute Walk Test
ACC	American College of Cardiology
ACT	Activated Clotting Time
ADL	Activities of daily living
AE	Adverse Event
AHA	American Heart Association
AKI	Acute Kidney Injury
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate aminotransferase
CABG	Coronary Artery Bypass Graft
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CIB	Clinical Investigator's Brochure
CIP	Clinical Investigational Plan
CMR	Cardiovascular Magnetic Resonance
COPD	Chronic obstructive pulmonary disease
CRF	Case Report Form
CT	Computed Tomography
CTA	Clinical Trial Agreement
CV	Cardiovascular
DAPT	Dual anti-platelet therapy
DSMB	Data Safety Monitoring Board
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EF	Ejection Fraction
eGFR	Estimated glomerular filtration rate
EROA	Effective regurgitant orifice area
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase

Abbreviation/Acronym	Definition
GI	Gastrointestinal
HF	Heart Failure
Hgb	Hemoglobin
ICF	Informed consent form
ICU	Intensive care unit
IFU	Instructions For Use
INR	International normalized ratio
IRB	Institutional Review Board
ISO	International Standardization Organization
ITT	Intention-to-treat
IVC	Inferior vena cava
KCCQ	Kansas City Cardiomyopathy Questionnaire
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MAE	Major Adverse Event
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
NYHA	New York Heart Association
PASP	Pulmonary Artery Systolic Pressure
PHTN	Pulmonary hypertension
PP	Per-protocol
QOL	Quality of Life
RA	Right atrium
RV	Right ventricle
SAE	Serious Adverse Event
SLDA	Single leaflet device attachment
STS	Society of Thoracic Surgeons
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
UADE	Unanticipated adverse device effect
VC	Vena contracta

APPENDIX D: SAMPLE INFORMED CONSENT FORM

[redacted]

has not been approved for commercial use by the U.S. Food and Drug Administration (FDA).

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