



Edwards

The CLASP Study

Edwards PASCAL Transcatheter Mitral Valve Repair System Study

Clinical Investigation Plan

Study Number: 2016-05

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Effective Date: August 20, 2018

CONFIDENTIAL

Study Sponsor:

Edwards Lifesciences LLC

One Edwards Way

Irvine, CA 92614 USA

[REDACTED]

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The following terms will be used synonymously:

Sponsor	Edwards
Edwards	Edwards Lifesciences LLC
Clinical investigation	(clinical) study, (clinical) trial
Clinical investigation device	study device, Edwards PASCAL system
Clinical investigation Plan (CIP)	(clinical) protocol, (study) plan, (study) protocol
Competent authority	regulatory authority, Ministry of Health, MoH
CRF	eCRF
EC	Ethics committee, Investigational Review Board, Regional Ethics Board



	Following completion of the primary cohort of 60 patients in the analysis population (up to 45 of which may be US patients), an additional 50 patients will be enrolled in the U.S. at up to 15 clinical sites.	
[REDACTED]	[REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]
Study Population:	Adult patients with clinically significant, symptomatic, mitral regurgitation despite optimal medical therapy and/or who are being considered by the heart team for standard mitral valve repair or replacement.	

Inclusion Criteria:	<ol style="list-style-type: none">1. Signed and dated ethics committee/institutional review board approved study consent form prior to study related procedures2. Eighteen (18) years of age or older3. New York Heart Association (NYHA) Functional Class II, III and ambulatory IV heart failure despite optimal medical therapy4. Candidate for surgical mitral valve repair or replacement as determined by a Heart Team evaluation5. For patients whose primary mechanism of mitral regurgitation is functional (secondary; FMR) in nature: Elevated BNP > 150 pg/ml or corrected NT-proBNP of 600 pg/ml measured within 90 days prior to enrollment or heart failure hospitalization within 12 months prior to enrollment. These criteria do not apply to patients whose primary mechanism of mitral regurgitation is degenerative (DMR) in nature.6. Clinically significant mitral regurgitation (3+ to 4+, as defined in section 18.0) confirmed by transesophageal echocardiography (TEE) within 90 days prior to intervention, or transthoracic echocardiography (TTE) within 60 days prior to intervention7. Left ventricular ejection fraction (LVEF) \geq 20% determined by TTE within 60 days prior to intervention8. The primary regurgitant jet is non-commissural. If a secondary jet exists, it must be considered clinically insignificant9. Patient agrees to return for all required post-procedure follow-up visits10. For patients whose primary mechanism of mitral regurgitation is functional (secondary; FMR) in nature: Six-minute walk test (6MWT) \geq 150 m and \leq 400 m within 60 days prior to intervention. These criteria do not apply to patients whose primary mechanism of mitral regurgitation is degenerative (DMR) in nature.
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Exclusion Criteria	<ol style="list-style-type: none">1. Patient in whom a TEE is contraindicated or screening TEE is unsuccessful2. Leaflet anatomy which may preclude PASCAL device implantation, proper device positioning on the leaflets, or sufficient reduction in mitral regurgitation that may include:<ul style="list-style-type: none">• Evidence of moderate to severe calcification in the grasping area.• Evidence of severe calcification in the annulus or subvalvular apparatus• Evidence of severe Barlow's disease• Presence of significant cleft or perforation in the grasping area• Flail width > 15mm and/or flail gap > 10mm• Leaflet mobility length < 8mm• Coaptation gap > 5mm• Transseptal puncture height < 3.5cm• LA diameter ≤ 35mm• Presence of two or more significant jets• Presence of one significant jet in the commissural area3. Mitral valve area (MVA) < 4.0 cm² as measured by planimetry (If MVA by planimetry is not measurable, PHT measurement is acceptable)4. Echocardiographic evidence of intracardiac mass, thrombus, or vegetation5. Clinical evidence of right sided congestive heart failure and/or echocardiographic evidence of severe right ventricular dysfunction6. LVEDD > 8.0 cm determined by TTE within 60 days prior to intervention7. End-stage Heart Failure with inotrope support and/or consideration for LVAD or heart transplant8. Untreated significant coronary artery disease / stenosis, unstable angina, evidence of acute coronary syndrome, myocardial infarction, transient ischemic attack or stroke within 30 days prior to intervention
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	<ol style="list-style-type: none">9. Clinically significant uncorrected valvular disease or left ventricular outflow obstruction, obstructive cardiomyopathy, poorly controlled rapid atrial fibrillation or flutter, poorly controlled symptomatic brady- or tachy-arrhythmias10. Any percutaneous cardiovascular intervention, carotid surgery, cardiovascular surgery or atrial fibrillation ablation within 90 days prior to intervention11. Implant of any rhythm management device (i.e., pacemaker, cardiac resynchronization therapy [CRT] with or without cardioverter-defibrillator [CRT-D]) within 90 days prior to intervention, or revision of any implanted rhythm management device within 90 days prior to intervention12. Need for emergent or urgent surgery for any reason or any planned cardiac surgery within the next 12 months13. Any prior mitral valve surgery or transcatheter mitral valve procedure14. Contraindication to transseptal catheterization15. Active endocarditis or active infections requiring current antibiotic therapy or last antibiotic treatment was administered within 14 days prior to intervention16. Active rheumatic heart disease or rheumatic etiology for MR17. Infiltrative cardiomyopathies (e.g., amyloidosis, hemochromatosis, sarcoidosis), hypertrophic cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, or any other structural heart disease causing heart failure other than dilated cardiomyopathy of either ischemic or non-ischemic etiology18. Tricuspid valve disease requiring surgery or severe tricuspid regurgitation19. Severe aortic stenosis (aortic valve area <1.0 cm²) or severe aortic regurgitation20. Absence of CRT with Class I indication criteria for biventricular pacing21. Uncontrolled hypertension (i.e., BP >180 mmHg systolic and/or >105 mmHg diastolic) or hypotension (i.e., BP <90 mmHg systolic)
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	<p>22. Pulmonary artery systolic hypertension >70mmHg</p> <p>23. Severe symptomatic carotid stenosis (>50% by ultrasound) or asymptomatic carotid stenosis (>70% by ultrasound)</p> <p>24. Severe Kidney Renal Disease with creatinine >2.5mg/dL and/or eGFR <30 mL/min/1.73 m²</p> <p>25. Presence of an occluded or thrombosed IVC filter that would interfere with the delivery catheter, or ipsilateral deep vein thrombosis is present</p> <p>26. Known hypersensitivity to nitinol or contraindication to procedural medications which cannot be adequately managed medically</p> <p>27. History of bleeding diathesis or coagulopathy or patient who refuses blood transfusions</p> <p>28. Pregnant or planning pregnancy within next 12 months. Note: Female patients of childbearing potential need to have a negative pregnancy test performed within 14 days prior to intervention and be adherent to an accepted method of contraception</p> <p>29. Severe COPD evidenced by oral steroid therapy or oxygen therapy</p> <p>30. Concurrent medical condition with a life expectancy of less than 12 months in the judgment of the Investigator</p> <p>31. Patient is currently participating or has participated in another investigational drug or device clinical study where the primary study endpoint was not reached at time of enrollment</p> <p>32. Patient is under guardianship</p>
<p>Primary Endpoints</p>	<p>Safety:</p> <p>Composite of major adverse events (MAE) defined as cardiovascular mortality, stroke, myocardial infarction, new need for renal replacement therapy, severe bleeding and re-intervention for study device related complications at 30 days.</p> <p>Performance:</p> <ul style="list-style-type: none">• 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.



	<ul style="list-style-type: none"> • Procedural success: device success with evidence of MR reduction \leq MR2+ at discharge and without the need for a surgical or percutaneous intervention prior to hospital discharge. Per patient analysis. • Clinical success: procedural success with evidence of MR reduction \leq MR2+ and without MAEs at 30 days. Per patient analysis.
<p>Secondary Endpoints and Clinical Outcomes:</p>	<ul style="list-style-type: none"> • Mitral regurgitation reduction at 30 days, 6 months, 1 year and annually thereafter over baseline • All-cause mortality at 30 days, 6 months, 1 year, and annually thereafter • Recurrent heart failure hospitalization at 30 days, 6 months, 1 year, and annually thereafter • Re-intervention rates for mitral regurgitation at 30 days, 6 months, 1 year and annually thereafter • Composite of major adverse events (MAE) defined as cardiovascular mortality, stroke, myocardial infarction, new need for renal replacement therapy, severe bleeding and re-intervention for study device related complications at 6 months, 1 year and annually thereafter • Change in Left Ventricular End Diastolic Volume (LVEDV) at 6 months and 1 year and annually thereafter over baseline • Change in Left Ventricular End Systolic Volume (LVESV) at 6 months and 1 year and annually thereafter over baseline • Change in Pulmonary Artery Systolic Pressure at 6 months and 1 year and annually thereafter over baseline • Change in 6MWT distance at 6 months and 1 year over baseline • Change in Quality of Life (QoL) score, as measured by Kansas City Cardiomyopathy Questionnaire (KCCQ), and EQ5D at 30 days, 6 months and 1 year and annually thereafter over baseline • Change in NYHA Functional Classification at 6 months and 1 year and annually thereafter over baseline • Change in BNP/NT-pro-BNP level at 6 months and 1 year and annually thereafter over baseline • Change in tricuspid regurgitation at 6 months and 1 year and annually thereafter over baseline



	<ul style="list-style-type: none">• Change in effective regurgitant orifice area (EROA) at 30 days, 6 months, 1 year and annually thereafter over baseline• Change in mitral regurgitant volume at 30 days, 6 months and 1 year and yearly thereafter over baseline
Study Committees:	<p>Independent Data Safety Monitoring Board (DSMB) / independent Clinical Events Committee (CEC)</p> <ul style="list-style-type: none">• The DSMB will consist of a minimum of three physician members and will be selected for their expertise in specific medical disciplines, including CT surgery, Interventional Cardiology, and Heart Failure. The DSMB will also include an experienced biostatistician with experience in clinical research.• The CEC is a defined group of physicians in clinical practice, inclusive of the CEC Chair, and will be further defined in the CEC Charter.
Echocardiography Core Laboratory:	



1 OVERVIEWS

1.1 Study Assessment Overview

Table 1: Study Assessments

Study Assessments	Screening/Baseline	Implant Procedure ¹ (Day 0)	Post Implant (within 12-24 hrs)	Discharge or 7 days Post- Procedure ²	1 Month (30 ± 7 days)	6 Month (180 ± 30 days)	1 Year (± 45 days)	Annual 2-5 Year (± 45 days)
Informed Consent	X							
Review of inclusion/exclusion criteria	X							
Medical History	X							
Logistic EuroSCORE-I, EuroSCORE-II, STS score	X							
Clinical Evaluation	X		X	X	X	X	X	X
NYHA Class Assessment	X				X	X	X	X
NIH Stroke Scale/Modified Rankin Scale ³	X			X	X	X	X	X
Health Status Questionnaires	X				X	X	X	
Six Minute Walk Test	X				X	X	X	
Safety Evaluation		X	X	X	X	X	X	X
CBC and Platelet count	X		X	X	X	X	X	X
Complete Metabolic Panel	X				X	X	X	X
BNP/NT-pro-BNP	X			X	X	X	X	X
βHCG ⁴	X							
Serum creatinine	X		X	X	X	X	X	X
Coagulation profile (PT or INR, PTT)	X		X	X				
Troponins and CK-MB	X		X	X				
ECG	X	X	X	X	X	X	X	X
Transesophageal Echocardiogram	X	X						
Transthoracic Echocardiogram	X			X	X	X	X	X
Procedural Angiography		X						
Invasive Hemodynamic Monitoring		X						
Magnetic Resonance Imaging (optional, as deemed appropriate by Investigator)	X				X	X	X	X

¹ Implant procedure must be scheduled within 60 days of baseline TTE and 90 days of baseline TEE

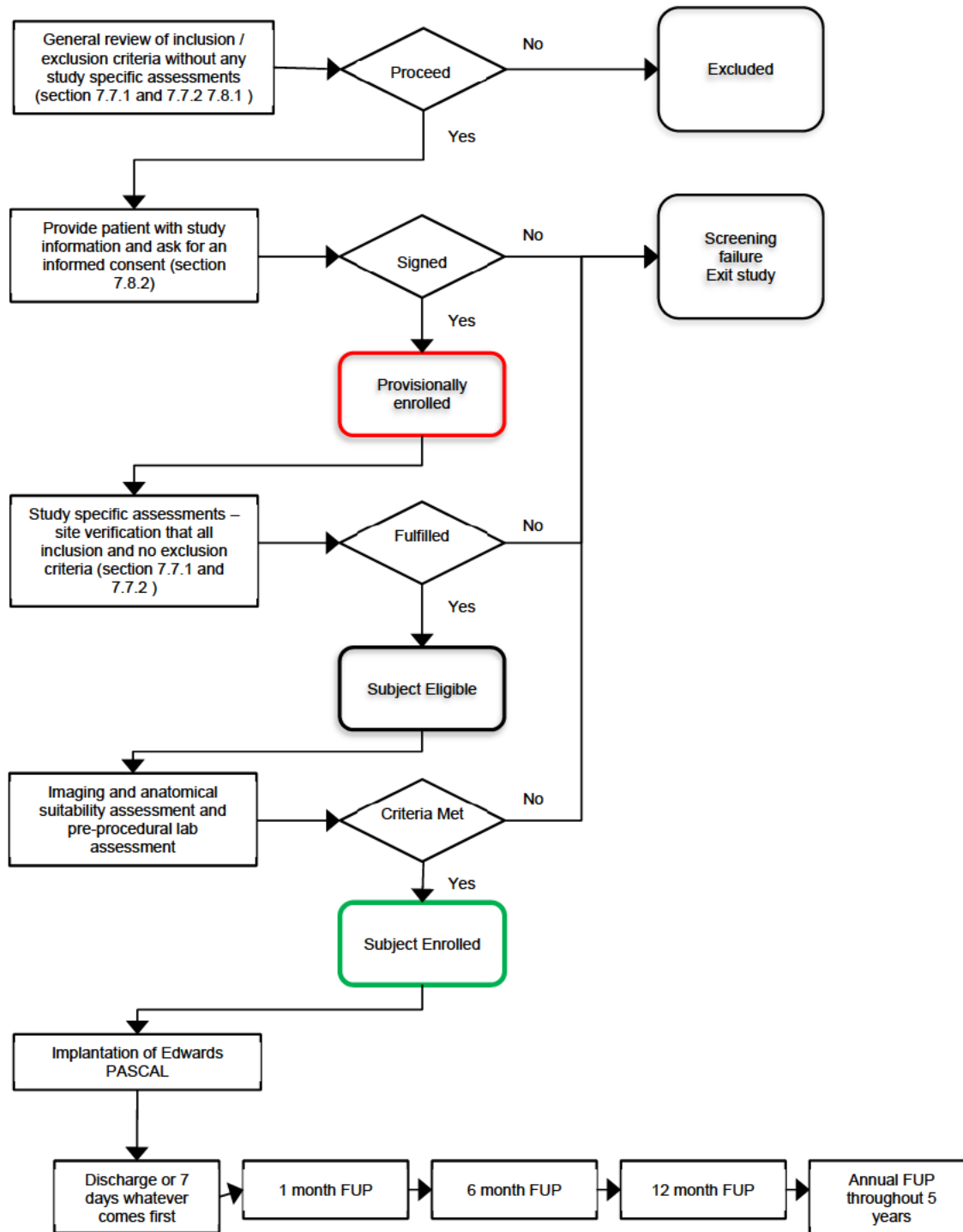
² Discharge or 7 days post-procedure, whichever comes first

³ Modified Rankin Scale (mRS) will be conducted at baseline for all patients with a history of stroke, and at each follow-up visit for all patients who experience a stroke at any time period during the trial. The assessment should also be completed closest to 90 days post event.

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

1.2 Enrollment Overview

Figure 1: Enrollment Overview



2 PRIMARY CONTACTS

2.1 Sponsor

[REDACTED]

[REDACTED]

2.2 Participating Sites

A current list of participating centers and a detailed list of contacts are filed at each site in the Investigator site file.

2.3 Core Laboratory

[REDACTED]

2.4 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) members are to be determined and will be documented in the DSMB charter.

2.5 Clinical Events Committee

The Clinical Events Committee (CEC) composition will be documented in the CEC charter.

[REDACTED]

3 INTRODUCTION

3.1 Mitral Regurgitation

Mitral regurgitation (MR), also known as mitral insufficiency, is the condition in which incompetency of the mitral valve causes abnormal backflow of blood from the left ventricle to the left atrium during the systolic phase of the cardiac cycle.

MR can have many underlying etiologies, but the majority of these can be divided into two major categories: degenerative and functional. Degenerative mitral valve regurgitation (DMR), also known as primary MR, refers to regurgitation resulting from structural abnormality of the mitral valve leaflets and/or valve apparatus. The most common causes of DMR is mitral valve prolapse, rheumatic disease, and endocarditis. In contrast, functional mitral regurgitation (FMR), also known as secondary MR, occurs when the valve and/or valve apparatus are structurally normal, but dysfunction, distortion, or dilation of the left atrial or ventricular chambers results in tethering of leaflets and/or mitral annular dilation that prevent leaflet coaptation. FMR can occur in the setting of underlying ischemic heart disease or heart failure with dilated cardiomyopathy.

3.2 Prevalence of Mitral Regurgitation

Mitral regurgitation is the most common valvular heart disease after aortic stenosis.

Approximately 2% of the population is affected, with 250,000 new diagnoses annually. The prevalence and severity of MR increases with age, with significant MR affecting nearly 10% of the U.S. population aged >75 years and associated with increased morbidity and mortality in the setting of left ventricular dysfunction and heart failure symptoms^{1, 2}.

Amongst those with severe MR, the predominant mechanism of MR has been shown to be up to 74% functional and 21% degenerative³. In patients with severe heart failure, the onset of FMR increases the hemodynamic stress on the failing left ventricle resulting in a cycle of progressive dilation and dysfunction and volume overload. Between 54 and 60% of patients with dilated cardiomyopathy have been reported to have FMR⁴.

3.3 Morbidity and Mortality Related to Mitral Regurgitation

Chronic MR imposes volume overload on the left ventricle (LV) which results in LV remodeling and cyclical worsening of MR. This may lead to worsening of left ventricular failure, pulmonary hypertension, atrial fibrillation and increased mortality.¹ Although MR may be tolerated for a long time in some patients, in others, progression of heart failure with LV muscle dysfunction may be more rapid⁵. The natural course of severe MR depends on many factors including, but not



limited to, the type of MR, presence of symptoms, LV function and presence of atrial fibrillation or pulmonary hypertension⁶.

Symptomatic patients with severe MR have an annual death rate of 5%⁷. The risk of death in subjects aged ≥ 70 years old with moderate/severe MR has been shown to be more than four-fold higher than that of age and sex matched subjects with absent/mild MR⁸.

Nearly 50% of patients with ischemic FMR develop heart failure or cardiac death within 5 years (three times more likely than post-MI patients without MR)⁹.

In patients with ischemic and non-ischemic cardiomyopathies and heart failure, MR independently predicts increased mortality, and mortality is directly associated with the degree of regurgitation⁷.

FMR has a 50% composite rate of mortality and heart failure (HF) hospitalization at 3 years, compared with 30% in HF patients without FMR¹⁰.

3.4 Current Treatment of Patients with Mitral Regurgitation

3.4.1 Medical Therapy

For chronic DMR patients without heart failure, medical treatment is limited to diuretics and nitrates to reduce afterload. Medical therapy for FMR patients with heart failure is focused on symptom relief from left-ventricular dysfunction. This includes diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin-receptor antagonists, beta blockers, and aldosterone antagonists. Although these drugs have been shown to improve the symptoms of heart failure and some have been shown to improve survival, there are no data that show that current medical therapies will reduce the severity or consequences of functional MR or reverse the progression of the underlying pathology.¹¹⁻¹³

3.4.2 Surgical Treatment

For DMR, surgical mitral valve repair or replacement is indicated in patients with symptoms and LVEF $>30\%$, or in asymptomatic patients with LVEF between 30 and 60% or LVESD ≥ 40 mm. Surgical repair of abnormal structural valve apparatus includes prolapsed leaflet resection, chordae reconstruction, leaflet augmentation, and cleft closure. Surgical options for treatment of symptomatic severe FMR include partial or complete annuloplasty and/or edge-to-edge leaflet repair. Surgery for FMR is generally only recommended when patients become unresponsive to optimal medical therapy and have adequate LV function ($>30\%$ LVEF), as the clinical benefit of surgical treatment for FMR is controversial¹⁵



Surgical mitral valve repair is preferred over replacement if a successful and durable repair can be achieved. Mitral valve replacement surgery is associated with a high incidence of complications including valve failure and bleeding due to the need for anticoagulants¹⁴. Although surgical repair and replacement options have been shown to be the standard treatment for MR in the surgically eligible population, it has been estimated that nearly 50% of patients with severe MR are not referred for surgery because they are prohibitively high risk due to advanced age, impaired left ventricular function or the presence of comorbidities¹⁵. In practice, isolated surgery for FMR is performed in less than 15% of eligible patients¹⁶.

3.4.3 Novel therapies

3.4.3.1 Cardiac resynchronization

Cardiac resynchronization therapy (CRT) may provide benefit for patients with chronic severe FMR in the presence of conduction abnormalities that may cause cardiac wall motion that exacerbates the MR. While this therapy has been shown to improve quality of life and exercise tolerance, it is applicable only to those with conduction abnormalities.

3.4.3.2 Percutaneous valve replacement

Several percutaneous mitral valve replacement technologies, either via trans-apical, trans-atrial, or trans-septal approaches, are in early stages of pre-clinical and clinical evaluation¹⁷⁻²⁰ indicating a trend in catheter based therapies to treat the high surgical risk MR patient population. None are yet commercially available.

3.4.3.3 Percutaneous valve repair

Percutaneous mitral valve repair therapies have raised interest due to the minimally invasive nature of the procedures. Various technologies have emerged and can be grouped by the treatment area: leaflet repair, direct annuloplasty or indirect annuloplasty via the coronary sinus, and chamber (LV) remodeling^{17, 18}.

The MitraClip System (Abbot Vascular, Menlo Park, CA) is a catheter-based technology that delivers a clip to grasp and COAPT the native mitral valve leaflets, based on the edge-to-edge surgical repair technique which approximates the mitral posterior and anterior leaflets to create a double orifice. MitraClip received CE mark 2008 (indicated for MR) and FDA approval in 2013 (indicated for severe symptomatic DMR in high-surgical risk population only). To date, the MitraClip has been implanted in more than 40,000 patients.



The MitraClip has demonstrated rates of procedural success greater than 90%, a good safety profile, left ventricular reverse remodeling, and improved clinical outcomes in a randomized study and large multi-center registries²¹⁻²⁵. The U.S. EVEREST II randomized controlled trial compared the MitraClip to conventional surgical treatment of MR in 258 patients in an operable population with mostly DMR. The study concluded that MitraClip was superior to surgery for safety but less effective in the reduction of MR.²³ Five-year results have recently been published and have shown that between 1- and 5-year follow-up, showing comparable and low rates of surgery for mitral valve dysfunction between the groups, strengthening the evidence for durability of MR reduction. At 1- and 5-year follow up, the mortality rates were similar between both groups (at 1-year 6% vs. 6% for MitraClip and Surgery, respectively; $p=1.0$ and at 5-years 20.8% vs. 26.8% for MitraClip and Surgery, respectively; $p=0.36$), but residual moderate or severe MR was higher in the MitraClip group (12.3% vs. 1.8%; $p=0.02$)²⁶.

Glower et al²⁷ reported results from the prospective multi-center EVEREST II high-risk registry (n=78) and the REALISM continued access high risk arm (n=273). Twelve-month data showed that MitraClip treatment significantly reduced MR, improved clinical symptoms and decreased left ventricular dimensions in this high-risk cohort.

The ACCESS-EU was a prospective, multi-center, nonrandomized post-approval study conducted in 567 patients in Europe. In this patient population, the procedure was effective with low hospital mortality and low adverse event rates²⁴.

In these studies, it was observed that 30-day safety performance outcomes after MitraClip implantation are similar to those at one year. Only complications related to the underlying disease such as mortality and re-hospitalizations continually increase. Glower et al discussed "In these high-risk patients, the results of MV (mitral valve) device placement appear to be very stable from 30 days to 12 months". Additionally, Feldman et al²⁶ discussed: "The landmark analysis of this device demonstrated that the clinical failures primarily occurred within the first 6 months, most of which were caused by inadequate MR reduction during the index procedure or early SLDA (single-leaflet device attachment)."

Other recent commercially available (in select regions) Mitral Valve repair devices include percutaneous direct annuloplasty using Cardioband (Valtech Cardio, Israel, recently acquired by Edwards, Irvine, CA, USA; CE mark 2015), direct annuloplasty using Mitralign (Mitralign Inc., Tewksbury, MA; CE mark 2016), indirect annuloplasty using Carillon (Cardiac Dimensions, Kirkland, WA; CE mark 2009), and percutaneous chordal repair using NeoChord (NeoChord, Minneapolis, Minnesota; CE mark 2013).



3.5 Rationale for Study and Device Use

Percutaneous approaches to treating MR are appealing for their potential to provide sufficient reduction in MR without the risks typically associated with open heart surgery. Additionally, as previously stated, nearly 50% of patients with severe MR are not referred or denied to surgery due to prohibitive risks, and the uncertainty of benefit from surgical repair or replacement. Percutaneous therapy provides an alternative treatment option for these high risk surgical candidates and in those whom medical therapy is suboptimal.

Edwards has developed a catheter-based technique for the delivery of a permanent implant to the mitral valve via a trans-septal access to grasp and approximate the anterior and posterior leaflets, creating a double orifice and thereby reducing MR, much like surgical repair and the MitraClip System procedure. The MitraClip procedure has already been shown to be a viable alternative for high risk MR patients. However, MitraClip treatment is limited to specific anatomies, and often requires multiple devices (at least 40% of cases require ≥ 2 devices^{21, 24, 25}) to treat large regurgitant jets, which adds to clinical risk and increases procedural time. Additionally, MitraClip often leaves significant residual MR as previously discussed. The Edwards PASCAL Transcatheter Mitral Valve Repair (TMVr) System is designed to address some of these limitations, including: a larger implant with wider paddles and independent Clasp control to address complex anatomies and regurgitant jets and to potentially reduce the number of implants required for adequate MR reduction; a Spacer in the center of the implant to act as a filler in the regurgitant orifice for reduction of MR; working length that allows maneuverability even with higher septal puncture heights; ergonomic controls similar to other Edwards transcatheter product lines which are already familiar to many interventional cardiologists.



3.6 Intended Use

The Edwards PASCAL System is intended for the percutaneous reconstruction of an insufficient mitral valve in patients with clinically significant, symptomatic mitral regurgitation and:

- New York Heart Association (NYHA) Functional Class II, III and ambulatory IV heart failure
- The primary regurgitant jet is non-commissural. If a secondary jet exists, it must be considered clinically insignificant

A Clinical Investigator's Brochure (CIB) has been prepared for the Edwards PASCAL System. This brochure provides the prior testing conducted on the system components.

3.7 Prior Clinical Studies

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3.8 Study Device

3.8.1 Device Description

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

5

⁵ The images in this section are representative of the original version of the PASCAL System

[REDACTED]

3.8.1.1 Edwards Mitral Valve Repair Implant System

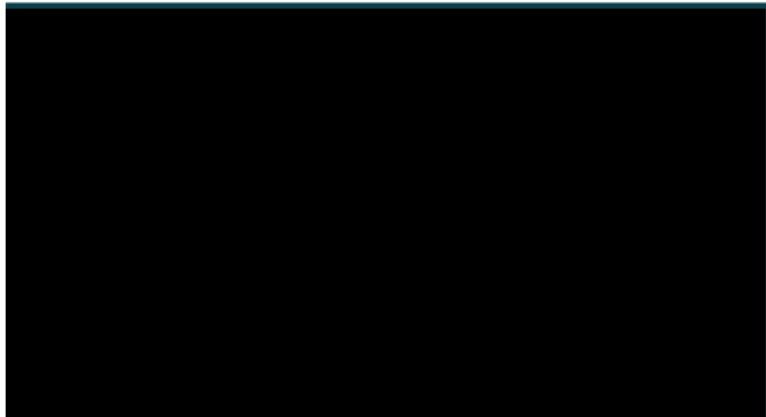


Figure 2: Implant System (Implant, Steerable Catheter, Implant Catheter), Guide Sheath, and Stabilizer

- **Implant Device** (Figure 3)

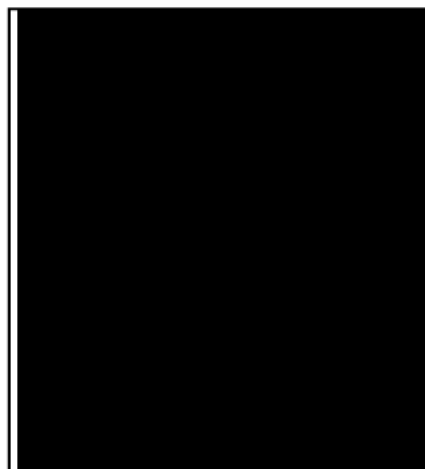
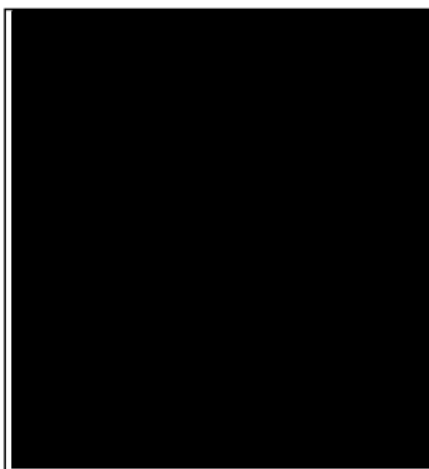


Figure 3: Implant



- **Steerable Catheter** (Figure 4)

[REDACTED]

- **Implant Catheter** (Figure 4)

[REDACTED]

[REDACTED]

- **Loader**

[REDACTED]

3.8.1.2 Edwards Mitral Valve Repair Guide Sheath

[REDACTED]

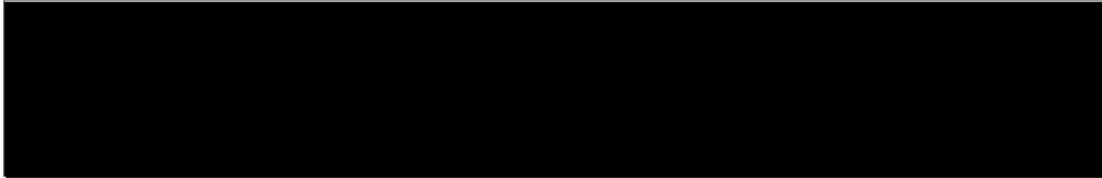


Figure 5: Guide Sheath



Figure 6: Introducer



Figure 7: Loader

3.8.1.3 Edwards Mitral Valve Repair Stabilizer

[REDACTED]

[REDACTED]



Figure 8: Stabilizer

3.8.1.4 Edwards Mitral Valve Repair Table

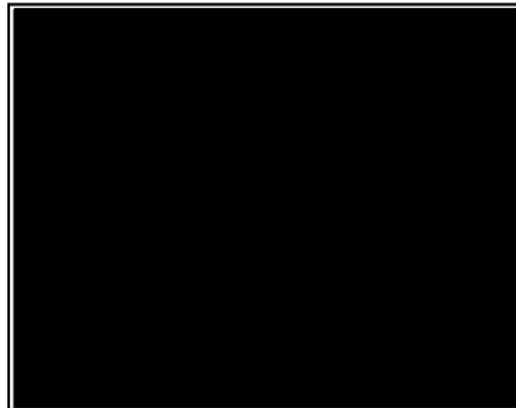


Figure 9: Table

4 DEVICE ACCOUNTABILITY

4.1 Device Shipments

Devices will be transported to the study center when the Clinical Study Agreement is in place, the study center has obtained applicable regulatory (e.g., Ethics Committee, Ministry of Health) approvals, and a patient eligible for implant has been identified.

Devices will be provided to the study center as needed for scheduled implant procedures. All investigational devices used in this study for investigational purposes will be labeled as such per regional requirements.



4.2 Device Accountability Records

All device shipments will have inventory and shipment records will be maintained by both the Study Sponsor and the study center. Devices may be hand carried to participating study centers by the Study Sponsor personnel and will be accompanied by delivery of investigational device documentation (packing lists, transfer of investigational product form, etc.). The Investigator (s) or designee will take inventory of the product and complete the delivery documentation with receipt date, condition of the device and signature. The Investigator will maintain a Device Accountability Log (as provided by the Sponsor) of all investigational devices documenting their receipt, disposition and return during this clinical study. The log will be kept with the documents for the clinical study and will be available for review during Study Sponsor monitoring visits. Upon Sponsor request or when enrollment has ended, Edwards PASCAL System components must be returned to Edwards Lifesciences and the date of return must be recorded on the log.

4.3 Device Storage

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

4.4 Device Return

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

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



4.5 Patient Implant Card

The patient implant card will be supplied with the device.

5 TRAINING

5.1 Investigator Device Training

[REDACTED]

[REDACTED]

5.2 Training of Investigational Center Personnel

[REDACTED]

5.3 Training Documentation

[REDACTED]

[REDACTED]

6 RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

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

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

6.1 Potential Risks

Complications associated with standard cardiac catheterization, the use of anesthesia and use of the PASCAL system could lead to reoperation, explant, permanent disability, or death.

The following anticipated adverse events have been identified as possible complications of the PASCAL system and/or implant procedure:

- Abnormal lab values;
- access site AV fistula or pseudoaneurysm;
- allergic reaction to anesthetic, contrast, heparin, Nitinol;
- anemia, may require transfusion
- angina or chest pain
- arrhythmias;
- atrial fibrillation;
- atrial septal defect requiring intervention;
- arterio-venous fistula;
- bleeding;
- cardiac arrest;
- cardiac failure/low cardiac output;
- cardiac injury including perforation, obstruction, or dissection that may require intervention;
- cardiogenic shock;

- chordal entanglement or rupture;
- coagulopathy, coagulation defect or disorder, bleeding diathesis;
- conversion to open valve surgery
- conduction system injury which may require permanent pacemaker implantation
- death;
- deterioration of native valve (leaflet tear/tearing, leaflet retraction, leaflet thickening, or other);
- device deterioration (wear, tear, fracture, calcification, or other);
- device migration (including single leaflet device attachment (SLDA), malposition or embolization requiring intervention;
- device thrombosis requiring intervention;
- emergency cardiac surgery;
- deep venous thrombosis;
- reaction to anti-platelet, anticoagulation agents or contrast media
- dyspnea;
- edema
- electrolyte imbalance;
- emboli/embolization including air, particulate, calcific material, or thrombus;
- endocarditis;
- esophageal irritation;
- esophageal perforation or stenosis;
- exercise intolerance or weakness;
- fever;
- failure to deliver PASCAL to the intended site;
- failure to retrieve any PASCAL system components;
- gastrointestinal bleeding or infarct;
- heart failure;
- heart murmur;
- hematoma;
- hemodynamic compromise;
- hemolysis;
- hemorrhage requiring transfusion or intervention;
- hypertension

- hypotension;
- Implantation of additional transcatheter mitral repair device
- infection;
- Inflammation
- Leaflet damage;
- mesenteric ischemia
- mitral valve stenosis
- mitral valve injury;
- multi-system organ failure;
- myocardial infarction;
- nausea or vomiting;
- nerve injury
- neurological symptoms, including dyskinesia, without diagnosis of TIA or stroke
- non-emergent reoperation;
- nonstructural implant dysfunction;
- obstruction of valvular structures, e.g. LVOT obstruction;
- pain or changes at the access site;
- papillary muscle damage;
- paralysis;
- PASCAL system component(s) embolization
- pericardial effusion, cardiac tamponade;
- peripheral ischemia;
- permanent disability;
- pleural effusion;
- prolonged ventilation;
- pulmonary edema;
- pulmonary embolism;
- renal failure;
- renal insufficiency;
- respiratory compromise, respiratory failure, atelectasis, pneumonia
- reoperation;
- restenosis;



- retroperitoneal bleed;
- septicemia, sepsis
- shock, e.g. anaphylactic or cardiogenic
- skin burn, injury or tissue changes due to exposure to ionizing radiation
- syncope;
- systemic peripheral ischemia;
- thromboembolic events, stroke, transient ischemic attack, clusters, or other neurological changes;
- thromboembolism (permanent or transient pulmonary and/or neurological events)
- transvalvular flow disturbances;
- urinary tract infection and/or bleeding
- vascular injury or trauma, dissection or occlusion, that may require intervention
- valvular regurgitation;
- vessel spasm
- ventricular wall, atrial wall or septal damage, abrasion, or perforation;
- wound dehiscence, delayed or incomplete healing;
- worsening of heart failure;
- worsening mitral regurgitation / valvular insufficiency

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



6.2 Risk Management

All efforts will be made to minimize the identified risks. Careful patient selection will be performed by the Heart Team¹¹ in collaboration with the Sponsor.

The Investigators selected at each site will include an Interventional Cardiologist or Surgeon who is an expert in mitral valve disease and experienced in performing transcatheter mitral valve repair and/or replacement, and skilled in percutaneous coronary interventions and structural heart interventions to assess patient risk and anatomical suitability. Each implanting physician will be thoroughly trained on the investigational device before first implantation in a patient. There will be strong collaboration between interventional cardiology or cardiac surgery and a designated team of nurses, technicians and colleagues from supporting medical disciplines (e.g., anesthesiologist, echocardiographer, and radiologist).

The procedure will be performed in an operating room, catheterization lab or hybrid operating room with fluoroscopic and echocardiographic imaging capabilities.

All adverse events will be thoroughly monitored and reviewed by the Study Sponsor and DSMB. Stopping rules will be applied for patient safety throughout enrollment.

6.3 Benefits

[REDACTED]

7 CLINICAL INVESTIGATION

7.1 Study Design

This is a multi-center (up to 20 sites initially), multi-national, prospective, single arm study. The analysis population will consist of 60 patients. No site will be allowed to enroll more than 20% of the analysis population in the primary cohort. All enrolled study patients will be assessed for clinical follow-up at the following intervals: 30 days, 6 months, 1 year and annually for 5 years post implant procedure. In addition, the study allows for 0 to 3 roll-in patients per site where allowed, for a total maximum of 60 roll-in patients. The overall study therefore allows for up to 120 patients: 60 in the analysis population, and up to 60 additional roll-in patients.

Following completion of the primary cohort of 60 patients in the analysis population (up to 45 of which may be US patients), an additional 50 patients will be enrolled in the U.S. at up to 15 clinical sites.

7.2 Study Objectives

The objectives of this clinical study are to:

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

7.3 Study Population

Adult patients with clinically significant, symptomatic, mitral regurgitation despite optimal medical therapy and/or are being considered by the heart team for standard mitral valve repair or replacement.

7.4 Study Duration

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

7.5 Primary Endpoints

Safety:

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

Performance:

- Device success: device is deployed as intended and the delivery system is successfully retrieved as intended at the time of the patient's exit from the cardiac catheterization laboratory. Per device analysis.
- Procedural success: device success with evidence of MR reduction \leq MR2+ at discharge and without the need for a surgical or percutaneous intervention prior to hospital discharge. Per patient analysis.
- Clinical success: procedural success with evidence of MR reduction \leq MR2+ and without MAEs at 30 days. Per patient analysis.

7.6 Secondary Endpoints and Clinical Outcomes

- Mitral regurgitation reduction at 30 days, 6 months, 1 year and annually thereafter over baseline
- All-cause mortality at 30 days, 6 months, 1 year, and annually thereafter
- Recurrent heart failure hospitalization at 30 days, 6 months, 1 year, and annually thereafter
- Re-intervention rates for mitral regurgitation at 30 days, 6 months, 1 year and annually thereafter
- Composite of major adverse events (MAE) defined as cardiovascular mortality, stroke, myocardial infarction, new need for renal replacement therapy, severe bleeding and re-intervention for study device related complications at 6 months, 1 year and annually thereafter
- Change in Left Ventricular End Diastolic Volume (LVEDV) at 6 months and 1 year and annually thereafter over baseline
- Change in Left Ventricular End Systolic Volume (LVESV) at 6 months and 1 year and annually thereafter over baseline
- Change in Pulmonary Artery Systolic Pressure at 6 months and 1 year and annually thereafter over baseline
- Change in 6MWT distance at 6 months and 1 year over baseline



- Change in Quality of Life (QoL) score, as measured by Kansas City Cardiomyopathy Questionnaire (KCCQ), and EQ5D at 30 days, 6 months and 1 year and annually thereafter over baseline
- Change in NYHA Functional Classification at 6 months and 1 year and annually thereafter over baseline
- Change in BNP/NT-pro-BNP level at 6 months and 1 year and annually thereafter over baseline
- Change in tricuspid regurgitation at 6 months and 1 year and annually thereafter over baseline
- Change in effective regurgitant orifice area (EROA) at 30 days, 6 months, 1 year and annually thereafter over baseline
- Change in mitral regurgitant volume at 30 days, 6 months and 1 year and yearly thereafter over baseline



7.7 Patients

7.7.1 Inclusion Criteria

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

1. Signed and dated ethics committee/institutional review board approved study consent form prior to study related procedures
2. Eighteen (18) years of age or older
3. New York Heart Association (NYHA) Functional Class II, III and ambulatory IV heart failure despite optimal medical therapy
4. Candidate for surgical mitral valve repair or replacement as determined by a Heart Team evaluation
5. For patients whose primary mechanism of mitral regurgitation is functional (secondary; FMR) in nature: Elevated BNP > 150 pg/ml or corrected NT-proBNP of 600 pg/ml measured within 90 days prior to enrollment or heart failure hospitalization within 12 months prior to enrollment. These criteria do not apply to patients whose primary mechanism of mitral regurgitation is degenerative (DMR) in nature.
6. Clinically significant mitral regurgitation (3+ to 4+, as defined in Section 18.0) confirmed by transesophageal echocardiography (TEE) within 90 days prior to intervention, **or** transthoracic echocardiography (TTE) within 60 days prior to intervention
7. Left ventricular ejection fraction (LVEF) \geq 20% determined by TTE within 60 days prior to intervention
8. The primary regurgitant jet is non-commissural. If a secondary jet exists, it must be considered clinically insignificant
9. Patient agrees to return for all required post-procedure follow-up visits
10. For patients whose primary mechanism of mitral regurgitation is functional (secondary; FMR) in nature: Six-minute walk test (6MWT) \geq 150 m and \leq 400 m within 60 days prior to intervention. These criteria do not apply to patients whose primary mechanism of mitral regurgitation is degenerative (DMR) in nature.

7.7.2 Exclusion Criteria

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

1. Patient in whom a TEE is contraindicated or screening TEE is unsuccessful



2. Leaflet anatomy which may preclude PASCAL device implantation, proper device positioning on the leaflets, or sufficient reduction in mitral regurgitation that may include:
 - Evidence of moderate to severe calcification in the grasping area.
 - Evidence of severe calcification in the annulus or subvalvular apparatus
 - Evidence of severe Barlow disease
 - Presence of significant cleft or perforation in the grasping area
 - Flail width > 15mm and/or flail gap > 10mm
 - Leaflet mobility length < 8mm
 - Coaptation gap > 5mm
 - Transseptal puncture height < 3.5cm
 - LA diameter ≤ 35mm
 - Presence of two or more significant jets
 - Presence of one significant jet in the commissural area
3. Mitral valve area (MVA) < 4.0 cm² as measured by planimetry (If MVA by planimetry is not measurable, PHT measurement is acceptable)
4. Echocardiographic evidence of intracardiac mass, thrombus, or vegetation
5. Clinical evidence of right sided congestive heart failure and/or echocardiographic evidence of severe right ventricular dysfunction
6. LVEDD > 8.0 cm determined by TTE within 60 days prior to intervention
7. End-stage Heart Failure with inotrope support and/or consideration for LVAD or heart transplant
8. Untreated significant coronary artery disease / stenosis, unstable angina, evidence of acute coronary syndrome, myocardial infarction, transient ischemic attack or stroke within 30 days prior to intervention
9. Clinically significant uncorrected valvular disease or left ventricular outflow obstruction, obstructive cardiomyopathy, poorly controlled rapid atrial fibrillation or flutter, poorly controlled symptomatic brady- or tachy-arrhythmias
10. Any percutaneous cardiovascular intervention, carotid surgery, cardiovascular surgery or atrial fibrillation ablation within 90 days prior to intervention
11. Implant of any rhythm management device (i.e., pacemaker, cardiac resynchronization therapy [CRT] with or without cardioverter-defibrillator [CRT-D]) within 90 days prior to intervention, or revision of any implanted rhythm management device within 90 days prior to intervention

12. Need for emergent or urgent surgery for any reason or any planned cardiac surgery within the next 12 months
13. Any prior mitral valve surgery or transcatheter mitral valve procedure
14. Contraindication to transseptal catheterization
15. Active endocarditis or active infections requiring current antibiotic therapy or last antibiotic treatment was administered within 14 days prior to intervention
16. Active rheumatic heart disease or rheumatic etiology for MR
17. Infiltrative cardiomyopathies (e.g., amyloidosis, hemochromatosis, sarcoidosis), hypertrophic cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, or any other structural heart disease causing heart failure other than dilated cardiomyopathy of either ischemic or non-ischemic etiology
18. Tricuspid valve disease requiring surgery or severe tricuspid regurgitation
19. Severe aortic stenosis (aortic valve area $<1.0 \text{ cm}^2$) or severe aortic regurgitation
20. Absence of CRT with Class I indication criteria for biventricular pacing
21. Uncontrolled hypertension (i.e., BP $>180 \text{ mmHg}$ systolic and/or $>105 \text{ mmHg}$ diastolic) or hypotension (i.e., BP $<90 \text{ mmHg}$ systolic)
22. Pulmonary artery systolic hypertension $>70 \text{ mmHg}$
23. Severe symptomatic carotid stenosis ($>50\%$ by ultrasound) or asymptomatic carotid stenosis ($>70\%$ by ultrasound)
24. Severe Kidney Renal Disease with creatinine $>2.5 \text{ mg/dL}$ and/or eGFR $<30 \text{ mL/min/1.73 m}^2$
25. Presence of an occluded or thrombosed IVC filter that would interfere with the delivery catheter, or ipsilateral deep vein thrombosis is present
26. Known hypersensitivity to nitinol or contraindication to procedural medications which cannot be adequately managed medically
27. History of bleeding diathesis or coagulopathy or patient who refuses blood transfusions
28. Pregnant or planning pregnancy within next 12 months. Note: Female patients of childbearing potential need to have a negative pregnancy test performed within 14 days prior to intervention and be adherent to an accepted method of contraception
29. Severe COPD evidenced by oral steroid therapy or oxygen therapy
30. Concurrent medical condition with a life expectancy of less than 12 months in the judgment of the Investigator

31. Patient is currently participating or has participated in another investigational drug or device clinical study where the primary study endpoint was not reached at time of enrollment
32. Patient is under guardianship

7.8 Study Procedures

7.8.1 Pre-screening

Adult patients with clinically significant, symptomatic, mitral regurgitation despite optimal medical therapy and/or are being considered by the heart team for standard mitral valve repair or replacement.

Prior to performing any study specific activities/evaluations, except the standard assessments for this population, the patient must be thoroughly informed about all aspects of the study and the patient must have provided written informed consent.

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

7.8.2 Study Informed Consent Process

The patient must sign the Study Informed Consent Form that is currently approved by the institution's overseeing IRB/EC prior to participation. Failure to provide Study informed consent renders the patient ineligible for the study. Study Informed consent must be obtained prior to any study related procedures.

It has to be emphasized that a patient's participation in the trial is voluntary and that the patient may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the patient is otherwise entitled.

Signed Screening Consent Form (where applicable) and Study Informed Consent Form must be retained by the Investigational Center for verification during on-site monitoring visits. The



Investigator will retain the original consent forms, a copy will be filed in the sites specific study files, and a copy of the Screening Consent Form (where applicable) and Study Informed Consent Form will be provided to the patient.

The consent forms will be written in the native language/languages of the patient and administered only by the Investigator or authorized designee. The Principal Investigator or delegated person administering the consent must sign and date the Study Informed Consent Form to indicate that the purpose, risks and benefits of the study were explained to the patient and that their signature was witnessed.

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

As the Study Sponsor, Edwards Lifesciences must approve any modifications to the Screening Consent (where applicable) and Study Informed Consent Form prior to submission to the ethics committee (EC)/institutional review board (IRB), and/or Competent Authority (as required).

7.8.3 Patient Enrollment

The enrollment overview is shown in Figure 1 in Section 1.2. A patient will be considered a "patient" and "provisionally enrolled" when they have signed the informed consent form. Provisionally enrolled patients will be reviewed by the Heart Team to assure that all inclusion criteria and none of the exclusion criteria are met at which point the patient will be considered "eligible". If a patient has signed the informed consent but are deemed not eligible, the patient is considered a "screen failure" and exit the study.

Eligible patients will be screened for imaging and anatomical suitability and if pre-procedural lab criteria are met. Once these criteria are met, the patient is considered "enrolled".

A Screening/Enrollment Log provided by the Sponsor, will be maintained at the study site. All patients assessed for study participation will be entered on the screening log. "Screen failures" will be recorded on the log with a failure reason.

The screening of patients qualifying for this study should be carried out in a sequential, prospective manner, such that all patients are offered the possibility of participating in the study and are therefore, evaluated according to the selection criteria defined in this protocol.

All patients that have signed the informed consent form, been assessed for study participation and deemed eligible for study participation by meeting the study criteria, will be assigned a



sequential patient ID number by the Study Sponsor. The patient ID number and initials (if applicable) shall be used to identify the patient on the site patient log in order to allow source verification with all study-related documents at the site.

7.8.4 Baseline Evaluation

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

Table 3: Baseline Evaluation Data

General Information	Clinical Information	Laboratory Measurements
<ul style="list-style-type: none"> • Informed consent • Inclusion/exclusion and other screening evaluation • Demographics 	<ul style="list-style-type: none"> • Medical history (e.g., co-morbidities, EuroSCOREs, STS score, prior cardiovascular interventions / surgeries) • Clinical evaluation (vital signs, height, weight) • NIH Stroke Scale/Modified Rankin Scale* • Concomitant Medication • NYHA classification • TTE and TEE measurements** • 12-lead ECG results • 6MWT results • KCCQ, EQ-5D • MRI results within 60 days of procedure (optional) 	<ul style="list-style-type: none"> • Within 30 days of procedure: Troponin CK-MB • Within 14 days of procedure: CBC and platelets CMP • Within 72 hours of procedure: Serum creatinine • Within 14 days of procedure: βHCG, if applicable • BNP or NT-pro BNP • PTT or PT/INR

*Modified Rankin Scale (mRS) will be conducted at baseline for all patients with a history of stroke and at each follow visit for all patient who had a stroke at any time period during the trial.

**TTE and TEE must be performed within 60 days and 90 days of procedure, respectively

7.8.5 Stroke Assessment and Quality of Life measurements

The following references will be used for stroke assessment and quality of life measurements.

- National Institute of Health (NIH) Stroke Scale Form
http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf
- Modified Rankin Scale Form



http://www.strokecenter.org/wp-content/uploads/2011/08/modified_rankin.pdf

- EuroQol (EQ – 5D)
<http://www.aaos.org/uploadedFiles/EQ5D3L.pdf>
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
<http://cvoutcomes.org/pages/3214>

7.8.6 Imaging Assessments

Imaging assessments (TTE, TEE) shall be done according to the current version of the core lab echocardiographic acquisition protocol Appendix B. Severity of baseline MR shall be defined as described in Section 18.0 and confirmed by the echo core lab prior to enrollment.

7.8.7 Recommended Antiplatelet / Anticoagulation Therapy

Recommendations for antiplatelet/anticoagulation therapy are detailed in the following sections. Alternative anticoagulation/antiplatelet regimens may be considered according to the needs of individual patients or a hospital's standard practice; these will not constitute a protocol deviation.

7.8.7.1 Pre Procedure Therapy

All patients are recommended to receive aspirin (at least 75-100 mg daily) prior to implant procedure. Patients on warfarin should be asked to discontinue use prior to implant procedure.

7.8.7.2 Procedural Therapy

Heparin will be administered at procedure start. During the procedure, activated clotting time (ACT) will be monitored. It is recommended that Heparin will be administered during the procedure as needed to maintain the patient's ACT at ≥ 250 seconds. The sheaths may be removed when ACT level is appropriate (e.g., reaches < 150 seconds) after implantation of the study devices.

7.8.7.3 Post Procedure Therapy

- Patients without other indication for therapeutic anticoagulation should receive antiplatelet therapy with aspirin (acetylsalicylic acid; ASA) (100 mg daily) for at least 6 months. Additionally patients should receive a combination of Clopidogrel (75mg daily) and ASA (100mg daily) for the first month post-intervention.
- In patients with other indications for therapeutic anticoagulation treatment (e.g. atrial fibrillation), triple therapy is not recommended for the first month post-intervention.



- In addition to the recommended anticoagulation/antiplatelet therapy, periprocedural endocarditis prophylaxis should be administered according to current guidelines⁶.

Table 4: Recommended antiplatelet and anticoagulation therapy

Medication	Pre-Procedure	Intra-Procedure	Post-Procedure	Until 1 Month Follow-Up	Until 6 Month Follow-Up
IV Heparin		X	X		
Aspirin (75-100 mg daily)	X		X	X	X
Clopidogrel (75 mg daily)				X	

7.8.7.4 Device Preparation

A description of device preparation and use is provided in the IFU with the CIB. Investigators must be familiar with the information described in the IFU prior to use of the Edwards PASCAL System. An Edwards Representative that has been trained on the preparation of the Edwards PASCAL System will be in attendance at all implant procedures.

7.8.7.5 Implant Procedure

Refer to the current IFU version for detailed information on the use of the Edwards PASCAL System. Delivery of the implant should be performed under general anesthesia with hemodynamic monitoring in an operating room or hybrid operating room with fluoroscopic and echocardiographic (2D and 3D) imaging capabilities.

The following study procedures will occur during the implant procedure:

- Safety Evaluation
- Transesophageal Echocardiogram
- Angiogram
- ECG
- Invasive Hemodynamic Monitoring, including left side heart pressure measurements and cardiac output pre- and post-implant

⁶ 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. J Am Coll Card, Vol 63, No 22, 2014. e57-185.



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.

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

Table 5: Procedure Information

General Information	Clinical Information	Post-Implant Laboratory Measurements
<ul style="list-style-type: none"> • Date of study procedure • Patient identification number • Name of implanting physicians • Access site • Timing of implant procedures • Study device identification & disposition 	<ul style="list-style-type: none"> • Fluoroscopy duration & contrast volume • TEE measurements • Angiographic imaging • Invasive Hemodynamic Monitoring measurements • ECG results • Adverse events • Device malfunction 	<ul style="list-style-type: none"> • Within 12-24 hours post implant: <ul style="list-style-type: none"> - Troponin - CK-MB - CBC and platelets - Serum creatinine - PTT or PT/INR

7.8.7.6 Post Implant Procedure

The following study procedures will be performed 12-24 hours post implant procedure:

- Clinical Evaluation (includes vital signs, weight and height)
- Safety Evaluation Clinical Laboratory Tests
- Standard 12-lead ECG

7.8.7.7 Discharge

The following study procedures will be performed at discharge or at 7 days of procedure, whichever comes first.

- Clinical Evaluation and Concomitant Medication
- Safety Evaluation
- NIH Stroke Scale
- Clinical Laboratory Tests
- Standard 12-lead ECG
- Comprehensive TTE



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

Table 6: Discharge Information

General Information	Clinical Information	Laboratory Measurements
<ul style="list-style-type: none"> • Discharge date 	<ul style="list-style-type: none"> • Clinical evaluation (vital signs, height, weight) • Concomitant medication (incl. antiplatelet/anticoagulant therapy) • Safety evaluation • NIH Stroke Scale/Modified Rankin Scale* • TTE measurements • 12 lead ECG results 	<ul style="list-style-type: none"> • CK • Troponin, if applicable • CK-MB, if applicable • BNP or NT-pro-BNP • CBC and platelets • Serum creatinine • PTT or PT/INR

7.8.7.8 Follow Up Visits

Follow-up visits will be conducted at 1 month, 6 months, and annually for 5 years post implant.

The following procedures will be conducted during follow up visits:

- Clinical Evaluation (includes vital signs, weight and height), concomitant medication and NYHA classification
- Administration of Health Status Questionnaires at 1 month, 6 months and 1 year
- Administration of 6MWT at 1 month, 6 months and 1 year
- Safety Evaluation
- NIH stroke scale/Modified Rankin Scale*
- Clinical Laboratory Tests (troponin (if applicable), CK-MB (if applicable), BNP or NT-pro-BNP, CBC and platelets, complete metabolic panel, serum creatinine, PTT or PT/INR)
- Standard 12-lead ECG
- Comprehensive TTE
- MRI (optional, as deemed appropriate by Investigator).

Post-procedure follow up visits will be performed on all implanted study patients at 1 month, 6 months, and annually for 5 years post implant procedure intervals as summarized in Table 7.



* Modified Rankin Scale (mRS) will be conducted at baseline for all patients with a history of stroke and at each follow visit for all patient who had a stroke at any time period during the trial. The assessment should be done closest to 90 days post event.

Table 7: Follow-Up Visit Windows

Scheduled Follow-up Interval	Follow-up Window
1 month (30 days)	± 7 days
6 months (180 days)	± 30 days
Annually up to 5 years	± 45 days

During the follow up visits, medical information and assessment results will be entered in the appropriate CRFs.

7.8.7.9 Unscheduled Follow-Up

An unscheduled follow-up is defined as a patient's on-site visit (for medical reasons / adverse event/"symptomatic") at cardiac departments (cardiology, cardiac surgery) of an investigational site or outside hospital. Any unscheduled follow-up shall be documented in the medical file and corresponding CRF pages shall be completed.

7.8.7.10 Withdrawal, Missed Visit, and Loss to follow-up

The Investigator will make every attempt to follow the patients at each of the required assessment periods. Patients may be withdrawn from the study for the following:

- **Patient Withdrawal**

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

- **Physician Withdrawal**

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

- **Missed Visit / 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 "missed visit" for that time interval. After two



documented unsuccessful attempts to schedule follow up visits sequentially (e.g., 1 year and 2 year follow-up), the patient will be considered “lost to follow-up.”

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

7.8.7.11 Patient Study Completion

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

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

- Patient signs informed consent form, is deemed eligible and considered provisionally enrolled but does not undergo the study procedure
- Patient undergoes study procedure and does not receive investigational device (will exit study at the 30 day follow up visit)
- Patient undergoes study device explant or removal (will exit study 30 days post-explant or removal)
- Patient withdraws participation from the study or is withdrawn from the study
- Patient is lost-to-follow-up
- Patient expiration



8 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

8.1 Reporting Procedure

Adverse events will be captured from the time of enrollment (after patient eligibility is confirmed, per section 7.8.3) until the study patient's participation has ended (i.e. completion of study or withdrawal of consent).

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 (but no later than 3 calendar days after awareness for patients at EU sites)

Each adverse event must be reported on a separate AE CRF. In the event that the EDC system is not in service or is 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
- Date of event
- Site's awareness date
- AE description
- Causal relationship to device and implant procedure, if known

The site will provide the Sponsor or designee 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.

Study patients will be carefully monitored during the clinical study for any possible adverse event. All adverse events will be fully investigated by the Investigator. Appropriate treatment for the patient will be initiated while the study follow up continues. Adverse events 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 attempt to assess the involvement of the investigational device and / or study procedure in the adverse event. All observations and clinical findings, including the nature or the severity, will be documented on the appropriate case report form.

The Investigator will report all adverse events to their local Institutional Review Board/Ethical Committee and / or National Regulatory Agency in accordance with the applicable requirements.



8.1.1 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 mitral regurgitation or interventional structural heart procedures, or are associated with customary, standard care of patients undergoing transcatheter cardiovascular intervention:

- Post-operative pain (within 48 hour of procedure) not requiring treatment or treated with non-opioids
- Post-anesthesia emesis, nausea, or headache (within 24 hours of procedure).
- 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 WBC in patient with infection)

- Pre-planned future surgical procedures not associated with the study procedure or device.
- Low grade temperature increase ($\leq 101^{\circ}\text{F}$ or 38.5°C) without signs or 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.
- Expected, non-clinically significant events such as non-clinically significant lab variances that do not require treatment.

This listing of findings is intended to provide guidance to the investigational 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.

8.1.2 Pre-existing condition

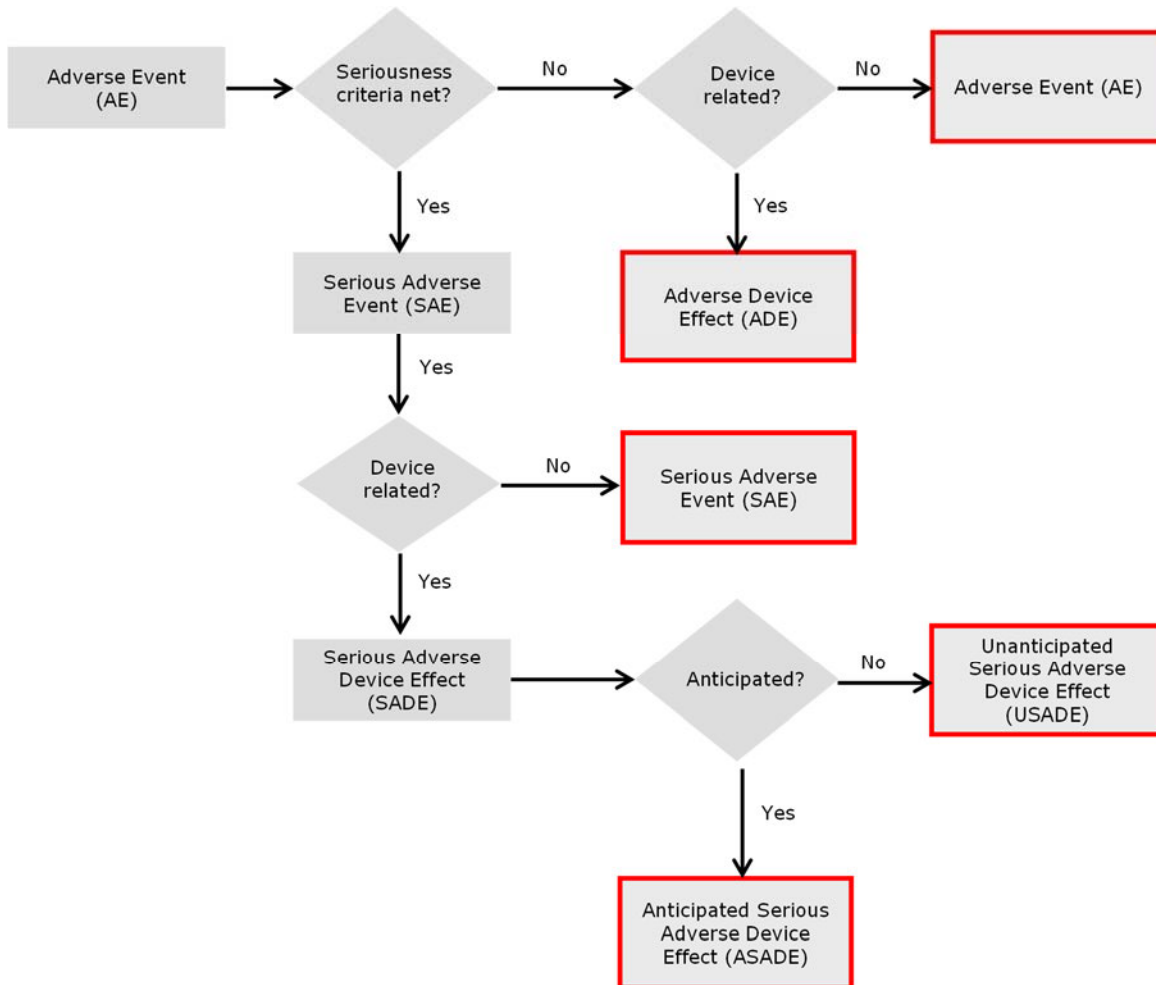


Pre-existing medical conditions or symptoms reported prior to subject enrollment will not be recorded as an AE. In the event there is a worsening in the pre-existing medical condition or symptoms due to the device, implant procedure, or study related procedures, then an AE must be recorded.



8.2 Adverse Event Definitions and Classification

Figure 10: Adverse Event Classification



8.2.1 Adverse Event

An adverse event (AE) is defined in ISO 14155:2011 as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in patients, users or other persons, whether or not related to the investigational medical device.

Note: anticipated adverse events are adverse events that have been identified as possible adverse events related to the investigational medical device or the study procedure. The anticipated events of this clinical study are summarized in Section 6.1.



8.2.2 Adverse Device Effect

An adverse device effect (ADE) is defined in ISO 14155:2011 as any adverse event related to the use of an investigational medical device. This definition includes:

- Adverse event resulting from insufficient or inadequate IFU, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
- Any event resulting from use error or from intentional misuse of the investigational medical device.

8.2.3 Serious Adverse Event

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

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

8.2.4 Serious Adverse Device Effect

A serious adverse device effect (SADE) is defined in ISO 14155:2011 as an adverse device effect that resulted in any of the consequences characteristics of a serious adverse event or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

8.2.5 Unanticipated Adverse Device Effect

Unanticipated adverse device effect (UADE) means 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 subjects. (21 CFR part 812.3 (s)).



8.2.6 Unanticipated Serious Adverse Device Effect

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

8.2.7 Adverse Event Causality Assessment

For each AE, the Investigator will determine whether the event is related to the device and/or the implant procedure, and whether the event meets the definition of a SAE as outlined in section 8.2.3

For the purpose of this study, each AE will be classified according to five different levels of causality per MEDEV 2.7/3 rev. 3 May 2015 as follows:

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 subject are not clearly due to use error;
- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

Possible: the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probable: the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be 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 subject 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 the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

The sponsor and the investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedures and the investigational 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.

8.2.8 Sponsor Assessment of Adverse Events

All AEs will be reviewed by the Sponsor's Clinical Safety department. Each AE will be assessed as to its relationship to the study device and/or implant procedure, whether it was anticipated or not anticipated, (based on the list of potential risks provided in section 6), and whether it qualifies as an SAE.

8.2.9 Device Deficiency and Malfunction

Device deficiency is defined in ISO 14155:2011 as an inadequacy of a medical device with respects to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labeling.

Device malfunction is defined in ISO 14155:2011 as a failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the IFU. All reported device observations, malfunctions or deficiencies for the Edwards PASCAL System are required to be documented on the appropriate eCRF. In the event of a suspected observation or device problem, 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.



8.3 Deaths and Explants

8.3.1 Patient Deaths

In the event of patient death, every effort should be made to obtain a copy of the autopsy report and/or death summary. Information on the cause of death and its relationship to the investigational device or study procedure will be determined by the Investigator. Copies of an autopsy report, if available, and/or a death summary are to be forwarded to the Study Sponsor. If a device is explanted during autopsy, the device should be returned to the Study Sponsor for analysis. Return kits for devices will be provided upon request by the clinical monitor.

8.3.2 Device Explants

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

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



9 STATISTICAL CONSIDERATIONS

9.1 Study Design and Sample Size

This is a multi-center, multi-national, prospective, and single arm study. A total of 60 patients will be enrolled in the study. This sample size is adequate to evaluate the safety and performance of the PASCAL System. Recent studies for CE marking of novel mitral repair technologies (listed in Table 8 below) have used sample size of 30 to 35 patients. A sample size of 30 patients is therefore appropriate to reasonably assess the safety profile and technical performance of the PASCAL device.

The analysis population will consist of 60 patients. No site will be allowed to enroll more than 20% of the analysis population in the primary cohort. In addition, the study allows for 0 to 3 roll-in patients per site, for a total maximum of 60 roll-in patients. The overall study therefore allows for up to 120 patients: 60 in the analysis population, and up to 60 additional roll-in patients.



Table 8. Safety and Performance studies for CE marking of novel devices for the treatment of mitral regurgitation.

Month, Year (CE Mark)	Study Title	Sample Size	Primary Outcome Assessment	Device/Sponsor
Sep, 2011	AMADEUS™ (CARILLON Mitral Annuloplasty Device European Union Study) Source: European Society of Cardiology	30	30 Day	Carillon / Cardiac Dimensions
Sep, 2015	Cardioband Adjustable Annuloplasty System for Transcatheter Repair of Mitral Valve Regurgitation Source: Clinical report on file at Edwards	31	30 Day	Cardioband/ Valtech, Inc.
Feb, 2016	Mitralign Percutaneous Annuloplasty First In Man Study Source: www.clinicaltrials.gov	35	30 Day	MPAS Implant/ Mitralign, Inc.





9.2 Analysis Population

- **Intent-to-treat population**

The intention-to-treat (ITT) population includes all patients in whom the study procedure has been attempted (i.e., incision).

- **Per-protocol population**

The per-protocol (PP) population includes all patients in whom the study device was introduced in the body, and do not have any major protocol deviations.

- **Roll-in population**

Up to three roll-in patients per site may be allowed, but not required (e.g., for sites with sufficient prior experience with the system). The study Sponsor will review each situation to determine when a site may start enrolling in the ITT population.

The PP population will be the primary analysis population for performance and safety assessment. The ITT population will be used for additional safety analysis. Subgroup analysis by etiology may be performed. For patients with mixed etiology, the echo core lab will determine the dominant etiology for analysis.

9.3 Statistical Analysis

A first analysis will be performed when 30 patients complete 30-day follow-up, and a second analysis when all patients in the primary cohort complete their 30-day follow-up. A pooled analysis of all patients from the primary cohort and additional cohort will also be performed. Descriptive statistics will be presented for all primary and secondary endpoints. For quantitative variables, the mean values, standard deviation, maximum and minimum will be calculated. The 95% confidence interval (CI) for the mean will be calculated when relevant.

For qualitative variables, absolute and relative frequencies are determined. Exact binomial 95% confidence interval for proportions will be calculated when relevant.

For combined and individual clinical endpoints the survival rate (and 95% CI) will be calculated using Kaplan-Meier estimator. Kaplan-Meier survival curves will also be presented when relevant.



9.4 Missing Data

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

10 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

10.1 Data Safety Monitoring Board (DSMB) and Clinical Events Committee (CEC)

10.1.1 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) will be the primary independent Data and Safety advisory board for the CLASP Study. The independent DSMB will have the responsibility to assess aggregate safety data (and if requested the critical performance endpoints) on an ongoing basis, evaluate trends of adverse events and their effect on trial conduct and device risk assessment, and to recommend to the sponsor whether to continue, suspend, modify or stop the clinical investigation. The DSMB will communicate all safety-related trial recommendations to the Sponsor.

The DSMB will consist of a minimum of three physician members that are medical experts in the areas of CV surgery, interventional cardiology, and heart failure. The DSMB will also include an experienced biostatistician. Its conduct will be governed by a written DSMB charter describing its rules of operation and responsibilities.

10.1.2 Clinical Events Committee (CEC)

The Clinical Events Committee (CEC) is an independent committee that will provide a standard, systematic and unbiased assessment of pre-determined endpoints to ensure that they are adjudicated uniformly by a single group, using the definitions specified in the Protocol and CEC Charter.

The CEC will consist of a minimum of three members and will be comprised of physicians with expertise in CV surgery, interventional cardiology, heart failure, and neurology.

The scope, procedures, and events classification system will be defined in a written CEC charter.



10.2 Core Laboratory

An echocardiography core laboratory will be used for the independent assessment of image findings. Standard measurement processes will be designed by the independent core laboratory and specified in written core laboratory guidelines. Each of the selected investigative sites will receive training on the acquisition, interpretation (in especially regarding patient selection) and transmission of images. Any additional (unscheduled) imaging data should be documented and sent to Edwards.

10.3 Monitoring

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.

10.3.1 Monitoring Methods

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

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



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

- Institutional Review Board/Ethics Committee and applicable regulatory body approvals have been obtained and documented,
- The Investigator (s) and study personnel are appropriately trained and clearly understand the study,
- The Investigator (s) and study personnel accept the obligations incurred in undertaking this clinical study,
- The Delegation of Authority form has been completed properly.

Periodic monitoring visits will be made at the enrolling study center in accordance with center enrollment rates and / or the monitoring plan. Upon termination or conclusion of the study, the study monitor will perform a close-out visit. Additional details will be included in the Monitoring Plan.

10.4 Data Management

A qualified third party service partner will be used to host the clinical study database. The hosting facility will have a multi-level protected environment, restricted access with high-end user recognition technology, and multi-point backup of critical data. Passwords will be issued to appropriate data management personnel to ensure confidentiality and protection of the data. The Study Sponsor's data management is responsible for providing a clean data set at the end of the clinical investigation. Queries should be resolved by the Investigator or a person designated by the Investigator in a timely manner. Data snapshots will be performed for interim analysis. When all data is complete, the database will be locked and data analyzed.

10.4.1 Data Collection Methods

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

10.4.2 Case Report Forms (CRFs)

Electronic case report forms (eCRFs) will be used to collect all patient data during the trial. 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.



The Investigator, or an individual designated by him/her, is responsible for recording all data from the trial onto the eCRFs on a dedicated website. All data entered may be subjected to data type verification and range checking. The operator is notified of queries that may occur, and depending on the data verification sub-routines (edit checks), the operator might need to resolve that queries before moving to the next entry field. The Investigator is required to provide an electronic signature on the appropriate eCRF pages to verify that he/she has reviewed the recorded data. If for any reason the eCRFs are unavailable, or access to the electronic database is limited, paper CRF forms must be completed and submitted to the sponsor. Completed eCRFs will be reviewed at the investigational site and remotely by authorized Edwards Lifesciences or designee personnel at regular intervals throughout the trial. If a query is discovered, the Clinical Research Coordinator will be notified. Corrections to the eCRFs will be made by the research Study Coordinator, approved by the Investigator or designee and verified by the sponsor.

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

10.4.3 Source Documentation Requirements

The Clinical Research Coordinator designated by the Investigator, and documented on the Delegation of Authority log, will perform primary data collection drawn from source documentation review (patient's medical record). Data to be collected for the study purposes must not be entered directly onto eCRFs. The data shall 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.

10.5 Patient Visits

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



The Investigator or designee shall keep a separate log of the patients' names and current contact information to facilitate their record keeping and ability to contact the patients for future follow-up. If a patient cannot be reached for a follow-up assessment, the Investigator will document the missed visit and effort made to contact the patient or the patient's primary health care provider. Patients who miss a visit will not be considered withdrawn, and an effort to contact them at the next follow-up visit interval will be made by the Investigator.

10.6 Vulnerable Population

Children or patients under guardianships are perceived as vulnerable population. Both subgroups are excluded from this study.

11 DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

11.1 Protocol Deviation

If an Investigator or designee contacts a Clinical Affairs representative to obtain prior approval for a change to the clinical study requirements, the approval or disapproval will be documented in writing. A copy of the approval or disapproval will be forwarded to the Investigator and a copy will be maintained in the study files.

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

- a) Subject implanted/treated with study device not having met eligibility criteria at the time of implant/treatment.
- b) Informed Consent not signed or signed after the initiation of non-standard of care, research related assessments.
- c) UADE not reported to IRB/EC/Sponsor within the required timeframe
- d) Unauthorized use/implant of an investigational device

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



11.2 Audits / Inspections

Study centers may be audited during the course of and after completion of the clinical investigation by Edwards or Edwards' designees, IRB/EC, competent authority or other applicable regulatory authorities.

The Investigator must provide the auditor with all clinical investigation documents including the medical records for all enrolled patients.

Edwards will evaluate any non-compliance and issue corrective actions, discontinue enrolment or, as last measure, close the clinical investigation site.

11.3 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 Study Sponsor. This binder must be made available during monitoring visits and audits.

12 STATEMENTS OF COMPLIANCE

12.1 Applicable Regulations and Guidelines

This clinical investigation will be conducted in compliance with the applicable regulations for the conduct of clinical investigations with human beings, especially with regard to:

- The Declaration of Helsinki (2013)
- ISO 14155:2011
- ICH/GCP current version
- All applicable local and national requirements in the participating countries

12.2 Ethics and Regulatory Bodies

Prior to start of the study, the CIP and other relevant study documents will be submitted for approval by the ethics and regulatory bodies per applicable regional regulations. Edwards will record changes to the CIP in amendments and submitted to ethics and regulatory bodies as applicable. Investigators and study personnel will be trained on all amendments.

All patients must be provided with a written informed consent which is approved by the site's ethics body. Edwards will provide a master English informed consent form and patient information sheet to be used in the study. Each site must provide Edwards with a copy of the clinical site's ethics approval letter or vote and the approved informed consent. The approval



letter must specify the documents for which approval has been granted. Approvals for the continuation of the trial at each clinical site must be kept current and notifications forwarded to Edwards.

12.3 Insurance

Patients who participate in this study will be insured for study related injuries according to local regulatory requirements. Edwards will organize appropriate insurance coverage which will be available throughout the entire study.

12.4 Data Protection and Patient Confidentiality

The Study Sponsor is dedicated to maintaining the confidentiality and privacy of patients who volunteer to participate in the study. Passwords are issued to appropriate personnel to insure confidentiality and protection of the database by allowing variable levels of access to the computer system. In addition, the Principal Investigator is responsible for ensuring confidentiality throughout the clinical study. Hard copies of source documents are to be maintained in a secure area with limited access and duration according to country specific guidelines and regulations. All patient identifiers will be obliterated from all copies of source documents that have been removed from the study site. Patient identifiers include, but are not limited to: patient's name, social security number or equivalent, and medical / hospital number. All study documents for the clinical study will identify the patient by a patient study identification number assigned by the Sponsor and patient initials (if applicable). Subject to the same confidentiality obligations as described above, patient data (including, but not limited to, imaging assessments) collected during the course of this investigation may be used in other Edwards research and development efforts.

12.5 Study Termination

Edwards will monitor the progression of the clinical investigation. If warranted, the clinical investigation may be suspended or discontinued early if there is an observation of serious adverse reactions presenting an unreasonable risk to the clinical investigation population. Edwards may terminate Investigator and site participation in the clinical investigation if there is evidence of failure to maintain adequate clinical standards, failure to comply with the clinical investigational plan, fraud or any other forms of misconduct.

In the event of clinical investigation termination or suspension, Edwards will send a report outlining the circumstances to the corresponding IRB/EC, regulatory body and all Investigators.



A suspended or terminated clinical investigation may not be re-initiated without approval of the corresponding IRB/EC and competent authority.

12.6 Investigator Reimbursement and Contracting

Edwards will reimburse efforts undertaken for inclusion and follow-up of patients, and documentation of patient data within the study. A contract with the principal Investigator and/or the respective hospital will be agreed on and signed prior to study start. Within this, an overall fee per patient, broken down to individual visits, will be included.

This patient fee will cover all expenses for material used and procedures to be performed according to the CIP.

The CIP, and any future changes thereof, will be part of the contract.

13 INVESTIGATOR RESPONSIBILITIES

13.1.1 General Duties

The Investigator shall ensure that all work and services described herein, or incidental to those described herein, shall be conducted in accordance with the highest standards of medical and clinical research practice and the applicable regulations. The Investigator shall be responsible for the day to day conduct of the clinical study and for the safety and well-being of patients enrolled. The Investigator will provide copies of the current study protocol to all staff responsible for study conduct.

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

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

13.1.2 Investigator Records

The Investigator will maintain the accurate, complete, and current records relating to participation in this clinical study. Study records including CRFs and supporting data, signed Clinical Study Agreement, protocols and protocol amendments, signed informed consents, device tracking logs, IRB approval letters, IRB submissions, correspondence, including required reports, and other documents pertaining to the conduct of the study must be kept on file by the



Investigator. If the Investigator wishes to assign the responsibility of maintaining the study files to someone else or move them to another location, he/she should consult with the Study Sponsor in writing regarding the change.

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

13.1.3 Investigator Reports

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

Anticipated and unanticipated serious adverse device effects occurring during the study will be reported as described in section 8.1.

Withdrawal of IRB/EC approval will be reported to the Sponsor within 5 working days

Annual progress reports will be submitted to the IRB/EC.

Deviation from the clinical study protocol. Deviations to protect the patient's life or physical well-being in an emergency will be reported to the Study Sponsor within 5 working days and to the IRB/EC according to their reporting policy.

Use of the study device without informed consent will be reported within 5 working days after the use occurs.

A final written report within three months of completion or termination of the trial.

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

13.2 Sponsor Responsibilities

13.2.1 General Duties

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

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



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

14 STUDY CHANGES

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

15 PUBLICATION POLICY

[REDACTED]

16 ACRONYMS

Acronym	Definition
ACE	Angiotensin converting enzyme
ACT	Activated clotting time
ADE	Adverse Device Effect
AE	Adverse Event
AR	Aortic Regurgitation
ASA	Acetylsalicyclic acid
ASE	American Society of Echocardiography
AV	Atrioventricular
BNP	B-type Natriuretic Peptide
CBC	Complete Blood Count
CEC	Clinical events committee
CI	Confidence interval
CIB	Clinical Investigator's Brochure
CIP	Clinical Investigation Plan.
CK	Creatinine Kinase
CKMB	Creatinine Kinase Muscle/Brain
cm	Centimeter
Cr	Creatinine
CRF	Case Report Form
CRT	Cardiac resynchronization therapy
dl	Deciliter
DSMB	Data Safety Monitoring Board
DMR	Degenerative/Primary Mitral Regurgitation
DVI	Doppler Velocity Index
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECHO	Echocardiography
EDC	Electronic Data Capture
EROA	Effective Regurgitant Orifice Area
EQ-5D	Five Dimensions Quality of Life Questionnaire
F	French
FDA	U.S. Food and Drug Administration
FIH	First-in-Human
FMR	Functional/Secondary Mitral Regurgitation
FUP	Follow-Up
Hg	Mercury
IABP	Intra-Aortic Balloon Pump

ICH/GCP	International Conference on Harmonization / Good Clinical Practice
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IFU	Instructions For Use
INR	Internationalized Normalized Ratio
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-Treat
IV	Intravenous
KCCQ	Kansas City Cardiomyopathy Questionnaire
LV	Left Ventricle
LVAD	Left Ventricular Assist Device
LVEDD	Left Ventricular End Diastolic Diameter
LVEDV	Left Ventricular End Diastolic Volume
LVEF	Left Ventricular Ejection Fraction
LVESV	Left Ventricular End Systolic Volume
LVOT	Left Ventricular Outflow Tract
m	Meter
MAE	Major Adverse Events
MD	Medical Doctor
mg	Milligram
MI	Myocardial Infarction
MLWHF	Minnesota Living With Heart Failure
mm	Millimeter
MR	Mitral Regurgitation
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
MV	Mitral Valve
MVA	Mitral Valve Area
MVARC	Mitral Valve Academic Research Consortium
MVR	Mitral Valve Replacement
N	Number
NIH	National Institutes of Health
NIHSS	National Institutes of Health Stroke Scale
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
OR	Operating Room
PCI	Percutaneous Coronary Intervention
PET	Polyethylene Terephthalate
PI	Principal Investigator



PP	Per-protocol
PT	Prothrombin Time
PTFE	Polytetrafluoroethylene
PTT	Partial Thromboplastin Time
QoL	Quality of Life
Q _p	Pulmonary Blood Flow
Q _s	Systemic Blood Flow
RBC	Red Blood Cell(s)
rHFH	Recurrent heart failure hospitalization
s	Second(s)
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAVR	Surgical Aortic Valve Replacement
SC	Steering Committee
Six (6) MWT	Six minute walk test.
STS	Society of Thoracic Surgeons
TEE	Trans-Esophageal Echocardiogram
TF	Transfemoral
TIA	Transient Ischemic Attack
TMVr	Transcatheter Mitral Valve Repair
TTE	Transthoracic Echocardiogram
USADE	Unanticipated Serious Device Effect
VSD	Ventricular Septal Defect
WBC	White Blood Cell(s)



17 DEFINITIONS

Access site (VARC-1)	Any location (arterial or venous) traversed by a guide-wire, a catheter or a sheath
Access site related complication (VARC-1)	Any adverse clinical consequence possibly associated with any of the access sites used during the procedure
Access site and Vascular Complications (M-VARC 2015)	<p>I. Vascular complications</p> <p>A. Major access site vascular complications, including:</p> <ul style="list-style-type: none"> 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 <p>B. Minor access site vascular complications, including:</p> <ul style="list-style-type: none"> 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)



	<p>II. Cardiac structural complications due to access-related issues</p> <p>A. Major cardiac structural complications, including:</p> <p style="padding-left: 40px;">i. Cardiac perforation* or pseudoaneurysm resulting in death, life-threatening bleeding, hemodynamic compromise, or tamponade, or requiring unplanned surgical or percutaneous intervention</p> <p>B. Minor cardiac structural complications, including:</p> <p style="padding-left: 40px;">i. Cardiac perforation* or pseudoaneurysm not meeting major criteria</p> <p>*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.</p>
<p>Acute Kidney Injury (AKI) (M-VARC 2015)</p>	<p>Acute kidney injury defined as maximal change in sCr from baseline to 7 days post-procedure</p> <p>Stages:</p> <p>Stage 1- Increase in sCr to 150%–199% (1.50–1.99× 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</p> <p>Stage 2- Increase in sCr to 200%–299% (2.00–2.99× increase vs. baseline) or urine output <0.5 ml/kg/h for ≥12 h but <24 h</p> <p>Stage 3- Increase in sCr to ≥300% (>3.0× 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.</p>
<p>Adverse Device Effect (ADE) (ISO 14155:2011)</p>	<p>Adverse event related to the use of an investigational medical device</p> <p>NOTE 1- This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.</p> <p>NOTE 2- This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.</p>



<p>Adverse Event (AE) (ISO 14155:2011)</p>	<p>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 NOTE 1- This definition includes events related to the investigational medical device or the comparator. NOTE 2- This definition includes events related to the procedures involved. NOTE 3- For users or other persons, this definition is restricted to events related to investigational medical devices.</p>
<p>Bleeding (M-VARC 2015)</p>	<p>I. Minor Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that meets ≥ 1 of the following: requiring nonsurgical medical intervention by a health care professional; leading to hospitalization or increased level of care; prompting evaluation; or requires 1 or 2 U of whole blood or packed RBC transfusion and otherwise does not meet criteria for major, extensive, or life threatening bleeding.</p> <p>II. Major Overt bleeding either associated with a drop in the hemoglobin of ≥ 3.0 g/dl or requiring transfusion of ≥ 3 U of whole blood or packed RBCs AND does not meet criteria of life-threatening or extensive bleeding.</p> <p>III. Extensive Overt source of bleeding with drop in hemoglobin of ≥ 4 g/dl or whole blood or packed RBC transfusion ≥ 4 U within any 24-h period, or bleeding with drop in hemoglobin of ≥ 6 g/dl or whole blood or packed RBC transfusion ≥ 4 U (BARC type 3b) within 30 days of the procedure.</p> <p>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.</p> <p>V. Fatal Bleeding adjudicated as being a proximate cause of death. Severe bleeding adjudicated as being a major contributing cause of a subsequent fatal complication, such as MI or cardiac arrest, is also considered fatal bleeding.</p>
<p>Cardiac Tamponade</p>	<p>Pressure on the heart that occurs when blood or fluid builds up</p>



	in the space between the heart muscle (myocardium) and the outer covering sac of the heart (pericardium).
Clinical Success	Procedural success with evidence of MR reduction \leq MR2+ and without MAEs at 30 days. Per patient analysis.
Coagulopathy	A pathologic condition that affects the ability of the blood to coagulate. Examples include hemophilia, drug-induced clotting disorder, thrombocytopenia and Von Willebrand's disease
Congestive Heart Failure (CHF) (STS)	<p>Diagnosis requires physician documentation or report of any of the following:</p> <ul style="list-style-type: none"> • Unusual dyspnea on light exertion • Recurrent dyspnea occurring in the supine position • Fluid retention; or the description of rales, jugular venous distension • Pulmonary edema on physical exam, or pulmonary edema on chest x-ray presumed to be cardiac dysfunction <p>A low ejection fraction alone, without clinical evidence of heart failure does not qualify as heart failure. An elevated BNP without other supporting documentation should not be reported as CHF</p>
Death (M-VARC 2015 Definition and Hicks JACC 2014)	<p>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.</p> <p>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.</p> <p>CV Death The primary cause of CV death will be categorized using the following choices:</p> <ul style="list-style-type: none"> ○ Arrhythmia and/or conduction system disturbance ○ Cardiovascular infection and sepsis (e.g. Endocarditis) ○ Device failure ○ Heart failure ○ Major bleeding ○ Myocardial Infarction



	<ul style="list-style-type: none"> ○ Stroke ○ Sudden, unexpected death / unknown ○ Tamponade ○ Thromboembolism ○ Other CV cause <p>If death was due to a heart failure, it will be sub-classified into:</p> <ul style="list-style-type: none"> ○ LV dysfunction ○ RV dysfunction ○ Biventricular dysfunction <p>Non-CV Death A diagnosis of non-CV death requires the primary cause to be clearly related to another condition due primarily to an identifiable non-CV cause or etiology. Specific diagnoses may include respiratory failure, pneumonia, trauma, suicide, or any other non-cardiovascular defined causes (e.g., liver disease, malignancies etc.) not included in the previous categories.</p> <p>Primary cause of non-CV death The primary cause of non-CV death will be categorized using the following choices:</p> <ul style="list-style-type: none"> ○ Adverse drug reaction or overdose ○ Cancer ○ Gastrointestinal ○ Liver failure ○ Non-cardiovascular infection and sepsis (e.g. pneumonia) ○ Pancreatic ○ Renal failure ○ Respiratory Failure ○ Trauma ○ Other non-CV cause
<p>Degenerative/ Primary Mitral Regurgitation (M-VARC 2015)</p>	<p>Abnormal backflow of blood from left ventricle to left atrium due to underlying degenerative/structural mitral valve pathology. Severity is as defined by ASE.</p>
<p>Device success</p>	<p>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.</p>
<p>Conversion to open mitral valve surgery during a transcatheter</p>	<p>Sub-classified as:</p> <ul style="list-style-type: none"> ○ Secondary to mitral valve apparatus damage or dysfunction, requiring surgical valve repair or replacement, or



procedure	<ul style="list-style-type: none"> ○ Secondary to procedural complications (such as cardiac perforation, removal of an embolized device, and so on)
Effective Regurgitant Orifice Area (ASE)	Cross-sectional area of the vena contracta of the regurgitant jet
Enrollment	Patient enrollment in this clinical study is established when a patient has signed the informed consent form agreeing to participate in the study and has been deemed eligible for study participation by meeting the study criteria.
Explant	Removal of the study device for any reason.
Functional/ Secondary Mitral Regurgitation (M-VARC 2015)	Abnormal backflow of blood from left ventricle to left atrium principally caused by global or regional left ventricular remodeling and/or severe left atrial dilation. Severity is as defined by ASE.
Heart Team	Multidisciplinary team consisting of local experts experienced in the care of patients with mitral valve disease. At a minimum, the heart team should include a heart failure/valve cardiologist, an interventional cardiologist skilled in the relevant access and device implantation procedures, a mitral valve cardiac surgeon, and an imaging specialist.
Implant procedure (Index procedure)	The procedure in which placement of the investigational device in the mitral valve regurgitant orifice takes place
Infection	Known infection requiring intravenous antibiotics for other than prophylaxis, and/or extended hospitalization
KCCQ	Kansas City Cardiomyopathy Questionnaire is an instrument used to quantify physical function, symptoms, social function, self-efficacy and knowledge, and quality of life.
Major Adverse Events (MAE)	Cardiac mortality, stroke, myocardial infarction, new need for renal replacement therapy, severe bleeding, and non-elective cardiovascular surgery for device related complications.
Mitral regurgitation	The condition in which incompetency of the mitral valve causes abnormal backflow of blood from the left ventricle to the left atrium during the systolic phase of the cardiac cycle.



<p>Myocardial Infarction (M-VARC 2015)</p>	<p>I. Periprocedural MI (≤ 48 h after the index procedure)</p> <p>A. In patients with normal baseline CK-MB (or cTn): The peak CK-MB measured within 48 h of the procedure rises to $\geq 10\times$ 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), or to $\geq 5\times$ULN with new pathological Q waves in ≥ 2 contiguous leads or new persistent LBBB, OR 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 $\geq 70\times$ 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), or $\geq 35\times$ ULN with new pathological Q waves in ≥ 2 contiguous leads or new persistent LBBB.</p> <p>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.</p> <p>II. Spontaneous MI (>48 h after the index procedure)</p> <p>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:</p> <p>A. Symptoms of ischemia</p> <p>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</p> <p>C. Imaging evidence of a new loss of viable myocardium or new wall motion abnormality</p> <p>III. MI associated with sudden, unexpected cardiac death</p> <p>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</p> <p>IV. Pathological findings of an acute myocardial infarction</p>
<p>New York Heart Association Classification (NYHA Class)</p>	<p>Class I: Patients with cardiac disease but without resulting limitations of physical activity.</p> <p>Class II: Patients with cardiac disease resulting in slight limitation of physical activity. Patients are comfortable at rest.</p>



	<p>Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.</p> <p>Class III: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation dyspnea, or anginal pain.</p> <p>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.</p>
Nonstructural Dysfunction	Abnormality extrinsic to the repair device that results in valve dysfunction (stenosis, regurgitation or both)
Patient	A person with the disease (mitral regurgitation) being screened to participate in the clinical study.
Pre-existing condition	A pre-existing condition is one that is present prior to enrollment in the trial
Procedural Success	Device success with evidence of MR reduction \leq MR2+ at discharge and without the need for a surgical or percutaneous intervention prior to hospital discharge. Per patient analysis.
Rehospitalization (M-VARC 2015 Definition and Sponsor)	<p>Rehospitalization</p> <p>For the purpose of this trial, rehospitalization 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. ER (Emergency Room) visits will be explicitly presented separately from the inpatient hospitalizations.</p> <p>Rehospitalizations will be classified as either:</p> <ul style="list-style-type: none"> ○ Admission to an inpatient unit (treated by a physician in a hospital for at least a 24 hour period) OR ○ Visit to an ER unit (typically less than 24 hours) AND diagnostic procedure and/or therapeutic intervention <p>Additionally, duration of admission will be indicated as lasting:</p> <ul style="list-style-type: none"> ○ < 24 hours OR ○ \geq 24 hours <p>All rehospitalizations will be classified to determine whether the hospitalization was related to:</p>



- **CHF (Congestive Heart Failure) hospitalization:** a hospital stay for ≥ 24 hours with signs and/or laboratory evidence of worsening heart AND administration of intravenous or mechanical heart failure therapies. An ER stay for ≥ 24 hours would qualify as a CHF hospitalization endpoint, even absent formal hospital admission, as such a prolonged stay represents a severe episode of heart failure.
- **Other CV hospitalization:** hospitalization due for coronary artery disease, acute myocardial infarction, hypertension, cardiac arrhythmias, cardiomegaly, pericardial effusion, atherosclerosis, stroke, or peripheral vascular disease without qualifying heart failure.
- **Non-CV hospitalization:** hospitalization that is not due to heart failure or other cardiovascular causes, as defined above.

Diagnostic Criteria of Heart Failure

The diagnosis of worsening heart failure is on the basis of:

- 1) Symptoms of worsening heart failure such as increased dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, decreased exercise tolerance, and/or history of weight gain
- 2) Physical examination evidence of worsening heart failure such as neck vein distention, the presence of a third heart sound, pulmonary rales, ascites or pedal edema, and/or hypotension or signs of worsening end-organ perfusion; and/or
- 3) Diagnostic evidence of worsening heart failure such as radiographic pulmonary congestion, natriuretic peptide levels greater than the upper limit of normal in the absence of conditions known to affect these values (e.g., renal dysfunction, infection), arterial oxygen desaturation or increasing oxygen requirements, and/or acidosis.

No single finding is necessarily diagnostic, and classification should be on the basis of all available clinical evidence.

Examples of intravenous Heart Failure therapies contributing to this definition would include:

- Bolus or continuous infusion of loop diuretic agents
- Continuous infusion of vasodilators such as Nitroglycerin, Nitroprusside, or Nesiritide



	<ul style="list-style-type: none"> ○ Inotropic agents such as Dobutamine ○ Inodilators such as Milrinone ○ Beta-agonists ○ Vasopressors such as Dopamine, Epinephrine, and Norepinephrine <p>Also included would be other invasive or mechanical heart failure treatments such as:</p> <ul style="list-style-type: none"> ○ Ultrafiltration ○ CRT (Cardiac Resynchronization Therapy) ○ Hemodynamic assist devices including intra-aortic balloon counterpulsation or left ventricular (LV) or biventricular assist devices <p>Treatment with intravenous antiarrhythmic medications or electrical cardioversion and/or ablation in the absence of other intravenous or invasive heart failure treatments would not per se constitute criteria for CHF hospitalization (but would qualify as a cardiovascular hospitalization). Similarly, a CHF exacerbation that can be managed solely by augmentation of oral heart failure therapies does not meet the pre-defined criteria for heart failure hospitalization.</p> <p>Patients hospitalized with heart failure meeting these criteria should further be subclassified into:</p> <ul style="list-style-type: none"> ○ 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. <p>Investigator may need to determine which diagnosis is of prevailing importance (e.g., exacerbation of COPD with bronchospasm and some element of heart failure, or major heart failure exacerbation with secondary bronchospasm). Only primary heart failure should be considered a valid criterion for heart failure hospitalization.</p>
Re-intervention	Any intervention on the previously implanted study device (repair, alteration, or replacement) or study procedure access site post-implant procedure.
Renal Failure	See “Acute Kidney Injury (AKI)”



Renal Replacement Therapy	Treatment that replaces the normal blood-filtering function of the kidneys (e.g. dialysis) due to renal failure (typically Stage 3 AKI)
Serious Adverse Device Event (SADE)	Per ISO 14155:2011: adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
Serious Adverse Event (SAE)	Per ISO 14155:2011: adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) led to fetal distress, fetal death or a congenital abnormality or birth defect NOTE Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.
Severe Bleeding	Severe bleeding is a major, extensive, life-threatening or fatal bleeding, as defined by MVARC.
Screen Failure	A patient who has signed the consent but, does not meet the inclusion criteria or who meets at least one of the exclusion criteria
Subject Withdrawal	A subject who decides not to participate in the study after signing an informed consent form and being enrolled.
Stroke and TIA (M-VARC 2015)	Stroke Diagnostic Criteria: 1) Acute episode of a focal or global neurological deficit with at least one of the following: <ul style="list-style-type: none"> • 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



	<p>2) Duration of symptoms:</p> <ul style="list-style-type: none">• A focal or global neurological deficit \geq 24 hours• A focal or global neurological deficit $<$ 24 hours if available neuroimaging indicates a new intracranial or subarachnoid hemorrhage (hemorrhagic stroke) or central nervous system infarction (ischemic stroke)• The neurological deficit results in death <p>3) No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences) to be determined by or in conjunction with designated neurologist.*</p> <p>4) Confirmation of the diagnosis by at least one of the following:</p> <ul style="list-style-type: none">• Neurologist or neurosurgical specialist, or• Neuroimaging procedure (CT scan or brain MRI)• Non-neurologist physician (if neurologist is not available)• Clinical presentation alone <p>Stroke types will be classified as:</p> <ul style="list-style-type: none">• Ischemic: an acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of the central nervous system tissue• Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage• Undetermined: if there is insufficient information to allow categorization as ischemic or hemorrhagic <p>TIA Acute episode of a focal or global neurological deficit fulfilling the following criteria:</p> <p>1) Resulting in at least one of the following:</p> <ul style="list-style-type: none">• 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
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	<p>2) Duration of deficit could be one of the following:</p> <ul style="list-style-type: none"> • A focal or global neurological deficit < 24 hours • Any available neuroimaging does not demonstrate a new hemorrhage or infarct <p>3) No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences) to be determined by or in conjunction with designated neurologist.*</p> <p>Notes: *Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies. #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.</p>
Tricuspid Regurgitation	Tricuspid Regurgitation (TR), tricuspid insufficiency or tricuspid incompetence describes a condition in which blood flow through the tricuspid valve flows in the incorrect direction during part of the cardiac cycle.
Unanticipated Adverse Device Effect (UADE) 21 CFR part 812.3 (s)	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 subjects.
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report NOTE Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.



18 CHRONIC MR SEVERITY GRADING BY ECHOCARDIOGRAPHY

This table is derived from the 2017 American Society of Echocardiography Native Valve Regurgitation Guidelines.

The only modification of note to the guidelines is the addition of a separate category for Trace MR. This category will be used to characterize regurgitation that is clinically insignificant and too little to quantify. In addition, the core lab overall has also subdivided the moderate MR category into mild-moderate and moderate-severe subcategories.

	Trace (0-1+)	Mild (1+)	Mild-Moderate (2+)	Moderate-Severe (3+)	Severe (4+)
Structural					
MV morphology	None or mild leaflet abnormality	None or mild leaflet abnormality	Moderate leaflet abnormality or moderate tenting	Moderate leaflet abnormality or moderate tenting	Severe valve lesions
LV and LA size	Usually normal	Usually normal	Normal or mild dilation	Normal or mild dilation	Dilated
Qualitative Doppler					
Color flow jet area	Small, central, narrow, brief	Small, central, narrow, brief	Variable	Variable	Large central jet (>50% of LA) or eccentric wall-impinging jet of variable size
Flow convergence	Not visible	Not visible, transient or small	Intermediate in size and duration	Intermediate in size and duration	Large throughout systole
CW Doppler jet	Faint	Faint/partial/parabolic	Dense but partial or parabolic	Dense but partial or parabolic	Holosystolic/dense/triangular
Semiquantitative					
Vena contracta width (cm)	< 0.3	< 0.3	Intermediate	Intermediate	≥ 0.7
Pulmonary vein flow	Systolic dominance	Systolic dominance	Normal or systolic blunting	Normal or systolic blunting	Minimal to no systolic flow / systolic flow reversal
Mitral inflow	A wave dominant	A wave dominant	Variable	Variable	E wave dominant (> 1.2 m/sec)
Quantitative					
EROA (cm ²)	< 0.2	< 0.2	0.20 – 0.29	0.30 – 0.39	≥ 0.40 (may be lower in secondary MR with elliptical EROA)
Regurg Vol (ml)	< 30	< 30	30 – 44	45 – 59	≥ 60 (may be lower in low flow conditions)
Regurg Fract (%)	< 30	< 30	30 – 39	40 – 49	≥ 50

Reference: Zoghbi et al. Recommendations for Noninvasive Evaluation of Native Valve Regurgitation. Journal of the American Society of Echocardiography. Volume 30, Number 4.



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