Edwards PASCAL Transcatheter Valve Repair System Registry: A multicenter observational registry with the Edwards PASCAL Transcatheter Valve Repair System

PASCAL REGISTRY

Registry Protocol
Registry Number: 2019-03
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Effective Date: May 10, 2019

Registry Sponsor:
Edwards Lifesciences, LLC
One Edwards Way
Irvine, CA 92614 USA

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REGISTRY SYNOPSIS

Title	Edwards PASCAL Transcatheter Valve Repair System Registry: A multicenter observational registry with the Edwards PASCAL Transcatheter Valve Repair System
Phase	Post Market Observational Registry
Sponsor	Edwards Lifesciences, LLC One Edwards Way Irvine, CA 92614
Sponsor Contact	[redacted]
Device Name	Edwards PASCAL Transcatheter Valve Repair System
Indications for Use	The Edwards PASCAL Valve Repair System is indicated for the percutaneous reconstruction of an insufficient mitral valve.
Background	This registry will collect prospective and retrospective clinical data on patients treated with the Edwards PASCAL Transcatheter Valve Repair System outside of the Post Market Clinical Follow-up (PMCF) study. Patients will be treated per standard of care at their medical facilities and a written informed consent will be collected to allow the data to be collected. This registry intends to enroll patients under commercial usage and will serve as a mechanism to collect clinical data to further characterize the safety, performance and effectiveness of the PASCAL Transcatheter Valve Repair System.
Registry Objectives	To expand the knowledge of safety, performance and effectiveness of the Edwards PASCAL Transcatheter Valve Repair System.
Registry Design	A post market, prospective and retrospective (where applicable), observational, single-arm, multicenter, registry. Data will be collected on patients receiving the implant in the commercial setting. Available clinical data will be collected prospectively, as it becomes available. Retrospective data collection is allowed for all patients treated in the commercial experience (where applicable). Data on patients will be collected as it becomes available.

Registry Design (cont.)	All participating patients will provide a written informed consent to allow data to be collected in compliance with local privacy laws and regulations.
Data Collection	Patient data, as per the CRF, will be collected. Clinical and echocardiographic data available from routine clinical records will be captured at the following time points: • Baseline: pre-procedural data • Procedural data: data collected as part of the procedure • Discharge data: data collected prior to discharge from hospital • 30 day visit: visit performed between discharge and up to 2 months post procedure • 1 year follow up: visit performed between 10 months and 14 months post procedure
Number of Patients	A minimum of 200 patients will be enrolled in the Registry.
Number of Medical Centers	A minimum of 10 sites in the European Union.
Outcome Measures	**Primary Safety Measures:** • Major Adverse Events (MAE) at 30 days. MAEs – composite of all-cause death, Myocardial Infarction, Stroke, Heart Failure Hospitalization, or complication requiring transcatheter or surgical intervention (repeat PASCAL or Mitral Valve Surgery) **Primary Performance Measure:** • MR reduction to ≤2+ at 30 days and 12 months **Secondary Measures:** 1. Adverse event assessment (all follow up visits) 2. EQ-5D-5L or KCCQ at baseline, 30 days and 12 months, if available 3. 6MWT at baseline, 30 days, and 12 months, if available 4. NYHA assessment at baseline, 30 days and 12 months, if available

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Statistical Analysis	No predefined statistical hypothesis testing will be performed. Only descriptive and summary statistical analysis will be provided for baseline/pre-procedure, procedure, and other follow-up outcome variables.
Enrollment Criteria (Inclusion)	Patients must meet **ALL** of the following criteria to be eligible for the registry: 1. Patients electively treated or electively intended to be treated with Edwards PASCAL Transcatheter Valve Repair System 2. Patients provided written informed consent to participate in the registry.
Enrollment Criteria (Exclusion)	Patients will be excluded from the Registry if they meet the following: 1. Patient is part of an ongoing Edwards Pre or Post Market Clinical study for the PASCAL Transcatheter Valve Repair System.

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1 INTRODUCTION

The PASCAL Transcatheter Valve Repair System is commercially approved in the EU.

1.1 Disease Process

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 is a disease frequently associated with increased morbidity and mortality, [1] and can be characterized by two distinct etiologies: degenerative mitral regurgitation (DMR), and functional mitral regurgitation (FMR). DMR is caused by damage to leaflets or other components of the valve apparatus (e.g. chordae tendinae, papillary muscles). FMR is driven by adverse left ventricular remodeling due to ischemic or non-ischemic myocardial disease.[2-4]

1.2 Anatomy and Pathophysiology of Mitral Regurgitation

The mitral valve is an atrioventricular valve, separating the left atrium from the left ventricle (**Figure 1**). In the normal mitral valve, mitral leaflets coapt during systole to prevent backflow of blood into the left atrium. The mitral apparatus consists of the mitral annulus, mitral leaflets, chordae tendinae, and papillary muscles. The valve itself is saddle-shaped and is a dynamic anatomical structure during the cardiac cycle, playing a crucial role in proper mitral valve coaptation.

Figure 1. The Anatomy and Structure of the Mitral Valve and Mitral Apparatus[5,6]

Initially in MR, patients experience a prolonged asymptomatic period, and if left untreated, may progress to moderate and then severe MR with symptoms such as decreased exercise tolerance and exertional dyspnea.[2] Eventually, chronic MR imposes volume overload on the left ventricle, which results in cyclical worsening of progressive left ventricular (LV) dilatation, LV remodeling, and cardiomyopathy. This may lead to worsening LV failure, pulmonary hypertension, atrial fibrillation and increased mortality.[1] Although MR may be tolerated for a long time in some patients, in others, the progression of heart failure with LV dysfunction may be more rapid.[7] The natural course of severe MR depends on many factors including, but is not limited to, the type of MR, the presence of symptoms, LV function and the presence of atrial fibrillation or pulmonary hypertension.[8] A study of 953 patients with mostly severe FMR (who were considered too high risk for surgery) and were treated with conservative therapy found an annual mortality rate of 26.2%.[9] Similarly, in high surgical risk patients with severe DMR and NYHA Class III/IV symptoms, annual mortality has been reported to be as high as 34%.[10] The risk of death in subjects aged ≥70 years old with moderate or severe MR has been shown to be more than four-fold higher than that of age- and sex-matched subjects with absent or mild MR.[11]

1.3 Etiology

MR can have many underlying etiologies, but the majority of these can be divided into two major categories: degenerative and functional.[12]

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. In the degenerated mitral valve, incomplete coaptation of the mitral leaflets occurs due to prolapse of the leaflets into the left atrium leading to volume overload of the left atrium. DMR is most commonly characterized by mitral valve prolapse (MVP) due to myxomatous degeneration. MVP may be caused by a focal abnormality of a mitral leaflet to involvement of both the anterior and posterior leaflets. MVP may also be due to a flail leaflet (***Figure 2***) which occurs when the leaflet edge, not just the body, is located in the left atrium with free motion.[13] This situation almost always denotes severe DMR and is strongly associated with adverse outcomes.[7,14] Thus, the spectrum of DMR may range from lesions from simple chordal rupture involving prolapse of an isolated segment to multi-segment prolapse involving one or both leaflets with significant excess tissue which is characteristic of Barlow's disease (***Figure 3***).[15,16]

Figure 2. Degenerative MR: Prolapse and Flail[17]

Figure 3. Spectrum of Degenerative Mitral Disease FED: fibroelastic deficiency[16]

In contrast, functional mitral regurgitation (FMR), also known as secondary MR, is most commonly a disease of the LV. FMR 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 prevents proper leaflet coaptation (***Figure 4***).

Figure 4. Mechanism of Functional Mitral Regurgitation: A) normal mitral valve B) ischemic mitral valve with pronounced posterior restriction in P3 after an episode of ventricular ischemia[18]

In summary, MR is nearly two separate diseases with different definitions, different therapies, and different outcomes,[19] thus, it is important to distinguish primary/DMR from secondary/FMR as therapeutic approaches and outcomes differ.[20]

1.4 Prevalence of Mitral Regurgitation

Mitral regurgitation (MR) is generally considered to be the most common heart valve disorder worldwide[21] with a high prevalence particularly in industrialized nations with aging populations. MR and aortic stenosis are the two most common VHDs in Europe and in the United States. Unfortunately, precise estimates of MR prevalence are difficult due to lack of large scale epidemiological studies, however, studies suggest the burden of MR is high.[22]

In a large prospective echocardiographic study of 79043 patients in the UK who were referred for echocardiography for suspected heart failure, approximately 12.5% had mitral regurgitation.[23]

The 2007 Euro Heart Survey was a large prospective study designed to assess the detailed clinical and echocardiographic characteristics of 5001 patients referred to hospital for the management of valvular heart disease. Among this cohort, the survey found that MR was the second most common valvular disease (after aortic stenosis) accounting for 32% of the valvular etiology as shown in ***Figure 5***. Despite this prevalence in the European population, the same study suggested that patients were frequently denied surgical treatment.[21]

Figure 5. Distribution of Valvular Heart Disease Etiologies' by European Region[24]

Similarly, in the United States, MR is the most common valvular heart disease affecting approximately 2 million individuals with 250,000 new diagnoses annually[22,25] or approximately 1.7-2% of the general population.[22] The Framingham Study reported a prevalence of 19% MR equal to or more than mild severity.[26] The prevalence and severity of MR increases with age, with significant MR affecting nearly 10-11% of the U.S. population aged >75 years and is associated with increased morbidity and mortality in the setting of left ventricular dysfunction and heart failure symptoms.[22,26,27] Due to the aging and growth of the US population, it is estimated that up to 4.0-5.0 million individuals will be affected by MR in 2030.[22]

Amongst those with severe MR, the predominant mechanism of MR has been shown to be up to 74% for functional MR (FMR) and approximately 21% for degenerative MR (DMR),[1] with some MR patient populations demonstrating upwards of 44% DMR.[21] While DMR represents the minority of MR patients, it does affect about 2% of the general population, with 4% of this subset experiencing severe DMR.[16,28]

FMR, in particular, may be underestimated since patients often present with heart failure due to left ventricular systolic dysfunction rather than with valvular disease itself.[29] Moreover, FMR is often clinically silent and may not be apparent unless echocardiography or other imaging is performed.[30] In Europe, FMR, has been shown to be prevalent in patients with non-ST segment elevation acute coronary syndrome.[31] Similarly, extrapolations of patients with heart failure in

the United States suggest that the burden of severe FMR is high in the community, particularly in patients with recent myocardial infarction.[24,32]

Despite the prevalence of MR in developed countries in the EU and the U.S. even in communities with well-equipped medical facilities and good access to treatment, the vast majority of patients with moderate-to-severe isolated mitral regurgitation are not referred for surgical treatment.[21] Given the high incidence of heart failure associated with MR, poor outcomes, and severe excess mortality across all subgroups (including patients with moderate MR), the authors strongly suggested that their data represented a "call for action" to expand MR treatment options in all subsets of patients.[21]

1.5 Diagnostic Assessments for Mitral Regurgitation

Transthoracic echocardiography (TEE) is the principal investigational tool used to assess the severity and mechanism of mitral regurgitation as well as the likelihood of repair, however if the TTE image is suboptimal, then transesophageal echocardiography (TOE/TEE) is recommended.[33]

Patients with DMR should be differentiated from patients with other forms of mitral disease such as FMR or rheumatic heart disease[16] as therapeutic approaches and outcomes differ.[20] Echocardiography is the diagnostic method of choice to assess MR, particularly for DMR, and is essential to identify the etiology and underlying lesions affecting leaflet morphology. The precise morphology classification is necessary to predict the success of leaflet repair surgery and can usually be ascertained from transthoracic echo (TTE). However, transesophageal echo (TEE) should be performed if TTE is inconclusive and is currently systematically performed prior to mitral repair surgery.

The severity of mitral regurgitation can be quantitated by several approaches, including calculation of regurgitant volumes and fraction from calculation of volume flow rate at two intracardiac sites, from the proximal isovelocity surface area, or by measurement of the vena contracta on color flow imaging.[6] Specific echocardiographic parameters that are important for clinical decision making are the degree of left ventricular dilation, left ventricular systolic function, left atrial enlargement, and pulmonary hypertension.[6]

In addition to echocardiography, emerging imaging technologies such as cardiac magnetic resonance imaging may provide new possibilities of imaging the entire mitral valvular apparatus and lend further diagnostic importance in the assessment of DMR.[34,35]

1.6 Treatments and Therapies for Mitral Regurgitation

The presence of MR leads to progressively more severe MR ("mitral regurgitation begets mitral regurgitation").[36] For DMR, the restoration of mitral competence with mitral repair removes the hemodynamic burden responsible for the eventual deterioration in left ventricular (LV) function,

[redacted]

may restore LV function if it was already depressed, and improves both the quality of life and longevity.[37-39]

Moreover, growing evidence suggests that earlier and aggressive surgical intervention with mitral valve repair for severe DMR in asymptomatic patients leads to better outcomes than "watchful waiting".[40-42] The development of even mild DMR symptoms by the time of surgical referral is associated with worse prognosis and deleterious changes in cardiac function, therefore, early surgery in these patients is justified.[43,44] Both the European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines and the American Heart Association (AHA)/American College of Cardiology (ACC) Guidelines for the Management of Valvular Heart Disease recommend early intervention for asymptomatic patients with severe degenerative mitral regurgitation.[33,36,45-47]

The current 2017 ESC/EACTS Guidelines for the Management of Valvular Heart Disease (***Figure 6***) also recommend mitral valve surgical repair (whenever possible) over valve replacement for symptomatic patients with chronic, severe DMR with ejection fractions >30%. For patients who are not candidates for surgery, medical therapy may be considered. Transcatheter mitral valve repair (TMVr) is currently considered to be a Class IIb recommendation in both Europe the U.S.[33,36] and should be discussed by the Heart Team in symptomatic patients who are at high surgical risk or are inoperable.[33]

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 treatments for FMR is controversial.[48,49] ESC/EACTS Guidelines recommend optimal medical therapy as the first step in FMR management, however if symptoms persist after optimization of conventional heart failure therapy, mitral valve intervention should be evaluated.[33]

[redacted]

Figure 6. 2017 ESC/EACTS Guidelines for the Management of DMR[33]

1.6.1 Surgical Intervention of the Mitral Valve

Surgical intervention is typically required to correct the leaflet pathology in patients with severe DMR. The current "gold standard" of treatment for DMR[50] is surgical mitral valve repair as it results in improved symptoms and is often curative. Surgical mitral valve repair is preferred over replacement as outcomes such as long-term survival, freedom from valve-related adverse events and preservation of left ventricular function have shown to favor repair.[51,52]

Surgery is traditionally performed through a full median sternotomy which requires extracorporeal circulation, however, right lateral mini-thoracotomy and partial sternotomy are performed in many centers.[53] Surgical repair of the abnormal structural mitral valve apparatus are based on three major targets, namely restitution of physiological leaflet motion, establishment of an adequate line of leaflet coaptation, and stabilization of the annulus while maintaining an adequate size of the mitral orifice.[50] Depending on the specific type of valvular lesion and degree of leaflet dysfunction underlying the DMR etiology, surgical mitral valve repair

techniques may include edge-to-edge repair of the anterior and posterior leaflets, annuloplasty, artificial chordal implantation or transfer, leaflet resection, papillary muscle repositioning, and commissural closure are performed.[51]

When performed before LV dysfunction has occurred, mitral repair maintains LV function and restores lifespan to normal when practiced in expert hands.[9,43] Unfortunately, it is estimated that up to 50-70% of DMR patients do not receive surgical mitral valve repair or replacement.[21,54] Indeed, a study of the Society of Thoracic Surgeons (STS), showed that the average U.S. surgeon performed fewer than half a dozen mitral operations of any kind in a year.[21,55]

While surgery is the standard of care for DMR, in patients with severe FMR, the presence of multiple comorbidities often precludes surgical repair due to age and or comorbidities preventing prolonged operative times. Mitral valve replacement with preservation of the subvalvular apparatus is favoured[33] as outcomes when the subvalvular apparatus is disrupted are worse.

In general, replacement is associated with worse outcomes than repair particularly for younger patients as the durability of repair has been demonstrated in several studies.[39,56-58] Silaschi et al. also demonstrated superior results of repair compared to replacement in both short and long term survival in elderly patients as have several previous studies and meta-analysis comparing repair to replacement.[59] While increased age and comorbidities may explain the higher mortality of replacement patients, the poorer outcomes may also be due to the lack of preservation of the subvalvular apparatus. This may indicate a need to consider increasing use of other interventional repair options as an alternative to surgical valve replacement in patients with FMR.[60]

1.6.2 Medical Management of Mitral Regurgitation

In symptomatic patients with chronic DMR in whom surgery is not performed or delayed, medical therapy for systolic dysfunction is considered reasonable, however no known medical therapy has been shown to alter the natural history of patients with severe primary mitral regurgitation. While diuretics and afterload reduction might relieve signs and symptoms of heart failure, the ultimate treatment is intervention.[56]

For patients who are symptomatic with severe primary mitral regurgitation, a standard regimen for heart failure, including beta-adrenergic blockade, angiotensin-converting inhibitors (ACE inhibitors) or angiotensin II receptor blockers (ARBs) is recommended to treat symptoms.[2] However, medical therapy has a limited role in the treatment of DMR as it fails to address the underlying pathology of mitral valve mechanical incompetence. Importantly, no medical treatment has been shown to be effective in preventing the consequences of volume overload in asymptomatic DMR[15] and should not delay consideration of surgical intervention in patients with symptoms or evidence of left ventricular systolic dysfunction.[6] In FMR patients, medical

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

1.6.3 Cardiac Resynchorization Therapy

Cardiac resynchronization therapy (CRT) may provide benefits for patients with chronic, severe FMR in the presence of conduction abnormalities. Conduction abnormalities can cause cardiac wall motion that exacerbates MR. It has been reported that CRT combined with an implantable cardioverter-defibrillator (ICD) can reduce death and hospitalizations for heart failure.[61] While this therapy has been shown to improve quality of life and exercise tolerance, it is applicable only to those with conduction abnormalities. Additionally, an increase in certain adverse events, such as lead interactions or dislodgements, and infections has been seen after CRT which can lead to prolonged hospitalization.[61]

1.6.4 Transcatheter Replacement of the Mitral Valve

Given the clinical need to treat high surgical risk patients with severe DMR, several percutaneous mitral valve replacement technologies, either via transapical, transatrial, or trans-septal approaches have been developed and are in the early stages of pre-clinical and clinical evaluation.[62,63] Early feasibility has been demonstrated with a few investigational devices, [64,65] however, no TMVR technologies for the indication of native mitral regurgitation are commercially available yet. Some of the challenges experienced in the initial phases of clinical validation include the mitral valve position, its proximity of the left ventricular outflow tract, complex anatomy, valve sealing, and prosthesis anchoring and annular retention.[63]

1.6.5 Transcatheter Mitral Valve Repair (TMVr)

Despite the excess mortality associated with MR, a significant number of patients with MR are not referred for surgery as they may be considered inoperable or at high surgical risk because of age or comorbidities. Moreover, recent evidence points towards a substantial unmet need for treatment of DMR, even in patients with normal ejection fractions, low comorbidity, and considered low risk for surgery.[21] Thus, the role of transcatheter therapy shows promise in providing MR patients another therapeutic option to surgery or medical treatment.

Various TMVr technologies have been developed and can be grouped by the treatment area: leaflet repair, direct annuloplasty or indirect annuloplasty via the coronary sinus, and chamber (LV) remodeling. The development of these TMVr techniques show promise as an important alternative treatment option for high-risk surgical patients with severe MR.

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Reports on MitraClip System

The MitraClip Delivery System (Abbott, Santa Clara, CA) received its CE-Mark in 2008 for the treatment of MR (FMR and DMR). In the U.S., the MitraClip system has only been approved to treat DMR patients, and is more specifically indicated "for the percutaneous reduction of significant symptomatic mitral regurgitation (≥ 3+) due to primary abnormality of the mitral apparatus [degenerative MR] in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team."[66]

The MitraClip System delivers a clip-based device via a transfemoral and transseptal route to create an edge-to-edge repair to coapt the mitral valve leaflets which is based on the surgical double-orifice technique, also known as the Alfieri repair[67,68] as shown in ***Figure 7***.

Figure 7. Alfieri Repair Using Edge-to-edge Suture Technique[67]

EVEREST I was the Phase I, early feasibility study (EFS) of the MitraClip System and enrolled 55 patients (93% DMR) across 11 sites in the United States. The results of this EFS demonstrated that percutaneous repair with the MitraClip System could be safely accomplished with low rates of morbidity and mortality with acute MR reduction ≤ 2+ in the majority of patients.[69] Following the EFS, was EVEREST II, which was a pivotal, randomized controlled trial (N=279) comparing the MitraClip System to surgical repair or replacement where approximately 75% of patients presented with DMR at baseline. The results of this trial further demonstrated that the TMVr procedure was associated with superior safety and similar improvements in clinical outcomes to surgery, although it was still less effective in reducing MR compared to surgery.[70] EVEREST II HRR (High Risk Registry) and the REALISM HR (High Risk) were both registry studies conducted to provide additional safety and performance data. Glower et al. presented the results for the high risk cohort in these registry studies and concluded that TMVr with MitraClip was feasible, relatively safe and was effective in reducing symptoms and improving clinical status in this high-risk group of patients who were unlikely to receive surgery to reduce MR. [71]

To date, the short and long-term (5-year)[72] clinical data have demonstrated that percutaneous mitral repair procedures are uniformly well tolerated even in high risk patients with over 60,000 patients worldwide having undergone the MitraClip procedure.[73] Accordingly, the 2017 update to AHA/ACC Guidelines for the Management of Valvular Disease, considers TMVr procedures to be a Class IIb recommendation for severely symptomatic patients (NYHA class III to IV) with chronic severe primary MR (stage D) who have "*favorable anatomy* for the repair procedure and a reasonable life expectancy but who have a prohibitive surgical risk…".[36]

There remains, however, a subset of patients seen in clinical practice with unfavorable anatomy due to leaflet morphology and other criteria that may not be suitable for the MitraClip procedure and may make TMVr technically more demanding.[74-76] The exclusion criteria used in the EVEREST II trial[70] excludes a sub-population of patients which present in real-world clinical practice. Franzen et al. demonstrated that patients who had severely abnormal mitral morphology or severe LV dysfunction (and thus, ineligible for EVEREST II), had lower rates of MitraClip device success, often required more than one clip, and had higher rates of clip detachment.[75] Lesevic et al. also showed that patients who did not fulfil the EVEREST II criteria were less likely to have device success and had higher rates of reintervention due to mitral valve dysfunction.[77] Due to the spectrum of DMR pathologies with different leaflet anatomies and tissue characteristics, expanded MitraClip application is currently limited by device factors which influence the device's gripping quality of the leaflets.[76] Moreover, the device is associated with some intrinsic characteristics and dimensions which limit maneuverability of the system and may restrict its use in complex anatomical settings.[76,78]

1.7 Prior Clinical Experience With the PASCAL System

1.7.1 Compassionate Use Experience of the PASCAL System in Treating Mitral Regurgitation

Praz et al. (2017) published the 30-day results of the PASCAL System in an early feasibility, first-in-man, compassionate use experience of 23 patients with severe MR with either FMR (52%) or DMR (26%) or mixed etiologies (22%). Despite the anatomical complexity of this compassionate use population, technical success was 96% while device success was in 76% of the cohort. The 6-month results with 29 patients (28% DMR) were presented by Webb (2017)[78] and demonstrated high rates of MR ≤ 2+ (95%) and NYHA I/II functional status (100%) and a low rate of second device requirement (25%). Major adverse events were low in this high risk/inoperable population; mortality was 0% and 10% during the procedure and at 30 days, respectively. [78] These early results demonstrate the safety and feasibility of TMVr with the PASCAL System in patients with complex anatomies and suggests that the device addresses an unmet clinical need in both DMR and FMR patients.[76]

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1.7.2 The CLASP Study

The Edwards PAS**C**A**L** Tr**A**n**S**catheter Mitral Valve Re**P**air System (CLASP) Study is a multi-national, prospective, single-arm study aimed to assess the clinical safety and outcomes of the PASCAL System in treating adult patients with clinically significant, symptomatic, mitral regurgitation despite optimal medical therapy (NCT03170349).

The primary safety endpoint is a composite of major adverse events at 30 days, which include cardiovascular mortality, stroke, myocardial infarction, new need for renal replacement therapy, severe bleeding, and re-intervention for study device-related complications. The primary performance endpoints of the study include device success, procedural success, and clinical success. Device success is defined as device deployment as intended and successful delivery system retrieval as intended at the time of the patient's exit from the cardiac catheterization laboratory. Analysis of device success was performed per device. Procedural success is defined as device success with MR severity ≤2+ at discharge (Echo Core Lab-evaluated) and without the need for a surgical or percutaneous intervention prior to hospital discharge. Procedural success was analyzed per patient. Clinical success is defined as procedural success with evidence of MR reduction MR ≤ 2+ and without MAEs at 30 days (analyzed per patient). Secondary endpoints of the study include clinical, safety, and functional outcomes at 30-day, 6 month, 1 year, and annual follow-up time points. All patients are assessed for clinical follow-up at 30 days, 6 months, 1 year, and annually for 5 years post-implant procedure. Patient follow-up is ongoing.

An independent core lab assessed all echocardiographic data. An independent clinical events committee (CEC) adjudicated safety events and a data safety monitoring board (DSMB) independently reviewed aggregate safety data and evaluated trends of adverse events and their effect on trial conduct and device risk assessment.

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In summary, the results of the CLASP study supports the safety and performance of the PASCAL System in treating patients with clinically significant, symptomatic, MR despite optimal medical therapy.

2 DEVICE

2.1 General Device Description

The Edwards PASCAL Transcatheter Valve Repair System is described in detail in the Instructions For Use (IFU). IFU will be provided to the sites and Ethics Committees (ECs) and a copy is part of the Trial Master File and Investigator Site File.

All devices used in this Registry are CE marked therefore device accountability records will not be maintained.

2.2 Device Components

The PASCAL System includes the following four main subsystems: the Implant System, the Guide Sheath, the Stabilizer and the Table.

Complete device description and components can be found with the product Instructions For Use (IFU).

3 REGISTRY OBJECTIVES AND DESIGN

3.1 Registry Objectives

The objective of the registry is to expand the knowledge of safety, performance and effectiveness of the Edwards PASCAL Transcatheter Valve Repair System.

This registry will collect prospective and retrospective clinical data on patients treated with the Edwards PASCAL Transcatheter Valve Repair System outside of the Post Market Clinical Follow-up (PMCF) study.

Patients will be treated per standard of care at their medical facilities and a written informed consent will be collected to allow the data to be collected. This registry intends to enroll patients under commercial usage and will serve as a mechanism to collect clinical data to further characterize the safety, performance and effectiveness of the PASCAL Transcatheter Valve Repair System.

3.2 Outcome Measures

3.2.1 Primary Safety Measures

- Major Adverse Events (MAE) at 30 days. MAEs – composite of all-cause Death, Myocardial Infarction, Stroke, Heart Failure Hospitalization, or complication requiring transcatheter or surgical intervention (repeat PASCAL or Mitral Valve Surgery)

3.2.2 Primary Performance Measure

- MR Reduction to ≤2+ at 30 days and 12 months

3.2.3 Secondary Measures

1. Adverse event assessment (all follow up visits)
2. EQ-5D-5L or KCCQ at baseline, 30 days and 12 months, if available
3. 6MWT at baseline, 30 days, and 12 months, if available
4. NYHA assessment at baseline, 30 days and 12 months, if available

3.3 Number of Planned Patients

All patients treated with the commercially available PASCAL Transcatheter Valve Repair System and who are not part of any ongoing PASCAL pre or post market study, will be asked to participate in this registry. A minimum of 200 patients are expedited to be enrolled in the registry at sites performing transcatheter valve repair where commercialized PASCAL Transcatheter Device is available.

A patient will be considered enrolled in the registry once the patient has signed the ICF and the procedure has begun (defined as PASCAL guide sheath is inserted into the vasculature).

3.4 Number of Planned Registry Sites

A minimum of 10 sites will be activated for the Registry.

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3.5 Inclusion Criteria

Patients must meet all of the following criteria to be eligible for the Registry:

1. Patients electively treated or electively intended to be treated with Edwards PASCAL Transcatheter Valve Repair System.
2. Patient provided written informed consent to participate in the registry.

3.6 Exclusion Criteria

Patients will be excluded from the Registry if they meet the following:

1. Patient is already part of an Edwards Pre or Post Market Clinical study for the PASCAL Transcatheter Valve Repair System.

3.7 Registry Exit Criteria and Procedures

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

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

- Completion per Protocol
- Withdrawal
    - Patient Withdrawal: The patient may voluntarily withdraw from the registry at any time, without penalty or loss of benefits to which they are otherwise entitled.
    - Physician Withdrawal: The Investigator also has the right to withdraw a patient if s/he feels it is in the best interest of the patient to do so.
    - Sponsore Withdrawal: The Sponsor may prematurely terminate the Registry.
- Death
- Device Reintervention or Explant
    - Patients who have a surgical reintervention where the device is explanted will be followed for 30 days post-reintervention or until resolution of any adverse events related to the procedure and then exited from the registry. Patients that have a percutaneous or surgical reintervention where the device remains in place will continue to be followed for the duration of the registry.

- Lost to Follow-up
    - If a patient cannot be reached for a follow-up visit, the Investigator will document the contact efforts made to the patient and/or effort to obtain hospital records in the appropriate electronic case report form. If the patient cannot be reached in any way, or misses a visit, the patient will be considered "unable to contact" for that time interval. After three (3) documented unsuccessful attempts to make contact prove unsuccessful, a certified letter will be sent to the patient's residence. If there is no response after the certified letter is sent, the patient will be considered "lost to follow-up".
    - For patients who are lost-to-follow-up or withdraw early, Edwards may request the site to search death registries as available or applicable per GDPR requirements and may request the site to obtain the death certificate, if applicable.

In all cases of withdrawal (as described above), no additional data will be collected.

All data collected up until the time of withdrawal will be analyzed and will be retained for the duration of the registry.

4 PROCEDURES AND METHODS

4.1 Site Personnel Training

To ensure uniform data collection and protocol compliance, training is required for relevant registry site personnel in accordance to roles outlined in the Individual Delegation of Authority Log.

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

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

4.2 Registry Training

An initiation visit for each participating investigation site or, alternatively, a training teleconference shall be conducted and documented by the sponsor or monitor at the beginning of the registry. A log shall be initiated identifying names, initials, signatures, functions, and designated authorizations for the principal investigator and members of the registry site team.

4.3 Informed Consent

The registry investigator(s) and/or delegated registry personnel will approach patients who are candidates for treatment with the PASCAL System to assess their interest in participating in the registry by providing them an overview of the registry. If patients are interested in allowing their data to be used for the registry, the patient will sign the EC-approved informed consent form (ICF) prior to any data being collected.

A patient will be considered enrolled in the registry once the patient has signed the ICF and the procedure has begun (defined as PASCAL guide sheath is inserted into the vasculature).

The Sponsor must approve any modifications to the Informed Consent Form prior to submission to the EC, and/or local regulatory agencies (as required).

Failure to provide informed consent renders the patient ineligible for the registry.

The consent form will be written in the native language of the patient and administered only by the Investigator or EC-approved persons.

The Investigator or delegated person administering the consent must sign and date the ICF to indicate that the purpose of the registry were explained to the patient.

The signed ICF must be retained by the registry site for verification during on-site monitoring visits.

4.4 Patient Treatment

Patients will be treated according to standard of care at their medical facilities and no additional tests or procedures will be performed.

4.5 Data Collected

Routine clinical (such as Medical History, Risk Factors, Medication, Clinical Status, Procedure Information and Safety data) and echocardiographic data available from clinical records will be collected for the following time points:

- Baseline: pre-procedural data
- Procedural data: data collected as part of the procedure
- Discharge data: data collected prior to discharge from hospital
- 30 day visit: visit performed between discharge and up to 2 months post procedure
- 1 year follow up: visit performed between 10 months and 14 months post procedure

4.6 Description of Data to Be Collected

Throughout the registry participation, sites will collect patient data per the relevant CRFs in the EDC, as available.

If a patient is followed up in a different location, an effort should be made to obtain copies of source documents from the outside medical facility and kept in the patient's registry file.

Please refer to registry CRF for specific patient level data collected in this registry.

4.7 Registry Termination and Close-Out

The investigator will be notified in writing upon termination/conclusion of the registry. The sponsor retains the right to suspend or terminate this registry at any time.

5 DATA COLLECTION AND REPORTING

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

5.1 Case Report Forms (CRFs)

Patient data will be recorded in a limited access secure electronic data capture (EDC) system. The investigator, or an individual designated by the investigator, is responsible for entering all data from the trial into the eCRFs hosted on a dedicated website. Electronic CRFs must be completed with as much information as possible for each patient, and signed electronically by the investigator and/or designee. The eCRFs should be completed at the first earliest opportunity.

All data entered may be subject to data validation checks (e.g. format, range checks). The site designee is notified of data discrepancies and will need to resolve those queries.

The investigator is required to provide an electronic signature on the appropriate eCRF pages which will serve as confirmation that the recorded data has been reviewed in compliance with local regulation.

[redacted]

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The sponsor or designee may perform source documentation verification. If further data discrepancies are discovered during the site visit, queries will be generated and will be addressed by the registry site.

5.2 Source Documentation Requirements and Record Retention

All data entered into the eCRFs must have source documentation available in the patient medical records. The data must be recorded from original source documents and available for review by the registry monitor. Regulations require that investigators maintain information in the registry 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.

The investigator will maintain, at the registry center, in original format all essential registry documents and source documentation that support the data collected on the registry subjects in compliance with relevant sections of ICH/GCP and ISO14155 guidelines. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product (or longer if required by local regulations). These documents will be retained for a longer period of time by agreement with the sponsor or in compliance with other local regulations. It is the sponsor's responsibility to inform the investigator when these documents no longer need to be maintained. The investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and the sponsor must receive written notification of this custodial change.

5.3 Quality Control and Assurance Procedures

Because of the potential for errors and inaccuracies in entering data into eCRFs, originals or photocopies of all relevant procedural records and reports, post-procedural examinations, laboratory and other test results may be kept on file in the investigator's patient registry files. Access to eCRFs and copies of test results must be available at all times for inspection by the registry monitor.

Registry sites may be monitored periodically by a registry monitor employed or contracted by Edwards for protocol adherence, accuracy of eCRFs, and compliance to applicable regulations. Evident patterns of non-compliance with respect to these standards may be cause for the site to

be notified in writing that they will be put on probation for a period of one month. If corrective actions are not subsequently undertaken, the registry site may be asked to withdraw.

The sponsor will provide data management through a secure, password protected EDC system accessible via the Internet. Passwords will be issued to appropriate data management personnel to ensure confidentiality and protection of the data by allowing variable levels of access to the computer system.

6 ADVERSE EVENT REPORTING AND ASSESSMENTS

The below described Adverse Events, Interventions and Surgeries will be captured in the eCRF for all registry patients from the time of procedure until the patient's participation has ended (i.e. completion of Registry or withdrawal of consent):

Intra or post procedure events:

Bleed/Vascular: Bleeding at Access Site, Hematoma at Access Site, Retroperitoneal Bleeding, Gastrointestinal Bleed, Gastro Urogenital Bleed, Other Bleed, Transseptal Complication.

Vascular: Major Vascular Complication, Minor Vascular Complication

Additional Procedures: Mitral Valve Re-intervention, Unplanned Other Cardiac Surgery or Intervention (not MVR), Unplanned Vascular Surgery or Intervention (for Bleeding or Access Site Complication), Atrial Septal Defect Closure Due To Transseptal Catheterization

At follow up visits (30 days through annual visits)

Cardiac events: Atrial Fibrillation (new onset), Endocarditis, Myocardial Infarction

Neuro Events: Transient Ischemic Attack, Ischemic Stroke, Hemorrhagic Stroke, Stroke (Undetermined Type)

Device/Delivery System Events: Device Embolization, Single Leaflet Device Attachment, Device Thrombosis, Other Device/Delivery System Related Event

Renal Events: New Requirement for Dialysis

Vascular: Major Vascular Complication, Minor Vascular Complication, Major Bleeding Event, Life Threatening bleeding

Additional Procedures: Mitral Valve Re-intervention, Unplanned Other Cardiac Surgery or Intervention (not MVR), Unplanned Vascular Surgery or Intervention (for Bleeding or Access Site Complication), Atrial Septal Defect Closure Due To Transseptal Catheterization

[redacted]

Readmission: Readmission – Heart Failure, Readmission – Cardiac (not Heart Failure), Readmission – Non-Cardiac

As the registry device is commercially approved, it is the investigator's responsibility to report any complaints as defined in local regulations to the Edwards Complaint Handling Unit To INTL_TMTT@edwards.com.

Edwards will be responsible for reporting to the National Competent Authority according to national requirements and in line with MEDDEV 2.12-1 (Medical Device Vigilance System).

7 RISKS AND BENEFITS

Patients participating in this observational registry study will undergo treatment with the PASCAL System.

No study-specific procedures will be performed. There are no increased risks related to the participation in this study. Potential complications associated with standard cardiac catheterization and use of anesthesia are listed in the IFU.

8 STATISTICAL ANALYSIS

All data will be analyzed by summary statistics without hypothesis testing based on the following convention:

Descriptive summaries will follow the conventions below.

- For continuous variables, summary statistics will include mean, median, standard deviation (SD), median, IQR, sample size, minimum, and maximum. If confidence limits are desired, they will be computed using the t-distribution or normal approximation.
- For ordinal data, the count and percentage of patients will be presented.
- For categorical and qualitative variables, summaries will include the count and percentage of patients who are in the particular category. If confidence limits are needed, they will be computed using the exact binomial distribution.
- Time-to-event variable summaries will include the number of events, the number of patients with the event and Kaplan-Meier estimates at given time points. Standard errors will be calculated using Greenwood's formula and SAS defaults will be used for confidence bands and transformations on S(t) for the confidence limits. Kaplan-Meier event rate plots will be presented via the cumulative hazard rate plotted against the days from implantation.

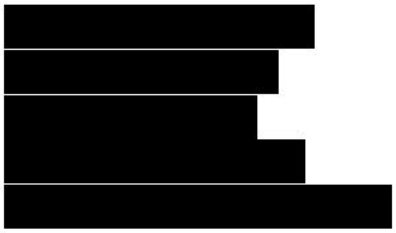
- All analyses will be performed using SAS® Software version 9.4 (SAS Institute, Inc., Cary, NC), unless otherwise specified.

Quality of Life (QoL) will be scored according to algorithms provided by the vendor. The various summary score produced by the algorithms will be analyzed as continuous variables. KCCQ clinical summary score and overall summary score and its changes from baseline will be summarized. SF36 Physical Component Summary Score and Mental Component Summary Score and its changes from baseline will be summarized descriptively.

9 MONITORING

The Sponsor, or its designee, may monitor and manage the data for the registry.

The clinical contact on behalf of the Sponsor will be:



9.1 Monitoring Methods

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

A registry monitor will be assigned to monitor the progress of the registry by the Sponsor. The registry monitor will remain in close contact with the registry site throughout the duration of the registry to provide any needed materials, (i.e. registry forms, etc.) answer any questions and ensure that proper staffing levels are being maintained by the Investigator. The registry monitor will be responsible for verifying that patients have signed the Informed Consent Form as required by regulations, reviewing the data recorded on the eCRFs and may visit the registry site periodically to observe registry progress and compliance with the registry protocol and regulations applicable to this registry.

9.2 Communication Procedures

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

10 ETHICAL AND REGULATORY CONSIDERATIONS

10.1 Applicable Regulations and Guidelines

The regulations listed in Table 1 must be observed to comply with the Sponsor policy for conduct of clinical studies; they also represent sound research practice. It is the responsibilities of the Investigator(s) to comply with the requirements set forth in their country-specific regulations.

Table 1. Applicable Regulations and Guidelines

Region	Clinical Information
Europe	• EN ISO 14155* Clinical investigation of medical devices for human subjects – Part 1: General requirements • Directive 93/42/EEC on Medical Devices (MDD) • Local laws as applicable • General Data Protection Regulation (EU) 2016/679 (GDPR) • Declaration of Helsinki • MEDDEV 2.12/2 rev2, Guideline on Post Market Clinical Follow-up Studies • MEDDEV 2.7.1 Clinical Evaluation: A Guide for Manufacturers and Notified Bodies • MEDDEV 2.12-1 Guidelines on a Medical Device Vigilance System • MEDDEV 2.7/4 Guidelines on Clinical Investigation

*Exception to ISO 14155: All devices used in this Registry are CE marked therefore device accountability records will not be maintained.

The registry shall not begin until the required approval/favorable opinion from the EC and applicable regulatory authorities have been obtained, where appropriate. Any additional requirements imposed by the EC or regulatory authorities shall be followed.

All patients should have valid medical insurance coverage.

10.2 Data Protection and Patient Confidentiality

The sponsor is dedicated to maintaining the confidentiality and privacy of patients who volunteer to participate in the registry. The investigator is responsible for maintaining confidentiality throughout the registry.

All data used in the analysis and reporting of this evaluation will be without identifiable reference to the patient (patient identifiers include, but are not limited to: patient's name/initials, social security number or equivalent, and medical/hospital number). Authorized personnel assigned by the sponsor will have access to the confidential files and will have the right to inspect and copy all records pertinent to this registry. All copies will be de-identified and anonymized for collection.

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

10.3 Ethics Committee (EC) Review of Registry Documents

The investigation shall not start until the required approval/favorable opinion from the EC or regulatory authority has been obtained, where appropriate. Any additional requirements imposed by the EC or regulatory authority shall be followed.

All patients must provide written informed consent in accordance with the investigational center's EC rules and regulations. A copy of the consent form from each center must be forwarded to the investigation sponsor for review and approval prior to submitting it to the institutional review committee. Each center must provide the investigation sponsor with a copy of the investigational center's EC approval letter (stating at a minimum, the registry name or identification number, protocol revision version and date being approved and an approval date) and the relevant information for the associated informed consent, prior to the initiation of enrollment at that center. If yearly approvals for the continuation of the investigation at each investigational center are required, they must also be forwarded to the investigation sponsor. The same document process and information must be completed should registry amendments be required.

10.4 Ethics Committee (EC) Approval

This protocol, the proposed ICF, other written patient information and any proposed advertising material must be submitted to the EC for written approval. A copy of the written EC approval of

the protocol and ICF must be received by the sponsor before recruitment of patients into the registry.

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

The investigator is responsible for obtaining annual EC approval and renewal throughout the duration of the registry if applicable. Copies of the investigator's reports and the EC continuance of approval must be sent to the sponsor.

10.5 Informed Consent

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

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

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

10.6 Investigator Responsibilities

The principal investigator (or designee)/institution should maintain the trial documents as specified in ISO 14155 or as required by applicable regulatory requirement(s). The principal investigator (or designee)/institution should take measures to prevent accidental or premature destruction of these documents.

10.6.1 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 registry and for the safety and well-being of patients enrolled. The

investigator will provide copies of the current registry protocol to all staff responsible for registry conduct.

The investigator is responsible for obtaining and maintaining EC approval for the registry at his/her registry site. If there is a change or addition of an investigator, all required documents must be updated, accordingly.

10.6.2 Ethics Committee Communication

The investigator shall:

- Provide the sponsor with copies of any registry-related communications between the principal investigator and the EC
- Comply with the requirements described in ISO 14155 Section 4.5
- Obtain the written and dated approval/favorable opinion of the EC for the registry before recruiting patients and implementing all subsequent amendments, if required
- Perform safety reporting as specified in ISO 14155 Section 9.8

10.6.3 Investigator Records

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

- Registry protocol and all amendments
- Signed registry agreement and any amendments
- EC approval letters, including continuing reviews and all amendments/changes
- EC approved informed consent documents
- All correspondence with another investigator, EC, sponsor, or monitor , including required reports

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

- Signed ICF
- All relevant source documentation for registry visits
- Supporting documentation of any adverse events

Upon registry completion, the registry files must be maintained in a known location for a period in accordance with local regulatory requirements. Changes in investigational site team shall be reported within 5 business days to the sponsor.

[redacted]

10.6.4 Investigator Reports

The investigator will prepare and submit the following accurate and complete reports to the registry Sponsor and/or EC in a timely manner:

- Withdrawal of EC approval will be reported to the Sponsor within 5 business days.
- Annual progress reports will be submitted to the EC as required.
- A final written report within one year of completion or termination of the registry.

10.7 Sponsor Responsibilities

10.7.1 General Duties

As the sponsor of this registry, Edwards Lifesciences has the overall responsibility for the conduct of the registry, including assurance that the investigation meets the regulatory requirements of the pertinent regulatory agencies.

In addition, the sponsor declares that no employee/affiliate of the sponsor or investigator will be included or encouraged to participate in this registry.

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

10.7.2 Sponsor Records

The sponsor will maintain accurate, complete, and current records relating to this registry. Registry records include CRFs, signed agreement, signed financial disclosure, protocols and protocol amendments, informed consent, EC approval letters, submissions, correspondence, including required reports, and other documents. The sponsor will maintain registry documentation during the registry and for a period in accordance with local regulatory requirements after the registry is terminated or completed, or the registry records are no longer required to support a regulatory submission. Storage of the registry records may be designated to a third party.

10.8 Registry Changes

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

[redacted]

10.9 Audits and Inspections

The registry may be subject to a quality assurance audit by the sponsor or a designee, as well as inspection by appropriate regulatory authorities. It is important that the investigator and relevant registry personnel are available during any audits and that sufficient time is devoted to the process. In the event of an audit by regulatory authorities, the investigator should contact the sponsor as soon as possible.

10.10 Publication Policy

[redacted]

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APPENDIX B: ABBREVIATIONS AND ACRONYMS

ACC	American College of Cardiology	ICF	Informed Consent Form
ACE	Angiotensin-Converting Inhibitor	IFU	Instructions For Use
ADE	Adverse Device Effects	ISO	International Standardization Organization
AE	Adverse Event	LV	Left Ventricle
AHA	American Heart Association	LVEF	Left Ventricle Ejection Fraction
ARB	Angiotensin II Receptor Blocker	MDD	Medical Device Directive
CLASP	Edwards PASCAL TrAnScatheter Mitral Valve RePair System Study	MEDDEV	Medical Device Vigilance System
CRF	Case Report Form	MR	Mitral Regurgitation
CRT	Cardiac Resynchronization Therapy	MSAE	Major Serious Adverse Event
DMR	Degenerative Mitral Regurgitation	MVP	Mitral Valve Prolapse
EC	Ethics Committee	NYHA	New York Heart Association
eCRF	Electronic Case Report Form	SADE	Serious Adverse Device Effect
EDC	Electronic Data Capture	SAE	Serious Adverse Event
ESC/ EACTS	European Society of Cardiology/European Association for Cardio-Thoracic Surgery	SLDA	Single Leaflet Device Attachment
FMR	Functional Mitral Regurgitation	STS	Society of Thoracic Surgeons
GCP	Good Clinical Practice	TEE	Transthoracic Echocardiography
GDPR	General Data Protection Regulation	TOE/TEE	Transesophageal Echocardiography
ICD	Implantable Cardioverter-Defibrillator	TMVr	Transcatheter Mitral Valve Repair Therapy