



## STATISTICAL ANALYSIS PLAN

Protocol Title:	<b>The CLASP Study</b> Edwards PASCAL TrAnScatheter Mitral Valve RePair System Study
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## GLOSSARY OF TERMS

Abbreviation	Definition
6MWT	Six-Minute Walk Test
AE	Adverse Event
CEC	Clinical Events Committee
CSR	Clinical Study Report
EF	Ejection Fraction
EFS	Early Feasibility Study
EOA	Effective Orifice Area
ITT	Intent-to-Treat
MAE	Major Adverse Event
MR	Mitral Regurgitation
NYHA	New York Heart Association
OUS	Outside of United States
SAP	Statistical Analysis Plan

## 1. INTRODUCTION

The statistical analysis plan (SAP) specifies the statistical methods to be implemented for the analysis of data collected within the scope of Edwards Lifesciences's Protocol with Study Number 2016-05, "The CLASP Study - Edwards PASCAL TrAnScatheter Mitral Valve RePair System Study", [REDACTED]

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## 2. STUDY DESIGN

### 2.1. Study Objectives

The objectives of this clinical study are to:

- Evaluate the safety and performance of the Edwards PASCAL Transcatheter Mitral Valve Repair (TMVr) System
- Provide guidance for future clinical study designs utilizing the Edwards PASCAL System
- Provide guidance for future Edwards PASCAL System development efforts

### 2.2. Study Design

This is a multi-center (up to 20 sites), 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. 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.

Of the total enrollment, 45 patients will be enrolled in the U.S. at up to 9 clinical sites. In the event that the 60-patient analysis cohort fills prior to the completion of the US EFS cohort, the US EFS cohort may continue to enroll until completed.

### 3. STUDY ENDPOINTS

#### 3.1. 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.

#### 3.2. 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

#### 4. ANALYSIS POPULATIONS

- **Intent-to-treat population**

The intention-to-treat (ITT) population includes all patients in whom the study procedure has been attempted (i.e., incision). The ITT population does not include roll-in patients.

- **Per-protocol population**

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

- **Implanted population**

The implanted population includes all patients in whom the study device was implanted in the body at the time of the patient's exit from the cardiac catheterization laboratory.

- **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. Additional analyses of performance and safety data using the implanted population will be performed if it is clinically meaningful in addition to the PP analysis. Subgroup analysis by etiology may be performed. For patients with mixed etiology, the echo core lab will determine the dominant etiology for analysis. All analyses will be performed separately for the roll-in population.

A first analysis will be performed when 30 patients complete 30-day follow-up, and a second analysis when all patients complete their 30-day follow-up.

## 5. DEFINITIONS

### 5.1. Analysis Dates

#### 5.1.1. Study Start Date

For a subject who have had study procedure attempted, the study start date is defined as the procedure date.

#### 5.1.2. Treatment Start Date

The treatment start date is defined as the procedure date.

#### 5.1.3. Last Information Date

The last information date is defined as the latest date assessed with any available information concerning the subject (e.g., most recent date out of: baseline assessment, procedure, discharge, all follow-up visits, laboratory tests, study termination, and adverse events). Last information date is used as censor date for survival analyses.

### 5.2. Visit Windows

The follow-up schedule and analysis windows are listed below.

- Post implant (within 24 hrs)
- Discharge visit (discharge or 7 days post-procedure, whichever comes first)
- 30-Day Visit  $\pm$  7 Days [23, 37 days]
- 6-Month Follow-up (180  $\pm$  30 days) [150, 210 days]
- 12-Month Follow-up (365  $\pm$  45 days) [320, 410 days]
- 2 years (730 days)  $\pm$  45 days [685, 775 days]
- 3 years (1095 days)  $\pm$  45 days [1050, 1140 days]

- 4 years (1460 days)  $\pm$  45 days [1415, 1505 days]
- 5 years (1825 days)  $\pm$  45 days [1780, 1870 days]

## 6. STATISTICAL ANALYSES

### 6.1. General Considerations

a. For continuous variables, summary statistics will include number of observations, mean, median, standard deviation, minimum, maximum, and 95% confidence intervals (based on normal distribution, unless otherwise specified) per table shells.

b. For categorical variables, summary statistics will include counts, percentages, and 95% Clopper-Pearson confidence intervals per table shells. In general, the denominator for the percentage calculation will be based on total number of subjects with evaluable data for a specified time point unless otherwise specified. Subjects with missing data will be excluded from the denominator.

c. Survival analysis techniques will be used to analyze the time-to-event variables. Summaries will include the number of subjects at risk, number of events, and number of subjects with the event. Subjects without events will be censored at their last known event-free time point. If this event-free time point occurs after the analysis time point, the days to event variable will be set equal to the analysis time point so that the subject will be included in the analysis. For subjects who did not have an event or early withdrawal and have not yet completed the analysis visit, they will be censored at their last information date. Time to first event curves will be constructed using Kaplan-Meier estimates and all post procedure results will be summarized with Kaplan-Meier estimates of event rates. Hazard ratios, confidence interval for the hazard ratios, and p-values may also be presented from a Cox proportional hazards model.

d. Descriptive statistics will be provided at each follow-up assessment, including change from baseline to subsequent time point for selected endpoints. Paired (i.e., subjects with available data at both baseline and respective time point) and unpaired data will be presented separately.

e. If insufficient data are available for summary statistics, then data will be provided only as listings.

f. Unless otherwise specified, descriptive analysis will be performed for all data. Nonparametric techniques may be used if the data does not meet the assumptions of parametric tests.

g. All analyses will be performed using SAS® Software version 9.4 or later (SAS Institute, Inc., Cary, NC).



## 6.2. Handling of Missing Data

All statistical analyses on the functional endpoints will be performed using only those patients with available data required for endpoint analysis. No missing value imputation will be performed.

No imputation will be done if the date variables are completely missing. For partial dates, only adverse event (AE) onset date will be imputed as follows:

- 1) If both month and day are missing
  - a. If the AE onset year is the same year as index procedure then use index procedure date to impute this AE onset date
  - b. Otherwise, assign January 1<sup>st</sup> for this AE onset date
- 2) If only day is missing
  - a. If the AE onset year and month are the same as the procedure ones then use the index procedure date to impute the AE onset date
  - b. Otherwise, assign '01' as the day for the AE onset date

## 6.3. Analyses of Primary Endpoints

### Safety:

The primary safety endpoint for this clinical study is a 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. The safety endpoints on composite of major adverse events shall be analyzed via the Kaplan-Meier method.

In addition to the safety endpoint analysis, a summary of the percentage of patients who experience an early adverse event ( $\leq 30$  day post-procedure) will be reported for all adverse events. Additionally, linearized rates will be used to summarize adverse events for the late ( $> 30$  days) post-procedure period. The linearized rates will be reported as the number of events occurring after the early post-procedure period per year of patient survival.

### Performance:

The device success, procedural success and clinical success will be summarized by counts and percentages.

#### 6.4. Analyses of Secondary Endpoints

Mitral regurgitation reduction from baseline at 30 days, 6 months, 1 year and annually thereafter will be summarized with counts and percentages.

All-cause mortality rates at 30 days, 6 months, 1 year, and annually thereafter and corresponding 95% confidence intervals will be computed using the Kaplan-Meier algorithm with the standard errors being computed using Greenwood's formula.

Recurrent heart failure hospitalization at 30 days, 6 months, 1 year, and annually thereafter will be analyzed using Poisson regression.

Re-intervention rates for mitral regurgitation at 30 days, 6 months, 1 year and annually thereafter will be summarized with counts and percentages.

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 will be summarized with counts and percentages.

Change from baseline in Left Ventricular End Diastolic Volume (LVEDV), Left Ventricular End Systolic Volume (LVESV), Pulmonary Artery Systolic Pressure, 6MWT distance, BNP/NT-pro-BNP level, effective regurgitant orifice area (EROA) and mitral regurgitant volume at the protocol specified timepoints in the secondary endpoints and clinical outcomes section will be summarized by mean and standard deviation for the PP population. For the analyses of six minute walk test (6MWT), subjects unable to perform the walk due to a medical reason will be considered to have walked an actual distance of zero.

Change from baseline 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 will be

summarized by mean and standard deviation. Patients that are missing a baseline or follow up values will be excluded from the analysis.

Change from baseline in NYHA Functional Classification at 6 months, 1 year and annually thereafter will be presented as shift from baseline for each of the pre-specified follow-up periods. Subjects that are missing a baseline or follow-up values will be excluded from the paired analysis.

Change from baseline in tricuspid regurgitation at 6 months, 1 year and annually thereafter will be summarized with counts and percentages.

#### 6.5. Poolability Analyses

Poolability will be assessed for the primary safety endpoint. The percentage of patients with MAE will be summarized separately for patients from North America (including sites in US and Canada) and the rest of the regions. The fisher's exact test will be applied to assess the poolability of data from these two regions. If p-value is great than 0.05 based on the fisher's exact test, then MAE data from North America and the rest of the regions are deemed poolable and the percentage of patients with MAE for all patients will be summarized. If data are not poolable, then data will be explored to identify differences between these two regions.

#### 6.6. Additional Analyses per FDA

Per FDA, the success rates based the following definitions will be summarized by counts and percentages.

FDA Device Success (30 day and all post-procedural intervals):

- Alive and stroke free, with
- Original intended device in place, and
- No additional surgical or interventional procedures related to access or the device since completion of the original procedure (i.e., exit from the cath lab/OR), and
- Intended performance of the device:
- Structural performance: No migration, embolization, detachment, fracture, hemolysis, thrombosis or endocarditis, etc., and
- Hemodynamic performance: Maintenance of relief of insufficiency without producing stenosis (stenosis = MV gradient > 5 mmHg; insufficiency = MR >2+), and
- Absence of para-device complications (e.g., leaflet, chordae or papillary muscle damage; LVOT gradient increase > 10 mmHg; hemodynamically significant ASD requiring closure)

FDA Procedural Success (30 day):

- Device success, and
- No device or procedure related SAE's (life threatening bleed; major vascular or cardiac structural complications requiring unplanned reintervention or surgery; stage 2 or 3 AKI (includes new dialysis); MI or need for PCI/CABG; severe HF or hypotension requiring IV inotrope, ultrafiltration or MCS; prolonged intubation > 48 hours)

FDA Technical Success (at exit from OR):

- Alive, with
- Successful access, delivery and retrieval of the device delivery system, and
- Deployment and correct positioning (including repositioning /recapture if needed) of the single intended device, and
- No need for additional unplanned or emergency surgery or re-intervention related to the device or access procedure

FDA Individual Patient Success (1 year):

FDA Device success and all of the following:

- No re-hospitalizations or re-interventions for the underlying condition (e.g., MR, HF)
- Return to prior living arrangement (or equivalent)
- Improvement vs. baseline in symptoms (e.g., NYHA Class improvement > 1 class)
- Improvement vs. baseline in functional status (e.g., 6MWT improvement > 25 meters)
- Improvement vs. baseline in QoL (e.g., KCCQ improvement > 10)

## 7. LIST OF KEY VARIABLES

The following parameters will be summarized. Other parameters may be added as deemed necessary.

### 7.1. Subject Enrollment and Disposition

Subject disposition will be summarized in a table. A subject level listing will also be provided.

### 7.2. Demographics and Baseline Characteristics

- Age (in years)
- Gender
- Body Mass Index (BMI)
- Tobacco use
- Logistic EuroSCORE I (%)
- EuroSCORE II (%)

- STS Mortality Score (%)
- NYHA Class
- 6 Minute Walk Test – Total distance of walk (m)

### 7.3. Medical History

- Cardiovascular Risk Factors
  - Angina
  - Aortic Aneurysm
  - Aortic Valve Disease
  - Arrhythmia and Conduction Defects
  - Atrial Septal Defect (ASD)
  - Cardiomyopathy
  - Carotid Artery Stenosis
  - Cardiogenic Shock
  - Coronary Artery Disease
  - Deep Vein Thrombosis (DVT)
  - Endocarditis
  - Heart Failure
  - Hypertension
  - Lower Extremity Edema > 2+
  - Myocardial Infarction (MI)
  - Mitral Valve Disease
  - Pericarditis
  - Peripheral Vascular Disease
  - Porcelain Aorta
  - Pulmonary Embolism (PE)
  - Pulmonic Valve Disease
  - Rheumatic Heart Disease
  - Syncope
  - Thromboembolic Disease
  - Tricuspid Valve Disease
  - Ventricle Septal Defect (VSD)
  - Stroke or Cerebrovascular Accident (CVA)
  - Transient Ischaemic Attack (TIA)
- Non-Cardiovascular Risk Factors
  - Amyotrophic Lateral Sclerosis (ALS)
  - Chronic Headache or Migraine
  - Dementia (including Alzheimer's)
  - Infectious (including Guillian-Barre Syndrome)
  - Multiple Sclerosis
  - Parkinson's
  - Seizure Disorder (including Epilepsy)
  - Spinal Cord Injury
  - Traumatic Brain Injury (TBI)

- Asthma
- Bronchitis
- Chronic Obstructive Pulmonary Disease (COPD)
- In-home oxygen use
- Chronic lung disease
- Emphysema
- Lung Infection (i.e. Pneumonia or TB)
- Pulmonary Hypertension
- Pulmonary Edema
- Pulmonary Fibrosis
- Pulmonary Embolism
- Cor Pulmonale
- Sleep Apnea
- Other pulmonary disease
- Diabetes (Type I, Type II)
- Dyslipidemia
- Other endocrine conditions
- Renal Disease
- Gastrointestinal Bleeding
- Variceal bleeding
- Crohn's Disease
- Ulcerative Colitis
- Cirrhosis
- Other gastrointestinal conditions
- Chronic Urinary Tract Infections
- Disease of the Prostate
- Cancer/Malignancy
- Coagulopathy (including haemophilia and factor deficiencies)
- Chronic Anemia
- Thrombocytopenia
- HIV/AIDS
- Subject currently taking immunosuppressants?
- Autoimmune Disorder
- Marfan's Syndrome
- Hostile Chest/ Chest Deformities
- Prior radiation treatment that precludes an open chest procedure

#### 7.4. Prior Interventions or Surgeries

- Prior Cardiovascular Interventions or Surgeries
  - Pacemaker or ICD implant
  - PCI/Stent
  - Coronary Artery Bypass Graft (CABG)
  - Electrophysiological procedures (EP procedures)
  - Previous valve replacement or repair
  - Carotid endarterectomy / Carotid stent

- Cardiac Devices
- Atrial Septal Defect (ASD) Repair
- Ventricular Septal Defect (VSD) Repair
- Cardiac Transplant
- Peripheral Vascular Intervention
- Implanted Inferior Vena Cava (IVC) Filter

#### 7.5. Procedure Information

- Type of anesthesia (Conscious sedation, General anesthesia)
- Access side through which device advanced (Left femoral vein, Right femoral vein)
- Total operative lab duration (min)
- Skin incision to Femoral vein access closure time (min)
- Femoral vein access closure method (Percutaneous closure device, Surgical closure of cut-down, Other)
- Cardiopulmonary bypass (Yes, No)
- Fluoroscopy duration (min)
- Volume of contrast used (ml)
- Pre-implant echocardiographic mitral regurgitation assessment (Site-Reported)
- Post-implant echocardiographic mitral regurgitation assessment (Site-Reported)
- Implant hospitalization length of stay (days)

#### 7.6. Device Usage and Malfunction

- Total number of study devices implanted
- Reason for additional implant(s) of study devices
- Number of non-study devices used
- Name of non-study device

#### 7.7. Safety Variables

Number of unique subjects who experienced adverse events will be reported by AE category for each analysis cohort.

Events will be adjudicated by the CEC according to the CEC Charter. The CEC adjudicated adverse events will be summarized by KM estimate and/or binary proportions.

Number of unique subjects who experienced heart failure rehospitalization will be reported.

#### 7.8. Primary Performance Endpoints

- Device Success (Per Device Analysis)
- Procedural Success (Per Patient Analysis)
- Clinical Success (Per Patient Analysis)

#### 7.9. Clinical Results

- New York Heart Association (NYHA) Functional Class
- Six Minute Walk Test (6MWT)
- Kansas City Cardiomyopathy Questionnaire (KCCQ) Scores
- EQ5D Scores

#### 7.10. Transthoracic Echocardiogram (TTE) & Transesophageal Echocardiogram (TEE) Parameters

##### Transthoracic Echocardiogram (TTE) Parameters

- Mitral annular calcification (Baseline only)
- MR Mechanism (Baseline only)
- LVEDD
- LVESD
- LVEDV
- LVESV
- Ejection Fraction (EF)
- Pericardial effusion
- Mitral Valve Area
- EROA (MR effective regurgitant orifice area)
- Regurgitant Volume
- Regurgitant Fraction
- MR Severity

##### Transesophageal Echocardiogram (TEE) Parameters



- Mitral annular calcification (Baseline only)
- MR Mechanism (Baseline only)
- MR Severity

## **8. CHANGES FROM PROTOCOL SPECIFIED ANALYSES**

Definition of Implanted population and related analysis were not in the protocol. They were added to the SAP due to the clinically meaningfulness of this population.

## **9. REFERENCES**

1. Clopper CJ, Pearson E. The Use of the Confidence or Fiducial Limits Illustrated in the Case of the Binomial. *Biometrika* 1934; 26:404-413.
2. SAS/STAT® 9.4 User's Guide, SAS Institute, Inc., Cary, NC.

## **10. TABLES, LISTINGS, and GRAPHS**

The tables, listings, and graphs shells will be provided in a separate document, namely the second part of the SAP.