Edwards Lifesciences

STATISTICAL ANALYSIS PLAN (SAP)

Clinical Protocol Title:	**Edwards PASCAL TrAnScatheter Valve RePair System in Tricuspid Regurgitation (CLASP TR) Early Feasibility Study**
Clinical Protocol Number:	Study Number: 2018-10 [redacted]
SAP Version:	[redacted]
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GLOSSARY OF TERMS

The following abbreviations are used throughout the document and shall not be defined elsewhere:

Abbreviation/Acronym	Definition
6MWT	6 Minute Walk Test
ACC	American College of Cardiology
ACT	Activated Clotting Time
ADL	Activities of daily living
AE	Adverse Event
AHA	American Heart Association
AKI	Acute Kidney Injury
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate aminotransferase
CABG	Coronary Artery Bypass Graft
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CIB	Clinical Investigator's Brochure
CIP	Clinical Investigational Plan

CMR	Cardiovascular Magnetic Resonance
COPD	Chronic obstructive pulmonary disease
CRF	Case Report Form
CT	Computed Tomography
CTA	Clinical Trial Agreement
CV	Cardiovascular
DAPT	Dual anti-platelet therapy
DSMB	Data Safety Monitoring Board
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EF	Ejection Fraction
EFS	Early Feasibility Study
eGFR	Estimated glomerular filtration rate
EROA	Effective regurgitant orifice area
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
HF	Heart Failure
Hgb	Hemoglobin
ICF	Informed consent form
ICU	Intensive care unit
IFU	Instructions For Use
INR	International normalized ratio
IRB	Institutional Review Board
ISO	International Standardization Organization
ITT	Intention-to-treat
IVC	Inferior vena cava
KCCQ	Kansas City Cardiomyopathy Questionnaire
LV	Left ventricle
LVEF	Left ventricular ejection fraction

MAE	Major Adverse Event
MI	Myocardial Infarction
MR	Mitral Regurgitation
mRS	Modified Rankin Scale
MSAE	Major Serious Adverse Event
MSCT	Multi-slice computed tomography
MV	Mitral Valve
MVARC	Mitral Valve Academic Research Consortium
NYHA	New York Heart Association
PASP	Pulmonary Artery Systolic Pressure
PHTN	Pulmonary hypertension
PP	Per-protocol
QOL	Quality of Life
RA	Right atrium
RV	Right ventricle
SAE	Serious Adverse Event
SLDA	Single leaflet device attachment
STS	Society of Thoracic Surgeons
TEE	Transesophageal echocardiography
TIA	Transient Ischemic Attack
TMVr	Transcatheter Mitral Valve Repair
TMVR	Transcatheter Mitral Valve Replacement
TR	Tricuspid Regurgitation
TTE	Transthoracic Echocardiography
TTVr	Transcatheter tricuspid valve repair
TTVR	Transcatheter tricuspid valve replacement
TV	Tricuspid valve
UADE	Unanticipated adverse device effect
VC	Vena contracta

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 Clinical Protocol Study # 2018-10, "Edwards PASCAL TrAnScatheter Valve RePair System in Tricuspid Regurgitation (CLASP TR) Early Feasibility Study " version A and provides detailed instructions as to how each analysis will be performed.

[redacted]

2. STUDY DESIGN

2.1 Study Objectives

The objectives of this early feasibility study are to:

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

2.2 Overall Study Design and Plan

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

A total of 15 patients will be enrolled in the study at up to 8 investigational sites in the US. All enrolled study patients will be assessed for clinical follow-up at the following intervals: discharge, 30 days, 6 months, 1 year and annually for 5 years post implant procedure.

A description of each study visit and required study procedures is included in the clinical protocol's Section 8. Procedures and Methods. In addition, a summary of required procedures is listed in Table 11, Schedule of Assessments of the clinical protocol.

3. STUDY ENDPOINTS

3.1 Safety Endpoint:

Safety will be analyzed as a composite endpoint of Major Adverse Events (MAEs) at 30 days which includes cardiovascular mortality, myocardial infarction (MI), stroke, renal complications requiring unplanned dialysis or renal replacement therapy, severe bleeding (includes fatal, life-threatening, extensive, or major bleeding, as defined by MVARC), unplanned or emergency re-intervention (either percutaneous or surgical) related to the device and major access site and vascular complications requiring intervention.

3.2 Performance Endpoints

3.2.1 Device Success

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

3.2.2 Procedural Success

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

3.2.3 Clinical Success

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

3.3 Echocardiographic, Clinical, and Functional Endpoints and Parameters

3.3.1 Echocardiographic Endpoints and Parameters

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

Additional echocardiographic parameters will be compared to baseline:

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

1. TR grade
2. Vena Contracta (2D)
3. EROA (PISA/2D or 3D/3D color Doppler)
4. Regurgitant volume
5. Tricuspid annular dimensions
6. TV inflow gradient

7. Cardiac output
8. Right ventricle dimensions
9. Right atrium volume
10. Left ventricular Ejection Fraction
11. Inferior Vena Cava dimensions/respiratory variations
12. Hepatic vein flow reversal
13. Pulmonary artery pressure (mean)
14. Right ventricular function

3.3.2 Clinical and Functional Endpoints and Parameters

Clinical and functional endpoints-assessed at baseline and at various time points, depending on the parameter (see Clinical Protocol Version A, Table 11)

A. All-cause mortality

B. Heart Failure Hospitalization

C. Unplanned or emergency re-intervention (either percutaneous or surgical) related to the device

D. Volume overload assessed by serial measurements of:

   1. Body weight
   2. Edema assessment (1+ to 4+)
   3. Ankle circumference measurement

4. Patient edema questionnaire.

E. Quality of Life and Functional status assessed by:

1. NYHA Classification
2. 6-Minute Walk Test (6MWT)
3. KCCQ
4. Short Form Health Survey (SF-36)

Clinical and Functional Parameters

A. Baseline Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale

B. Baseline Katz Index of Independence in Activities of Daily Living (Katz ADL)

C. Baseline Patient Preference Survey

D. Electronic Diary (eDiary): Administered via a handheld device as follows:

1. Baseline: Question(s) will be administered daily for a minimum of 2 weeks before the index procedure and then paused at time of admission for index procedure.
2. Post discharge: Starting post discharge, question(s) will be administered daily for 7 days, every other week, to the 12-month follow-up visit.
3. 12-month follow-up visit: Starting at the 12-month follow-up visit, question(s) will be administered daily for a week, up to 7 days.

E. Activity Monitoring*: Administered via a wearable monitor as follows:

1. Baseline: Activity monitoring will occur for a minimum of 2 weeks before the index procedure and then paused at time of admission for index procedure
2. 30 days post discharge

3. 2 weeks at 3 months, 6 months, 9 months, and 12 months post index procedure.

F. General Clinical and Laboratory Parameters assessed by:

1. Creatinine, BUN, uric acid, and eGFR
2. Liver Panel (Albumin, Bilirubin, ALP, ALT, AST, GGT)

G. Diuretic medications and doses (No change in diuretics are allowed for at least 3 months post procedure unless patient presents with severe hypotension.)

3.3.3 Additional Safety Assessments

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

4. ANALYSIS POPULATIONS

The analysis cohorts are defined below:

4.1 Intention-to-Treat (ITT) Population

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

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

4.2 As-Treated (Implanted) Population

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

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

4.3 Per-Protocol (PP) Population

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

Additional analyses of performance and safety data using the PP population will be performed if it is clinically meaningful in addition to the as-treated analysis.

5. DEFINITIONS

5.1 Analysis Dates

5.1.1. Study Start Date

For a patient who has the study implant procedure attempted, the study start date is defined as the study implant procedure date (day 0).

5.1.2. Treatment Start Date

The treatment start date is defined as the study implant procedure date (day 0).

5.1.3. Last Information Date

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

5.2 Visit Windows

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

- Discharge visit (discharge or 7 days post-procedure, whichever comes first)
- 30-Day Visit ± 7 Days [23, 37 days]
- 6-Month Follow-up (180 ± 30 days) [150, 210 days]
- 12-Month Follow-up (365 ± 45 days) [320, 410 days]
- 2 years (730 days) ± 45 days [685, 775 days]
- 3 years (1095 days) ± 45 days [1050, 1140 days]
- 4 years (1460 days) ± 45 days [1415, 1505 days]
- 5 years (1825 days) ± 45 days [1780, 1870 days]

6. STATISTICAL ANALYSIS

6.1 General Conventions

- For continuous variables, data will be summarized using the number of observations, mean, median, standard deviation, minimum, maximum, and 95% confidence intervals (based on normal distribution) per table shells. Nonparametric techniques may be used if the data

does not meet the assumptions of parametric tests.

- For categorical variables, data will be summarized using the number of observations, percentage, and 95% Clopper-Pearson confidence intervals per table shells. In general, the denominator for the percentage calculation will be based on total number of patients with evaluable data for a specified time point unless otherwise specified. Patients with missing data will be excluded from the denominator.
- For time-to-event variables, survival analysis will be used to analyze the data. Summaries will include the number of patients at risk, and number of patients with the event. Patients 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 patient will be included in the analysis. For patients 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.
- For selected variables, in addition to descriptive summary statistics at each follow-up assessment, change from baseline to subsequent time point will be summarized. Paired (i.e., patients with available data at both baseline and respective time point) and unpaired data will be presented separately for selected variables. In general, patients with missing baseline or following-up values will be excluded from the analysis unless otherwise specified.

- If insufficient data are available for summary statistics, then data will be provided only as listings.
- 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 analysis on the endpoints will be performed using only those patients with available data required for endpoint analysis. No missing value imputation will be performed unless otherwise specified.

7. SUMMARY OF BASELINE INFORMATION

7.1 Patient Enrollment and Accountability

Patient disposition including numbers and percentages will be summarized. A patient level listing will also be provided.

7.2 Demographics and Baseline Characteristics

Patient demographics, age, sex, race, and other demographic variables are summarized descriptively. For baseline characteristics, efficacy/safety measures that describe the disease characteristics at baseline are summarized descriptively. The measures to be summarized depend on the study indication and measures collected at screening and/or baseline.

7.3 Medical History and Prior Intervention

Following medical history and prior intervention will be summarized by number and percentage. Other medical history and prior intervention variables may be added as deemed necessary.

7.3.1 Cardiovascular Risk Factors

- Number of hospitalizations for heart failure in the last 12 months
- Number of days hospitalized for heart failure in the last 12 months
- Angina
- Aneurysm
- Atrial Flutter/Fibrillation
- Flutter/Fibrillation Ablation
- Ventricular Tachyarrhythmia
- Conduction Defects/Heart Block
- Congestive Heart Failure (CHF)
- Atrial Septal Defect (ASD)
- Ventricular Septal Defect (VSD)
- Carotid Artery Stenosis
- Carotid Surgery
- Carotid Intervention
- Cardiogenic Shock

- Coronary Artery Disease (>50 Stenosis)
- Deep Vein Thrombosis (DVT)
- Dyslipidemia or Hyperlipidemia
- Endocarditis
- Hypertension
- Hypotension
- Myocardial Infarction (MI)
- Peripheral Vascular Disease
- Rheumatic Heart Disease
- Stroke
- Transient Ischemic Attack (TIA)

7.3.2 Non-Cardiovascular Risk Factors

- Chronic Lung Disease
- COPD
- Asthma
- Pulmonary Hypertension
- Pulmonary Edema
- Pulmonary embolism
- Other pulmonary disease

- Diabetes
- Thyroid Disease
- Renal Disease
- Gastrointestinal or esophageal bleeding
- Cirrhosis or other liver disease
- Other gastrointestinal or hepatobiliary conditions
- Cancer/Malignancy
- Coagulopathy
- Chronic Anemia
- Thrombocytopenia
- Dementia (including Alzheimer's)
- HIV/AIDS
- Patient immunocompromised
- Autoimmune Disorder
- Frailty
- Smoking
- Alcohol consumption

7.3.3 Prior Cardiovascular Interventions or Surgeries

- Pacemaker, ICD or CRT (cardiac resynchronization Therapy)

- PCI/Stent
- Coronary Artery Bypass Graft (CABG)
- Prior Aortic Valve (AV) surgery/intervention
- Prior Mitral Valve (MV) surgery/intervention
- Prior Pulmonic Valve (PV) surgery/intervention
- Cardiac Transplant
- Other cardiovascular interventions or surgery

7.4 Procedural Information

Following procedural information will be summarized by mean and standard deviation for continuous variables and by counts and percentages for categorical variables.

- Skin incision to Femoral vein access closure time (min)
- Fluoroscopy Time (min)
- Volume of Contrast Used (ml)
- Implant Access Approach
- Device permanently implanted
- Device implanted as intended
- Reintervention Required
- Device Malfunction

- Implant hospitalization length of stays: Days form index procedure to discharge of index procedure

8. STATISTICAL ANALYSIS OF STUDY ENDPOINTS

8.1 Safety and Performance Endpoints

Safety:

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

Performance:

All performance endpoints will be summarized by counts and percentage.

The device success endpoint will be evaluate for the ITT and AT cohorts, per device analysis.

The procedure success endpoint will be assessed for the ITT and AT cohort, per patient analysis. Only device-related intervention will be considered when calculating procedure success.

The clinical success endpoint at 30 days will be summarized for the ITT and AT cohort, per patient analysis. CEC adjudicated data will be used for MAEs.

Additional Safety Assessments at 30 days will be summarized by counts and percentages for the ITT and AT cohort.

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

8.2 Echocardiographic, Clinical and Functional Endpoints

8.2.1 Echocardiographic Endpoints and Parameters

Echocardiographic data will be evaluated by a core laboratory. TTE parameters will be assessed at baseline, discharge, 30 days, 6 months, 1 year and annually until 5 years post procedure. TEE parameters will be assessed at start and end of implant procedure. The change from baseline for selected items will be presented as shift from baseline for each of the pre-specified follow-up periods. Patients that are missing a baseline or follow-up values will be excluded from the analysis.

8.2.2 Clinical and Functional Endpoints and Parameters

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.

Heart failure re-hospitalization rates at 30 days, 6 months, 1 year, and annually thereafter will be summarized with counts and percentages .

Re-intervention rates for tricuspid 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, MI, stroke, renal complications requiring unplanned dialysis or renal replacement therapy, severe bleeding, unplanned or emergency re-intervention (either percutaneous or surgical) related to the device and major access site and vascular complications requiring intervention at 6 months, 1 year and annually thereafter will be summarized with counts and percentages.

Change from baseline in NYHA Functional Classification and Edema assessment at 30 days, 6 months, 1 year and annually thereafter will be presented as shift from baseline for each of the pre-specified follow-up periods. Patients that are missing a baseline or follow-up values will be excluded from the paired analysis.

Change from baseline in Quality of Life (QoL) score, as measured by Kansas City Cardiomyopathy Questionnaire (KCCQ), Short Form Health Survey (SF-36) and six minute walk test (6MWT) as well as weight, ankle circumference measurement and patient edema questionnaire at 30 days, 6 months and corresponding follow-up visits will be summarized by mean and standard deviation. Patients that are missing a baseline or follow up values will be excluded from the analysis. For the analyses of 6MWT, patients unable to perform the walk due to a medical reason will be considered to have walked an actual distance of zero.

eDiary assessments and Activity Monitoring will be summarized using descriptive statistics based on data types and for each pre-specified follow-up periods.

9. ANALYSIS OF SAFETY

9.1 Deaths

Summary of all-cause mortality is provided in section 8.2.2.

9.2 Adverse Events

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

When adverse event (AE) date is used to derive variables for analysis, missing dates will be imputed as follows:

- If the AE year is unknown, then no imputation will be performed.
- If the AE month is unknown, then
  - If the AE year matches the year of the index procedure/randomization*, then impute the month and day using the index procedure/randomization date.
  - Otherwise, assign "January".
- If the AE day is unknown, then:
  - If the AE month and year match the month and year of the index procedure/randomization, then impute the day using the index procedure/randomization date.
  - Otherwise, assign "01".

For study that all patients have intervention, use index procedure date. For study that some patients have intervention, some patients have medical therapy, use randomization date.

10. 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.

11. PEER REVIEW REQUEST, PER SAP INSTRUCTION ([redacted])

Yes	Name of Reviewer:	No	Reason Peer Review not Needed:
☑	[redacted]	☐	

12. APPENDIX

The Rev number has been changed [redacted] The footer was removed from the original document, but should have been there and no content changes have been made.