Edwards Lifesciences

STATISTICAL ANALYSIS PLAN (SAP)

Clinical Protocol Title:	Edwards PASCAL Transcatheter Valve Repair System Registry: A multicenter observational registry with the Edwards PASCAL Transcatheter Valve Repair System
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GLOSSARY OF TERMS

ABBREVIATION	DEFINITION OR DESCRIPTION
6MWT	6 Minute Walk Test
CI	Confidence Interval
CSR	Clinical Study Report
ITT	Intention-to-treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
MAE	Major Adverse Event
MR	Mitral Regurgitation
MV	Mitral Valve
NYHA	New York Heart Association
QoL	Quality of Life
SAP	Statistical Analysis Plan
SD	Standard Deviation
STS	Society of Thoracic Surgeons

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 #2019-03, "Edwards PASCAL Transcatheter Valve Repair System Registry: A multicenter observational registry with the Edwards PASCAL Transcatheter Valve Repair System" [redacted]

Results obtained from the analyses specified in the SAP will become the basis of the clinical study report (CSR) for this protocol. Any deviations from the SAP must be documented in the CSR.

2. STUDY DESIGN

2.1 Study Objectives

The objective of the study is to expand the knowledge of safety, performance and effectiveness of the usage of Edwards PASCAL Transcatheter Valve Repair System in the treatment of patients with an insufficient mitral valve.

2.2 Overall Study Design and Plan

This is a post market, prospective and retrospective (where applicable), observational, single-arm, multicenter, registry study of the Edwards PASCAL Transcatheter Valve Repair System for the percutaneous reconstruction of patients with an insufficient mitral valve.

A minimum of 200 patients will be enrolled in the registry at over 10 sites in the Europe.

Patients will be treated per standard of care at their medical facilities and a written informed consent will be obtained to allow the data to be collected. This registry will 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.

A description of each study visit and required study procedures is included in the clinical protocol Section 4: Procedures and Methods.

3. OUTCOME MEASURES

3.1 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 Primary Performance Measure

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

3.3 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

4. ANALYSIS POPULATIONS

The analysis cohorts are defined below:

4.1 Intention-to-Treat (ITT) Population

The intention-to-treat (ITT) population includes all enrolled patient.

4.2 Implanted Population

The implanted population is a subset of ITT population and includes all patients in whom the PASCAL Transcatheter Device is implanted.

The implanted population will be the primary analysis population for this study.

5. DEFINITIONS

5.1 Analysis Dates

5.1.1. Reference Start Date and Day 0

The reference start date is defined to be the date of the index procedure. The index procedure is defined as the time of the PASCAL guide sheath is inserted into the vasculature. If a patient has multiple procedure forms, we will present information on the procedure with the first date when the site has indicated that the PASCAL guide sheath is inserted into the vasculature. If no form has this indicated, then the procedure information corresponding to the date of the first procedure will be used.

The reference start date is considered to be Day 0.

5.1.2. Last Participation Date

The last participation date is defined as the latest date assessed with any available information concerning the patient (e.g., latest date out of: baseline assessment, procedure, discharge, follow-up visit, unscheduled visit, echo data, laboratory tests collection, study exit when exit reason is not lost to follow-up, and adverse event occurrence).

5.1.3. Last Participation Day

Last Participation Day = Last Participation Date – Reference Start Date

Note: Last Participation Day is used as the censor day for Kaplan-Meier analysis.

5.1.4. Study Day

Study Day = Current Date – Reference Start Date

5.2 Visit Windows

An assessment is considered scheduled if the assessment is identified by a nominal visit name (e.g., “Discharge”, “30 day”, and “1 year”) regardless if the actual visit date is within the protocol defined visit window. An assessment is considered unscheduled if no nominal visit name is identified. Unless specified, measurements collected from unscheduled assessments should be excluded from analyses. Disposition status will be summarized using occurrence date instead of nominal visit.

6. STATISTICAL ANALYSIS

6.1 General Conventions

[redacted]

- For continuous variables, summary statistics will include mean, median, standard deviation (SD), 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 or later (SAS Institute[1], Inc., Cary, NC), unless otherwise specified.

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.

Partial onset event dates are imputed for safety data using the result in the earliest event date possible. This imputation will only be performed as needed such as date variable is used in the variable derivation. However, no imputed dates will be presented in the listings.

- If the adverse event year is unknown, then the date will be imputed using the procedure date
- If the adverse event month is unknown, then:
    - If the adverse event year matches the year of the procedure date, then impute the month and day using the procedure date
    - Otherwise, assign 'January'
- If the adverse event day is unknown, then:
    - If the adverse event month and year match the month and year of the procedure date, then impute the day using the procedure date
    - Otherwise, assign '01'

For missing data due to patient withdrawal or lost to follow-up in the analyses of time-dependent endpoints, including the primary safety measures, primary performance measure, and secondary measures, the censoring mechanism will automatically account for censored data in the Kaplan-Meier analysis.

7. SUMMARY OF BASELINE INFORMATION

7.1 Patient Enrollment and Accountability

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

7.2 Demographics and Baseline Characteristics

[redacted]

Patient demographics, including age, sex, race, are summarized descriptively. Baseline characteristics that describe the disease state and patient condition at baseline are summarized descriptively. The characteristics to be summarized depend on the study indication and measures collected at baseline.

7.3 Medical History and Prior Intervention

Medical history and prior interventions grouped by event types (cardiovascular, cardiovascular intervention and surgeries, and non-cardiovascular) will be summarized by counts and percentages.

7.4 Procedural Information

Procedural information will be summarized including, but not limited to, the type of anesthesia, procedure duration, and the number of implanted devices, by mean and standard deviation for continuous variables and by counts and percentages for categorical variables.

7.5 Baseline Risk Assessments

The following baseline assessments will be summarized by sample size, mean, standard deviation for continuous variable, and counts and percentages for categorical variable.

- STS Risk Score (MV Repair, MV replacement)
- EuroSCORE II
- NYHA Classification

8. STATISTICAL ANALYSIS OF STUDY ENDPOINTS

[redacted]

8.1 Primary Safety Measures

The primary safety measure for this study is a composite endpoint of Major Adverse Events (MAEs) at 30 days. No hypotheses testing will be performed for this endpoint. The composite MAE and each individual MAE will be summarized by counts, percentage and 95% Confidence Interval (CI) of the percentage for the ITT and implanted population.

8.2 Primary Performance Measure

The primary performance measure is MR reduction to ≤2+ at 30 days and 12 months. The count and percentage of patients who are in each severity category will be summarized.

8.3 Secondary Measures

Safety Measures

All AEs and SAEs with onset on or after the procedure date (Day 0) will be summarized using type of event by early events (⩽ 30 days) and late events (> 30 days). Summaries of incidence rates (counts and percentages) will be prepared, where data is available.

Functional and Quality of Life Measures

Quality of Life (QoL) as measured by EQ-5D and KCCQ, will be scored according to algorithms provided by the vendor. The various summary scores produced by the algorithms will be analyzed as continuous variables. EQ-5D and KCCQ overall summary scores, and their changes from baseline to 30 days and 12 months will be summarized. Patients that are missing a baseline or follow up values will be excluded from the analysis.

Count and percentage of patients in each NYHA Class will be summarized. Change from baseline will be presented as a shift from baseline to 30-day and 12-month follow-up. Patients that are missing baseline or follow-up values will be excluded from the paired analysis.

Summary statistics, including mean, median, SD, and sample size, for 6MWT will be presented. Change in 6MWT at 30 days and 12 months over baseline will be summarized. Patients that are missing baseline or follow-up values will be excluded from the paired analysis. Patients unable to perform the walk due to a medical reason will be considered to have walked a distance of 0 m.

9. ANALYSIS OF SAFETY

9.1 Deaths

The primary cause of death will be summarized descriptively by counts and percentages at 30 days and 1 year. No statistical testing will be performed.

9.2 Adverse Events

As described in section 8.3.

10. CHANGES FROM PROTOCOL SPECIFIED ANALYSES

N/A.

11. REFERENCES

1. SAS/STAT® 9.4 User's Guide, SAS Institute, Inc., Cary, NC.

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