Edwards Lifesciences

Statistical Analysis Plan

Protocol Title:	Early Feasibility Study of the Edwards FORMA Tricuspid Transcatheter Repair System
Protocol Number:	2014-04 version M
SAP Version:	3.0
SAP Date:	April 1, 2019
SAP Author:	[redacted]

[redacted]

TABLE OF CHANGES

SAP version 2.0	SAP version 3.0	Reason for Change
3.4 Other Endpoint: Echocardiographic parameters	Updated the wording to be exactly matched with protocol [redacted]	[redacted]
4. Analysis Population	Added "Rev[redacted] and after" to be more clear for analysis population.	[redacted]
4.3 Per-protocol Population	Cha[redacted] protocol pop[redacted]on to be consisten[redacted]	[redacted]
7.1 Patient Enrollment and Accountability	Removed wording to be consistent with TMTT standard table shells.	[redacted]
8.4.1 Echocardiographic parameters	Updated the wording to be exactly matched with protocol Rev[redacted]	[redacted]
8.4.2 Clinical parameters	Change SF-36 to SF-12	Corrected error.
8.4.3 Additional Safety Analysis	Removed "DMC adjudicated AEs and SAEs"	Per safety adjudication rule update, only MAE and study endpoints will be CEC

[redacted]

		adjudicated. AE and SAE will no longer require CEC adjudication.
9. Changes From Protocol Specified Analyses	Updated per Rev [redacted]	Per protocol Rev [redacted]

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GLOSSARY OF TERMS:

ABBREVIATION	DEFINITION OR DESCRIPTION
AKI	Acute Kidney Injury
AT	As-treated population
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
CI	Confidence Interval
CIP	Clinical Investigational Plan
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EROA	Effective Regurgitant Orifice Area
HF	Heart Failure
ITT	Intent-to-treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQOS	KCCQ Overall Summary Score
KM	The Kaplan-Meier Method
Max	Maximum
Min	Minimum
MCS	Mechanical Circulatory Support
NYHA	New York Heart Association
PCS-12	Physical Health Summary score
PE	Pericardial Effusion
PP	Per protocol
PPM	Permanent Pacemaker
QoL	Quality of Life
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Standard deviation
SF-12	Medical Outcomes Study 12-Item Short-Form Health Survey
SVC	Superior Vena Cava
TV	Tricuspid Valve
TR	Tricuspid Regurgitation
VCW	Vena Contracta Width

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 Protocol, study #2014-04, Early Feasibility Study of the Edwards FORMA Tricuspid Transcatheter Repair System, and provides detailed instructions as to how each analysis will be performed. This SAP v3.0 is based on Protocol Rev M.

Results obtained from the analyses specified in the final approved version of the SAP will become the basis of the clinical study report (CSR) for this study. Any deviations from the final approved version of the SAP must be substantiated by sound statistical reasoning and documented in the CSR.

2. STUDY DESIGN

2.1 Study Objectives

The objectives of this early feasibility study are to:

- Evaluate the safety and function of the Edwards FORMA System
- Provide guidance for future clinical study designs utilizing the Edwards FORMA System
- Provide guidance for future FORMA System development efforts.

2.2 Overall Study Design and Plan

This is a multi-site, prospective, early feasibility study. 60 patients will be enrolled in the study. All enrolled study patients will be assessed for clinical follow-up at the following intervals: 1 month, 6 months, 1 year and annually for 3 years post implant procedure.

2.3 Sample Size Consideration

This clinical study will enroll 60 patients. This sample size was established based on typical sample size for early feasibility studies and no statistical justification was utilized.

2.4 Patient Enrollment

All patients enrolled under Revision [redacted] and later of the Clinical Protocol, will be consented, treated and followed according to the requirements described in protocol Revision [redacted] and later. Patients enrolled under previous versions of the Clinical Protocol [redacted] will not be required to re-consent under Revision [redacted], those patients will be followed according to the requirements of the protocol version to which they were consented.

3. STUDY ENDPOINTS

3.1 Safety Endpoints

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

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.

3.2.2 Procedural success

Device success with evidence of tricuspid regurgitation (TR) reduction as evidenced by a relative reduction in EROA of ≥ 30% from baseline to discharge and without the need for a surgical or percutaneous intervention prior to hospital discharge.

3.3.3 Clinical success

Procedural success without MAEs at 30 days. (MAEs: cardiovascular mortality, myocardial infarction, new need for renal replacement therapy, severe bleeding, re-intervention and major access site and vascular complications).

3.3 FDA Success Endpoints

Per FDA Request, the following success endpoints will also be summarized in reports.

3.3.1 FDA Device Success (at 1 month and all post-procedure follow-up visit intervals):

- Alive, with
- Original intended device in place, and
- No additional surgical or interventional procedures related to access or the device, and
- Intended performance of the device:

  a) No migration, detachment, hemolysis, thrombosis or endocarditis and

b) Expected hemodynamic performance (i.e., TR reduction of one grade and TV gradient ≤ 5mmHg)

c) No para-device complications (i.e., PPM, PE, SVC or subclavian thrombosis, damage to subvalvular apparatus of TV)

3.3.2 FDA Procedural Success (at 1 month): Safety

- Device Success, and
- None of the following device or procedure related SAE's:
  - a) Life threatening bleeding
  - b) Major vascular or cardiac structural complications requiring intervention,
  - c) Pericardial effusion requiring drainage or surgery (includes tamponade),
  - d) Stage 2 or 3 AKI (includes new dialysis).
  - e) Severe heart failure or hypotension requiring IV inotrope, ultrafiltration or MCS.
  - f) Prolonged intubation > 48 hours

3.3.3 FDA Individual Patient Success (at 6-months & 1 year): Effectiveness

- Device Success and all of the following:
  - a) No re-hospitalizations or re-interventions for the underlying condition (e.g. HF or TR)
  - b) Improvement vs. baseline in symptoms (e.g. NYHA Class improves from baseline)
  - c) Improvement vs. baseline in functional status (e.g. 6MWT improves from baseline)
  - d) Improvement vs. baseline in QoL (e.g. SF-12, KCCQ improves from baseline)

3.4 Other Endpoint: Echocardiographic 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 3 years post procedure.

1. TR grade- qualitative assessment
2. Vena Contracta (2D)
3. EROA (PISA/2D or 3D/3D color doppler)
4. Regurgitant volume
5. Tricuspid annular diameter (end-diastolic – S-L)
6. Tricuspid annular area (2D/3D mid-diastolic)
7. Tenting area and distance
8. Forward stroke volume
9. RV dimensions
10. Right atria volume
11. Left ventricular Ejection Fraction
12. Inferior Vena Cava dimensions/respiratory variations
13. Hepatic vein flow reversal
14. Pulmonary artery pressure (peak)
15. Right ventricular function

4. ANALYSIS POPULATIONS

This clinical study will enroll 60 patients. This sample size was established based on typical sample sizes for early feasibility studies and no statistical justification was utilized.

It was decided that from an analysis perspective, data from the first 30 patients (patient enrolled before Rev L) and second 30 patients (Patient enrolled under Rev L and after) will be analyzed together and also separately by sub-groups of before rev L and rev L and after, where applicable.

The analysis population will be grouped into three analysis cohorts that in total comprise all the patients in whom the study procedure has been attempted (vascular access obtained) in this study. The analysis cohorts are defined below:

4.1 Intent-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. at least skin incision to introduce the FORMA System).

4.2 As-Treated (AT) Population

The As-Treated population (AT) is a subset of the 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.

4.3 Per-protocol Population

The Per-Protocol (PP) population is a subset of the As-Treated (implanted) population in whom there are no inclusion/exclusion criteria-related protocol deviations.

The AT population will be the primary analysis population for performance and safety assessment. The ITT population will be used for device success, and additional safety analyses. Additional analyses of performance and safety data using the PP population will also be performed, if there is a clinically meaningful difference in sample size from the as-treated population.

5. DEFINITIONS

5.1 Analysis Dates and Days

- 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 the first interventional access-related puncture (arterial) is established.

The reference start date is considered to be day 0.

- Last Participation Date

The Last Participation Date is defined as the last date the patient is seen (e.g. maximum of the last date of procedure date, discharge date, follow-up visit date, exit date, adverse event date, and laboratory test date).

- Last Participation Day

Last Participation Day = Last Participation Date – Reference Start Date

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

5.2 Visit Windows

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

- Discharge visit (discharge day)
- 30-Day Visit ± 7 Days [23, 37 days]
- 6-Month Follow-up (180 ± 30 days) [150, 210 days]
- 1 year 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]

6. DATA AND ANALYSIS CONVENTIONS

6.1 General Conventions

- For continuous variables, summary statistics will include 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 ordinal data, the count and percentage of patients will be presented.
- For categorical and qualitative variables, summary statistics will include 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.
- Survival analysis techniques will be used to analyze the time-to-event variables. Summaries will include the number of patients at risk, number of events, number of patients with the event, and Kaplan-Meier estimates at given time points. 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 participation date. 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.
- [redacted]

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.

7. SUMMARY OF BASELINE INFORMATION

7.1 Patient Enrollment and Accountability

Patient enrollment for the ITT and AT groups will be summarized by each site and in total.

Disposition of patients at each follow up interval will be summarized in a table. If a patient discontinues prematurely from the study, the reason for discontinuation must be documented. The Study Exit case report form will be completed to document the reason for withdrawal.

7.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics, including but not limited to age, sex, and NYHA at baseline, will be summarized by counts and percentages for the ITT and AT populations.

7.3 Medical History and Prior Intervention

Medical history and prior interventions will be summarized by counts and percentages. Cardiovascular Medical History and Risk Factors, Non-Cardiovascular Medical History and Risk Factors, and Prior Cardiovascular interventions or Surgeries will all be summarized.

7.4 Procedural Information

Procedural information will be summarized including but not limited to procedure duration, duration of fluoroscopy time, volume of contrast used, and implantation status. In addition, the number of days spent in the ICU and total hospitalization for the index hospitalization will be summarized in a different table.

8. ANALYSIS OF STUDY ENDPOINTS

8.1 Safety Endpoint

Safety will be analyzed as a composite endpoint of Major Adverse Events (MAEs) at 30 days.

The MAE endpoint and its components will be summarized by counts and percentage for the AT cohort. Data Monitoring Committee (DMC) adjudicated data will be used in the analysis.

8.2 Performance Endpoints

All performance endpoints will be summarized by counts and percentages.

Device success is based on procedure data only. It will be evaluated for the ITT and AT cohorts at the time of the patient's exit from the cardiac catheterization laboratory.

The procedure success endpoint will be assessed for the AT cohort. The endpoint and its components will be assessed at the index procedure hospital discharge.

The clinical success endpoint at 30 days will be summarized by counts and percentages for the AT cohort. DMC adjudicated data will be used for MAEs. The endpoint and its components will be assessed at the 1 month follow-up interval.

8.3 FDA Endpoints

FDA Device Success, FDA Procedural Success, and FDA Individual Patient Success will be summarized by counts and percentages for the overall success variable and each of their individual components.

8.4 Additional Analysis

8.4.1 Echocardiographic parameters

Echocardiographic data will be provided by a core laboratory. TTE parameters will be assessed at baseline, discharge, 30 days, 6 months, 1 year and annually until 3 years post procedure. TEE parameters will be assessed at the start and the end of the initial implant procedure. The change from baseline for selected items will be presented as a shift from baseline for each of the pre-specified follow-up periods (paired analysis). Patients that are missing baseline or follow-up values will be excluded from the paired analysis. Patients that undergo any type of repair or replacement procedure for the tricuspid valve will be excluded from analysis at the time of the reintervention.

8.4.2 Clinical parameters

Re-hospitalization rates will be assessed at 1 month, 6 months and annually up to 3 years.

Time to first Heart Failure Re-hospitalization will be assessed via the Kaplan-Meier method for the AT cohort. In addition, the HF Re-hospitalization rate (number of HF Re-hospitalization per patient-year) will be analyzed.

Patient specific functional status (NYHA Class), exercise capacity (6MWD), and quality of life (SF-12 and KCCQ) metrics will be assessed at baseline, 1 month, 6 months, and 1 year and beyond.

Patients that undergo any type of repair or replacement procedure for the tricuspid valve will be excluded from analysis at the time of the reintervention. Only data up to the point of reintervention will be used.

8.4.3 Additional Safety Analysis

Site-reported adverse events (AEs) and serious adverse events (SAEs) will be summarized by early events (<=30 days) and late events (>30 days) for the ITT cohort. In addition, a listing of all the AEs and SAEs for the entire study population will be provided.

8.4.4 Sub-group Analysis

Subgroup analysis by enrollment (i.e., patients enrolled prior to Protocol Rev L vs. the remaining patients) will be performed, whenever applicable.

9. CHANGES FROM PROTOCOL SPECIFIED ANALYSES

Protocol version M had changed the definitions of per protocol population, in addition to that, the wording on echocardiographic parameters Section had also changed. This new version of the SAP incorporates those changes to be consistent with the protocol Rev M. The wording of “Rev L and after” in this version replaced “Rev L” in SAP 2.0 will help clarify the patient population available for analysis.

10. REFERENCES

Clopper CJ, Pearson E. The Use of the Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika 1934; 26:404-413.