Edwards Lifesciences

The SPACER Trial – Repair of Tricuspid Valve Regurgitation using the Edwards

FORMA TricuSPid TrAnsCatheter REpaiR System

Statistical Analysis Plan (Methodology)

Version 1.0

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1. GLOSSARY OF TERMS

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

6MWT	6-Minute Walk Test
ADS	Analysis Data Set
AE	Adverse Event
AKI	Acute Kidney Injury
BMI	Body Mass Index
BNP	Brain Natriuretic Peptide
CI	Confidence Interval
CIP	Clinical Investigational Plan
CSR	Clinical Study Report
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EROA	Effective Regurgitant Orifice Area
HF	Heart Failure
IC	Informed Consent
IP	Implant population
ITT	Intent-to-treat analysis population
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
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis Software
SD	Standard deviation
SF-12	Medical Outcomes Study 12-Item Short-Form Health Survey
SVC	Superior Vena Cava
TV	Tricuspid Valve
TR	Tricuspid Regurgitation
US	United States
VCW	Vena Contracta Width

2. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

2.1 Purpose of the Statistical Analysis Plan

The statistical analysis plan (methodology) provides detailed description of the planned analysis and methodology for Study #2015-09, the SPACER Trial – Repair of Tricuspid Valve Regurgitation using the Edwards FORMA Tricuspid Transcatheter Repair System. This SAP is based on Clinical Investigation Plan Rev C.G.

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2.2 Study Objectives

The purpose of the study is to assess the safety and device performance of the Edwards FORMA Tricuspid Transcatheter Repair System in patients with clinically significant, symptomatic, tricuspid regurgitation who are at high surgical risk for standard tricuspid repair/replacement.

2.3 Study Design

This is a multi-center (⩽12), international, prospective, single arm, safety study designed to assess the safety and device performance of the FORMA System.

A total of seventy-eight (78) subjects will be enrolled in the study. All implanted 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. Centers that do not have experience with the investigational device will be allowed a single “roll-in” subject to become familiar with the study device and procedure.

2.3.1 Primary Endpoint:

The primary endpoint for the study will assess the all-cause mortality of the as treated cohort at 30 days compared to a literature derived Performance Goal based on high-risk surgical outcomes for tricuspid repair/replacement.

2.3.2 Secondary Endpoints and Clinical Outcomes:

The following secondary endpoints and clinical outcomes will also be assessed:

Technical Success (at exit from procedure room):

- Alive, with
- Successful access, delivery and removal of the delivery systems, and

- Deployment and correct positioning of the intended device, and
- No need for additional emergency surgery or re-intervention related to the device or access procedure

Device Success (at 1 month, 6 months & annually):
- Alive, with
- Original intended device in place, and
- No additional surgical or interventional procedures related to the device, and
- TR reduction (assessment made by change in EROA) compared to baseline and TV gradient $\leq$ 5mmHg

Procedural Success (at 1 month):
- Device Success, and
- None of the following device or procedure related SAEs:
- Life threatening bleeding
- Major vascular or cardiac structural complications requiring intervention
- Pericardial effusion requiring drainage or surgery (includes tamponade)
- Stage 2 or 3 acute kidney injury (includes new dialysis).
- Severe heart failure or hypotension requiring IV inotrope, ultrafiltration or mechanical circulatory support
- Prolonged intubation > 48 hours

Clinical Outcomes (at 1 month, 6 months & annually)
- Re-hospitalization rates for the underlying condition (heart failure)
- Re-intervention rates for the underlying condition (tricuspid regurgitation)
- Change in Tricuspid Regurgitation (assessment made by change in EROA) from baseline
- Change in peripheral edema as assessed by subject weight loss (kilograms) from baseline
- Change in NYHA Class from baseline
- Change in 6 minute walk test distance (meters) from baseline
- Change in Quality of Life as assessed by the SF-12 and KCCQ questionnaires from baseline

2.4 Analysis Populations

The analysis population will be grouped into four analysis cohorts that in total comprise all subjects enrolled in this study. The analysis cohorts are defined below:

- Enrolled Cohort: all subjects enrolled in the study
- As Treated (AT) Cohort: all subjects who are enrolled and undergo the study procedure (chest incision)
- Implanted Cohort: all subjects who undergo the study procedure (chest incision), receive and retain the investigational device upon leaving the procedure room
- Roll-In Cohort: first subject enrolled and treated at a center that does not have previous device or procedure experience and is classified as a “roll-in” subject

The primary endpoint will be reported based on the AT cohort. For the secondary endpoints and clinical outcomes, technical success analysis will be performed for the AT cohort, while device success, procedure success and clinical outcomes analyses will be performed for the implanted cohort. Roll-In subjects will be analyzed separately. Subject listings for adverse events, deaths will include all enrolled subjects.

For subjects with major protocol violations, which include but are not limited to study criteria and informed consent violations, a secondary analysis will be conducted in which those subjects will be excluded from the implanted cohort analyses.

3. STATISTICAL ANALYSIS

3.1 General Considerations

Baseline demographics, medical history, procedural data, adverse event data, and endpoint data will be analyzed using descriptive statistics.

Continuous variables will be summarized using means, standard deviations, medians, ranges, and 95% confidence intervals for the mean based on normal distribution.

Binary variables will be summarized with counts, percentages, and 95% Clopper-Pearson confidence intervals.

Time to event variables will be analyzed using Kaplan–Meier estimates.

Nonparametric techniques may be used if the data does not meet the assumptions of parametric tests.

3.2 Primary Endpoint Analysis

A performance goal of 18% was pre-specified for the 30-day rate of all-cause mortality in TVR (Tricuspid Valve Regurgitation) subjects treated with the Edwards FORMA Tricuspid Transcatheter Repair System, which was based on review of literature and early clinical studies. The hypothesis for the primary endpoint is as follows:

H0: $\pi \geq 18\%$
HA: $\pi < 18\%$

Where π represents the all-cause mortality rate at 30 days.

The primary endpoint for this clinical study is all-cause mortality at 30 days post-implant procedure in the as treated (AT) cohort population. A one-sided 95% confidence interval for 30 day mortality will be computed using the Kaplan-Meier algorithm with the standard errors being computed using Greenwood's formula. The null hypothesis shall be rejected at alpha = 0.05 if the upper confidence limit is less than 0.18.

3.3 Additional Endpoint Analysis

Kaplan Meier estimates will be performed at the pre-specified follow-up times to project the estimates for time-related safety endpoints. The rate of freedom from all-cause mortality at 6 month, 1 year, 2 years, and 3 years will be estimated in addition to the primary endpoint which is established at 30 days post procedure.

Echocardiographic data will be analyzed by a core laboratory. The improvement from baseline for selected items 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 analysis.

Subjects that undergo any type of repair or replacement procedure for the tricuspid valve will be excluded from the implant cohort analyses at the time of the re-intervention.

The average overall (general) quality of life at baseline, 1 month, 6 months and annually for 3 years and the changes from baseline to follow up will be summarized by mean and standard deviation for the implanted cohort. Patients that are missing a baseline or follow up values will be excluded from the analysis.

3.4 Follow-up and Analysis Time points

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

- Procedure (day 0)
- Discharge (discharge days = discharge date – implant date)
- 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 [1055, 1140 days]

3.5 Missing Data Handling

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.

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 1st 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

3.6 Analysis Software

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4. VARIABLE LIST FOR TABLE SHELLS

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

4.1 Demographics, Subject Characteristics, and Procedure Assessments

4.1.1 Demographics and Clinical Evaluation

- Age (in years)
- Gender
- Race/Ethnicity
- Body Mass Index (BMI)
- NYHA Class

4.1.2 Medical History

- Arrhythmia
- Cancer
- Carotid artery stenosis
- Coagulopathy
- Coronary artery disease
- Diabetes
- Hyperlipidemia
- Hypertension
- Liver Disease
- Myocardial infarction
- Pacemaker/ICD
- Peripheral vascular disease
- Prior Percutaneous Coronary Intervention
- Prior CABG
- Prior Valve Implant
- Pulmonary Disease
- Pulmonary Hypertension
- Stroke

- TIA

4.1.3 Procedure Information

- Time from Skin Incision to Closure Time (min)
- Time from Sheath Insertion to Device Lock (min)
- Fluoroscopy Time (min)
- Volume of Contrast Used (ml)

  Implant Access Approach
  - Left subclavian/axillary vein
  - Right subclavian/axillary vein
- Spacer Size
  - 12mm
  - 15mm
  - 18mm
- Device permanently implanted
- Device implanted as intended
- Reintervention Required
- Device Malfunction

4.1.3 Implant Hospitalization Length of Stay (in days)

Days from index procedure to discharge of index procedure.

4.2 Primary Endpoint Analysis

- All-cause mortality at 30 days post-implant procedure

4.3 Additional Endpoint Analysis

The following secondary endpoints and clinical outcomes will also be assessed

4.3.1 Technical Success (at exit from procedure room):

- Alive, with

- Successful access, delivery and removal of the delivery systems, and
- Deployment and correct positioning of the intended device, and
- No need for additional emergency surgery or re-intervention related to the device or access procedure

4.3.2 Device Success (at 1 month, 6 months & annually):

- Alive, with
- Original intended device in place, and
- No additional surgical or interventional procedures related to the device, and
- TR reduction (assessment made by change in EROA) compared to baseline and TV gradient ≤ 5mmHg

4.3.3 Procedural Success (at 1 month):

- Device Success, and
- None of the following device or procedure related SAEs:
    - Life threatening bleeding
    - Major vascular or cardiac structural complications requiring intervention
    - Pericardial effusion requiring drainage or surgery (includes tamponade)
    - Stage 2 or 3 acute kidney injury (includes new dialysis).
    - Severe heart failure or hypotension requiring IV inotrope, ultrafiltration or mechanical circulatory support
    - Prolonged intubation > 48 hours

4.3.4 Clinical Outcomes (at 1 month, 6 months & annually)

- Re-hospitalization rates for the underlying condition (heart failure)
- Re-intervention rates for the underlying condition (tricuspid regurgitation) Change in Tricuspid Regurgitation (assessment made by change in EROA) from baseline
- Change in peripheral edema as assessed by subject weight loss (kilograms) from baseline
- Change in NYHA Class from baseline
- Change in 6 minute walk test distance (meters) from baseline
- Change in Quality of Life as assessed by the SF-12 and KCCQ questionnaires from baseline

4.4 Transthoracic Echocardiogram (TTE) Parameters

- RA Area (cm2)
- RV End Diastolic Area (cm2)
- RV End Systolic Area (cm2)
- RA Volume (ml)
- RVED Volume (ml)
- RVES Volume (ml)
- RV EF (%)
- TAPSE (cm)
- RV Free Wall Thickness (cm)
- TV Annular Area 2D (cm2)
- TV Annular Area 3D (cm2)
- TV mean gradient (mmHg)
- LV EF (%)
- TR Vena Contracta inflow (cm)
- TR Vena Contracta Short Axis (cm)
- PISA EROA (cm2)
- Tricuspid Regurgitant volume (ml)
- Tricuspid Regurgitant EROA 2D (cm2)
- Tricuspid Regurgitant EROA 3D (cm2)
- Tricuspid Regurgitant RF (%)
- Jet Area (cm2)
- TR Jet VTI (cm)
- Tricuspid Leaflet Motion
- Tricuspid Leaflet Thickening
- Thrombus
- Pericardial Effusion
- Non-Study Valves AS
- Non-Study Valves AR
- Non-Study Valves MR
- Overall baseline TR

5. 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® 9.3 User's Guide, SAS Institute, Inc., Cary, NC.