TRI-REPAIR
Tricuspid Regurgitation Repair with Cardioband Transcatheter System
Study TR1-1

Statistical Analysis Plan (Methodology)

Version 1.0

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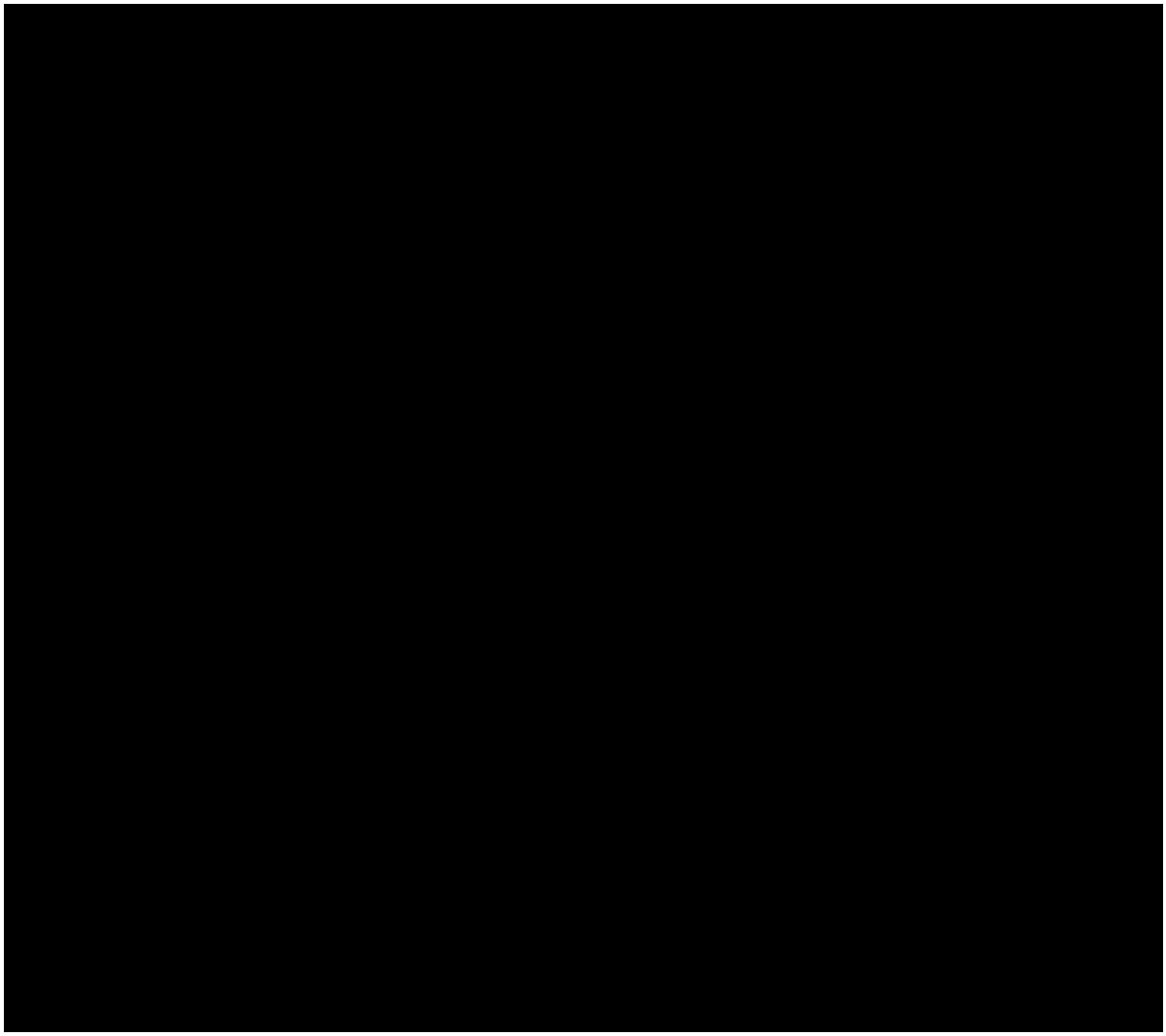
[redacted]

Edwards Lifesciences LLC
One Edwards Way
Irvine, CA 92614

Approved By:



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1 SYNOPSIS OF STUDY DESIGN AND PROCEDURES

1.1 Purpose of the statistical analysis plan (SAP)

The SAP (methodology) provides detailed description of the planned analyses and methodology for Study TR1-1 (TRI-REPAIR – Tricuspid Regurgitation (TR) Repair with Cardioband Transcatheter System). This SAP is based on the study protocol for TR1-1 Rev 05, dated May 25, 2017.

[redacted]

1.2 Study objectives

The objectives of this early feasibility study are to assess the safety and technical success of the Cardioband system for the procedure of symptomatic chronic functional tricuspid regurgitation.

1.3 Study design

This clinical investigation is a single arm, multi-center, prospective study with intra-subject comparisons. Candidates for Cardioband TR procedure are symptomatic subjects with functional tricuspid valve repair. Subjects are selected upon clinical conditions and severity of TR. Anatomical feasibility is assessed by Echocardiography and/or other exams (such as computerized tomography and angiography) according to the site common practice. Subjects will be screened and enrolled according to the study inclusion and exclusion criteria.

Subjects will undergo tricuspid valve repair with Cardioband implanted via transcatheter procedure under Transoesophageal/Intracardiac echocardiography (TEE/ICE) and fluoroscopy guidance. Post-procedure clinical care will be performed according to standard management of valve repair; Clinical follow-up including standard post-procedural management of surgical valve repair and Transthoracic Echo (TTE) assessment of the degree of Tricuspid regurgitation will be obtained at hospital discharge, 30 days, 6, 12 and 24 months post-index procedure.

As the follow up at 30 days is of most importance in terms of the subject's safety, the first 3 subjects will have to complete 30 days follow up before the recruitment of additional subjects. In relation to the first 3 subjects, recruitment will continue in case of elongated hospitalization or complications that are unrelated to the study device as will be judge by the study clinical event committee.

1.4 Sample size

A sample size of up to 60 patients is considered adequate to further confirm the safety and performance of the Cardioband System in TR patients. Considerable clinical data on the safety of clinically equivalent devices exists. This will enable a comparison of clinical data obtained in this study with literature data from prior studies.

1.5 Sample Size Justification

Reference values for calculations are based on a literature review of predicate devices and clinical experience in previous Valtech adjustable and mitral annuloplasty devices. A sample size of 60 subjects allows accurate estimates of risk associated the device (even for rare events). The sample size was selected through the width of the two-sided 95% exact confidence interval of the potential adverse event rates. [redacted]

2 STUDY ENDPOINTS

2.1 Primary endpoints

Safety

Primary safety endpoints will be measured at hospital discharge and 30 days post-procedure.

1. Major serious adverse events (MSAEs)

    - Death
    - Myocardial infarction
    - Cardiac tamponade
    - Device related cardiac surgery
    - Stroke

Technical success

Primary technical success endpoints will be measured throughout the procedure and at discharge.

1. Successful Cardioband procedure
2. Cardioband completely implanted
3. Any reduction in septolateral diameter

2.2 Secondary endpoints*

Secondary endpoints will be measured at baseline, discharge, 1, 6, 12, and 24 months post procedure.

1. Tricuspid regurgitation
2. Effective regurgitant orifice area (EROA)
3. Regurgitant volume
4. Tricuspid annular plane systolic excursion (TAPSE)
5. New York Heart Association (NYHA) Class
6. Six Minute Walk Test (SMWT)
7. Kansas City Cardiomyopathy Questionnaire (KCCQ)
8. Left ventricular ejection fraction (LVEF)
9. N terminal pro B type natriuretic peptide (NT-pro BNP)
10. GOT aka aspartate aminotransferase (AST), GPT aka alanine transaminase (ALT), bilirubin
11. Blood urea nitrogen (BUN) creatinine clearance
12. Diuretic therapy

**Note. Although originally included in the protocol, secondary endpoints:*

(a) Left ventriculuar end diastolic volume index (LVEDVI)
(b) Left ventricular end systolic volume index (LVESVI)
(c) Activity by wearable device

will not be analyzed due to their limited relevance to main study objectives

Table 2. Summary of primary and secondary endpoints

Endpoint	Baseline	Discharge	1 Month	6 Months	12 Months	24 Months
MSAE		x	x			
Technical success		x				
Tricuspid regurgitation	x	x	x	x	x	x
EROA	x	x	x	x	x	x
Regurgitant volume	x	x	x	x	x	x
TAPSE	x	x	x	x	x	x
NYHA	x	x	x	x	x	x
SMWT	x	x	x	x	x	x
KCCQ	x	x	x	x	x	x
LVEF	x	x	x	x	x	x
NT-pro BNP	x	x	x	x	x	x
AST	x	x	x	x	x	x
ALT	x	x	x	x	x	x
Bilirubin	x	x	x	x	x	x
BUN	x	x	x	x	x	x
Diuretic therapy	x	x	x	x	x	x

2.3 Analysis populations

Two analysis cohorts will be defined as below:

- Intent-to-treat (ITT) cohort includes all subjects who signed informed consent, met eligibility criteria, and for whom the study procedure has been attempted.
- As-treated cohort is a subject of the ITT cohort and includes all subjects for whom the study device is implanted and remains in the position at the time of the subject's exit from the procedure room.

The primary safety analysis will be performed on both cohorts with due consideration given to the required follow-up intervals for each cohort. All other analyses will be performed on the as-treated cohort.

3 STATISTICAL ANALYSIS

3.1 General considerations

There are no pre-specified hypotheses for this study.

Continuous variables will be summarized with means, standard deviations, medians, ranges, and 95% confidence intervals for the mean based on a normal distribution. Categorical variables will be summarized with counts and percentages, accompanied by 95% Clopper-Pearson (i.e., exact method) confidence intervals. In addition, graphs may be created for certain endpoints as appropriate.

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

3.2 Primary endpoint analysis

Safety

1. Major serious adverse events (MSAEs)

   Death, myocardial infarction, cardiac tamponade, device related cardiac surgery, and stroke. Percentage of occurrences at discharge and 30-day post-procedure will be summarized in tables.

Technical

1. Successful Cardioband procedure
2. Cardioband completely implanted
3. Any reduction in septolateral diameter

   Technical success is defined as meeting success criteria in all three categories. Percentage of success at discharge will be summarized in tables.

3.3 Secondary endpoint analysis

Secondary endpoints will be measured at baseline, discharge, 1, 6, 12, and 24 months post-procedure. Descriptive statistics will be presented at each 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. Importance will be given to the 30 day and 6 month follow-ups.

1. Tricuspid regurgitation (TR)

   TR from Core Lab will be categorized into two grading systems and summarized in tables:

   a. 0 = none, 1 = mild, 2 = moderate, 3 = severe

   b. (Pending availability form Core Lab) 0 = none, 1 = mild, 2 = moderate, 4 = severe, 5 = massive, 6 = torrential. This grading system has more granular detail and it's recommended by Hahn and Zamorano (2017).

2. Effective regurgitant orifice area (EROA)

   Descriptive statistics for regurgitant area (cm^2) from Core Lab will be summarized in tables.

3. Regurgitant volume

   Descriptive statistics for regurgitant volume (mL) from Core Lab will be summarized in tables.

4. Tricuspid annular plane systolic excursion (TAPSE)

   Descriptive statistics for distance of systolic excursion of the right ventricle annular plane towards the apex (cm) from Core Lab will be summarized in tables.

5. Left ventricular ejection fraction (LVEF)

   Descriptive statistics for LVEF (%) from Core Lab will be summarized in tables.

6. New York Heart Association (NYHA) Class

   NYHA will be categorized into classes (1 = no limitation of physical activity, 2 = slight limitation of physical activity, 3 = marked limitation, 4 = unable to carry any physical activity without discomfort) and summarized in tables.

7. Six Minute Walk Test (SMWT)

   Descriptive statistics for distance (m) walked will be summarized in tables.

8. Kansas City Cardiomyopathy Questionnaire (KCCQ) Short form-12

   Descriptive statistics for clinical summary scores will be summarized in tables.

9. N terminal pro B type natriuretic peptide (NT-pro BNP)

   Descriptive statistics for NT-pro BNP (ng/L) will be summarized in tables.

10. GOT aka aspartate aminotransferase (AST), GPT aka alanine transaminase (ALT), bilirubin

    Descriptive statistics for AST (U/L), ALT (IU/L), and bilirubin (µmol/L) will be summarized in tables.

11. Blood urea nitrogen (BUN) creatinine clearance

    Descriptive statistics for BUN (mg/dL) will be summarized in tables.

12. Diuretic therapy

    Raw data for number of subjects currently taking each type of diuretic drug and dosage level will be presented in listings.

3.4 Missing data handling

All statistical analysis on primary and secondary endpoints will be performed using only available data. No missing value imputation will be performed.

3.5 Analysis software

Unless otherwise specified, SAS® Version 9.3 or higher will be the default software for analysis. Other statistical or graphic packages may be used.

4 VARIABLE LIST FOR TABLE SHELLS

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

4.1 Subject disposition, baseline characteristics, and procedure information

4.1.1 Number of subjects enrolled by site

- Site number
- Site name
- Total subjects per site
- Date of first subject implanted
- Date of last subject implanted

4.1.2 Subject dispositions at 30 days and 6 months

- Total number of subjects
- Died before follow up
- Withdrew consent
- Lost to follow up
- Eligible for visit
- Follow up completed within window (30 ± 14 days vs 180 ± 30 days)
- Follow up completed outside window
- Follow up not performed

4.1.3 Demographics and Baseline Characteristics

- Age
- Gender
- Body mass index
- Society of Thoracic Surgeons (STS) score
- EuroSCORE II
- NYHA class
- NYHA class grouped
- LVEF by Core Lab
- FTR Etiology

4.1.4 Prior cardiovascular interventions or surgeries

- Valve surgery
- Percutaneous transcatheter valve replace/repair other than tricuspid
- Coronary artery bypass graft (CABG)
- Percutaneous coronary intervention
- Any cardiac devices without electrodes
- Any cardiac devices with electrodes

4.1.5 Non-cardiovascular risk factors

- Diabetes
- Dyslipidemia
- Systemic hypertension
- Peripheral vascular disease
- Peripheral vascular intervention
- Chronic lung disease (moderate to severe)
- Chronic renal disease
- eGFR
- Chronic liver disease
- Chronic anemia
- History of endocarditis
- Thyreosis
- Ongoing inotropic support
- Elevated pulmonary pressure (> 35 mmHg)
- Pulmonary pressure
- Frailty score
- Prior stroke
- Prior transient ischemic attack
- Carotid surgery
- Carotid intervention
- History of smoking
- Active malignancy
- Any other relevant medical conditions

4.1.6 Cardiovascular risk factors

- Coronary artery disease
- Previous MI
- Angina pectoris
- Congestive heart failure
- Aortic valve
- Mitral valve
- Pulmonic valve
- Atrial flutter/fibrillation
- Flutter/fibrillation ablation
- Ventricular tachyarrhythmia

4.1.7 Implant procedure information

- Cardioband implanted

- Procedure outcome
- Any septolateral reduction
- Total Cardioband TR time
- Total procedure time
- Total fluoro exposure
- Ventilated for more than 40 hours
- Cardioband implant size

4.1.8 Implant hospitalization length of stay
- Implant hospitalization length of stay
- ICU length of stay

4.2 Safety endpoints

4.2.1 Major serious adverse events
- Any major serious adverse event
- Death
- Myocardial infarction
- Cardiac tamponade
- Device related cardiac surgery
- Stroke

4.2.2 Re-hospitalization due to heart failure at 12 months
- Number of CHF-related hospitalizations in the 12 months prior to procedure
- Total number of CHF-related hospitalizations in the 12 months prior to procedure
- Number of HF re-hospitalizations in the 12 months post discharge
- HF Re-hospitalization rate

4.3 Clinical endpoints

4.4.1 Technical success
- Cardioband implanted
- Successful procedure
- Any septolateral reduction

4.4.2 Vital signs
- BMI
- Weight

4.4.3 Other clinical endpoints
- NYHA
- Six Minute Walk Test
- Edema
- KCCQ

4.5 Adverse events

4.5.1 Adverse events reported by site

4.5.2 Serious adverse events adjudicated by CEC

4.5.3 Major serious adverse events after 30 day post procedure

4.6 Echocardiogram parameters by Core Lab

4.6.1 Transthoracic echocardiogram (TTE) parameters at 30 day and 6 months

- Triscuspid valve regurgitation degree
- Quantitative doppler TR EROA
- PISA EROA
- PISA radius
- TR vena contracta min
- TR vena contracta max
- TV annulus mid diastolic diameter
- TV annulus mid diastolic diameter inflow view
- TV annulus mid diastolic area
- TV annulus diastolic area
- TR regurgitant volume
- RV TAPSE
- LVEF
- LVOT doppler stroke volume
- Pulmonary artery pressure
- Right atrial pressure

4.6.2 Intra procedure transesophageal echocardiogram (TEE) parameters

- TR severity
- TR vena contracta min
- TR vena contracta max
- TV annulus mid diastolic diameter
- TV annulus mid diastolic diameter inflow view

4.7 Protocol deviations

5 REFERENCES

1. Clopper, C.J. and Pearson, E. (1934). The Use of the Confidence or Fiducial Limits Illustrated in the Case of the Binomial. *Biometrika*, 26, 404-413.
2. SAS/STAT® 9.3 User's Guide, SAS Institute, Inc., Cary, NC.
3. Hahn, R.T. and Zamorano, J.L. (2017). The need for a new tricuspid regurgitation scheme. Eur Heart J Cardiovasc Imaging, *jex139*, https://doi.org/10.1093/ehjci/jex139