Edwards Lifesciences

STATISTICAL ANALYSIS PLAN

Protocol Title:	**(Annular ReduCtion for Transcatheter Treatment of Insufficient Mitral ValvE (ACTIVE)**: A prospective, multicenter, randomized, controlled pivotal trial to assess transcatheter mitral valve repair with Edwards Cardioband System and guideline directed medical therapy (GDMT) compared to GDMT alone in patients with functional mitral regurgitation (FMR) and heart failure
Protocol Number:	2017-05 Rev E
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1. INTRODUCTION

This statistical analysis plan (SAP) specifies the statistical methods to be implemented for the analysis of data collected within the scope of Edwards Lifesciences's Protocol ACTIVE 2017-05[redacted] and provides detailed instructions as to how each analysis will be performed.

[redacted]

2. STUDY DESIGN

2.1 Study Objective

The objective of this study is to evaluate the efficacy and safety of transcatheter mitral annular reduction for functional mitral regurgitation (MR) plus guideline directed medical therapy (GDMT) compared to GDMT alone.

2.2 Overall Study Design and Plan

This study is a prospective, randomized, multicenter clinical evaluation of the Edwards Cardioband System for the treatment of clinically significant functional mitral regurgitation in MR patients who are treated in accordance with current ACC/AHA valve guidelines. The study design incorporates a roll-in cohort to provide experience in use of the Edwards Cardioband System prior to randomizing patients into the pivotal study cohort at a given investigational site. The roll-in cohort will include a maximum of three patients per site (e.g. if 75 sites used, a maximum of 225 roll-in patients). Data for the roll-in patients will be presented and analyzed as a separate cohort. All patients are followed for 30 days, 6 months, 1 year, and annually for a total of five years post-index procedure or randomization in the case of the Control population.

2.3 Randomization and Blinding

Randomization is ideally performed within seven days prior to the scheduled procedure, but no more than 14 days prior. If a patient is randomized to Control, the scheduled interventional case is cancelled and the patient is notified that they have been enrolled in the Control/medical therapy arm of the trial and will not need to undergo an interventional procedure. The process of randomizing after a case is scheduled has been implemented to ensure that the time frame between randomization and actual treatment is minimized. Eligible patients will be randomly assigned in a 2:1 ratio to either Device group or Control group, respectively.

Randomization schedule will be generated using the Balance module in Medidata RAVE, the Electronic Data Capture System for the study. Randomization will be stratified by (a) site and (b) baseline ischemic vs non-ischemic disease. This randomization schedule will be masked to patients, site personnel, study team, and sponsor as defined in the Randomization and Blinding Plan. Only the unblinded statistician and designates will be privy to the masked randomization scheme.

All analyses of data by the study statistician/programmer will be conducted blinded to treatment assignment (similar to the conduct of blinded clinical study to the extent possible), until the time of database lock for the primary endpoint analysis. Analyses of unblinded data such as DSMB analysis will be performed by a separate non-study or independent statistician/SAS programmer.

2.4 Sample Size Consideration

This study randomizes up to 375 eligible patients at up to 75 sites in North America and Europe on a 2:1 randomization

ratio to the Edwards Cardioband System + GDMT (Device group) or to GDMT alone (Control group). Data will be available at 30 days, 6 months, 1 year, and long-term follow-up annually through 5 years is planned for all patients. Therefore, it is expected that a maximum of 600 patients will be enrolled (up to 375 pivotal patients plus up to 225 roll-in patients).

3. HYPOTHESIS AND STUDY ENDPOINTS

Transcatheter mitral valve repair with the Edwards Cardioband System, combined with GDMT will reduce MR and improve MR symptoms and functional capacity in patients with functional MR as compared with GDMT alone.

3.1 Co-Primary Hypothesis 1

H_0: $P_{Device}(T=1) - P_{Control}(T=1) = 0$
H_1: $P_{Device}(T=1) - P_{Control}(T=1) \neq 0$

where

H_0 = Null hypothesis
H_1 = Alternative hypothesis
P_{Device} = Proportion of patients in the Device group with MR ≤ 2+
$P_{Control}$ = Proportion of patients in the Control group with MR ≤ 2+
T = Time (years)

The co-primary hypothesis 1 tests the superiority in reducing MR of the Device group relative to the Control group via two independent proportions z-test with two-sided alpha = .05.

3.2 Co-Primary Hypothesis 2

H_0: The hierarchical composite ranking of the co-primary endpoints 2 does not differ by treatment
H_1: The hierarchical composite ranking of the co-primary endpoints 2 does differ by treatment

The co-primary hypothesis 2 tests the superiority of the Device group relative to the Control group for the hierarchical sequence of the four co-primary endpoints 2 (see section 2.2) via the Finkelstein-Schoenfeld test (Finkelstein and Schoenfeld, 1999). The Finkelstein-Schoenfeld test is a generalization of the Gehan Wilcoxon test. See statistical analysis in section 3 for details.

3.3 Primary Efficacy Endpoints (1 Year)

a. Co-primary efficacy endpoint 1:
   Prevalence of MR ≤ 2+ at 1 year

b. Co-primary efficacy endpoint 2:
   i. Time to all-cause death
   ii. Number of heart failure hospitalizations
   iii. Improvement in Six Minute Walk Test (6MWT) relative to baseline (≥ 40 meters improvement)
   iv. Improvement in Kansas City Cardiomyopathy Questionnaire (KCCQ) relative to baseline (≥ 10 points improvement)

Co-primary efficacy endpoint 1 must meet statistical significance in order to proceed to co-primary efficacy endpoints 2. This approach does not require any adjustment for multiplicity. The co-primary efficacy endpoints were chosen in order to capture the ability of the Edwards Cardioband System to effectively reduce MR (co-primary endpoint 1) and improve clinical outcomes (co-primary endpoints 2).

3.4 Primary Safety Endpoints – Device Group Only (30 Days)

Overall rate of device and procedure related major adverse events (MAEs), which includes:

a. Death
b. Stroke
c. Myocardial infarction
d. Pericardial effusion requiring drainage
e. Left circumflex coronary artery injury requiring intervention
f. Mitral valve reintervention
g. Access site and vascular complications requiring intervention

The primary safety endpoints were chosen to detect any concerns relating to safety of the Edwards Cardioband System implantation procedure.

3.5 Secondary Safety Endpoints – Device Group Only (30 Days)

Individual rates of the following adverse events:

a. Death
b. Stroke
c. Myocardial infarction
d. Pericardial effusion requiring drainage
e. Left circumflex coronary artery injury requiring intervention
f. Mitral valve reintervention
g. Access site and vascular complications requiring intervention
h. Need for a new permanent pacemaker

3.6 Secondary Endpoints – Powered (1 Year)

The following key secondary efficacy endpoints will be tested between Device and Control group in hierarchical order to account for multiplicity:

a. MR ≤ 1+
b. NYHA class
c. KCCQ
d. 6MWT
e. SF-36v2 Health Survey (SF-36)
f. Heart failure hospitalizations
g. Cardiovascular death
h. All-cause mortality

3.7 Other Secondary Endpoints

The following outcomes will be assessed between Device and Control, where appropriate:

For the Device Arm:

1. Device Success (measured at 30 days): 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).

2. Procedural Success (measured at 30 days): Device success with evidence of MR reduction ≤ 2+ at discharge and without the need for a surgical or percutaneous intervention prior to hospital discharge (per patient analysis).

3. Clinical Success (measured at 30 days): Procedural success with evidence of MR reduction ≤ 2+ and without MAEs* at 30 days (per patient analysis).

**Major adverse events (MAE) defined as death, stroke, myocardial infarction, pericardial effusion requiring drainage, left circumflex coronary artery injury requiring intervention, mitral valve reintervention and access site and vascular complications requiring intervention.*

4. Responder analysis percentage of patients who achieve:

a. MR ≤ 2+ and
b. Meets at least two of the following criteria:

i. Improvement vs. baseline in symptoms (e.g., NYHA Class improvement ≥ 1)
ii. Improvement vs. baseline in functional status (6MWT improvement ≥ 30 meters)
iii. Improvement vs. baseline in QoL (KCCQ improvement ≥ 5 points)

For both the Device and Control Arms:

1. Patient success (measured at 1 year) is defined as

a. Patient remains alive and stroke free,
b. No re-hospitalizations (or equivalents) for HF, and
c. Patient meets at least two of the following criteria:

i. Improvement vs. baseline in symptoms (e.g., NYHA Class improvement ≥ 1)
ii. Improvement vs. baseline in functional status (6MWD improvement ≥ 30 meters)
iii. Improvement vs. baseline in QoL (KCCQ improvement ≥ 5 points)

2. Mean daily steps (measured at 1 year):

Mean daily steps measured during the hours of 6am to 10pm, via an activity monitoring device, during a one month collection period following the 1 year follow-up visit. Patient Success (evaluated at 1 year post index procedure).

3.8 Echocardiography Endpoints (Annually Through 5 Years)

Key echocardiography parameters by echo core lab assessment at 30 days, 6 months, and yearly at 1 to 5 years:

a. MR severity
b. LVEDVi
c. LVESVi
d. TAPSE
e. Mitral valve effective orifice area (EOA)
f. Left ventricular ejection fraction (LVEF)
g. Stroke volume
h. Left atrial volume
i. Tricuspid regurgitation severity
j. Estimated pulmonary artery pressure

3.9 Long Term Outcomes (Through 2, 3, 4, 5 Years)

The following outcomes will be collected yearly at 2 to 5 years:

a. NYHA
b. SMWT
c. Heart failure hospitalizations
d. Cardiovascular death
e. Surgical mitral valve replacement or surgical repair
f. Transcatheter based mitral valve interventions
g. All-cause mortality
h. Cardiac transplantation
i. Mechanical hemodynamic support (e.g., LVAD)
j. Number of days alive and out of hospital
k. NT-proNBP level
l. Need for new permanent pacemaker
m. KCCQ
n. SF-36

3.10 Long Term Safety Outcomes (1 Year)

a. Stroke
b. Transient ischemic attack
c. Major vascular complications
d. Renal complications

4. ANALYSIS POPULATIONS

4.1 Enrolled Population

Any patient who has signed informed consent will be included as part of the enrolled population. Should a patient be considered ineligible after signing consent and before randomization, the reason for failure will be documented, and the patient will be exited from the study. For roll-in patients, the enrolled population will be based on those who signed informed consent, met eligibility criteria, and had the procedure attempted. Serious adverse events (SAEs) will be reported for all enrolled patients through study exit.

4.2 Intent-to-Treat Population (Safety Analysis)

The intent-to-treat population (ITT) will consist of all patients who have signed informed consent and have been randomized. Patients that have entered the procedure room but have not received an implant attempt (passing of any Edwards Cardioband System component past the skin) will be deregistered and followed through 30 days for safety purposes only.

4.3 Modified Intent-to-Treat Population (Efficacy Analysis)

The modified intent-to-treat population (mITT) will consist of all patients randomized to the Control Group and all patients randomized to the Device group that have had the Edwards Cardioband System implanted. The mITT population represents the primary analysis population for this study. The randomization will continue until 375 mITT patients are enrolled.

A separate summary of the safety on all screen failure patients shall be provided as part of the study final report.

4.4 Device Implant Population

The device implant population is defined as the subset of the mITT population consisting of those patients for whom any part of the Edwards Cardioband System is implanted and remains in position (i.e., absence of any anchor detachment). This population will be utilized as a secondary analysis population.

5. DEFINITIONS

5.1 Analysis Dates and Days

- Study start date is defined as the procedure date.
- Last information date is defined as the most recent date assessed with any available information concerning the patient (e.g., most recent date out of: baseline assessment, procedure, discharge, follow-up visits, laboratory tests, study termination, and adverse events). Last information date is used as censor date for survival analyses.
- Study day = Date – Study start date

5.2 Visit Windows

Assessments are considered by their nominal visit name (e.g., "30 days" and "1 year") regardless of whether the actual visit date is within the protocol defined visit window.

- 30 Days: Day 23 – Day 37
- 6 Months: Day 166 – Day 194
- 1 Year: Day 320 – Day 410
- 2 Years: Day 670 – Day 790
- 3 Years: Day 1035 – Day 155
- 4 Years: Day 1400 – Day 1520
- 5 Years: Day 1765 – Day 1885

6. DATA AND ANALYSIS CONVENTIONS

6.1 General Conventions

All data collected will be summarized overall and by treatment groups.

For continuous variables (e.g., age, percent diameter stenosis, and lesion length), results within treatment group will be summarized with the numbers of observations, means, medians, standard deviations, minimums, maximums, and 95% confidence intervals per table mockups. Differences between the treatment groups, where specified, will be summarized with the differences of the two means and 95% confidence intervals for the difference between the means, and p-values based on a t-test. The distributions within each group will be tested for normality using the Shapiro-Wilks test and if normality cannot be assumed then a Wilcoxon rank-sum test and 95% confidence interval of the median will be presented. The confidence interval for the difference of two means will be calculated under the assumption of unequal variances.

For categorical variables (e.g., gender, in-hospital event rates, and angina status), results within treatment group will be summarized with patient counts and percentages. Differences between the two treatment groups, where specified, will be

summarized with the difference in percentages, the asymptotic 95% confidence interval for the difference of two percentages, and a p-value based on a chi squared test. If 20% or more of the expected cell frequencies are less than 5, a Fisher's exact test will be used to test for differences in proportions.

For the determination of event rates in-hospital, the number of all patients in the patient population will be used as the denominator. For variables ascertained at follow-up, the denominator will be only those patients who had follow-up performed at that time point. Unless otherwise noted, patients with missing data are excluded from the denominator.

Survival analysis techniques will be used to analyze the time-to-event variables. 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 the time of their last follow-up. Time to first event curves will be constructed using Kaplan-Meier estimates and all post discharge 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.

Covariate analyses and variables of interest, as well as possible subgroup analyses of interest, may be performed to gain more clinical insight.

Descriptive statistics will be presented at each assessment, including change from baseline to subsequent time point for selected endpoints. Paired (i.e., patients with available data at both baseline and respective time point) and unpaired data will be presented separately.

6.2 Handling of Missing Data

No imputation of missing data will be performed. Reasonable efforts will be made to obtain complete data for all patients. Missing observations, however, will occur due to patients lost to follow-up or noncompliance with required assessments. The reasons for missing data will be evaluated (e.g. patient is deceased, lost to follow up, missed visit, etc.). In addition, the distribution of prognostic factors between patients with data and those without data will be examined to evaluate any potential sources of bias. Any missing observations will be described in detail and evaluated for assessment of possible bias.

7. SUMMARY OF BASELINE INFORMATION

7.1 Patient Enrollment and Accountability

The patient enrollment table will include both ITT and mITT populations. Patients from each site will be summarized separately. The patient disposition table will include total number of patients divided into the following categories: visit not yet due, death, explant, withdrew from study, lost to FU, visit completed, and visit not performed. Patients are considered eligible for follow-up if their visit window is open and prior to FU visit window, they are alive, not explanted, did not withdraw from study, and are not lost to FU. Each follow-up visit will have its own disposition section.

7.2 Demographics and Baseline Characteristics

The demographics and baseline characteristics table will contain descriptive summaries of age, sex, race, height, weight, resting blood pressure, STS mortality score, NYHA class, and KCCQ.

7.3 Medical History and Prior Intervention

The medical history table will include patient counts of various conditions and interventions available from the CRF.

7.4 Baseline Risk Assessments

The baseline risk assessment table will include patient counts of various risk factors available from the CRF.

7.5 Procedural Information

The procedure information table will contain descriptive summaries of procedure time, device disposition, number of patients permanently implanted, Cardioband implant size, and number of anchors.

8. STATISTICAL ANALYSIS OF STUDY ENDPOINTS

8.1 Co-Primary Hypothesis 1

H_0: $P_{Device}(T=1) - P_{Control}(T=1) = 0$
H_1: $P_{Device}(T=1) - P_{Control}(T=1) \neq 0$

where

H_0 = Null hypothesis
H_1 = Alternative hypothesis
P_{Device} = Proportion of patients in the Device group with MR ≤ 2+ at 1 year
$P_{Control}$ = Proportion of patients in the Control group with MR ≤ 2+ at 1 year
T = Time (years)

The co-primary hypothesis 1 tests the superiority in reducing MR of the Device group relative to the Control group via Chi-Square test for two independent proportions with two-sided alpha = .05. Co-primary efficacy endpoint 1 must meet statistical significance in order to proceed to co-primary efficacy endpoints 2. This approach does not require any adjustment for multiplicity.

8.2 Co-Primary Hypothesis 2

H_0: None of the four co-primary endpoints 2 are improved by treatment
H_1: At least one of the four co-primary endpoints 2 is improved by treatment

i. Time to all-cause death within the first year
ii. Number of heart failure hospitalizations within the first year
iii. Improvement in Six Minute Walk Test (6MWT) at 1 year relative to baseline (≥ 40 meters improvement)
iv. Improvement in Kansas City Cardiomyopathy Questionnaire (KCCQ) at 1 year relative to baseline (≥ 10 points improvement)

The co-primary hypothesis 2 tests the superiority of the Device group relative to the Control group for the hierarchical sequence of the four co-primary endpoints 2 via the Finkelstein-Schoenfeld test (Finkelstein and Schoenfeld, 1999). The Finkelstein-Schoenfeld test is a generalization of the Gehan Wilcoxon test. Each patient pair is compared in descending order of the endpoints until one member of the pair shows superiority. While the example comparison given in the table below shows a Device patient being compared to a Control patient it should be noted that a pairwise comparison is made for every patient in Device group versus every patient in Control group.

Table 1. Hierarchy of co-primary endpoints 2

Comparison of each potential patient pair (e.g. 1 from Device group and 1 from Control group)	How Event is Assessed
Step 1	
If 1 or both patients die due to cardiovascular (CV) cause	
Patient in Device group dies first due to CV cause	Favors Control
Patient in Control group dies first due to CV cause	Favors Device
Both patients die on the same day due to CV cause	Go to Step 2
If neither of the patients die due to CV cause	Go to Step 2
Step 2	
If no ranking yet available	
Patient in Device group had more heart failure hospitalizations	Favors Control
Patient in Control group had more heart failure hospitalizations	Favors Device
Both patients had equal number heart failure hospitalizations	Go to Step 3
Step 3	
If no ranking yet available	
Patient in Device group but not patient in Control group improved 6 minutes walking distance ≥ 40 meters compared to baseline	Favors Device
Patient in Control group but not patient in Device group improved 6 minutes walking distance ≥ 40 meters compared to baseline	Favors Control
Both patients improved 6 minutes walking distance ≥ 40 meters compared to baseline	Go to step 4
Neither of the patients improved 6 minutes walking distance ≥ 40 meters compared to baseline	Go to step 4
Step 4	
If no ranking yet available	
Patient in Device group (but not Control) improved KCCQ score ≥10 points compared to baseline	Favors Device
Patient in Control group (but not Device)improved KCCQ score ≥10 points compared to baseline	Favors Control
Both patients improved KCCQ score ≥10 points compared to baseline	Tie
None of the patients improved KCCQ score ≥10 points compared to baseline	Tie

The following rules are applied with the pairwise comparative outcome assessment:

- If any one of the patients in a patient pair is missing data for a variable included in the hierarchy then the pair will be considered a tie in regards to that variable/level and will proceed to the next level in the hierarchy.
- The time dependent events are censored at exactly 1 year after randomization.
- Patients who are censored during the first year (includes patients who are lost to follow-up as well as patients who die due to non-cardiovascular causes) will be compared to other patients using available data up until the time at which the patient was censored. In other words, the number of heart failure hospitalizations up until the censoring time will be compared between the patient pair.
- Inclusion of hospitalizations is based on adjudication by the Clinical Events Committee (CEC).
- The index hospitalization for Edwards Cardioband System implant in patients randomized to Device group is not counted as heart failure related hospitalization. However, if the hospital stay is prolonged beyond 5 days because of a heart failure (HF) complication, it is counted as a HF-related hospitalization. This rule is also applies to surgical mitral annuloplasty or replacement that is performed during follow-up in patients randomized to Control.
- Hospitalizations beginning prior to the exact 1 year time point are counted for analysis of frequency of hospitalization.

- The 6MWT and KCCQ data from the 1-year visit are used regardless of whether the visit is before or after the exact 1 year time point.
- If clinical follow-up of one or both patients is censored, the pairwise outcome assessment is performed on the basis of those events that occurred during the smaller of the two follow-up times. For example, if a Control patient experiences an event on a particular day, and the Device patient is censored on that day or a later day, then the pair favors Device.

The Finkelstein-Schoenfeld method is a simple non-parametric statistical test for analyzing the impact of treatment which combines multiple events (e.g., death and hospitalizations) with longitudinal measures of clinical effect (e.g., 6MWT and KCCQ). The test is based on a Wilcoxon rank sum test. We define a score, μ_{ij}, which is chosen to reflect whether patient i has had the more favorable outcome than patient j by following the hierarchy of scoring provided in table 1. If one of the patients has the more favorable outcome, his score is +1 and the other patient has a score of -1. If it is not possible to assign either patient as having the better outcome, then both patients get a score of 0.

This is a score test based on the sum of scores for the Device group. Suppose there are N total patients in the trial, let D_i = 1 for patients in Device group and D_i = 0 for patients in the Control group. Using the μ_{ij} for every pair of patients defined above, we assign a score to each patient, $U_i = \sum_{i \neq j} \mu_{ij}$. The test is now based on

$$T = \sum_{i=1}^{N} U_i D_i.$$

Finkestein and Schoenfeld refers to this test as the generalization of the Gehan Wilcoxon (GGW) test. The null hypothesis is that none of the endpoints in table 1 are different between Device and Control group. The alternative hypothesis is that at least one endpoint in table 1 is different between Device and group.

Let m be the number of patients in the Device group. The mean of T is zero and its variance is

$$V = \frac{m(N-m)}{N(N-1)} \left(\sum U_i^2\right).$$

The hypothesis of interest is tested by comparing $L = \frac{T}{\sqrt{V}}$ to the normal distribution. Hence, we are looking for a z-score that is indicative of a significant difference ($p < .05$) between the Device and Control groups.

8.3 Primary and Secondary Safety Endpoints (30 Days)

Overall rates of device and procedure related major adverse events (MAEs) though 30 days post procedure (i.e., primary safety endpoints) as well as the components will be calculated, along with 95% confidence intervals.

8.4 Key Secondary Efficacy Endpoints (1 Year)

Secondary efficacy endpoints will be tested in hierarchical order after the primary endpoints to address multiplicity and preserve alpha at the .05 level. When one of the endpoints does not achieve statistical significance in favor of the Device group, no further testing of subsequent endpoints will be conducted.

a. Mitral regurgitation (MR)

Superiority test of Device group versus Control group via the chi-square statistic, for the difference in the prevalence of MR ≤ 1+ at one year, with a two-sided alpha of 0.05. The null (H_0) and alternative (H_1) hypotheses are:

H_0: $P_{Device} - P_{Control} = 0$

H_1: $P_{Device} - P_{Control} \neq 0$

P_{Device} and $P_{Control}$ are the prevalence of MR ≤ 1+ at one year in the Device and Control groups, respectively.

b. New York Health Association (NYHA)

Superiority test of Device group versus Control group via the Chi-square statistic, for the difference in the proportion of subjects with NYHA class I/II at one year, with a two-sided alpha of 0.05. The null (H_0) and alternative (H_1) hypotheses are:

H_0: $P_{Device} - P_{Control} = 0$

H_1: $P_{Device} - P_{Control} \neq 0$

P_{Device} and $P_{Control}$ are the proportion of subjects with NYHA I/II at one year in the Device and Control groups, respectively. Fisher's Exact Test will be performed if assumptions for the Chi-square test are not met.

c. Kansas City Cardiomyopathy Questionnaire (KCCQ)

KCCQ scores at baseline and 1 year will be quantified as continuous variables ranging from 0 to 100 and the difference between the two time points will be calculated. This difference (i.e., delta) will be analyzed with paired T statistic with a two-sided alpha of 0.05. The null (H_0) and alternative (H_1) hypotheses are:

H_0: $\Delta_{Device} = \Delta_{Control}$

H_1: $\Delta_{Device} \neq \Delta_{Control}$

Δ_{Device} and $\Delta_{Control}$ represent mean deltas for the Device and Control groups, respectively.

d. Six Minute Walk Test (6MWT)

The 6MWT distance at baseline and 1 year will be quantified as continuous variables measured in meters and the difference between the two time points will be calculated. This difference in distance (i.e., delta) will be analyzed with paired T statistic with a two-sided alpha of 0.05. The null (H_0) and alternative (H_1) hypotheses are:

H_0: $\Delta_{Device} = \Delta_{Control}$

H_1: $\Delta_{Device} \neq \Delta_{Control}$

Δ_{Device} and $\Delta_{Control}$ represent mean deltas for the Device and Control groups, respectively.

e. SF-36v2 Health Survey (SF-36)

SF-36 score at baseline and 1 year will be quantified as continuous variables ranging from 0 to 100 and the difference between the two time points will be calculated. This difference (i.e., delta) will be analyzed with paired T statistic with a two-sided alpha of 0.05. The null (H_0) and alternative (H_1) hypotheses are:

H_0: $\Delta_{Device} = \Delta_{Control}$

H_1: $\Delta_{Device} \neq \Delta_{Control}$

Δ_{Device} and $\Delta_{Control}$ represent mean deltas for the Device and Control groups, respectively.

f. Heart Failure Hospitalizations

The number of heart failure hospitalizations between day 0 and day 365 post procedure will be quantified as recurrent events and analyzed with a survival analysis intensity model (Andersen and Gill, 1982). The null (H_0) and alternative (H_1) hypotheses are:

H_0: HR = 1
H_1: HR ≠ 1

HR represents hazard rate for Device group relative to Control group. A two-sided alpha of 0.05 will be used.

g. Cardiovascular Mortality

Cardiovascular mortality rate up to 365 days will be compared between the Device and Control groups using time-to-event analysis and log-rank test. The null (H_0) and alternative (H_1) hypotheses are:

H_0: HR = 1
H_1: HR ≠ 1

HR represents hazard rate for Device group relative to Control group. A two-sided alpha of 0.05 will be used.

h. All-Cause Mortality

All-cause mortality rate up to 365 days will be compared between the Device and Control groups using time-to-event analysis and log-rank test. The null (H_0) and alternative (H_1) hypotheses are:

H_0: HR = 1
H_1: HR ≠ 1

HR represents hazard rate for Device group relative to Control group. A two-sided alpha of 0.05 will be used.

8.5 Additional Secondary Endpoints (1 Year)

Additional secondary endpoints: technical, device, procedural, and patient success, and responder analysis will be compared between Device and Control groups and descriptively summarized with patient counts, percentages, and confidence intervals.

8.6 Key Echocardiography Endpoints (5 Years)

Descriptive statistics for key echocardiography endpoints will be compared between Device and Control groups.

8.7 Long Term Outcomes (5 Years)

Descriptive statistics for long term outcomes will be compared between Device and Control groups.

8.8 Long Term Safety Outcomes (5 Years)

Descriptive statistics for long term safety outcomes will be compared between Device and Control groups.

8.9 Adherence and Retention

Adherence to protocol requirements and patient dispositions will be summarized by treatment.

8.10 Interim Analysis

The sample size will be re-estimated when at least 40% of patients have undergone 1 year primary efficacy endpoint assessment. This re-estimated will be conducted through simulation in the following steps:

a. Data from the sample that has completed the study will be treated as fixed and retained in each simulation
b. Data from patients who have not completed the study will be simulated, under the assumption that the observed data in the sample from (a) is representative of the true population value for the four co-primary endpoints 2 (see section 3.2.2).
c. Data from (a) and (b) will be combined and the Finkelstein-Schoenfeld methodology will be conducted and resulting probability will be calculated.
d. Steps (a) through (c) will be repeated 10,000 times.
e. The proportion of the 10,000 iterations for which the resulting probability from the Finkelstein-Schoenfeld test is less than .05, will be taken as the estimate of conditional power.

If the conditional power is < 90% than the sample size will be re-estimated to include the number of patients necessary to achieve 90% conditional power. The group allocation ratio of 2:1 (Device vs Control) will be retained. Increase in the sample size will be at the discretion of the sponsor and pursuant to FDA approval. Additional scenarios (e.g., conditional power is < 80%) may be requested.

8.11 Determination of Sample Size

Co-primary endpoint 1

Using PASS software and a test for two independent proportions 375 enrolled patients give us >99% power to detect a difference between the groups using the following assumptions:

1. Proportion in control arm who meet the criteria for MR reduction (MR ≤ 2+) is 10%.
2. Proportion in treatment arm who meet the criteria for MR reduction (MR ≤ 2+) is 70%.
3. A two-sided significance level (alpha) of 0.05.
4. A 2:1 treatment allocation ratio between Edwards Cardioband System (Device group) and control group.
5. Data will be available for 60% of the randomized patients (accounting for mortality and lost to follow-up).

Co-primary endpoint 2

Assuming up to 20% dropout, a total of 375 enrolled patients will ensure at least 300 patients with evaluable data. Based on 5,000 trial simulations using SAS software (version 9.4), it is estimated that 300 evaluable patients will provide 87% power to detect superiority of treatment vs. control using the Finkelstein-Schoenfeld test and the following assumptions:

1. All-cause mortality of 20% within the first year in both groups (Control and Device).

2. Cardiovascular mortality of 15% within the first year in both groups (Control and Device).

3. Number of heart failure hospitalizations within the first year:
   a. 60% of the patients in the Control and 70% in the Device group will not have HF hospitalization.

b. 10% of the patients in the Control group and 10% of the patients in the Device group will have one HF hospitalization.
c. 10% of the patients in the Control group and 5% in the Device group will have two HF hospitalizations.
d. 10% of the patients in the Control group and 5% in the Device group will have three HF hospitalizations.
e. 5% of the patients in the Control group and 5% in the Device group will have four HF hospitalizations.
f. 5% of the patients in the Control group and 5% in the Device group will have five or more HF hospitalizations.

4. Improvement in 6-minute walk test at one year vs. baseline:
   10% of the patients in the Control group and 50% of the patients in the Device group will have an improvement in 6 minutes walking distance of 40 meters or more compared to their baseline result.

5. Improvement in KCCQ score at one year vs. baseline:
   10% of the patients in the Control group and 50% of the patients in the Device group will have an improvement in KCCQ score of 10 points or more compared to their baseline result.

6. A two-sided significance level (alpha) of 0.05.
7. A 2:1 treatment allocation ratio between Device group and Control group.

9. ANALYSIS OF SAFETY

9.1 Deaths

Cardiovascular and all-cause death will be descriptively summarized in tables and analyzed with Kaplan-Meier estimates (depending on data sufficiency).

9.2 Adverse Events

Site reported and CEC adjudicated adverse events will be descriptively summarized in tables and listings for the ITT population. MedDRA codes will be provided in addition to seriousness, relation to device, and relation to procedure. Both patient and event counts will be summarized.

10. CHANGES FROM PROTOCOL SPECIFIED ANALYSES

The only difference between this SAP 3.0 and protocol rev E is that updated definition of enrolled population for roll-in patients is more meaningful from a device/procedure evaluation perspective. It will be included in future protocol updates.

11. REFERENCES

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.

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

Finkelstein, D.M. and Schoenfeld, D.A. (1999). Combining Mortality and Longitudinal Measures in Clinical Trials. *Statistics in Medicine, 18*, 1341-1354.

12. APPENDIX

N/A

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

Yes	Name of Reviewer:	No	Reason Peer Review not Needed:
☐		☑	SAP will be reviewed by biostats director