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.

Short Title: Edwards Cardioband System ACTIVE Pivotal Clinical Trial

Protocol Number: 2017-05
[redacted]
Date: April 20, 2018

Sponsor: Edwards Lifesciences

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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).
Short Title	Edwards Cardioband System ACTIVE Pivotal Clinical Trial
Device Name	Edwards Cardioband System
Intended Use	The Edwards Cardioband System is indicated for transcatheter mitral valve repair to treat functional mitral valve regurgitation.
Study Hypothesis	Transcatheter mitral valve repair with the Edwards Cardioband System will reduce mitral regurgitation (MR) and improve symptoms, functional capacity, and/or quality of life in patients with symptomatic functional MR.
Study Objective	Evaluate the efficacy and safety of transcatheter mitral annular reduction for functional MR plus guideline directed medical therapy (GDMT) compared to GDMT alone.
Study Design and Methods	Prospective, multicenter 2:1 randomized trial [(Edwards Cardioband System + GDMT (Device group)) vs. GDMT (Control group)].
Number of Study Patients	Pivotal cohort: approximately 375 patients Roll-in cohort: up to 3 patients per study site Up to 600 patients, including 375 pivotal cohort patients and up to 3 roll-in patients per center, at 75 centers (pending FDA approval).
Number of Study Sites	A maximum of 75 study sites located in North America. Additional sites in Europe may also participate in the study, contributing a maximum of 50% of enrollees.
Estimated Timeline	[redacted]

	[redacted]
Primary Efficacy Endpoint	**<u>Co-Primary Efficacy Endpoints evaluated at 1 year follow-up</u>:** • Co-primary endpoint I 1. Prevalence of MR ≤ 2+ at one year • Co-primary endpoint II Hierarchical comparison between the Device and Control groups using Finkelstein-Schoenfeld methodology: 1. Time to all-cause death 2. Number of heart failure hospitalizations 3. Improvement in 6 Minute Walk Test (6MWT) vs. baseline (≥ 40 meters improvement) 4. Improvement in Kansas City Cardiomyopathy Questionnaire (KCCQ) at one year vs. baseline (≥ 10 points improvement) The co-primary endpoints will be analyzed in a hierarchical order where co-primary endpoint I must meet statistical significance in order to proceed to co-primary endpoint II. This approach does not require any adjustment for multiplicity.
Primary Safety Endpoint [Device Group only]	**<u>Primary Safety Endpoint</u>:** Overall rate of device and procedure related Major Adverse Events (MAEs) through 30 days post procedure (including 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.
Secondary Safety Endpoints (through 30 Days) [Device Group only]	1. Death 2. Stroke 3. Myocardial infarction 4. Pericardial effusion requiring drainage 5. Mitral valve reintervention 6. Access site and vascular complications requiring intervention 7. Left circumflex coronary artery injury requiring intervention 8. Need for a new permanent pacemaker

Secondary Endpoints (through 1 year) (Hierarchical Testing)	The following key secondary efficacy endpoints will be tested in comparison to control in a hierarchical order to preserve statistical power. 1. MR ≤ 1+ 2. NYHA Class 3. Kansas City Cardiomyopathy Questionnaire (KCCQ) 4. 6 Minute Walk Test (6MWT) 5. SF-36v2 Health Survey (SF-36) 6. Heart failure hospitalizations 7. Cardiovascular death 8. All-cause mortality
Other Secondary Endpoints:	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 to ≤ MR2+ 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 ≤ MR2+ and without MAEs* at 30 days (per patient analysis). **Major adverse events (MAE) is 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 (6MWD 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, and 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.
Echocardiography Parameters (through 5 years)	Key echocardiography parameters by echo core lab assessment at 30 days, 6 months, yearly at 1-5 years (see Echo protocol for full details). 1. MR severity 2. LVEDVi 3. LVESVi 4. TAPSE 5. Mitral valve effective orifice area (EOA) 6. LV ejection fraction 7. Stroke volume 8. Left atrial volume 9. Tricuspid regurgitation severity 10. Estimated pulmonary artery pressure

Long-term Outcomes (through 2, 3, 4, 5 years)	1. NYHA 2. 6 Minute Walk Test (at two years only) 3. Heart failure hospitalizations 4. Cardiovascular death 5. Surgical mitral valve replacement or surgical repair 6. Transcatheter based mitral valve interventions 7. All-cause mortality 8. Cardiac transplantation 9. Mechanical hemodynamic support (e.g. LVAD) 10. Number of days alive and out of hospital 11. NT-proBNP level 12. Need for new permanent pacemaker **<u>Quality of Life (assessment with generic and disease-specific measures)</u>:** 1. Kansas City Cardiomyopathy Questionnaire (KCCQ) 2. SF-36v2 Health Survey (SF-36)	
Long-term Safety Outcomes (through 1 year)	1. Stroke 2. Transient Ischemic Attack (TIA) 3. Major Vascular Complications (MVC) 4. Renal Complications	
Inclusion Criteria (ALL must be present; reference Section 6.2 for further guidance)	1.	Eighteen (18) years of age or older;
	2.	Clinically significant functional MR (≥ 3+ by echocardiography) as assessed by the core lab;
	3.	Stable heart failure medications as determined by local heart team;
	4.	Elevated BNP > 150 pg/ml or corrected NT-proBNP > 600 pg/ml within past 90 days or heart failure hospitalization within past 12 months;
	5.	Symptomatic heart failure patients with measured baseline 6 minute walk test (6MWT) between 150 and 400 meters;
	6.	Patient is deemed appropriate for Edwards Cardioband System by the Heart Team at the investigational site and the Central Screening Committee;

	7.	Patient is able and willing to give informed consent and follow protocol procedures, and comply with follow-up visit compliance.
Exclusion Criteria (ALL must be absent)	1.	Primarily degenerative MR;
	2.	LVEF ≤ 20% and LVEDD > 80 mm by transthoracic echocardiography as measured by core lab;
	3.	Mitral annular calcification that would impede implantation of device as assessed by core lab;
	4.	Infiltrated cardiomyopathies (e.g., amyloidosis, hemochromatosis, sarcoidosis), hypertrophic cardiomyopathy, constrictive pericarditis, or any other structural heart disease causing heart failure other than dilated cardiomyopathy of either ischemic or non-ischemic etiology;
	5.	Recent hemodynamic instability (e.g. need for inotropic support or intra-aortic balloon pump or other hemodynamic support device);
	6.	Right sided heart failure or echocardiographic evidence of severe right ventricular dysfunction per core lab assessment;
	7.	Estimated pulmonary artery systolic pressure (PASP) > 70 mmHg assessed by site based on echocardiography or right heart catheterization, unless active vasodilator therapy in the catheterization lab is able to reduce the pulmonary vascular resistance (PVR) to < 3 Wood units or between 3 and 4.5 Wood units with V wave less than twice the mean of the pulmonary capillary wedge pressure;
	8.	Other severe valve disorders requiring intervention;
	9.	Need for emergent or urgent surgery for any reason or any planned cardiac surgery within the next 12 months;
	10.	Mitral valve anatomy which may preclude proper Edwards Cardioband System access, use and/or deployment;
	11.	Any prior or other planned mitral valve procedure;
	12.	Patient in whom a TEE is contraindicated or screening/baseline TEE is unsuccessful;
	13.	Echocardiographic evidence of intracardiac mass, thrombus or vegetation;
	14.	Severe liver cirrhosis (Childs-Pugh C or MELD > 12);
	15.	Active systemic infection, including active endocarditis;

	16.	Untreatable hypersensitivity or contraindication to any of the following: • Aspirin and Clopidogrel and Ticlopidine, OR • Heparin and Bivalirudin, or Warfarin, OR • Nitinol Alloys (nickel and titanium) or contrast media;
	17.	Any recent percutaneous coronary, carotid, endovascular intervention, carotid surgery, or cardiac surgery;
	18.	Recent implant or revision of any rhythm management device (i.e., pacemaker, cardiac resynchronization therapy [CRT] with or without cardioverter-defibrillator [CRT-D]);
	19.	Resting systolic blood pressure < 90 or > 160 mmHg after 3 consecutive measurements;
	20.	Recent CVA or TIA;
	21.	Previous stroke with permanent disability (modified Rankin score > 2);
	22.	Severe renal insufficiency with eGFR ≤ 25 mL/min or requiring chronic renal replacement therapy;
	23.	Contraindication to transseptal catheterization;
	24.	Concurrent medical condition with a life expectancy of less than 12 months in the judgment of the investigator;
	25.	Pregnant or planning pregnancy within next 12 months;
	26.	Known bleeding or clotting disorders or patient refuses blood transfusion;
	27.	Severe COPD in whom the primary mechanism of dyspnea is pulmonary disease rather than heart failure;
	28.	Recent myocardial infraction (per WHO definition);
	29.	Patient has been approved to participate and is currently enrolled in, or has participated in another investigational drug or device clinical study where the primary study endpoint was not reached at time of enrollment;
	30.	Any condition, in the opinion of the Investigator, making it unlikely the patient will be able to complete all protocol procedures

		(including compliance with guideline directed medical therapy) and follow-up visits;
	31.	Other medical, social, or psychological conditions that preclude appropriate consent and follow-up, including patients under guardianship.
Sample Size & Endpoint Analysis		**<u>Co-primary endpoint I</u>** Using PASS software and a test for two independent proportions 375 enrolled patients with up to 20% attrition provides > 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. **<u>Co-primary endpoint II</u>** Assuming up to 20% attrition, a total of 375 enrolled patients will ensure at least 300 patients with evaluable data. Based on 10,000 trial simulations using SAS software (version 9.4), it is estimated that 300 evaluable patients will provide > 90% 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 minute 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 the Device group and Control group. The sample size will be re-estimated when at least 40% of patients have undergone 1 year primary efficacy endpoint assessment. If the conditional power is <90% then 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 (such as 80% power) may be requested. All event rates above are conservative estimates based on previous experience with the Edwards Cardioband System, as well as on data on patients with functional mitral regurgitation who underwent catheter based treatment with the CE marked CARILLON® device (Cardiac Dimensions, Kirkland, WA) or the MitraClip® device (Abbott Vascular, Santa Clara, CA) from two registries (Sentinel[1] and ACCESS-EU[2]) and three studies (EVEREST II[3,4], TRAMI[5-7], TITAN[8]).

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Echo Core Lab	[redacted]
CT Core Lab	[redacted]
Economic Data Collection Core Lab	[redacted]

	[redacted]
Clinical Events Committee (CEC)	A group of individuals with pertinent expertise that reviews clinical study endpoints to determine whether the endpoints meet protocol-specified criteria.
Data Safety Monitoring Board:	An independent data monitoring committee that may be established by the sponsor to assess, at intervals, the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

Table 1: Schedule of Study Visits and Patient Assessments

Test/ Assessment	**Screening/ Baseline**	**Random -ization**	**Pre-Index Procedure- Edwards Cardioband System** (Device group only; timing: per local institutional standard of care)	**Index Procedure- Edwards Cardioband System** (Device group only)	**Post- Edwards Cardioband System Procedure, Pre-Discharge** (Device group only)	**30 Day F/U (±7 days)**	**180 Day F/U (± 14 days)**	**1 Year F/U (±45 days)**	**2 Year F/U (± 60 days)**	**3, 4, 5 Year F/U (± 60 days)**
Study Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10, 11, 12**
Study Consent	X									
Medical Hx/ NYHA Class	X					X	X	X	X	X
STS Score	X									
Cardiovascular Medications	X			X	X	X	X	X	X	X
Targeted Physical Exam	X					X	X	X	X	X
12-Lead ECG	X				X	X	X	X		
Transthoracic Echo (TTE)	X				X	X	X	X	X	X
Transesophageal Echo (TEE)	X			X						
Cardiac CT Imaging	X									
Randomization		X								
Pregnancy Test (for females of childbearing potential only)	X[1]		X							

Test/ Assessment	**Screening/ Baseline**	**Random -ization**	**Pre-Index Procedure- Edwards Cardioband System** (Device group only; timing: per local institutional standard of care)	**Index Procedure- Edwards Cardioband System** (Device group only)	**Post- Edwards Cardioband System Procedure, Pre-Discharge** (Device group only)	**30 Day F/U (±7 days)**	**180 Day F/U (± 14 days)**	**1 Year F/U (±45 days)**	**2 Year F/U (± 60 days)**	**3, 4, 5 Year F/U (± 60 days)**
Study Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10, 11, 12**
Complete Blood Count (WBC, RBC, HCT, Hgb, platelet count)	X		X				X	X		
Coagulation Panel (PT, PTT; INR for patients on vitamin-K antagonist)	X		X							
Chemistry Panel (BUN, CO_2, Creatinine, Glucose, Cl, K, Na, AST (GOT), ALT (GPT), GGT, serum Total Protein, Albumin, Total Cholesterol, Triglycerides, HDL Cholesterol, Uric Acid	X		X				X	X		

Test/ Assessment	**Screening/ Baseline**	**Random -ization**	**Pre-Index Procedure- Edwards Cardioband System** (Device group only; timing: per local institutional standard of care)	**Index Procedure- Edwards Cardioband System** (Device group only)	**Post- Edwards Cardioband System Procedure, Pre-Discharge** (Device group only)	**30 Day F/U (±7 days)**	**180 Day F/U (± 14 days)**	**1 Year F/U (±45 days)**	**2 Year F/U (± 60 days)**	**3, 4, 5 Year F/U (± 60 days)**
Study Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10, 11, 12**
Cardiac biomarkers (troponins or CK/CK-MB)			X[2]		X[2]					
NT-Pro-BNP or BNP	X					X	X	X	X	X
Modified Rankin Scale	X				X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
NIHSS	X[3]				X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
KCCQ	X					X	X	X	X	X
SF-36	X					X	X	X	X	X
6 Minute Walk Test (6MWT)	X					X	X	X	X	
Safety Primary Endpoint						X				
Efficacy Primary Endpoint								X		
Adverse Events	X	X	X	X	X	X	X	X	X	X
Clinical Frailty Scale©	X									
Patient Preference Survey	X									

Test/ Assessment	**Screening/ Baseline**	**Random -ization**	**Pre-Index Procedure- Edwards Cardioband System** (Device group only; timing: per local institutional standard of care)	**Index Procedure- Edwards Cardioband System** (Device group only)	**Post- Edwards Cardioband System Procedure, Pre-Discharge** (Device group only)	**30 Day F/U (±7 days)**	**180 Day F/U (± 14 days)**	**1 Year F/U (±45 days)**	**2 Year F/U (± 60 days)**	**3, 4, 5 Year F/U (± 60 days)**
Study Visit No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10, 11, 12**
Activity Monitoring[4]	X	X	X		X	X	X	X		
Economic Data Collection[5]			X	X	X					

(1) Perform pregnancy test prior to Cardiac CT, as required

(2) Cardiac biomarkers: Collection for all patients undergoing Edwards Cardioband System implantation

(3) If the patient experiences a stroke during the study, Neurological Assessments including NIH Stroke Scale (NIHSS) and Modified Rankin Scale should additionally be performed within 90 days from the date of the stroke by a neurologist, a neurology fellow, or designee.

(4) Activity monitoring will be collected continuously from baseline to the 6 month visit. At 6 months if compliance is low an additional 1 month of monitoring will be issued. A month of continuous monitoring will be reinitiated at the 1 year follow-up visit

(5) Economic Data Collection will collect patient billing records for the index procedure.

ABBREVIATIONS

6MWT	6 Minute Walk Test	LVEDVi	Left Ventricular End-Diastolic Volume index
ADE	Adverse Device Effects	LVEF	Left Ventricle Ejection Fraction
ACC	American College of Cardiology	LVESVi	Left Ventricular End-Systolic Volume index
AE	Adverse Event	MAE	Major Adverse Events
AHA	American Heart Association	MI	Myocardial Infarction
CABG	Coronary Artery Bypass Graft	MR	Mitral Regurgitation
CDS	Edwards Cardioband Delivery System	MRS	Modified Rankin Scale
CEC	Clinical Events Committee	MSAE	Major Serious Adverse Event
CHF	Congestive Heart Failure	NIHSS	National Institutes of Health Stroke Scale
COPD	Chronic obstructive pulmonary disease	NT-proBNP	N-terminal pro b-type natriuretic peptide
CRF	Case Report Form	NYHA	New York Heart Association
CRT	Cardiac Resynchronization Therapy	QOL	Quality of Life
CSC	Central Screening Committee	RO	Radiopaque
CT	Computerized Tomography	SADE	Serious Adverse Device Effect
DSMB	Data Safety Monitoring Board	SAE	Serious Adverse Event
EF	Ejection Fraction	SAT	Size Adjustment Tool
FDA	Food and Drug Administration	SD	Standard Deviation
GC	Guide Catheter	SF-36	The Short Form (36) Health Survey
GCP	Good Clinical Practice	SOC	System Organ Class
GDMT	Guideline Directed Medical Therapy	SOP	Standard Operating Procedure
HF	Heart Failure	TAPSE	Tricuspid annular plane systolic excursion
IC	Implant Catheter	TEE	Transesophageal echocardiography
ICD	Implantable Cardioverter-Defibrillator	TF	Transfemoral
IDS	Implant Delivery System	TMVr	Transcatheter Mitral Valve Repair
ISO	International Standardization Organization	TSS	Transseptal Steerable Sheath
KCCQ	Kansas City Cardiomyopathy Questionnaire	TTE	Transthoracic Echocardiography
LVEDD	Left Ventricle End-Diastolic Dimension		

1 INTRODUCTION

The objective of this clinical trial is to evaluate the safety and efficacy of the Edwards Cardioband System for transcatheter mitral annular reduction in patients with functional mitral regurgitation. Specifically, the interventional transcatheter mitral annular reduction using Edwards Cardioband System plus guideline directed medical therapy (GDMT) will be compared to GDMT alone. The study protocol will ensure consistency in performing the procedure, patient management, and results of the procedure. The results of this study shall be used to support a PMA application for approval of the Edwards Cardioband System when indicated for transcatheter mitral annular reduction to treat functional mitral valve regurgitation.

1.1 Background on Mitral Regurgitation and Treatment Options

Mitral regurgitation (MR) is a disease frequently associated with increased morbidity and mortality,[9] and can be characterized by two distinct etiologies: degenerative mitral regurgitation (DMR), and functional mitral regurgitation (FMR). DMR is caused by damage to the leaflets or other components of the mitral valve apparatus (e.g. chordae tendinae, papillary muscles). FMR is driven by adverse left ventricular remodeling due to ischemic or non-ischemic myocardial disease.[10-14] Current guidelines are reluctant to advise isolated valve surgery for FMR as the prognostic benefit of surgical valve repair or replacement in typical heart failure patients is unclear.[10-12,15] Recent reports suggest that even patients in need of surgical coronary revascularization may not benefit from concomitant mitral valve surgery.[16,17] Therefore, surgical treatment of FMR is restricted to the small group of patients who require concomitant bypass surgery, or who have a high predicted rate for surgical success for open heart surgery. On the other hand, optimized medical therapy is of limited efficacy in patients with significant FMR for the reduction of heart failure related morbidity and mortality.[10-12,15,18-20] Consequently, reliable and predictable treatment for most patients with symptomatic FMR is lacking, and there is an unmet need for alternative, catheter-based, minimally invasive approaches. The edge-to-edge mitral valve repair with the MitraClip system offers an effective and safe treatment option for non-surgical patients with either DMR or FMR.[5] This direct approach on the mitral valve leaflets reduces MR severity and is associated with relief of heart failure related symptoms in up to 80% of treated patients.[1] However, the MitraClip system has been developed for the treatment of DMR,[21] and long-term outcomes data on FMR are missing.

More importantly, an idealized interventional approach enables direct treatment of the underlying pathophysiologic mechanism of FMR without interfering with the otherwise unaffected MV leaflets. To date, Edwards Cardioband System is the only catheter-based

direct mitral annular reduction system.[22] Other catheter-based, indirect approaches include the CE marked CARILLON®, by Cardiac Dimensions (Kirkland, WA), and the MitraClip® by Abbott (Santa Clara, CA).

1.2 Device Concept

The Edwards Cardioband System is a sutureless direct transcatheter mitral annual reduction device designed for mitral valve repair by a transvenous transseptal procedure. Edwards Cardioband is deployed and fixed along the posterior annulus of the mitral valve, and is then sized to reduce the mitral annulus under echocardiography.

1.3 Device Preclinical Testing

The Edwards Cardioband System has been evaluated both in bench-top testing and preclinical animal testing. Bench-top testing has been performed to demonstrate the mechanical integrity, as well as biocompatibility, of the implant and its delivery system. Testing has also been performed to support the long term mechanical durability of the implant via simulated use conditions.

Preclinical animal testing of MR devices is challenging since there is no suitable animal model that replicates the diseased human mitral valve anatomy. Although large animal models, such as ovine or swine, have limitations in being able to fully evaluate MR devices these models can nevertheless provide valuable information about device deliverability, performance and functionality. Edwards thus conducted several acute and chronic preclinical animal studies in an ovine model which have demonstrated the successful feasibility of the Edwards Cardioband System. In a chronic 90 and 120 day GLP study, 6 animals received implantation with the Edwards Cardioband System, and 3 animals underwent surgical implantation of a control device with a surgical annuloplasty band. Four test and 2 control animals were euthanized and necropsied 90 days after implantation, while remaining animals were terminated on Day 120. The results of this study showed neither the test nor control articles caused a clinically significant effect on hemodynamic parameters as evaluated by serial ecardiography at Day 90 or Day 120 post-implantation in this non-disease animal model. Based on microscopic examination on Day 90 and Day 120, both test and control devices were well integrated with a fibrous pannus covering the devices. Based on the study results, the Edwards Cardioband System appears to have an acceptable safety profile for clinical use.

1.4 Prior Clinical Experience with the Edwards Cardioband System

The Edwards Cardioband System received CE Mark in September 2015. The CE Mark was based on the results of a prospective multicenter clinical trial conducted in Europe. This trial of [redacted] patients demonstrated the safety and effectiveness of Edwards Cardioband System in mitral annular reduction as a highly effective first-line treatment option for reducing mitral regurgitation (MR) and improving quality of life scores. The Edwards Cardioband System was shown to significantly reduce annular size, with significant improvement in MR acutely, at 6- and 12- months.[23,24] Study patients will be followed for a total duration of [redacted] years and is currently ongoing with the last patient reaching the [redacted] follow up in [redacted].

[redacted]

Based on the encouraging experience to date, Edwards Lifesciences believes that a multi-center, prospective, randomized pivotal clinical trial for treatment of functional mitral regurgitation is reasonable and warranted.

2 Device Description

[redacted]

[redacted]

2.1 Edwards Cardioband System Principles of Operation

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Table 2: Edwards Cardioband System Implant Sizes

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Refer to the device Instructions for Use for additional device information.

2.2 Device Traceability

Each Edwards Cardioband System component is identified by serial/lot number. The use of the identifiers facilitates full traceability during and after the clinical investigation. A log of all system components shall be maintained for the trial to ensure full traceability for each item delivered, used and/or returned during the course of the clinical investigation.

3 STUDY OBJECTIVE

The objective of this clinical trial is to evaluate the safety and efficacy of the Edwards Cardioband System for transcatheter mitral annular reduction in treating patients with functional mitral regurgitation. Specifically, the transcatheter mitral annular reduction using Edwards Cardioband System plus guideline directed medical therapy (GDMT) will be compared to GDMT alone. The study protocol will ensure consistency in performing the procedure, patient management, and results of the procedure. The results of this study shall be used to support a PMA application for approval of the Edwards Cardioband System when indicated for transcatheter mitral annular reduction to treat functional mitral valve regurgitation.

3.1 Hypothesis

Transcatheter mitral valve repair with the Edwards Cardioband System, combined with guideline directed medical therapy (GDMT), will reduce mitral regurgitation (MR) and improve

MR symptoms and functional capacity in patients with functional MR as compared with GDMT alone.

4 STUDY DESIGN

This 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.[10,11]

This investigational plan incorporates a roll-in cohort to provide experience in the 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. In the event that a roll-in procedure needs to be prematurely terminated prior to full placement of the system, the treating physician may opt to re-attempt the Edwards Cardioband procedure at a later time (typically after 30 days) for this roll-in patient. In such instances, screening and baseline assessments will be repeated as necessary to ensure that they fit within the prescribed timeframes.

This trial 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). Primary endpoint data will be available at 30 days (safety) and 1 year (efficacy), and long-term follow-up 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).

A flow chart of the study (Figure 4) is provided on the following page to illustrate the overall design of the trial. Upon confirmation of patient eligibility, confirmatory testing shall be performed and a technical review of the case is performed by the Edwards Clinical support team to assist with device sizing and case planning with the operator(s). The study will utilize a Central Screening Committee (CSC) to evaluate each patient prior to enrollment. Patients shall then be scheduled for the procedure.

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. As depicted in the flowchart, all

patients are followed for 30 days, 6 months, 1 year and annually for a total of 5years post-index procedure or randomization in the case of the control population.

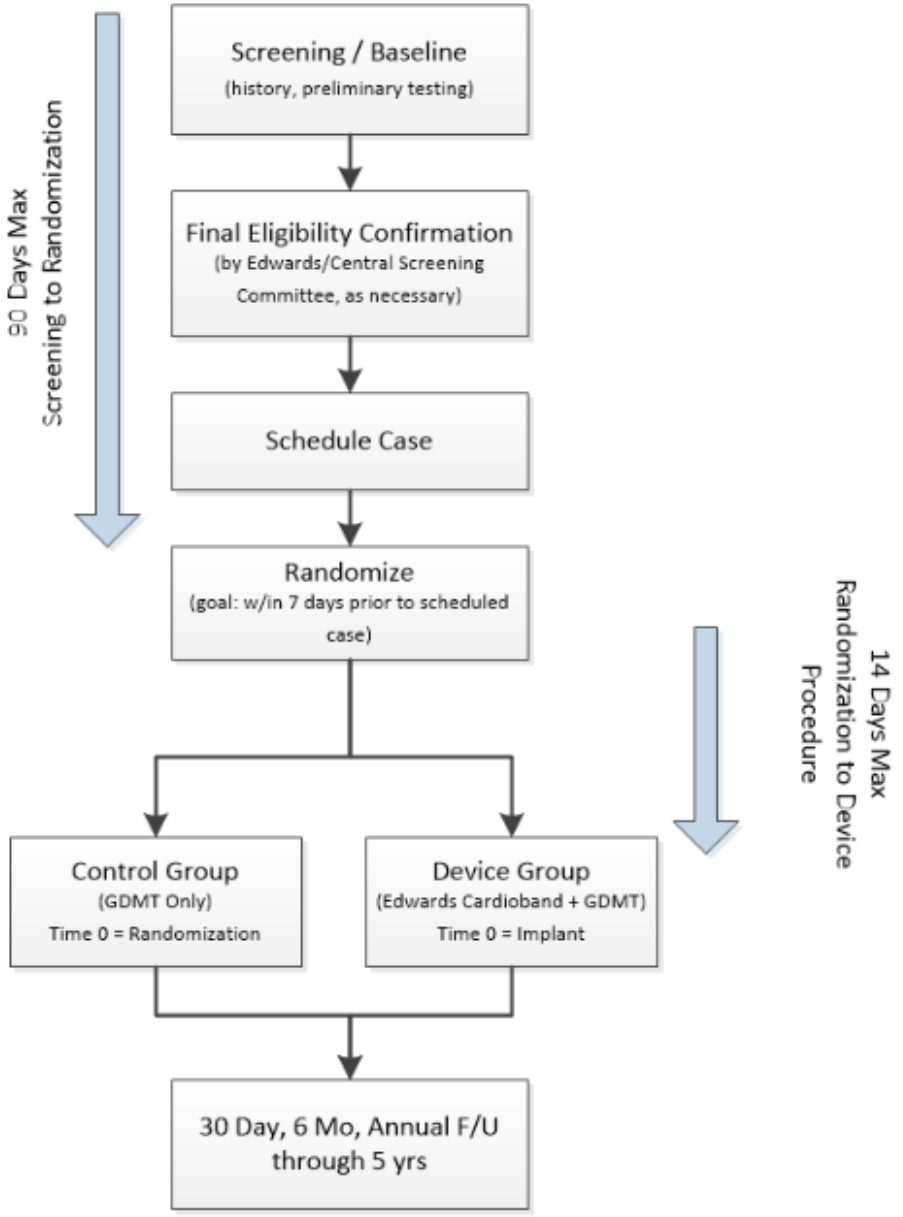

Figure 4: Clinical Study Design Flowchart

5 STUDY ENDPOINTS

5.1 Co-Primary Efficacy Endpoints (evaluated at 1 year)

- Co-primary endpoint I:
    1. Prevalence of MR ≤ 2+ at one year.
- Co-primary endpoint II:

    Hierarchical comparison between the Device and Control groups using Finkelstein-Schoenfeld methodology:

    1. Time to all cause death
    2. Number of heart failure hospitalizations
    3. Improvement in 6 Minute Walk Test (6MWT) vs. baseline (≥ 40 meters improvement)
    4. Improvement in Kansas City Cardiomyopathy Questionnaire (KCCQ) at one year vs. baseline (≥ 10 points improvement)

The co-primary endpoints will be analyzed in a hierarchical order where the co-primary endpoint I must meet statistical significance in order to proceed to co-primary endpoint II. 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 I) as well as its ability to improve clinical outcomes through reducing MR (co-primary endpoint II).

5.2 Primary Safety Endpoint (Evaluated through 30 Days post procedure) [Device Group only]

Overall rate of device and procedure related Major Adverse Events (MAEs) through 30 days post-procedure (including 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. The primary safety endpoint was chosen to detect any concerns relating to safety of the Edwards Cardioband System implantation procedure.

5.3 Secondary Safety Endpoints (through 30 Days) [Device Group only]

1. Death
2. Stroke
3. Myocardial infarction
4. Pericardial effusion requiring drainage
5. Mitral valve reintervention
6. Access site and vascular complications requiring intervention
7. Left circumflex coronary artery injury requiring intervention
8. Need for a new permanent pacemaker

5.4 Secondary Endpoints through 1 Year (Powered):

The following key secondary efficacy endpoints will be tested in comparison to control in a hierarchical order to preserve statistical power.

1. MR ≤ 1+
2. NYHA Class
3. Kansas City Cardiomyopathy Questionnaire (KCCQ)
4. 6 Minute Walk Test (6MWT)
5. SF-36v2 Health Survey (SF-36)
6. Heart Failure Hospitalizations
7. Cardiovascular mortality
8. All-cause mortality

5.5 Other Secondary Endpoints:

The following outcomes will be assessed for 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 ≤ MR2+ 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 ≤ MR2+ 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 (6MWD 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, and
   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)

5.6 Echocardiography Parameters (through 5 years)

Key echocardiography parameters by echo core lab assessment at 30 days, 6 months, yearly at 1-5 years (see Echo protocol for full details):

1. MR severity
2. LVEDVi
3. LVESVi
4. TAPSE
5. Mitral valve effective orifice area (EOA)
6. LV ejection fraction
7. Stroke volume
8. Left atrial volume
9. Tricuspid regurgitation severity
10. Estimated pulmonary artery pressure

5.7 Long-term Outcomes (Through 2,3,4,5 Years)

1. NYHA
2. 6 Minute Walk Test (at two years only)
3. Heart failure hospitalizations
4. Cardiovascular death
5. Surgical mitral valve replacement or surgical repair
6. Transcatheter based mitral valve interventions
7. All-cause mortality
8. Cardiac transplantation
9. Mechanical hemodynamic support (e.g. LVAD)
10. Number of days alive and out of hospital
11. NT-proBNP level
12. Need for new permanent pacemaker

Quality of Life (assessment with generic and disease specific measures):

1. Kansas City Cardiomyopathy Questionnaire (KCCQ)
2. SF-36v2 Health Survey (SF-36)

5.8 Long-term Safety Outcomes (through 1 year)

1. Stroke
2. Transient ischemic attack (TIA)
3. Major vascular complications (MVC)
4. Renal complications

6 PATIENT POPULATION AND SELECTION

6.1 Patient Population

Adult patients age ≥ 18 years at time of screening with primarily functional MR (≥ 3+) and symptomatic heart failure despite guideline directed medical therapy (GDMT) should be considered for inclusion in this trial. Patient will be considered enrolled in the study at the time written informed consent form (ICF) is signed and will be assigned a patient ID in the electronic data capture (EDC) system. Patients that sign the ICF, but are found ineligible during the screening process, will be considered screen failures. Screen failures will not be counted towards enrolled roll-in patients or the pre-planned sample size (i.e., the enrollment will continue until the pre-planned 375 non-screen failures are enrolled). If a patient is identified as a screen failure during the index procedure (prior to placement of the system into the body), the patient shall be followed for 30 days for the purposes of safety evaluations only and will be reported upon as a separate Screen Failure cohort safety analysis.

In studied populations the average age of patients with mitral regurgitation is 67 (± 12.7) years[4]. This study is expected to enroll patients with baseline characteristics (e.g. age) similar to previously studied populations, and results are expected to be generalizable to individuals qualifying for Medicare based on age criteria.

6.2 Inclusion Criteria

Patients must meet all of the following criteria to be eligible for the study:

Inclusion Criteria #	Criteria	Window/Guidance
1.	Eighteen (18) years of age or older;	As of date of signature on informed consent
2.	Clinically significant functional MR (≥ 3+ by echocardiography) as assessed by the core lab;	
3.	Stable heart failure medications as determined by local heart team;	Stable for 30 days prior to procedure date (further details in Section 8.3)
4.	Elevated BNP > 150 pg/ml or corrected NT-proBNP > 600 pg/ml within past 90 days or heart failure hospitalization within past 12 months;	Elevated BNP or NT-proBNP measured no earlier than 90 days prior to date of informed consent OR heart failure hospitalization within past 12 months prior to informed consent.
5.	Symptomatic heart failure patients with measured baseline 6 minute walk test (6MWT) between 150 and 400 meters;	
6.	Patient is deemed appropriate for Edwards Cardioband System by the Heart Team at the investigational site and the Central Screening Committee;	
7.	Patient is able and willing to give informed consent and follow protocol procedures, and comply with follow-up visit compliance.	

6.3 Exclusion Criteria

Patients will be excluded from the study if they meet any of the following:

Exclusion Criteria #	Criteria	Window/Guidance
1.	Primarily degenerative MR;	
2.	LVEF ≤ 20% and LVEDD > 80 mm by transthoracic echocardiography as measured by core lab;	Within 30 days of submission to image transfer system and 60 days of procedure
3.	Mitral annular calcification that would impede implantation of device as assessed by core lab;	
4.	Infiltrated cardiomyopathies (e.g., amyloidosis, hemochromatosis, sarcoidosis), hypertrophic cardiomyopathy, constrictive pericarditis, or any other structural heart disease causing heart failure other than dilated cardiomyopathy of either ischemic or non-ischemic etiology;	
5.	Recent hemodynamic instability (e.g. need for inotropic support or intra-aortic balloon pump or other hemodynamic support device);	Within 30 days prior to procedure date
6.	Right sided heart failure or echocardiographic evidence of severe right ventricular dysfunction per core lab assessment;	Per baseline TTE
7.	Estimated pulmonary artery systolic pressure (PASP) > 70 mmHg assessed by site based on echocardiography or right heart catheterization, unless active vasodilator therapy in the catheterization lab is able to reduce the pulmonary vascular resistance (PVR) to < 3 Wood units or between 3 and 4.5 Wood units with V wave less than twice the mean of the pulmonary capillary wedge pressure;	
8.	Other severe valve disorders requiring intervention;	
9.	Need for emergent or urgent surgery for any reason or any planned	From date of

Exclusion Criteria #	Criteria	Window/Guidance
	cardiac surgery within the next 12 months;	signature of informed consent
10.	Mitral valve anatomy which may preclude proper Edwards Cardioband System access, use and/or deployment;	
11.	Any prior or other planned mitral valve procedure;	
12.	Patient in whom a TEE is contraindicated or screening/baseline TEE is unsuccessful;	
13.	Echocardiographic evidence of intracardiac mass, thrombus or vegetation;	
14.	Severe liver cirrhosis (Childs-Pugh C or MELD > 12);	
15.	Active systemic infection, including active endocarditis;	Within 30 days prior to procedure date
16.	Untreatable hypersensitivity or contraindication to any of the following: • Aspirin and Clopidogrel and Ticlopidine, OR • Heparin and Bivalirudin, or Warfarin, OR • Nitinol Alloys (nickel and titanium) or contrast media;	
17.	Any recent percutaneous coronary, carotid, endovascular intervention, carotid surgery, or cardiac surgery;	Within 30 days prior to procedure date
18.	Recent implant or revision of any rhythm management device (i.e., pacemaker, cardiac resynchronization therapy [CRT] with or without cardioverter-defibrillator [CRT-D]);	Within 90 days prior to signing informed consent
19.	Resting systolic blood pressure < 90 or > 160 mmHg after repeated measurements;	Repeated = 3 consecutive

Exclusion Criteria #	Criteria	Window/Guidance
		measurements
20.	Recent CVA or TIA;	Within 30 days prior to procedure date
21.	Previous stroke with permanent disability (modified Rankin score > 2);	
22.	Severe renal insufficiency with eGFR ≤ 25 mL/min or requiring chronic renal replacement therapy;	
23.	Contraindication to transseptal catheterization;	
24.	Concurrent medical condition with a life expectancy of less than 12 months in the judgment of the investigator;	
25.	Pregnant or planning pregnancy within next 12 months;[1]	
26.	Known bleeding or clotting disorders or patient refuses blood transfusion;	
27.	Severe COPD in whom the primary mechanism of dyspnea is pulmonary disease rather than heart failure;	
28.	Recent myocardial infraction (per WHO definition);	Within 30 days prior to procedure date
29.	Patient has been approved to participate and is currently enrolled in, or has participated in another investigational drug or device clinical study where the primary study endpoint was not reached at time of enrollment;	

[1] Female patients of childbearing potential need to have a negative pregnancy test performed within 14 days prior to intervention and be adherent to an accepted method of contraception

Exclusion Criteria #	Criteria	Window/Guidance
30.	Any condition, in the opinion of the Investigator, making it unlikely the patient will be able to complete all protocol procedures (including compliance with guideline directed medical therapy) and follow-up visits;	
31.	Other medical, social, or psychological conditions that preclude appropriate consent and follow-up, including patients under guardianship.	

6.4 Patient Screening Overview

All patients who have been diagnosed with symptoms of heart failure and mitral regurgitation should be screened for eligibility. Patient will be consented and evaluated against eligibility criteria and baseline testing, as appropriate. Patient eligibility will be reviewed by both the local Heart Team and the study Central Screening Committee (CSC). All potential patients screened for the study will be captured on the site's Screening Log. If a patient does not meet all eligibility criteria, the log shall specify the reason for exclusion. A summary of the screening/enrollment process is provided in Figure 4.

If local IRB approval is obtained, a screening consent form may be implemented to enable the collection of standard assessments for this population (e.g., CT, TEE and TTE.). Data collected from screening assessments may be used to simultaneously assess the patient's anatomic eligibility for this Study using the Cardioband ACTIVE System or other Edwards Clinical Studies using a transcatheter mitral repair or replacement study device. If local IRBs do not allow the use of a screening consent form, all screening assessments will be described under the applicable standard study Informed Consent Form.

6.5 Informed Consent Procedures

Informed consent shall be obtained in writing from the patient or their legally authorized representative and the process shall be documented before any procedure specific to the clinical investigation is applied to the patient. If during the course of the study assessments, a patient is found not to be eligible for inclusion in the study, the patient or their representative should be notified and the reason for ineligibility documented on the screening log/form, and the patient will be exited from the study. Any patient enrolled into the roll-in cohort shall sign the Roll-In ICF which is different from the ICF designated for the randomized study patients.

The general process for obtaining informed consent (for both screening and study consents, as applicable) is as follows:

- Ensure that the principal investigator or his/her authorized designee conducts the informed consent process;
- Include all aspects of the clinical investigation that are relevant to the patient's decision to participate throughout the clinical investigation;
- Avoid any coercion or undue improper influence on, or inducement of, the patient to participate;
- Not waive or appear to waive the patient's legal rights;
- Use native non-technical language that is understandable to the patient;
- Provide ample time for the patient to read and understand the informed consent form and to consider participation in the clinical investigation;
- Include personally dated signatures of the patient and the principal investigator, or an authorized designee responsible for conducting the informed consent process;
- Provide the patient with a copy of the informed consent form and any other written information; and,
- Ensure important new information is provided to new and existing patients throughout the clinical investigation.

6.6 Screening / Baseline (Pre-Randomization)

Patients who are considered qualified for potential study eligibility will undergo assessments by the local Heart Team as outlined below after signing the appropriate consent form (screening and/or study consent).

- Informed Consent Form (screening and/or study consent)
- Medical History
- NYHA Class
- STS Score
- Cardiovascular Medications assessment
- Modified Rankin score

- Targeted physical examination
- 12-lead ECG
    - The baseline rhythm will be documented if patients have atrial rhythm (sinus, paroxysmal atrial fibrillation (AF), persistent AF, long-standing AF, and/or permanent AF)
- Transthoracic echocardiogram (TTE); (performed in accordance with core lab imaging acquisition protocol)
- Transesophageal echocardiography (TEE); (performed in accordance with core lab imaging acquisition protocol)
- Cardiac CT Imaging (performed in accordance with core lab imaging acquisition protocol)
- Pregnancy Test (for female patients of child bearing potential)
- Coagulation Panel (PT, PTT; INR for patients on Vitamin-K antagonist)
- Complete Blood Count (WBC with differential, RBC, HCT, Hgb, platelet count)
- Chemistry Panel (BUN, CO_2, Creatinine, Glucose, Cl, K, Na, AST (GOT), ALT (GPT), GGT, serum Total Protein, Albumin, Total Cholesterol, HDL Cholesterol, Uric Acid)
- NT-Pro-BNP or BNP
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- SF-36v2 Health Survey (SF-36)
- 6 Minute Walk Test (6MWT)
- Adverse Events (adverse events will be collected from the time patient signs informed consent until they complete or exit the study)
- Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale©
- Patient Preference Survey
- Activity Monitoring initiation with daily data collection through the 180 day follow-up visit.[2] Patients may opt out of activity monitoring during the informed consent process or at any time after by notifying the investigator.

[2] Activity Monitoring components to be implemented at system launch. Patients enrolled prior to system launch will not be required to participate in these assessments.

- Patients will be asked to wear the device as much as possible as waking and sleep activity data will be collected. Daily compliance tracking will be measured as a minimum of 8 hours activity data collection between 6am to 10pm.
- If the enrolled patient becomes a screen failure at any time after the screening/baseline visit, the patient will be instructed to return the activity monitoring equipment.

Note: The procedures required for Screening/Baseline confirmation may be conducted during more than one visit.

Table 3. Screening/Baseline Assessment Windows

Assessment	Window
TTE	Within 30 days prior to submission to image transfer system and within 60 days prior to procedure*
TEE	Within 90 days prior to submission to image transfer system
Cardiac CT	Within 180 days prior to submission to image transfer system

*If TTE is more than 60 days from the procedure, a repeat TTE will be required.

Note: For TTE, TEE and cardiac CT, pre-existing images of adequate quality capturing required anatomy for assessment can be used. If imaging is deemed incomplete or inadequate for assessment, repeat imaging may be required.

6.7 Technical Feasibility Assessment of Edwards Cardioband System Implantation by Sponsor

The Sponsor will review applicable patient data collected at Screening and Baseline Visits (e.g. cardiac CT) to determine the technical feasibility of implanting the Edwards Cardioband System. The Sponsor may also assist the site in determining the most appropriate implant size for the patient.

6.8 Central Screening Committee Determination

After the Central Screening Committee (CSC) has reviewed all screening and baseline assessments and reached a decision on eligibility, the decision will be communicated to the site. The site will proceed to scheduling the case for approved patients in accordance with institutional procedures.

7 Randomization Procedure

Patients will be prospectively randomized into the clinical study. Randomization will occur only after the patient provides informed consent, completes all required screening and baseline procedures, and satisfies the study eligibility criteria (including eligibility determination by the Central Screening Committee). Randomization shall be performed after cases have received final approval from the CSC and Sponsor and the case has been scheduled at the institution.

Eligible patients will be randomly assigned in a two to one (2:1) ratio to either treatment with Edwards Cardioband System + Guideline Directed Medical Therapy (Device Group) versus Guideline Directed Medical Therapy alone (Control Group).

Randomization assignment will be generated via the randomization module of the EDC system. Randomization scheme will be based on random blocks and will be stratified by:

- study center
- baseline ischemic vs. non-ischemic disease

This randomization schedule (list) will be masked to study patients, site personnel, study team and Sponsor. Only the un-blinded statistician and designates will be privy to the masked randomization scheme.

A patient is not considered randomized until the randomization assignment has been dispensed. If at any time after randomization a patient becomes ineligible or withdraws, the patient is still considered randomized.

8 TREATMENT (EDWARDS CARDIOBAND SYSTEM INDEX PROCEDURE / GDMT)

8.1 Prior to Index Procedure (for patients assigned to Device group only; timing per local institutional standard of care)

Note: The goal is to conduct the Edwards Cardioband System index procedure within 7 days of the date of randomization. Randomization should occur as close as possible prior to the scheduled procedure to minimize the amount of time between randomization and procedure.

The following data must be collected prior to the index procedure, according to the local institutional standard of care.

- Pregnancy Test (for females of child bearing potential)

- Complete Blood Count
- Coagulation Panel
- Chemistry Panel
- Cardiac Biomarkers (troponins or CK/CK-MB)
- Adverse Events

8.2 Edwards Cardioband System Index Procedure (for patients assigned to Device group only)

The following data must be collected during the index procedure:

- Transesophageal Echo (TEE)
- Procedural details
- Adverse Event Assessment
- Anticoagulation/ antiplatelet therapy administered intra-procedure.

Note: If, during the assessment of the patient at any time between the randomization and the time of the procedure, it is determined that the patient is no longer eligible for the study, the patient shall be withdrawn and will not be counted towards the pre-planned sample size (i.e. the enrollment will continue until the pre-planned 375 non-screen-failures are enrolled). A patient who is determined to be a screen-failure on the day of procedure and received diagnostic procedures in the procedure room, shall be followed for 30 days for the purposes of safety.

The mitral valve reduction procedure will be performed in a transcatheter manner to deliver and deploy the Edwards Cardioband System. The Edwards Cardioband System procedure may be performed in a standard operating room, hybrid operating room, or cardiac catheterization lab. In any of these settings emergency equipment and resources including adequate blood products, external defibrillator paddles, proper anesthesia administration, and monitoring capabilities must be available. The team performing the Edwards Cardioband System procedure will include an anesthesiologist, an interventional cardiologist or surgeon experienced in transseptal and transcatheter valve procedures, and an echocardiographer as per local standard of care.

Note: A recommended technique is presented in the following sections. It is recognized that individual patient anatomic variation or surgical/interventional conditions may necessitate modifications to the outlined procedures. However, to the extent possible, physicians should adhere to the procedure steps

8.2.1 Antithrombotic Therapy

To protect patients from bleeding or thromboembolic events, a recommended process for antithrombotic therapy is provided below. Investigators may utilize their institutional procedures for anticoagulation/ antiplatelet therapy, in recognition of various agents available as well as individual patient factors such as CHA_2DS_2-VASC score.

8.2.1.1 During Index Procedure

- IV unfractionated heparin with a target ACT ≥ 250 seconds or bivalirudin (no ACT monitoring necessary)

8.2.1.2 Post-Index Procedure

- Aspirin (ASA) 75 – 100 mg daily by mouth, indefinitely
- Clopidogrel 75 mg daily by mouth, for 6 months
- If oral anticoagulation is indicated, no clopidogrel is necessary unless indicated for post-PCI indication. If anticoagulation is given along with clopidogrel (for example due to a PCI history and indication) ASA may be discontinued at investigator's discretion.

To monitor anticoagulation for patients on vitamin-K antagonists, International Normalized Ratio (INR) should be measured at each follow up visit. Additional INR testing may be performed according to institutional practice or the physician's discretion.

8.2.2 Antibiotic Prophylaxis

It is recommended that all patients undergoing device implant be prophylactically treated for endocarditis per AHA recommendations.[26]

8.2.3 Patient Preparation in Procedure Room

Prior to draping, place the booster plate associated with the Edwards Cardioband System under the patient's leg in the region of the knee, and adjust booster apparatus per IFU.

The patient is prepped and draped for a standard transseptal procedure.

Non-sterile, external defibrillator pads are placed behind the right shoulder and on the left flank, away from femoral insertion sites. Alternatively, if sterile external defibrillator pads are available, one can be placed over the sternum and one directly posterior on the back.

General anesthesia or conscious sedation is induced and the patient ventilated according to patient's hemodynamic condition and institutional practices. Due to the duration of the

procedure an anesthesiologist should administer sedation/anesthesia. General anesthesia is encouraged to facilitate use of transesophageal echocardiography.

8.2.4 Implantation Procedure

Note: Prior to preparation and loading of the Edwards Cardioband System, the serial number of the implant should be recorded on the supplied Patient Implant Card. Similarly, the serial number of the implant should be recorded in hospital records.

The major steps for Edwards Cardioband System utilization are outlined below. Refer to the Instructions for Use (IFU) for complete details on device preparation and use:

1. [redacted]

8.2.5 Edwards Cardioband System/MR Assessment

After implantation of the Edwards Cardioband System, transesophageal echocardiography should be performed per the Echocardiography Core Lab study manual to assess mitral regurgitation after performing device reduction.

8.2.6 Index Procedure Completion and Tissue Closure

Once all maneuvers are complete, catheters and sheaths are withdrawn. The end of the procedure is defined as the time that the final catheter or sheath is withdrawn from the vasculature (does not include intravenous or other indwelling catheters used for medication delivery or patient monitoring). Catheter insertion site hemostasis and dressings should be performed according to institutional techniques.

8.2.7 Index Procedure through Discharge

The patient should arrive wearing the activity monitor wrist watch at time of the index procedure hospitalization period. The patient will be asked to wear the activity monitor wrist watch through the hospitalization and allowed to remove the device during tests, evaluations, the index procedure, and as required by the treating physician. At index hospitalization discharge the patient should be wearing the activity monitor.

The following assessments will be recorded prior to, or at time of discharge (or at 30 days post index procedure, whichever comes first).

- Cardiovascular medications
- 12-lead ECG
- Transthoracic Echocardiography
- Cardiac Biomarkers (troponins or CK/CK-MB) [pre-intervention and post-index procedure: approximately 12-24 hours, 36-48 hours, 72 hours or at discharge if earlier. Thereafter, if cardiac biomarkers remain elevated, collect daily until values show a decline or patient is discharged.]
- Neurological Assessments:

Neurological Assessment will be conducted by a neurologist, a neurology fellow, or designee. Every effort should be made to have a neurologist or neurology fellow perform the neurological assessments, or alternatively, a trained research team member certified in stroke assessment, which consist of:

  - NIHSS

  - Modified Rankin Scale (mRS): mRS can be obtained by a certified research team member via phone interview with the patient or caregiver member if the patient is unable to visit the research office.

- Adverse Events

For purposes of this study, hospital discharge is defined as the date of discharge, or 30 days following the post-index procedure if patient remains in hospital, whichever occurs first.

8.3 Guideline Directed Medical Therapy (for both Device and Control groups)

Patients with a documented intolerance to Guideline Directed Medical Therapy (GDMT) will be eligible for study inclusion. All patients (i.e. whether assigned to Device and Control groups) shall continue to receive stable Guideline Directed Medical Therapy as directed by current heart failure guidelines (including use of cardiac resynchronization therapy, as indicated).[27,28] This implies that the GDMT regimen in principle remains unchanged until primary efficacy endpoint, unless medically warranted. Changes to GDMT (doubling or halving of dose) will be documented including whether these occurred due to improvement, deterioration, or no change in the patient's condition. Medical management should continue under the direction of a heart failure specialist at regular intervals according to current heart failure guidelines.[27,28]

9 FOLLOW-UP EVALUATIONS

Follow-up evaluations will be scheduled for 30 days, 180 days, 1 year, 2 years, 3 years, 4 years, and 5 years.

- For patients assigned to the Device group, the follow-up visits are scheduled based on the date of the Edwards Cardioband System index procedure.
- For patients assigned to the Control group, the follow-up visits are scheduled based on the date of randomization.
- Note: A patient in the Control group may be offered an opportunity to receive an Edwards Cardioband System after they have been followed for a minimum of 1 year and completed their primary efficacy endpoint assessment. At the time of their 1 year follow-up visit, if the patient chooses to receive the investigational device, they will be evaluated in accordance with the eligibility criteria (including concurrence by the site Heart Team and the CSC). If the patient is still eligible for enrollment, he/she will be offered an opportunity to receive the device. If the patient receives the Edwards Cardioband System implant, he/she shall be followed in accordance with the clinical

protocol schedule or at a minimum for two years if the product has received PMA Approval. This group shall be summarized as a separate cohort.

9.1 Thirty (30) Day Follow-Up Evaluation

An evaluation will be scheduled for 30 day follow-up (±7 days). The following assessments will be performed:

- Medical History
- NYHA Class
- Cardiovascular Medications
- Targeted Physical Exam
- 12-lead ECG
- Transthoracic Echocardiography
- NT-Pro-BNP or BNP
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- SF-36v2 Health Survey (SF-36)
- 6 Minute Walk Test (6MWT)
- Continued Activity Monitoring data collection from baseline to the 180 day follow-up. The patient should be wearing the activity monitor wrist watch at time of the 30 day follow-up visit.
- Neurological Assessments:

Neurological Assessment will be conducted by a neurologist, a neurology fellow, or designee. Every effort should be made to have a neurologist or neurology fellow perform the neurological assessments, or alternatively, a trained research team member certified in stroke assessment, which consist of:

  - NIHSS
  - Modified Rankin Scale (mRS): mRS can be obtained by a certified research team member via phone interview with the patient or caregiver member if the patient is unable to visit the research office.

- Adverse Events

If the patient reports any adverse events that are potentially serious during the follow-up period, the patient should return to the investigator's facility for further evaluation of the event.

9.2 One Hundred Eighty (180) Day Follow-Up Evaluation

An evaluation will be scheduled for 180 day follow-up (± 14 days). The following assessments will be performed:

- Medical History
- NYHA Class
- Cardiovascular Medications
- Targeted Physical Exam
- 12-lead ECG
- Transthoracic Echocardiography
- Complete blood count (no WBC differential necessary)
- Chemistry panel
- NT-Pro-BNP or BNP
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- SF-36v2 Health Survey (SF-36)
- 6 Minute Walk Test (6MWT)
- Neurological Assessments

Neurological Assessments will be conducted by a neurologist, a neurology fellow, or designee. Every effort should be made to have a neurologist or neurology fellow perform the neurological assessments, or alternatively, a trained research team member certified in stroke assessments, which consist of:

    - NIHSS
    - Modified Rankin Scale (mRS): mRS can be obtained by a certified research team member via phone interview with the patient or caregiver member if the patient is unable to visit the research office.

- Continued Activity Monitoring data collection from baseline to the 180 day follow-up.
    - At the 180 day follow-up visit, the patient will return the Activity Monitoring Devices. If a patient's daily wear compliance rate (minimum 8 hours between 6am to 10pm) is less than 50% in the 30 days prior to the visit, an additional month (30 days) of Activity Monitoring will be completed. Devices will be returned following the month of Activity Monitoring.

- Adverse Events

If the patient reports any adverse events that are potentially serious during the follow-up period, the patient should return to the investigator's facility for further evaluation of the event.

9.2.1 Primary Endpoint Compliance

In order to ensure completeness of the primary endpoints at 12-month study visit, the investigational sites are advised to schedule the visit as early in the window (+/- 45 days) as possible to ensure compliance in the event a visit needs to be rescheduled for any reason.

9.3 One (1) Year Follow-Up Evaluation

An evaluation will be scheduled for the 1 year follow-up (± 45 days). The following assessments will be performed:

- Medical History
- NYHA Class
- Cardiovascular Medications
- Targeted Physical Exam
- 12-lead ECG
- Transthoracic Echocardiography
- CBC (no WBC differential necessary)
- Chemistry panel
- NT-Pro-BNP or BNP
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- SF-36v2 Health Survey (SF-36)
- 6 Minute Walk Test (6MWT)
- Adverse Events

If the patient reports any adverse events that are potentially serious during the follow-up period, the patient should return to the investigator's facility for further evaluation of the event.

- Neurological Assessments

Neurological Assessments will be conducted by a neurologist, a neurology fellow, or designee. Every effort should be made to have a neurologist or neurology fellow perform the neurological assessments, or alternatively, a trained research team member certified in stroke assessment, which consist of:

  - NIHSS
  - Modified Rankin Scale (mRS): mRS can be obtained by a certified research team member via phone interview with the patient or caregiver member if the patient is unable to visit the research office.
- Activity Monitoring data collection will be restarted at the time of the 1 year visit. The patient will be provided Activity Monitoring devices and following a month (30 days) of data collection will be instructed to return the device.

9.4 Two (2) Year Follow-Up Evaluation

An evaluation will be scheduled for the 2 year follow-up (± 60 days). The following assessments will be performed:

- Medical History
- NYHA Class
- Cardiovascular Medications
- Targeted Physical Exam
- Transthoracic Echocardiography
- NT-Pro-BNP or BNP
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- SF-36v2 Health Survey (SF-36)
- 6 Minute Walk Test (6MWT)
- Adverse Events

If the patient reports any adverse events that are potentially serious during the follow-up period, the patient should return to the investigator's facility for further evaluation of the event.

- Neurological Assessments

Neurological Assessments will be conducted by a neurologist, a neurology fellow, or designee. Every effort should be made to have a neurologist or neurology fellow perform the neurological

assessments, or alternatively, a trained research team member certified in stroke assessment, which consist of:

- NIHSS
- Modified Rankin Scale (mRS): mRS can be obtained by a certified research team member via phone interview with the patient or caregiver member if the patient is unable to visit the research office.

9.5 Three (3) to Five (5) Year Annual Follow-Up Evaluations (± 60 days)

The following assessments will be performed on an annual basis at three, four and five years (±60 Day):

- Medical History
- NYHA Class
- Cardiovascular Medications
- Targeted Physical Exam
- Transthoracic Echocardiography
- NT-Pro-BNP or BNP
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- SF-36v2 Health Survey (SF-36)
- Adverse Events

If the patient reports any adverse events that are potentially serious during the follow-up period, the patient should return to the investigator's facility for further evaluation of the event.

- Neurological Assessments

Neurological Assessments will be conducted by a neurologist, a neurology fellow, or designee. Every effort should be made to have a neurologist or neurology fellow perform the neurological assessments, or alternatively, a trained research team member certified in stroke assessment, which consist of:

- NIHSS
- Modified Rankin Scale (mRS): mRS can be obtained by a certified research team member via phone interview with the patient or caregiver member if the patient is unable to visit the research office.

9.6 Study Exit

If the patient exits the study prior to completing the required assessments, the Study Exit CRF must be completed.

10 Schedule of Study Visits and Patient Assessments

Evaluation of patients enrolled in this study will include all tests and procedures listed in the Schedule of Study Visits and Patient Assessments as outlined in Table 4.

Table 4: Schedule of Study Visits and Patient Assessments

Test/ Assessment	**Screening/ Baseline**	**Random -ization**	**Pre-Index Procedure- Edwards Cardioband System** (Device group only; timing: per local institutional standard of care)	**Index Procedure- Edwards Cardioband System** (Device group only)	**Post- Edwards Cardioband System Procedure, Pre-Discharge** (Device group only)	**30 Day F/U (±7 days)**	**180 Day F/U (± 14 days)**	**1 Year F/U (±45 days)**	**2 Year F/U (± 60 days)**	**3, 4, 5 Year F/U (± 60 days)**
Study Visit No.	**1**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11, 12, 13**
Study Consent	X									
Medical Hx/ NYHA Class	X					X	X	X	X	X
STS Score	X									
Cardiovascular Medications	X			X	X	X	X	X	X	X
Targeted Physical Exam	X					X	X	X	X	X
12-Lead ECG	X				X	X	X	X		
Transthoracic Echo (TTE)	X				X	X	X	X	X	X
Transesophageal Echo (TEE)	X			X						
Cardiac CT Imaging	X									
Randomization		X								
Pregnancy Test (for females of childbearing potential only)	X[1]		X							

Test/ Assessment	**Screening/ Baseline**	**Random -ization**	**Pre-Index Procedure- Edwards Cardioband System** (Device group only; timing: per local institutional standard of care)	**Index Procedure- Edwards Cardioband System** (Device group only)	**Post- Edwards Cardioband System Procedure, Pre-Discharge** (Device group only)	**30 Day F/U (±7 days)**	**180 Day F/U (± 14 days)**	**1 Year F/U (±45 days)**	**2 Year F/U (± 60 days)**	**3, 4, 5 Year F/U (± 60 days)**
Study Visit No.	**1**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11, 12, 13**
Complete Blood Count (WBC, RBC, HCT, Hgb, platelet count)	X		X				X	X		
Coagulation Panel (PT, PTT; INR for patients on vitamin-K antagonist)	X		X							
Chemistry Panel (BUN, CO_2, Creatinine, Glucose, Cl, K, Na, AST (GOT), ALT (GPT), GGT, serum Total Protein, Albumin, Total Cholesterol, Triglycerides, HDL Cholesterol, Uric Acid)	X		X				X	X		

Test/ Assessment	**Screening/ Baseline**	**Random -ization**	**Pre-Index Procedure- Edwards Cardioband System** (Device group only; timing: per local institutional standard of care)	**Index Procedure- Edwards Cardioband System** (Device group only)	**Post- Edwards Cardioband System Procedure, Pre-Discharge** (Device group only)	**30 Day F/U (±7 days)**	**180 Day F/U (± 14 days)**	**1 Year F/U (±45 days)**	**2 Year F/U (± 60 days)**	**3, 4, 5 Year F/U (± 60 days)**
Study Visit No.	**1**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11, 12, 13**
Cardiac biomarkers (troponins or CK/CK-MB)			X[2]		X[2]					
NT-Pro-BNP or BNP	X					X	X	X	X	X
Modified Rankin Scale	X				X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
NIHSS	X[3]				X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
KCCQ	X					X	X	X	X	X
SF-36	X					X	X	X	X	X
6 Minute Walk Test (6MWT)	X					X	X	X	X	
Safety Primary Endpoint						X				
Efficacy Primary Endpoint								X		
Adverse Events	X	X	X	X	X	X	X	X	X	X
Clinical Frailty Scale©	X									
Patient Preference Survey	X									

Test/ Assessment	Screening/ Baseline	Random -ization	Pre-Index Procedure- Edwards Cardioband System (Device group only; timing: per local institutional standard of care)	Index Procedure- Edwards Cardioband System (Device group only)	Post- Edwards Cardioband System Procedure, Pre-Discharge (Device group only)	30 Day F/U (±7 days)	180 Day F/U (± 14 days)	1 Year F/U (±45 days)	2 Year F/U (± 60 days)	3, 4, 5 Year F/U (± 60 days)
Study Visit No.	**1**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11, 12, 13**
Activity Monitoring[4]	X	X	X		X	X	X	X		
Economic Data Collection[5]			X	X	X					

(1) Perform pregnancy test prior to Cardiac CT, as required

(2) Cardiac biomarkers: Collection for all patients undergoing Edwards Cardioband System implantation

(3) If the patient experiences a stroke during the study, Neurological Assessments including NIH Stroke Scale (NIHSS) and Modified Rankin Scale should additionally be performed within 90 days from the date of the stroke by a neurologist, a neurology fellow, or designee.

(4) Activity monitoring will be collected continuously from baseline to the 6 month visit. At 6 months if compliance is low an additional 1 month of monitoring will be issued. A month of continuous monitoring will be reinitiated at the 1 year follow-up visit.

(5) Economic Data Collection will collect patient billing records for the index procedure.

All testing should be conducted at the investigational site to the extent possible. Follow-up testing may be performed at another site only if it is not possible for the patient (or the patient refuses) to return to the investigational site. In such cases, the Investigator may arrange for the study-required testing to be completed by the patient's local physician. However, it remains the responsibility of the study Investigator to ensure collection of appropriate information. Copies of source documents from the local physician must be obtained and kept in the patient's study file.

11 ADVERSE EVENTS

Potential risks to the patients are listed in the Clinical Risk/Benefit Analysis Section (see **Appendix 1- Clinical Risk/Benefit Analysis**).

Patients will be carefully monitored during the study for possible adverse events (AEs). During each clinical follow-up visit, the investigator or designee will determine AE occurrences. Each adverse event is considered to be either anticipated or unanticipated as described below. The site is required to report all adverse events that occur during the study. The investigator will classify the AEs based on the definitions as follows:

11.1 General Adverse Event Definitions

Adverse event: is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in patients, users, or other persons, whether or not related to the investigational medical device.

An adverse event can be further identified by a condition as noted below:

a) A unique symptom or event that is a change from the patient's baseline status

b) A series of symptoms or events that can be categorized as a single entity based on definitions found herein

c) A specific diagnosis responsible for a clinical change

d) A worsening or exacerbation of a pre-existing condition

11.2 Serious Adverse Events

A serious adverse event (SAE) is an adverse event that:

- Results in death

- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is an important medical event which may jeopardize the patient, and may require medical or surgical intervention to prevent one of the above outcomes

11.2.1 Unanticipated Adverse Device Effect

Unanticipated adverse device effect (UADE) is defined in accordance with 21 Code of Federal Regulations (CFR) Part 812.3 as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

11.3 Adverse Event Assessment

Adverse events in an implanted patient will be assessed by the Investigator for causality to the investigational device or index procedure.

Investigational Device Related Adverse Event: An adverse event, which in the judgment of the Investigator, results from use of the Edwards Cardioband System.

Procedure Related Adverse Event: An adverse event which, in the judgment of the Investigator, results as a consequence of the index (i.e. Edwards Cardioband System) procedure.

11.4 Events Expected to Occur with Edwards Cardioband System Index-Procedure

For purposes of this study, the following events are not considered reportable adverse events because they are normally expected to occur in conjunction with treatment of mitral regurgitation or structural heart interventional procedures, or are associated with customary, standard care of patients undergoing minimally invasive cardiovascular intervention:

- Chest pain without associated enzyme/ECG changes.
- Post-procedure pain (within 48 hour of procedure and treated with non-opioids).
- Post-anesthesia emesis, nausea, or headache (within 48 hours of procedure).

- Electrolyte imbalance without clinical sequelae and not requiring correction following the index procedure.
- Pre - Planned future Surgical Procedures.
- Low grade temperature increase (≤ 101°F or 38.5°C) without signs of infection.
- Dizziness: Imprecise term commonly used to describe various symptoms such as faintness, giddiness, imbalance, lightheadedness, unsteadiness or vertigo (in the initial 48 hours post procedure).
- Elevated White Blood Count, outside the standard laboratory normal value, without signs and symptoms of infection.
- Minor, localized tenderness, swelling, induration, oozing, etc. at access site(s).
- Sinus bradycardia/tachycardia that does not require treatment or intervention.
- Systolic or diastolic blood pressure changes that do not require treatment or intervention.
- Hyperglycemia: the use of insulin in a diabetic patient in the post op period.
- Non-clinically significant lab variances.
- Non-clinically significant events.

This listing of events is intended to provide guidance to the investigational sites for the purpose of adverse event reporting. The Investigator at the investigational site should utilize his/her own clinical judgment in evaluating adverse experiences, and may decide that the above events should be reported as adverse events.

11.5 Adverse Event Reporting Requirements

11.5.1 General Reporting Requirements (All Adverse Events)

All adverse events (i.e. serious or non-serious, anticipated or unanticipated) must be recorded on the Adverse Event eCRF by the investigator (or designee) and all device deficiencies must be reported to the Sponsor, with the exception of those adverse events identified in Section 11.4. The report should include: start date of the adverse event, treatment, resolution, and assessment of both the seriousness and the relationship to the investigational device and the procedure.

The following principles must also be adhered to by the Investigator:

- Completion of separate Adverse Event forms to document each event
- Completion of separate forms for each device observation/ deficiency
- The forms must be electronically signed by the Investigator, and
- Additional information related to adverse events as requested by the Sponsor
- It is the responsibility of the Investigator to inform their IRB/EC of serious adverse events as required by their IRB/EC procedures and in conformance with applicable regulatory requirements.

In the event of a suspected device observation or deficiency, the device shall be returned to Sponsor for analysis. Instructions for returning the investigational device will be provided by the Sponsor.

11.5.2 Reporting Requirements (Non-Serious Adverse Events)

All non-serious adverse events should be reported by the Investigator (or designee) by submitting the Adverse Event eCRF to the Sponsor within 7 calendar days of learning of the adverse event, or at the Sponsor's request. In the event that the electronic system is not available, the event should be reported by email to TMTT_Safety@edwards.com with the following minimum information:

- Study site number
- Patient ID number
- Date of event
- Site's awareness date
- Adverse event description
- Causal relationship to the device and Implant procedure

The AE eCRF should be submitted as soon as possible thereafter.

11.5.3 Reporting Requirements (Serious Adverse Events)

All serious adverse events should be reported by the Investigator (or designee) by submitting the Adverse Event eCRF to the Sponsor, within 3 calendar days of learning of the adverse event.

In the event that the electronic system is not available, the event should be reported as noted above in section 11.5.2.

The Investigator (or designee) shall provide source documents related to the serious and/or unanticipated adverse event as requested by Sponsor or their designee. Furthermore, the Investigator shall report the event to the IRB/EC in accordance with local/institutional requirements. The Sponsor will evaluate all serious adverse events for reportability as an unanticipated adverse device effect in accordance with 21 CFR Part 812.46(b)3. The investigator and Sponsor will comply with reporting requirements per 21 CFR Part 812.150. A Sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's/EC's and participating investigators within 10 working days after the Sponsor first receives notice of the event. Thereafter the Sponsor shall submit additional reports concerning the event as FDA requests.

Finally, the Investigator should follow all unresolved serious adverse events until the events are resolved, the patient is lost to follow-up, the patient has withdrawn consent, or the adverse event is otherwise explained.

11.6 Patient Death

Patient death during the investigation should be reported to Sponsor or designee within 3 calendar days of Investigator's knowledge of the death. The Adverse Event that resulted in death should be entered in the database on the Adverse Event form within 3 calendar days and include a brief description of the relevant details of the death. The electronic Adverse Event eCRF must be electronically signed by the Investigator. A copy of the death records, death certificate and an autopsy report (if performed) should be sent to the Sponsor as soon as possible or designee within 10 days following the death. In addition, patient death must be reported to the IRB/EC in accordance with IRB/EC requirements.

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[3] Unanticipated adverse device effect is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

11.7 Treatment Failures & Device Malfunctions

All suspected device deficiencies, malfunctions or failures of the Edwards Cardioband System should be documented on the appropriate eCRF. In the event of a suspected deficiency or other device issue, the device shall be returned to the Sponsor to the extent possible for analysis. Instructions for returning the investigational device will be provided by the Sponsor. F

11.8 Sponsor Reporting

A summary of adverse events will be reported to the applicable regulatory authority at least annually, or as required per applicable regulatory authority.

Sponsor or their designee is responsible for the classification and reporting of adverse events and ongoing safety evaluation of the clinical investigation in accordance with and the relevant regulatory requirements, as applicable.

12 Patient Withdrawal / Discontinuation

12.1 Patient Withdrawal/ Discontinuation/ Premature Study Termination

Once the patient has been enrolled in the study, he/she may withdraw his/her consent to participate in the study at any time without jeopardy or prejudice. Participation in this clinical investigation is entirely voluntary. Likewise, there may be a reason identified by the Investigator that deems the patient no longer suitable for the study. In either case, the Investigator should contact the study Sponsor, or its designee, to discuss the circumstances for discontinuation/withdrawal. Reasons for discontinuation or withdrawal may include, but are not limited to the following:

- The Investigator feels that the patient can no longer fully comply with the requirements of the study or if any of the study procedures would not be in the best interest of the patient.
- The patient is lost to follow-up. A patient will be considered “lost to follow-up” and terminated from the study when all of the following criteria have been met:
    - Failure to complete the remainder of the scheduled study visits without due cause; and
    - Documentation of three unsuccessful attempts to contact the patient via phone/email and/or registered mail.

- The patient withdraws their consent for participation in the study.
- The patient incorrectly randomized in the study and treatment has not been initiated; or
- The Sponsor prematurely terminates the study. Circumstances under which the Sponsor can suspend or stop this trial include, but are not limited to, low study enrollment or new information regarding safety or efficacy.

12.2 Data Collection & Follow-Up for Discontinued/Withdrawn Patients

All randomized patients are considered eligible for the assigned treatment and protocol defined follow-up and will be required to adhere to the assessment schedule outlined in Table 4. Patients may withdraw at any time from the clinical study without jeopardy or prejudice. If a patient terminates from the study, the reason for study termination will be recorded. If termination is a result of an adverse event or death, an Adverse Event eCRF will also be completed. Patients who withdraw consent after treatment will not be required to undergo follow-up after withdrawal, but will still be considered part of the patient cohort.

Every attempt will be made to conduct an exit/final visit prior to a patient terminating from the study. The reason for early discontinuation/ termination will be documented in the source documents and eCRFs.

12.3 Patients Lost to Follow-Up

All reasonable efforts (at least 3 contact attempts via phone/email and/or 2 registered letters) will be made to obtain complete data for all patients, before they are considered lost to follow-up. When possible, Social Security files and the National Death Index should be consulted in an attempt to ascertain mortality status for losses to follow-up. Missing observations may occur due to patients who are lost to follow-up, or demonstrate noncompliance with the required assessments.

13 DATA ANALYSIS

13.1 Statistical and Analytical Plans

A formal Statistical Analysis Plan (SAP) will include all statistical strategies and details necessary for performing the interim and final analyses.

13.2 Statistical Hypotheses

Co-Primary Endpoint I

The hypothesis test is designed to show superiority of Edwards Cardioband System (Device group) to Control group for the primary endpoint via the chi-square statistic, for the difference in the prevalence of MR ≤ 2+ at one year, with a two-sided alpha of 0.05. The null (H_0) and alternative (H_A) hypotheses are:

H_0: $P_{CardB}(T) - P_{Control}(T) = 0$

H_A: $P_{CardB}(T) - P_{Control}(T) \neq 0$.

P_{CardB} and $P_{Control}$ are the estimates of the prevalence of MR ≤ 2+ at T=one year in the Device and Control groups, respectively.

Co-Primary Endpoint II

The hypothesis test is designed to show superiority of Edwards Cardioband System (Device group) to Control group for the hierarchical sequence of the components of the co-primary endpoint, as analyzed via the Finkelstein Schoenfeld test. The Finkelstein-Schoenfeld test is a Generalized Gehan Wilcoxon (GGW) test. See section on primary endpoint analysis for details.

The null hypothesis is that none of the components in the hierarchy are improved by the treatment whereas the alternative hypothesis is that at least one of the components are improved by the treatment.

13.3 Analysis Populations

13.3.1 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. Serious adverse events (SAEs) will be reported for all enrolled patients through study exit.

13.3.2 Intent-to-Treat (ITT) Population – for safety analysis

The Intent-to-Treat population (ITT) [full analysis set (FAS)] 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.

13.3.3 Modified Intent-to-Treat population (mITT) - for 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 Edwards Cardioband System (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.

13.3.4 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.

13.4 Statistical Methods

13.4.1 General Approach

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, 25th and 75th percentiles, minimums, and maximums per the table mockups. Differences between the treatment groups, where specified, will be summarized with the differences of the two means, 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 such as 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 the variables of interest, as well as possible subgroup analyses of interest, will be pre-specified in the study SAP.

13.4.2 Analysis of the Primary Endpoints (Efficacy)

The co-primary endpoints will be analyzed in a hierarchical order where endpoint I must meet statistical significance in order to proceed to endpoint II. This approach does not require any adjustment for multiplicity.

Co-primary endpoint I

The proportion of patients who meet the criteria for reduction of mitral regurgitation (MR ≤ 2+) at one year follow-up.

The comparison of co-primary endpoint I between Device and Control groups will be performed using a Chi-Square-test for two independent proportions.

Co-primary endpoint II

Conditional on the first co-primary endpoint meeting statistical significance, co-primary endpoint II will be analyzed using the non-parametric method described by Finkelstein and Schoenfeld. Briefly, each patient pair is compared in descending order of the endpoints until one member of the pair shows superiority. As specified above, these endpoints are:

1. Time to all-cause death within the first year
2. Number of heart failure hospitalizations within the first year
3. Improvement of 6-Minute Walk Test at one year vs. baseline (≥ 40 meters improvement)
4. Improvement in Kansas City Cardiomyopathy Questionnaire (KCCQ) score at one year vs. baseline (≥10 point improvement).

The specifics of the procedure will be provided in greater detail within the statistical analysis plan (SAP).

The Finkelstein-Schoenfeld method starts by a comparative outcome assessment for all patient pairs. 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 versus every other patient.

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 all-cause	
Patient in Device group dies first due to all-cause	Favors Control
Patient in Control group dies first due to all-cause	Favors Device
Both patients die on the same day due to all-cause	Go to Step 2
If neither of the patients die due to all-cause	Go to Step 2

Comparison of each potential patient pair (e.g. 1 from Device group and 1 from Control group)	How Event is Assessed
Step 2	
If no ranking yet available	
Patient in Device group had more hospitalizations** for HF	Favors Control
Patient in Control group had more hospitalizations** for HF	Favors Device
Both patients were hospitalized** equal number of times	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

*** Only hospitalizations for heart failure are counted*

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) 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 complication, it is counted as a HF-related hospitalization. This rule is also applies to surgical mitral annuloplasty or replacement that are 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. Specifically, 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.

Details of the pairwise comparative outcome assessment process with full scenario analyses are provided in the Statistical Analysis Plan (SAP).

The Finkelstein-Schoenfeld test statistic is a Generalized Gehan Wilcoxon (GGW) test that requires information about the pairwise outcome assessment of all pairwise comparisons, including those within the Device and Control groups.[29]

13.4.3 Analysis of the Safety Endpoints

The overall rates of device and procedure related Major Adverse Events (MAEs) through 30 days post procedure, (primary safety endpoint) as well as the components and secondary safety endpoints, will be calculated, with 95% confidence intervals.

13.4.4 Key Secondary Endpoints (through 1 year)

The following secondary efficacy endpoints will be tested in a hierarchical order after the primary endpoints have passed (i.e., achieved statistical significance at pre-specified alpha level), in order to address multiple testing and control family-wise error. When one of the endpoints does not achieve statistical significance at two-sided alpha = 0.05

in favor of the Device group, no further testing of subsequent endpoints will be conducted.

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_A) hypotheses are:

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

H_A: $P_{CardB} - P_{Control} \neq 0$.

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

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_A) hypotheses are:

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

H_A: $P_{CardB} - P_{Control} \neq 0$.

P_{CardB} 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.

Kansas City Cardiomyopathy Questionnaire (KCCQ)

The 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 T statistic with a two-sided alpha of 0.05. The null (H_0) and alternative (H_A) hypotheses are:

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

H_A: $\Delta_{CardB} \neq \Delta_{Control}$

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

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 T statistic with a two-sided alpha of 0.05. The null (H_0) and alternative (H_A) hypotheses are:

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

H_A: $\Delta_{CardB} \neq \Delta_{Control}$

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

36-Item Short Form 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 T statistic with a two-sided alpha of 0.05. The null (H_0) and alternative (H_A) hypotheses are:

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

H_A: $\Delta_{CardB} \neq \Delta_{Control}$

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

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.[30] The null (H_0) and alternative (H_A) hypotheses are:

H_0: HR = 1

H_A: HR ≠ 1

HR represents hazard rates for Device group relative to Control group, respectively. Two-sided alpha of 0.05 will be used.

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_A) hypotheses are:

H_0: HR = 1

H_A: HR ≠ 1

HR represents hazard rates for Device group relative to Control group, respectively. Two-sided alpha of 0.05 will be used.

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_A) hypotheses are:

H_0: HR = 1

H_A: HR ≠ 1

HR represents hazard rates for Device group relative to Control group, respectively. Two-sided alpha of 0.05 will be used.

13.4.5 Analysis of Additional Secondary Endpoints

Analysis of additional secondary endpoints will be performed using descriptive statistics. Details of these analyses will be provided in the SAP.

13.4.6 Adverse Events Analyses

Adverse events (AE) will be summarized by treatment for the FAS population and mITT and AEs will be summarized by severity and relatedness. Serious AEs will be presented in a listing.

13.4.7 Adherence and Retention Analyses

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

13.4.8 Demographics, Baseline Characteristics, Laboratory and Medication, Medical History, and Procedure Characteristics and Concomitant Medication

Intervention groups should be compared on baseline and procedure characteristics, including demographics and laboratory measurements, using descriptive statistics, as well as change from baseline where appropriate.

13.4.9 Interim Analyses and Safety Monitoring

An interim analysis will be performed for the purpose of sample size re-estimation and will be described in the SAP.

Periodic safety analyses are to be performed during the trial as required by the appropriate regulatory authorities, and under the review the DSMB. Details will be provided in the DSMB charter.

13.5 Determination of Sample Size

Co-primary endpoint I

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 II

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.

All event rates above are conservative estimates based on previous experience with the Edwards Cardioband System, as well as on data on patients with functional mitral regurgitation who underwent catheter based treatment with the CE marked CARILLON® device (Cardiac Dimensions, Kirkland, WA) or the MitraClip® device (Abbott Vascular, Santa Clara, CA) from two registries (Sentinel[1] and ACCESS-EU[2]) and three studies (EVEREST II[3,4], TRAMI[5-7], TITAN[8]).

13.6 Treatment of Missing or Spurious Data

Reasonable efforts will be made to obtain complete data for all patients; however, missing observations 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.

For the purpose of the primary efficacy endpoint no imputation of missing data will be performed. As described in **Section 13.2** the FS analysis considers for each hierarchical level patient pairs with missing data for any one of the patients as ties on that level.

Any missing observations will be described in detail and evaluated for assessment of possible bias. Sensitivity analysis of primary safety and efficacy outcomes will be conducted using methods such as multiple imputation and tipping point analysis. Details will be provided in the SAP.

13.7 Blinding

All analyses of data by the study statistician/programmer will be conducted blinded to treatment assignment (similar to the conduct of a 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.

14 STUDY OVERSIGHT

14.1 Central Screening Committee

A Central Screening Committee (CSC) will be established under the direction of the Sponsor. The role of the CSC is to review key information on patients and establish their final eligibility for participation in the study.

14.2 Clinical Events Committee (CEC)

Independent, non-investigator physicians will form a Clinical Events Committee (CEC) and act as adjudicators under the direction of the Sponsor. This CEC will be responsible for the review and validation of reported adverse events that occur over the course of the study per the CEC Charter. The CEC shall classify each of these adverse events based on severity and association to the device and/or procedure. During the review of events, every effort will be made to keep the CEC blinded to the patient's treatment randomization. A CEC Charter will be developed prior to the start of study enrollment. The CEC Charter shall include consistent definitions for each type of event and shall outline the review process.

14.3 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will be assembled prior to patient enrollment. The DSMB will be comprised of experienced physician practitioners and a biostatistician who are not investigators in the trial.

In the safety monitoring role, the DSMB will establish a charter including a mission statement, operating procedures, and proposed monitoring criteria for the study, including any required interim analysis time points for assessing safety and proposed study stopping rules. Written minutes of all meetings shall be developed after each DSMB meeting and major conclusions (i.e. the assessment for study continuation vs. stopping) shall be documented. Meeting summaries shall be included in reports to the IRB's / EC's as appropriate.

14.4 Echocardiography Imaging Core Laboratory

An independent echocardiographic imaging core laboratory will be utilized for assessment of echocardiograms. Echocardiogram image acquisition shall be performed in accordance with the core laboratory's recommended protocol which is provided to the sites.

14.5 Cardiac CT Core Laboratory

An independent cardiac CT core laboratory will be utilized at the discretion of the Sponsor to supplement assessment of cardiac CT. Cardiac CT acquisition shall be performed in accordance with the core laboratory's recommended protocol which is provided to the sites.

14.6 Economic Data Collection Core Lab

An independent core laboratory will be used for the collection of hospital billing data for patients randomized to treatment with the Cardioband device, and for the conduct of a detailed health economic analysis that will include analysis of index and re-hospitalization characteristics collected during the trial, as well as projection of long-term outcomes in a disease simulation model.

15 Administrative Responsibilities

This clinical trial will be performed in accordance with Good Clinical Practice Guidelines, the Code of Federal Regulations (Title 21 CFR Parts 812, 50, 54, 56; Title 45 CFR Part 46); MDD, ISO 14155, and other local/national regulations as applicable.

15.1 Institutional Review Board (IRB)/ Ethics Committee (EC) Approval

The Clinical Investigational Plan shall be reviewed and approved by FDA and the Investigator's Institutional Review Board/Ethics Committee prior to patient enrollment. All proposed changes to the investigational plan must be reviewed by the Sponsor and/or their authorized agent, prior to implementation. Significant changes to the investigational plan must be approved in writing by the Sponsor, the IRB/EC and FDA/regulatory authority, prior to implementation. A significant change is one which may increase the risk or present a new risk to a patient, or which may adversely affect the scientific validity of the study.

Prior to shipment of the investigational study devices, a signed copy of the IRB/EC approval letter identifying the clinical study and investigational site is required to be submitted to the Sponsor signifying study approval. Investigators are responsible for obtaining and maintaining annual renewal of the study by their IRB/EC (or according to renewal schedule imposed by the IRB/EC). Evidence of renewal and continued IRB/EC approval must be provided to Sponsor or their designee accordingly.

15.2 Informed Consent

If the patient meets all clinical eligibility criteria, the patient (and/or their authorized legal representative) should be approached to obtain written informed consent. The background of the proposed study and the benefits and risks of the procedures and study should be explained to the patient or the patient's legally authorized representative. The patient or patient's legally authorized representative must sign the consent form prior to enrollment. Failure to obtain signed informed consent renders the patient ineligible for the study. All enrolled patients will complete the appropriate consent form that has been approved by the FDA/regulatory authority, the institutional review board (IRB)/ ethics committee (EC) and the Sponsor. Copies of the signed informed consent shall be kept in the patient's medical records and study files. A copy of the informed consent form must be given to each patient (or their authorized legal representative) enrolled in the study.

Modifications to the Informed Consent must have approval from the Sponsor, the IRB/EC, and FDA/regulatory authority as required.

15.3 Confidentiality

All information and data sent to the Sponsor or their authorized designees concerning patients or their participation in this study will be considered confidential. All data used in the analysis and reporting of this evaluation will be used in a manner without identifiable reference to the patient.

The Investigator must assure that the patient's anonymity will be maintained and that the confidentiality of records and documents which could identify patients will be protected, respecting the privacy of and confidentiality rules in accordance with applicable regulatory requirements, including provisions of the Health Insurance Portability and Accountability Act (HIPAA) and its current regulations, as applicable.

- Patients must be identified only by their assigned study number, or and other identifiers as needed and in accordance with local laws, on all CRFs and other records and documents submitted to Sponsor, and other authorised parties.
- The Investigator will keep a Patient Identification List with complete identification information (name, address, contact number, informed consent version number) on each patient.
- Documents not for submission to Sponsor such as patient written informed consent forms should be maintained by the Investigator in strict confidence.

The patient should also be informed about the use of his/ her health information collected during the study (study data). Subject to the same confidentiality obligations as described above, patient data (including, but not limited to, imaging assessments) collected during the course of this investigation may be used in other Edward's research and development efforts.

15.4 Data Monitoring and Quality Control

The Sponsor, or its designee, will monitor and manage the data for the investigational study.

The clinical contact on behalf of the Sponsor will be:

[redacted]

15.4.1 Training

The training of clinical site personnel will be the responsibility of the Sponsor, Edwards Lifesciences.

Device & Procedure Training

The Edwards Cardioband System implantation procedure may only be performed by qualified Investigators, who are familiar with structural heart procedures and techniques. A formal training program consisting of didactic and interactive sessions will be performed with participating investigators, and applicable study personnel identified, at each site prior to patient treatment.

This investigational plan incorporates a roll-in population 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 population will include a maximum of three patients per site who undergo the Edwards CardioBand System procedure.

Sponsor or affiliated personnel shall be available to assist with the technical aspects of the device/procedure. Training will be documented.

Clinical Investigation Training

To ensure uniform data collection and protocol compliance, appointed Sponsor personnel will perform study initiation visits to review the clinical protocol, techniques for the identification of eligible patients, instructions on in-hospital data collection, methods for soliciting data from alternative sources, and schedules for follow-up with study site personnel. Specific training related to the usage of the device and procedure will be provided separately. Training will be documented. It is ultimately the responsibility of the Investigator to ensure all clinical site personnel participating in this trial are trained.

15.4.2 Electronic Case Report Forms

Electronic Case Report Forms (eCRFs) will be used to collect all patient data during the course of the study. eCRFs must be fully completed for each patient and electronically signed by the Investigator when complete.

Federal Regulations and Good Clinical Practice Guidelines require that Investigators maintain information in the study patient's medical records that corroborate data collected on the eCRFs. In order to comply with these regulatory requirements, the following information should be maintained:

- Medical history/physical condition of the study patient before involvement in the study sufficient to verify protocol entry criteria.
- Dated and signed notes on the day of entry into the study including the study investigator, study name, patient number assigned and a statement that consent was obtained.
- Dated and signed notes from each study patient visit with reference to the CRFs for further information, if appropriate (for specific results of procedures and exams).
- Information related to adverse events.
- Study patient's condition upon completion of or withdrawal from the study.
- Discharge summaries/procedure reports.

15.4.3 Data Reporting

The Investigator or designated individual shall be responsible for recording all study data on the electronic case report forms (eCRFs) supplied by Sponsor or their authorized representatives.

The Investigator is required to electronically sign the eCRFs to verify that he/she has reviewed and agrees with the recorded data. All protocol deviations shall be documented and a justification for any missed assessments provided on the Protocol Deviation eCRF.

Completed eCRFs will be verified by the monitor at the investigational sites at regular intervals throughout the study. The Investigator will allow the monitor and/or representative of the Sponsor, and any regulatory body to review and inspect the study files, patient eCRFs, patient medical records and other related study documents as required.

15.4.4 Data Review

eCRFs will be reviewed for completeness and clarity. Missing or unclear data will be investigated by the monitor and will be retrieved, clarified and entered by study personnel as necessary throughout the study. The Sponsor, or their authorized representatives may request additional documentation from the investigator such as physician procedure notes or physician written summaries when adverse events are observed and reported. Adverse events reported during the study shall be adjudicated by the Clinical Events Committee (CEC) per the CEC Charter.

Development of the primary database for the study will be performed by Sponsor or designee. Sponsor or designee will also be responsible for the quality control of the database and confirming the overall integrity of the data.

15.5 Sponsor Record & Report Maintenance

15.5.1 Sponsor Records

The Sponsor must maintain the following records, at a minimum (as specified in 21 CFR Part 812.140 or other national regulations as applicable):

- Clinical protocol and all amendments
- Signed Clinical Study Agreement

- Institutional Review Board/Ethics Committee Approval Letter(s) including IRB/EC-approved informed consent(s) (including any revisions)
- CV for all investigators
- Correspondence relating to this study
- Correspondence with the IRB/EC
- IRB/EC membership list and/or assurance number
- Investigational site authorized study personnel signature list
- Device Instructions for Use
- Lab certification, including a set of the lab's normal range for tests performed
- Printed copy of blank set of CRFs and instructions for completion
- Patient Screening & Enrollment Log
- Site Visit Log (e.g. for Monitor sign-in)
- Insurance certificate (as required)
- Investigational Device Accountability Log with invoices, including: date, quantity, lot numbers of all devices, device returns and identification of all persons the device was used on
- Adverse Event Log
- Reports (includes Adverse Event reports and final reports from Investigator and Sponsor)
- All essential correspondence relating to the trial (including correspondence with another sponsor, a monitor, an investigator, an IRB/EC, or FDA)/regulatory authority.

15.5.2 Sponsor Reports

The Sponsor is responsible for the preparation of reports, the accuracy of the data contained in those reports, the review of and the submission of the reports listed in Table 5 (as specified in 21 CFR Part 812.150, ISO 14155, and other local/national regulations as applicable):

Table 5: Sponsor Reports

Report	Submit to	Description
Unanticipated Adverse (Serious) Device Effects (UADE or USADE)	IRB/EC, Investigators, FDA, and local regulatory agencies, where applicable	Sponsor will report on any confirmed unanticipated adverse device effect evaluation as soon as possible but no later than within 10 working days after first receiving notice of the effect and in compliance with local regulatory requirements, as applicable.
Withdrawal of IRB/EC approval	IRB/EC, Investigators, FDA, and local regulatory agencies, where applicable	Notification, when appropriate, is made within 5 working days after Sponsor receives notice of withdrawal of IRB/EC approval.
Withdrawal of FDA approval	IRB/EC, Investigators	Notification is made within 5 working days after Sponsor receives notice of withdrawal of FDA approval.
Current Investigator List	FDA and local regulatory agencies, where applicable	The Sponsor will submit a current list of the names and addresses of all participating investigators at 6 month interval, beginning 6 months after approval of IDE.
Progress Report	IRB/EC, Investigators, FDA	A progress report is submitted annually.
Recall and Device Disposition	IRB/EC, Investigators, FDA, and local regulatory agencies, where applicable	Notification is made within 30 working days of Sponsor request that an Investigator return, repair or otherwise dispose of any devices. Such

Report	Submit to	Description
		notification will state why the request was made.
Final Report	IRB/EC, Investigators, FDA	Notification is made within 30 working days of the completion or termination of the investigation. A final report is submitted within six months after trial completion or termination.
Failure to obtain Informed Consent	FDA	Notification is made within 5 working days after Sponsor receipt of such notification indicating Informed Consent was not obtained.
Emergency Deviations from Clinical Trial Protocol	FDA, IRB/EC and local regulatory agencies, where applicable	Notification is made within 5 working days after Sponsor learns of an emergency deviation from the Clinical Trial Protocol where the deviation was made to protect the life or physical wellbeing of a patient.
Significant risk device determinations	FDA	Notification is made within 5 working days after the sponsor first learns of the IRB's determination

A Sponsor shall, upon request by a reviewing IRB/EC or FDA/regulatory authority, provide accurate, complete, and current information about any aspect of the investigation.

The Sponsor may delegate all or some of these responsibilities.

15.6 Investigator Record & Report Maintenance

The Principal Investigator (or designee)/Institution should maintain the trial documents as specified in ISO 14155, 21 CFR Part 812.140 or as required by applicable regulatory requirement(s). The Principal Investigator (or designee)/Institution should take measures to prevent accidental or premature destruction of these documents.

15.6.1 Investigator Records

The Principal Investigator (or designee) must maintain the following records for each patient enrolled in the study:

- Signed patient consent form(s)
- Copy of final completed eCRFs
- All lab and testing results
- Record of any complications, adverse events, device deficiencies and/or malfunctions, with supporting documentation
- Procedure reports, progress notes, physician and/or nursing notes, and patient office files
- Records pertaining to patient deaths throughout the course of the study (including death records, death certificate and autopsy report, if performed)
- Any other records that FDA/regulatory authority or ISO 14155 requires to be maintained by regulation or by specific requirement for a category of investigations or a particular investigation.

15.6.2 Investigator Reports

Investigators are required to prepare and submit the following complete, accurate and timely reports on this clinical investigation as applicable (see Table 6).

Table 6: Investigator Responsibilities for Preparing and Submitting Reports

Type of Report	Prepared by Investigator for	Time of Notification
Case Report Forms	Sponsor or designee	Within 14 working days
Serious/ Unanticipated Adverse Event	Sponsor/designee	Within 3 calendar days of knowledge or as required by IRB/EC
Serious/ Unanticipated Adverse Event	IRB/EC and FDA/regulatory authority (as required)	Within 10 working days or as required by IRB/EC
Adverse Event (device related or not)	Sponsor/designee	Within 7 calendar days

Type of Report	Prepared by Investigator for	Time of Notification
Adverse Event (device related or not)	IRB/EC and FDA/regulatory authority (as required)	Within 10 working days or as required by IRB/EC
Device deficiency or observation/malfunction	Sponsor or designee	Within 2 calendar days of knowledge or as required by IRB/EC
Patient death during the course of the study	Sponsor/designee, IRB/EC	Within 3 calendar days of knowledge or as required by IRB/EC
Patient withdrawal	Sponsor or designee	Within 24 hours of knowledge
Withdrawal of IRB/EC or FDA/regulatory authority approval	Sponsor or designee	Within 24 hours of knowledge
Deviations from the investigational protocol	Sponsor/designee, IRB/EC	Within 24 hours of occurrence or knowledge
Medical Emergencies	Sponsor/designee, IRB/EC and FDA/regulatory authority	Within 24 hours of occurrence
Informed consent not obtained	Sponsor/designee, IRB/EC	Within 24 hours of knowledge
Final summary report	Sponsor/designee, IRB/EC and FDA/regulatory authority	Within 3 months of study completion
Other information upon the request of Sponsor, IRB/EC and/or FDA/regulatory authority	As appropriate	As requested

15.7 Investigator Record Retention

Investigator files containing all records and reports of the investigation should be retained for a minimum of two (2) years after the completion/ termination of the investigational study, or as required by applicable regulations. They may be discarded upon written notification by the Sponsor. To avoid error, the Principal Investigator

should contact Sponsor, before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained.

In addition, in accordance with the Clinical Study Agreement, the Sponsor should be contacted if the Principal Investigator plans to leave the investigational site so that appropriate arrangements for file custodianship can be made.

15.8 Investigator's & Sponsor's Annual & Final Reports

Each year an annual summary report shall be prepared by the Investigator which provides a summary of the number of patients treated to date as well as other pertinent clinical information associated with the investigational procedure. The annual report is required to be provided to the IRB/EC and the Sponsor or their authorized agent.

The Sponsor or their designee will be responsible for preparing a compilation of all of the participating site results for submittal as an annual progress report to the FDA/regulatory authority.

Upon completion and/or termination of the study a final report shall be prepared. This report will contain a critical evaluation of all data collected during the course of the investigation at each institution. The Sponsor or its designee is responsible for preparing this compilation to Investigators for submittal as a final report to their reviewing IRB/EC. The Sponsor or its designee will also provide this final report to FDA/regulatory authority.

15.9 Investigational Site Monitoring

The Sponsor is responsible for monitoring the safety and effectiveness of this study. The Sponsor may utilize the services of a CRO or independent contractors to facilitate the monitoring process. The study will be monitored according to applicable provisions of Sponsor's or designee's clinical monitoring procedures and in compliance with Title 21 CFR Part 812 or other applicable national regulations.

15.10 Deviations from Clinical Protocol & Medical Emergencies

The Investigator will not deviate from the clinical protocol without the prior written approval of Sponsor except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the patient's risk or affect the validity of the study. In medical emergencies, prior written approval for protocol

deviations will not be required, but Sponsor or their designee must be notified within 24 hours of occurrence.

15.11 Investigational Site Termination

The Sponsor reserves the right to terminate an investigational site from the study for any of the following reasons including, but not limited to:

- Failure to obtain Informed Consent
- Failure to report Serious Adverse Events in a timely manner (e.g. within 24 hours of knowledge)
- Repeated protocol violations
- Repeated failure to complete Case Report Forms
- Failure to enroll an adequate number of patients

16 Publication Policy

[redacted]

APPENDIX A: CLINICAL RISK/ BENEFIT ANALYSIS

Edwards Lifesciences

Protocol Number: 2017-05

Clinical Risk/ Benefit Analysis

1.0 SUMMARY

The objective of this clinical trial is to evaluate the safety and efficacy of the Edwards Cardioband System for transcatheter mitral annular reduction in treating patients with functional mitral regurgitation.

Risks to patients undergoing the Edwards Cardioband System procedure are listed below. The risks of participation are offset by the significant potential for clinical and functional benefits to patients with functional mitral regurgitation that comes through improving mitral valve function.

2.0 POTENTIAL BENEFITS

The potential benefit to study patients outweighs the risks of participation in this study. The benefits may include but are not limited to, the following:

- Clinical improvement (e.g. NYHA Class, 6 minute walk test)
- Functional improvement (e.g. mitral valve function)
- Overall advancement of medical and scientific knowledge which may benefit future patients with similar conditions may be gained through this clinical study.

There may also be other benefits that are unforeseen at this time.

3.0 POTENTIAL RISKS

Adverse events that are anticipated in this clinical study are believed to be consistent with those associated with other minimally invasive surgical and catheter-based procedures. Complications may occur at any time during the procedure, post-procedure or follow-up period.

Anticipated or potential adverse events that may occur during the study are listed in Table 7. These events may be associated with the Edwards Cardioband System, transcatheter procedure, stress-induced tests (e.g. TEE, TTE, MSCT scan, exercise tolerance, etc.), ancillary procedures or may occur in the heart failure population over time. Possible outcomes of the adverse events include reoperation, explant of the Edwards Cardioband, permanent disability or death. There may also be other risks that are unforeseen at this time.

Table 7: Anticipated or Potential Adverse Events

Abnormal laboratory values (e.g. electrolyte imbalance)
Allergic reaction/hypersensitivity to contrast media, medication, or device materials
Anaphylactic shock
Anemia including hemolytic anemia
Anesthesia reactions
Angina pectoris
Arrhythmias and conduction system disorders (e.g. ventricular or atrial tachycardia or fibrillation; AV block) which may require permanent pacemaker implantation
Atrial septal defect requiring intervention
Bleeding
Cardiac arrest
Cardiac Tamponade
Cardiogenic shock
Cardiovascular injury (e.g. damage of ventricle, ventricular septal perforation, myocardium or valvular structures including annulus rupture)
Cerebrovascular event (e.g. TIA, Stroke, neurologic changes)
Circumflex Artery Occlusion
Circumflex Artery Perforation
Conversion to an open cardiac surgery, including extracorporeal circulation
Coronary Artery Occlusion
Coronary Artery Perforation
Death
Deep venous thrombus (DVT)
Device associated endocarditis
Device dehiscence

Device embolization, migration, malposition, or deployment in unintended location
Device explantation
Device malfunction/ mechanical failure of device, delivery system and/or accessories
Device thrombosis
Dyskinesia, paralysis, permanent disability (new onset or worsening)
Dyspnea
Edema
Emboli/ Embolization (e.g. air, calcific material, thrombus)
Esophageal irritation or injury (e.g. perforation)
Exercise intolerance or weakness
Failure of the valvular apparatus due to progression of disease
Failure to deliver the device to the intended site
Fever
Groin hematoma
Heart failure or low cardiac output
Heart murmur
Hematoma
Hemodynamic compromise
Hemolysis
Hemorrhage
Hospitalization for heart failure
Hypertension
Hypotension
Implantation of second transcatheter mitral repair device
Implantation of surgical annuloplasty device
Inadequate repair of the valvular structure
Infection including endocarditis and septicemia
Inflammation
Mitral stenosis
Mitral valve injury, or worsening of mitral regurgitation
Multi-system organ failure
Myocardial infarction
Nausea/vomiting
Nerve injury
Non-structural device dysfunction (e.g., regurgitation)
Pain

Perforation or damage of vessels or tissue, myocardium or valvular structures
Pericardial effusion, may require drainage
Peripheral edema
Peripheral ischemia
Pleural effusion
Pneumonia
Prolonged ventilation
Pulmonary edema
Pulmonary embolism
Renal insufficiency or failure
Re-operation or emergency cardiac surgery
Respiratory compromise or respiratory failure
Retroperitoneal bleeding
Right heart failure
Stroke
Structural deterioration or degeneration of device (e. g. tear, suture line disruption, breakage, wear, calcification, anchor detachment)
Syncope or dizziness
Thrombus formation
Transvalvular flow disturbance
Vascular access (e.g. femoral entry site) complications (e.g. bleeding, hematoma, arteriovenous fistula, arterial occlusion, pseudoaneurysm, wound healing disorder, pain)
Vascular damage (e.g. perforation, dissection, contrast media extravasation, spasm)
Vessel spasm
Worsening heart failure symptoms

4.0 MINIMIZATION OF RISKS

Measures which will be taken to minimize risks related to the study include:

- Investigators in this study will be selected based on their experience in treating patients with mitral regurgitation and performing structural heart interventional procedures.

- Investigators will be trained in proper procedure performance and device operation prior to patient treatments. Training will include didactic and hands-on training with the Edwards Cardioband System.
- Well-defined clinical study protocol, including specific inclusion/ exclusion criteria to enroll appropriate patients in the trial.
- A Central Screening Committee (CSC) ensures final eligibility of patients for participation in the study.
- Close patient monitoring during the implant procedure and follow-up period.
- Ongoing monitoring of study data and results, including the use of independent Clinical Events Committee (CEC) and Data Safety Monitoring Board (DSMB).

5.0 CONCLUSION

This clinical study is justified because the study Sponsor and clinical Investigators believe the potential benefits outweigh the potential risks.

APPENDIX B: STUDY DEFINITIONS

Endpoints identified in the Clinical Events Committee (CEC) Charter will be adjudicated by the independent Clinical Events Committee. A detailed CEC Charter will further define the endpoint definitions. In case of inconsistency between the protocol and the CEC Charter, the CEC Charter will be the final determining document.

ACCESS SITE

Any location (arterial or venous) traversed by a guide-wire, a catheter or a sheath.

ACCESS SITE AND VASCULAR COMPLICATIONS REQUIRING INTERVENTION

Complications (i.e. dissection, perforation, arteriovenous fistula, pseudoaneurysm, retroperitoneal hemorrhage, thromboembolism etc.) requiring intervention (percutaneous or surgical).

ATRIAL FIBRILLATION (AF) – Heart Rhythm Society Guidelines

Paroxysmal: Recurrent (≥ 2) atrial fibrillation episodes that terminate spontaneously within 7 days.

Persistent: Atrial fibrillation that is sustained beyond 7 days, or lasting less than 7 days but necessitating pharmacologic or electrical cardioversion.

Longstanding Persistent AF: Continuous atrial fibrillation of greater than 1 year duration.

Permanent: Atrial fibrillation in which cardioversion has failed or not been attempted.

BLEEDING (MVARC)

Minor

Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that meets ≥ 1 of the following: requiring nonsurgical medical intervention by a health care professional; leading to hospitalization or increased level of care; prompting evaluation; or requires 1 or 2 units of whole blood or packed red blood cell (RBC) transfusion and otherwise does not meet criteria for major, extensive, or life threatening.

Major bleeding

Overt bleeding either associated with a drop in the hemoglobin level of ≥ 3.0 g/dl or requiring transfusion of ≥3 units of whole blood or packed RBC AND does not meet the criteria of life-threatening or extensive bleeding.

Extensive

Overt source of bleeding with drop in hemoglobin of ≥ 4 g/dl or whole blood or packed RBC transfusion

Life-threatening

Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating surgery or intervention, or intramuscular with compartment syndrome OR bleeding causing hypovolemic shock or hypotension (systolic blood pressure < 90 mm Hg lasting > 30 min and not responding to volume resuscitation) or requiring significant doses of vasopressors or surgery.

Fatal bleeding

Bleeding adjudicated as being a proximate cause of death. Severe bleeding adjudicated as being a major contributing cause of a subsequent fatal complication, such as MI or cardiac arrest, is also considered fatal bleeding.

CARDIOVASCULAR DEATH (MVARC)

Cardiovascular death is defined as any of the following contributing conditions:

- Heart failure (sub-classified into left ventricular vs. right ventricular dysfunction)
- Myocardial infarction
- Major bleeding
- Thromboembolism
- Stroke
- Arrhythmia and conduction system disturbance
- Cardiovascular infection and sepsis (e.g., mediastinitis and endocarditis)
- Tamponade
- Sudden, unexpected death
- Other cardiovascular
- Device failure

- Death of unknown cause (adjudicated as cardiovascular)

Non cardiovascular Death (MVARC)

Any death in which the primary cause of death is clearly related to another condition:

- Non cardiovascular infection and sepsis (e.g., pneumonia)
- Renal failure
- Liver failure
- Cancer
- Trauma
- Homicide
- Suicide
- Other noncardiovascular

FUNCTIONAL MITRAL REGURGITATION

Mitral regurgitation (≥3+ must be present for inclusion) accompanied by global or regional left ventricular wall motion abnormalities AND dilatation of the mitral annulus, with no significant abnormalities of the mitral apparatus, except mild focal thickening thought to be related to aging. No leaflet flail or other evidence of degenerative MR may be present, even in the presence of global or regional LV systolic dysfunction.

HEART TEAM

The local "Heart Team" (in accordance with MVARC) will consist of a multidisciplinary team which will assess the appropriateness of the patient for the protocol and as a minimum will consist of a heart failure/valve cardiologist, an interventional cardiologist skilled in the relevant access and device implantation procedures, a mitral valve cardiac surgeon and an imaging specialist.

HOSPITALIZATION (ALL-CAUSE)

Defined as admission to inpatient unit or ward in the hospital for ≥ 24 hours, including emergency department stay. Hospitalizations planned for pre-existing conditions are excluded unless there is worsening of baseline condition.

HEART FAILURE HOSPITALIZATION

Both of the following additional criteria are present:

- Symptoms, signs and/or laboratory evidence of worsening heart failure
- Administration of intravenous or mechanical heart failure therapies

Patients hospitalized with heart failure are further sub-classified as:

- Primary heart failure hospitalization, including heart failure secondary to other cardiac related hospitalization such as for myocardial infarction.
- Secondary heart failure hospitalization - heart failure has occurred during an otherwise non-cardiac related hospitalization.

OTHER CARDIOVASCULAR HOSPITALIZATION

Including hospitalizations such as for coronary artery disease, acute myocardial infarction, hypertension, cardiac arrhythmias, cardiomegaly, pericardial effusion, atherosclerosis, stroke, or peripheral vascular disease without qualifying heart failure.

NON-CARDIOVASCULAR HOSPITALIZATION

Hospitalizations that are not due to heart failure or other cardiovascular hospitalizations, as defined above.

LEFT CIRCUMFLEX ARTERY INJURY REQUIRING INTERVENTION

Injury to the left circumflex (LCX) artery which requires intervention may include occlusion, perforation, laceration, dissection, ligation, suture or anchor misplacement. Other potential causes may include a thrombus or hematoma formation due to surgical trauma. Vasospasm of the LCX artery is excluded in this definition unless it requires percutaneous intervention.

MITRAL VALVE STENOSIS

Defined as a mitral valve orifice area of less than 1.5 cm^2 as measured by the Echocardiography Core Laboratory.

MYOCARDIAL INFARCTION

Myocardial infarction (MI) classification and criteria for diagnosis is defined as follows:[31]

1. Peri-procedural MI (≤ 48 hours after Edwards Cardioband System procedure)

1.1. In patients with normal baseline CK-MB (or cTn):

Peak Creatinine Kinase myocardial b fraction (CK-MB) measured within 48 hours of Edwards Cardioband System implantation rises to ≥10x of the local laboratory upper limit of normal (ULN) *plus* new ST-segment elevation or depression of ≥1 mm in ≥ 2 contiguous leads (measured 80 ms after the J-point) or to ≥5x ULN with new pathological Q waves in ≥2 contiguous leads or new persistent LBBB.

1.2. In patients with elevated baseline CK-CB (or cTn):

The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level *plus* new ECG changes as described above.

1.3. In patients without CK-MB measurements and a normal baseline cTn,

A Cardiac Troponin (cTn (I or T)) level measured within 48 h of the PCI rises to ≥70x the local laboratory ULN *plus* new ST-segment elevation or depression of ≥1 mm in ≥ 2 contiguous leads (measured 80 ms after the J-point) OR ≥ 35x ULN with new pathological Q waves in ≥ 2 contiguous leads or new persistent LBBB.

2. Spontaneous MI (> 48 hours after Edwards Cardioband System procedure)

Detection of rise and/or fall of cardiac biomarkers (preferably cTn) with at least one value above the 99th percentile of the upper reference limit (URL) or ULN in the absence of URL, together with at least one of the following:

2.1. Symptoms of ischemia

2.2. ECG changes indicative of new ischemia (new ST – segment or T- wave changes or new LBBB) or new pathological Q waves in 2 contiguous leads

2.3. Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

3. MI associated with sudden, unexpected cardiac death

Sudden cardiac death or cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST-segment elevation or new LBBB and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurs before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood.

4. Pathological findings of an acute myocardial infarction

MODIFIED RANKIN SCALE SCORE DESCRIPTIONS

0: No symptoms at all

1: No significant disability despite symptoms; able to carry out all usual duties and activities

2: Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance

3: Moderate disability; requiring some help, but able to walk without assistance

4: Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance

5: Severe disability; bedridden, incontinent and requiring constant nursing care and attention

6: Dead

NEW YORK HEART ASSOCIATION CLASSIFICATION (NYHA CLASS)

Class I	Patients with cardiac disease but without resulting limitations of physical activity.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. Patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. Patients are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

PERICARDIAL EFFUSION REQUIRING DRAINAGE

Major pericardial effusion requiring drainage, also known as cardiac tamponade (CT) is a life-threatening, slow or rapid compression of the heart due to the pericardial accumulation of fluid, pus, blood, clots or gas as a result of inflammation, trauma, rupture of the heart, aortic dissection or iatrogenic causes (invasive procedure-related).[32] Cardiac tamponade meets the MVARC definition for device-related technical failure issues and complications and the MVARC definition for life threatening bleeding in a critical organ.[31]

REINTERVENTION

Any intervention on the previously implanted study device (repair, alteration or replacement)

STROKE and TIA

Acute episode of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke.

Cases will be categorized as either

1) Stroke – Duration of a focal or global neurological deficit ≥24 hours; OR <24 hours, if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death

2) TIA – Duration of a focal or global neurological deficit <24 hours, any variable neuroimaging does not demonstrate a new hemorrhage or infarct

Stroke classification

Ischemic – An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue

Hemorrhagic – An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage

A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic

Stroke definitions

Disabling stroke – a mRS score of 2 or more at 90 days and an increase of at least one mRS category from an individual's pre-stroke baseline

Non-disabling stroke – a mRS score of less than 2 at 90 days or one that does not result in an increase of at least one mRS category from an individual's pre-stroke baseline

Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence of cerebral infarction based upon neuroimaging studies (CT scan or Brain MRI).

RENAL COMPLICATIONS (Long-Term)

Long-term Renal Complication is defined as onset of renal replacement therapy

ACCESS SITE AND VASCULAR COMPLICATIONS (MVARC)

I. Vascular complications

A. Major access site vascular complications, including:

i. Aortic dissection or aortic rupture, or

ii. Access site-related† arterial or venous injury (dissection, stenosis, ischemia, arterial, or venous thrombosis including pulmonary emboli, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, retroperitoneal hematoma, atrial septal defect‡), irreversible nerve injury, or compartment syndrome resulting in death; hemodynamic compromise; life-threatening, extensive, or major bleeding (MVARC bleeding scale); visceral ischemia; or neurological impairment, or

iii. Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage, or

iv. Unplanned endovascular or surgical interventions resulting in death; life-threatening, extensive, or major bleeding (MVARC bleeding scale); visceral ischemia; or neurological impairment

B. Minor access site vascular complications, including:

i. Access site arterial or venous injury (dissection, stenosis, arterial, or venous thrombosis including pulmonary emboli, ischemia, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, retroperitoneal hematoma, atrial septal defect‡) not resulting in death; life-threatening, extensive, or major bleeding (MVARC scale); visceral ischemia; or neurological impairment, or

ii. Distal embolization treated with embolectomy and/or thrombectomy not resulting in amputation or irreversible end-organ damage, or

iii. Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication, or

iv. Vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)

II. Cardiac structural complications due to access-related issues

A. Major cardiac structural complications, including:

i. Cardiac perforation* or pseudoaneurysm resulting in death, life-threatening bleeding, hemodynamic compromise, or tamponade, or requiring unplanned surgical or percutaneous intervention

B. Minor cardiac structural complications, including:

i. Cardiac perforation* or pseudoaneurysm not meeting major criteria

**Including the left ventricle, left atrium, coronary sinus, right atrium, and right ventricle*

†May arise from the access procedure per se or complications from vascular closure devices

‡Meeting pre-specified criteria for a hemodynamically significant shunt, or requiring unplanned percutaneous or surgical closure

APPENDIX C: ECONOMIC DATA COLLECTION CORE LAB

An independent core laboratory will be used for the collection of hospital billing data for patients randomized to treatment with the Cardioband device, and for the conduct of a detailed health economic analysis that will include analysis of data collected during the trial, as well as projection of long-term outcomes in a disease simulation model. This study component aims to collect bills, along with other data, to evaluate the economic value of the Cardioband ACTIVE trial intervention arm versus control group. Under no circumstances will billing data from any single patient or institution be identified or shared with any outside party.

Economic Data Collection

The ACTIVE trial will include a prospectively planned health economic study component designed to assess the potential health economic value of the Cardioband intervention arm versus the control arm. Throughout this trial, Baim Institute will be acting on behalf of Edwards to obtain and analyze copies of subject hospital bills for patients treated with the Cardioband system (roll-ins and patients randomized to Cardioband). Specifically, Baim Institute will be seeking a UB-04 Summary bill and an Itemized Bill for each initial hospitalization. Bills will not be collected for patients randomized to the control group, since they are not automatically hospitalized.

Detailed resource utilization data, including information on all hospitalizations and residential care services will be collected on all study patients. In addition, patients randomized to the Cardioband procedure who are willing to participate in the economic study will provide separate, written consent for the collection of hospital billing data for the admission during which the Cardioband procedure is performed.

“In-trial” health care costs will be calculated for all study patients using a combination of resource-based and cost-accounting methods. The cost of index hospitalizations for Cardioband procedures will primarily be derived from the collected hospital billing data. The costs of follow-up hospitalizations will be estimated on the basis of measured data regarding those admissions, and national reimbursement for similar clinical events. If there are important differences in medical therapy observed between the groups during the trial, these may be considered, if the clinical data allow. A long-term health economic model comparing the cost-effectiveness of Cardioband to medical therapy in the study population will then be constructed. The preferred horizon for the model will be lifetime.

The long-term health economic model will combine empirical data on costs, survival and quality of life from the initial 12-month in-trial period, combined with long-term projections of those same parameters. Projections of survival will be uncertain given the size and duration of the study and varied survival functions and assumptions will need to be explored in scenario and sensitivity analysis. Projections of long-term quality of life and health care costs will be derived from in-trial data, where possible, supplemented with estimates from external literature (e.g. from patients with functional mitral regurgitation treated in other trials) as needed. Plausible ranges for all important model parameters will be estimated and the impact of variation in those parameters will be assessed with appropriate sensitivity analyses.

Billing Data Collection

Bills will need to be collected from your hospital billing department, and sent to the EQOL Group at the Baim Institute. A separate Medical Billing Release (MBR) Form from Baim Institute will be provided along with the site's Informed Consent Form. We request the Study Coordinators fax or email a copy of the MBR form to the Baim Institute team and mail the original MBR form to Baim Institute.

Sites will scan & email or fax bills using the information listed below. The MBR form and bills will arrive at Baim Institute through a secure system used for the transmission of source documents for many clinical trials. All billing data will be completely de-identified by the EQOL Group at Baim Institute immediately upon receipt. This billing information will be handled in a strictly confidential manner and used only for research purposes. No hospital name or subject identifiers will be disclosed or used in any format in reports or publications generated with these data.

[redacted]

APPENDIX D: INSTRUCTIONS FOR THE SIX MINUTE WALK TEST

The patient should be instructed to sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts.

The assessors will instruct the patient as follows per ATS 2002 Guidelines for the Six Minute Walk Test:

“The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I’m going to show you. Please watch the way I turn without hesitation.”

Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

“Are you ready to do that” I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don’t run or jog. Start now, or whenever you are ready.”

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