

		<b>Clinical Investigation Plan</b>	<b>Protocol # CP 18-01 Rev. C</b>
--	--	--	---

## CARDIOVALVE

### CLINICAL INVESTIGATION PLAN

#### EARLY FEASIBILITY STUDY OF THE CARDIOVALVE SYSTEM FOR MITRAL REGURGITATION (AHEAD)

Protocol Number: CP 18-01  
Revision C

Effective Date:

US SPONSOR

AUG 08 2019

Initials TB Date 05 Aug 2019

Boston Biomedical Associates  
100 Crowley Dr., Suite 216  
Marlborough, MA 01752

MANUFACTURER

Cardiovalve Ltd.

Terminal Center, 1 Yahadut Canada St., Or Yehuda 6037501, Israel

#### CONFIDENTIAL MATERIAL:

THIS DOCUMENT IS THE PROPERTY OF THE SPONSOR AND IS CONFIDENTIAL AND PROPRIETARY. THE INFORMATION CONTAINED HEREIN IS BELIEVED TO BE ACCURATE AND COMPLETE AS OF THE DATE OF PREPARATION. THE CONTENTS OF THIS DOCUMENT MAY NOT BE REPRODUCED WITHOUT PRIOR EXPRESSED CONSENT BY THE SPONSOR.

**INVESTIGATOR AGREEMENT - SIGNATURE PAGE**

The signature below constitutes the approval of this CIP/Protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable regulations and ICH guidelines.

Investigational Site Name: \_\_\_\_\_

Investigator Designation (please select as appropriate):

☐ Principal Investigator  
Investigator

☐ Physician Sub-Investigator

☐ Non-Physician Sub-

Investigator Name (*Print*): \_\_\_\_\_

Investigator Signature: \_\_\_\_\_

Date of Signature (*DD-Month-YYYY*): \_\_\_\_\_

**PRINCIPAL CONTACTS*****US Sponsor:***

Boston Biomedical Associates  
Lauren Baker, PhD President and CEO\_  
[lbaker@boston-biomedical.com](mailto:lbaker@boston-biomedical.com)  
Office: 508-351-8632 ext. 201

***Manufacturer***

Cardiovalve Ltd.  
Terminal Center, 1 Yahadut Canada St., Or Yehuda  
6037501, Israel  
Phone: +972 76 5396000  
Fax: +972 76 5396001

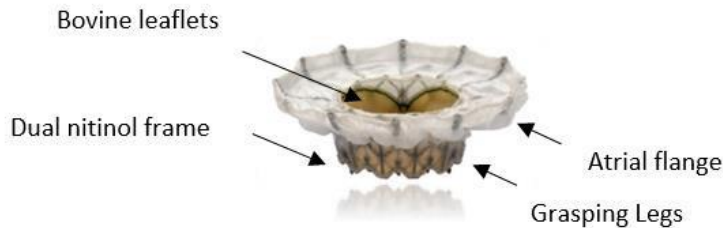
## TABLE OF CONTENTS

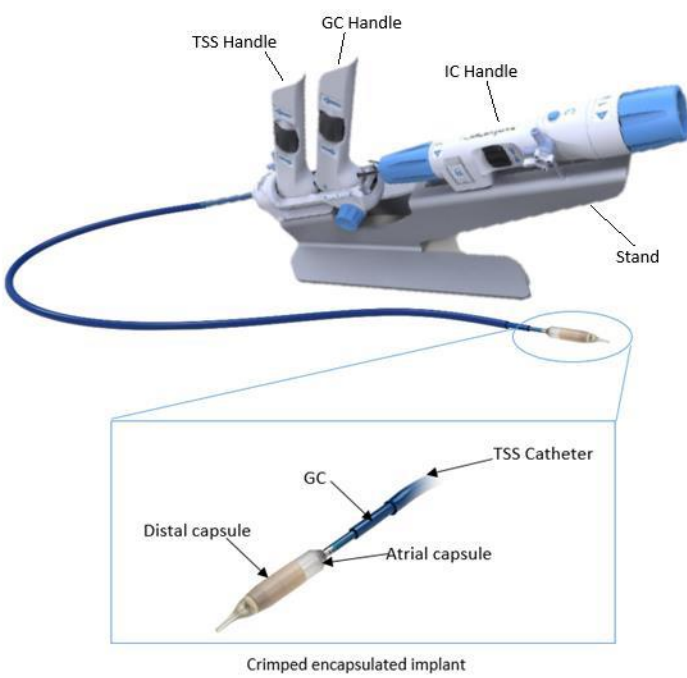
<b>1</b>	<b>SYNOPSIS.....</b>	<b>7</b>
<b>2</b>	<b>INTRODUCTION .....</b>	<b>14</b>
2.1	CLINICAL NEED .....	14
2.2	TREATMENT GUIDELINES.....	14
2.3	DEVELOPMENT OF TRANSCATHETER MITRAL VALVE INTERVENTIONS .....	15
2.3.1	<i>Cardiovalve Solution</i> .....	16
2.3.2	<i>The Unique Features of the Product</i> .....	16
2.4	CARDIOVALVE INNOVATION .....	17
<b>3</b>	<b>INVESTIGATIONAL DEVICE DESCRIPTION.....</b>	<b>17</b>
3.1	THE CARDIOVALVE IMPLANT .....	19
3.2	THE CARDIOVALVE DELIVERY SYSTEM (DS) .....	20
3.3	THE CARDIOVALVE ACCESSORIES .....	23
3.4	VALVE SIZES .....	24
3.5	DEVICE MATERIALS.....	25
3.6	IMPLANT PROCEDURE .....	25
<b>4</b>	<b>RISK BENEFIT ANALYSIS.....</b>	<b>26</b>
4.1	ANTICIPATED CLINICAL BENEFITS.....	26
4.2	ANTICIPATED OR POTENTIAL ADVERSE EVENTS.....	28
4.3	POTENTIAL ADVERSE EVENTS IN TRANSCATHETER MITRAL REGURGITATION TRIALS .....	29
4.4	RISK ANALYSIS AND RISK MITIGATION .....	31
4.5	RISK TO BENEFIT RATIONALE .....	32
<b>5</b>	<b>OBJECTIVES OF THE CLINICAL INVESTIGATION .....</b>	<b>33</b>
5.1	PRIMARY PERFORMANCE ENDPOINT.....	33
5.2	PRIMARY SAFETY ENDPOINT .....	33
5.3	SECONDARY PERFORMANCE ENDPOINTS .....	33
<b>6</b>	<b>STUDY DESIGN .....</b>	<b>34</b>
6.1	STUDY DURATION .....	34
6.2	STUDY POPULATION .....	34
6.2.1	<i>Inclusion Criteria</i> .....	35
6.2.2	<i>Exclusion Criteria</i> .....	35
<b>7</b>	<b>PROCEDURES AND METHODS.....</b>	<b>37</b>
7.1	TRAINING OF INVESTIGATIONAL CENTER PERSONNEL.....	37
7.2	SUBJECT SCREENING.....	37
7.3	SUBJECT ENROLMENT.....	37
7.4	ELEVATED RISK FOR OPEN-HEART SURGERY CRITERIA.....	38
<b>8</b>	<b>MEDICATION AND STUDY VISITS.....</b>	<b>38</b>
8.1	GUIDELINE DIRECTED HF THERAPY .....	39
8.2	SCREENING/BASELINE EVALUATION (DAY -45 TO 0) .....	40

8.3	IMPLANT PROCEDURE .....	41
8.4	FOLLOW-UP EVALUATION.....	42
8.4.1	Post-procedure follow-up .....	42
8.4.2	Discharge.....	43
8.4.3	30 Days, 3-Months, 6-Months Post-Procedure.....	43
8.4.4	30 Days, 12-Months Post-Procedure.....	43
8.4.5	30 Days, 6-Months, 12 Months Post-Procedure, Annually for a total of 5 years Post-Procedure.....	43
8.4.6	6-Months, 12 Months Post-Procedure, Annually for a total of 5 years Post- Procedure.....	43
8.4.7	30 Days, 3-Months, 6-Months, 12 Months Post-Procedure, Annually for a total of 5 years Post- Procedure .....	43
8.5	SCHEDULES OF TREATMENTS AND ASSESSMENTS.....	45
<b>9</b>	<b>ADVERSE EVENTS.....</b>	<b>47</b>
9.1	GENERAL ADVERSE EVENT DEFINITIONS .....	47
	<i>SERIOUS ADVERSE EVENTS</i> .....	47
	<i>Unanticipated Serious Adverse Device Effect</i> .....	47
9.2	ADVERSE EVENT CLASSIFICATION.....	48
9.3	ADVERSE EVENT SEVERITY .....	49
9.4	EVENTS EXPECTED TO OCCUR WITH CARDIOVALVE INDEX-PROCEDURE .....	49
9.5	ADVERSE EVENT REPORTING REQUIREMENTS.....	50
9.5.1	General Reporting Requirements (Non-Serious Adverse Events).....	50
9.5.2	Reporting Requirements (Serious Adverse Events).....	51
9.6	SUBJECT DEATH.....	52
9.7	TREATMENT FAILURES & DEVICE MALFUNCTIONS .....	52
9.8	SPONSOR REPORTING.....	52
<b>10</b>	<b>STATISTICAL CONSIDERATIONS.....</b>	<b>52</b>
10.1	STATISTICAL OVERVIEW.....	52
10.2	ANALYSIS POPULATION .....	52
10.3	INTERIM AND FINAL ANALYSES .....	53
10.4	TREATMENT OF MISSING OR SPURIOUS DATA .....	53
<b>11</b>	<b>DATA HANDLING AND RECORD KEEPING.....</b>	<b>53</b>
11.1	DATA MANAGEMENT PROCEDURES.....	54
11.2	DATA RETENTION .....	54
11.3	INVESTIGATOR RECORDS .....	54
<b>12</b>	<b>INVESTIGATOR REPORTS.....</b>	<b>56</b>
<b>13</b>	<b>QUALITY CONTROL AND ASSURANCE.....</b>	<b>57</b>
13.1	SITE AND INVESTIGATOR SELECTION.....	57
13.2	INVESTIGATOR RESPONSIBILITIES.....	57
13.3	PROTOCOL DEVIATIONS.....	58
13.4	PROTOCOL DEVIATION PROCESS .....	59
13.5	CORRECTIVE/PREVENTIVE ACTION.....	59
<b>14</b>	<b>STUDY OVERSIGHT .....</b>	<b>59</b>
14.1	SUBJECT SCREENING COMMITTEE .....	59

14.2	CLINICAL EVENTS COMMITTEE (CEC)	59
14.3	DATA MONITORING COMMITTEE	60
14.4	ECHOCARDIOGRAPHIC CORE LABORATORY	60
<b>15</b>	<b>ETHICS/PROTECTION OF HUMAN SUBJECTS</b>	<b>60</b>
15.1	STATEMENTS OF COMPLIANCE	60
15.2	INSTITUTIONAL REVIEW BOARD (IRB)	61
15.3	INFORMED CONSENT PROCESS	61
15.3.1	<i>Subject Unable to Read or Write</i>	61
15.3.2	<i>New Information</i>	62
15.4	SUBJECT CONFIDENTIALITY	62
<b>16</b>	<b>CLINICAL INVESTIGATIONAL PLAN/PROTOCOL AMENDMENTS</b>	<b>62</b>
<b>17</b>	<b>TERMINATION OF STUDY OR STUDY SITE PARTICIPATION</b>	<b>62</b>
<b>18</b>	<b>PUBLICATION POLICY</b>	<b>63</b>
<b>19</b>	<b>BIBLIOGRAPHY</b>	<b>63</b>
<b>20</b>	<b>APPENDIX 1: ACRONYMS</b>	<b>65</b>
<b>21</b>	<b>APPENDIX 2: GENERAL DEFINITIONS OF ADVERSE EVENTS</b>	<b>68</b>
<b>22</b>	<b>APPENDIX 3: DEFINITIONS OF ADVERSE EVENT ACCORDING TO MVARC</b>	<b>78</b>
<b>23</b>	<b>APPENDIX 4: GUIDELINES FOR SURGICAL RISK ASSESSMENT IN MR</b>	<b>85</b>

## 1 SYNOPSIS

<b>Study Title</b>	Early Feasibility Study of the Cardiovalve System for Mitral Regurgitation (AHEAD)
<b>ID/Rev.</b>	CP 18-01, Rev. C
<b>US Sponsor</b>	Boston Biomedical Associates 100 Crowley Drive, Suite 216 Marlborough, MA 01752
<b>Manufacturer</b>	Cardiovalve Ltd. Terminal Center, Yahadut Canada 1 St. Or Yehuda 6037501, Israel 30
<b>Investigational Device</b>	Cardiovalve System, comprised of: 1) Cardiovalve Implant; 2) Cardiovalve Delivery System (DS); 3) Cardiovalve Accessories
<b>Cardiovalve Implant</b>	<p>The Cardiovalve implant is based on a classic, proven design of three bovine pericardium leaflets which results in normal hemodynamic flow. The leaflets are sutured via a Dacron fabric to a dual self-expanding nitinol frame design which creates 24 grasping points that fixate the device to the native mitral annulus. The Dacron fabric is also used to cover the nitinol frame for promoting atraumatic interface with the heart tissue and enhanced sealing. The Cardiovalve implant is available in sizes medium, large and X-large.</p> 
<b>Cardiovalve Delivery System</b>	<p>The catheter assembly is comprised of the Transseptal Steerable Sheath (TSS), Guide Catheter (GC), Capsule shaft (CS), Implant Catheter (IC) and Torque Shaft (HSS). The catheter assembly is introduced to the mitral valve via transfemoral (venous) transseptal access. Using dual steering capability of the TSS and GC, the implant is positioned concentrically relative to the mitral native plane and co-aligned with the apex to base axes. The CS and HSS control the deployment sequence of the implant, by manipulating the capsule which houses the crimped implant.</p>

	 <p style="text-align: center;">Crimped encapsulated implant</p>
<b>Intended Use</b>	The Cardiovalve System is intended for use in symptomatic patients with severe mitral regurgitation
<b>Study Design</b>	Study is a prospective, multicenter, open label, early feasibility study
<b>Study Objective</b>	The objective of this study is to evaluate the safety and technical performance of the Cardiovalve System to successfully treat patients with severe symptomatic mitral regurgitation
<b>Study population</b>	Patients with symptomatic severe mitral regurgitation
<b>Sample Size</b>	A maximum of 15 mITT subjects
<b>Investigational sites</b>	<p>Up to 5 centers in the U.S. will participate in this feasibility study.</p> <p><b>Columbia University Medical Center</b> Investigator: Tamim Nazif, MD</p> <p><b>Piedmont Heart</b> Investigator: Chris Meduri, MD</p> <p><b>Baylor Scott &amp; White</b> Investigator: Robert Smith, MD</p> <p><b>Pinnacle Health Cardiovascular Institute</b> Investigators: Hemal Gada, MD and Mubashir Mumtaz, MD</p> <p><b>Montefiore Medical Center</b> Investigator: Mohamed Azeem Latib, MD</p>
<b>Study Duration</b>	Study Enrollment Start Date: Q4 2018

	Estimated Study Enrollment End Date: Q4 2019 Estimated Study Follow Up Completion: Q4 2024 Subjects will undergo evaluations at post procedure (48 hours), discharge (or 7-days), 30 days, 3 months, 6 months, 12 months, 24 months and up to 5 yr after the index procedure.
<b>Primary Performance Endpoint (evaluated at 30 days post index procedure)</b>	Cardiovalve Technical Success defined as: <ul style="list-style-type: none"> <li>• Successful access, delivery and retrieval of the delivery system; and</li> <li>• Successful deployment and correct positioning of the first intended implant; and</li> <li>• Freedom from emergency surgery or reintervention related to the device or access procedure</li> </ul> Without any procedural mortality, stroke, and device dysfunction (Central MR grade > 1 or paravalvular leak moderate or severe, mean mitral gradient > 6 mm Hg, LVOT obstruction (gradient increase $\geq 10$ mm Hg)) at 30-day follow up.
<b>Safety Endpoint (Evaluated at 30 days)</b>	The ability of the Cardiovalve to be implanted without Major Device Related Adverse Events through thirty (30) days including: <ul style="list-style-type: none"> <li>• Death (Cardiovascular mortality vs non-cardiovascular);</li> <li>• Reintervention (operative or transcatheter) due to progressive or recurrent MR or device related complications;</li> <li>• Disabling stroke;</li> <li>• Myocardial infarction (MVARC definition);</li> <li>• Major access site and vascular complications</li> <li>• Fatal or life-threatening bleeding (MVARC Type III-V)</li> <li>• Arrhythmia and conduction disorder requiring permanent pacing;</li> <li>• Renal Failure requiring dialysis;</li> <li>• Cardiac tamponade</li> <li>• All other SAE's and device/procedure-related AE's will be summarized throughout the follow-up duration.</li> </ul>
<b>Secondary Performance Endpoints (Patient Success) (Evaluated at 30 days, 90 days, and</b>	<ul style="list-style-type: none"> <li>• MR severity</li> <li>• Change in LV End diastolic volume index (LVEDVI)</li> <li>• Change in LV end-systolic volume index (LVESVI)</li> <li>• Changes in NYHA functional Class</li> </ul>

<b>180 days post procedure)</b>	<ul style="list-style-type: none"> <li>• 6-minute walk test distance</li> <li>• Kansas City Cardiomyopathy Questionnaire score</li> </ul>
<b>Major Inclusion Criteria</b>	<ol style="list-style-type: none"> <li>1. <math>85 \geq \text{Age} \geq 18</math> years</li> <li>2. Symptomatic severe MR confirmed by the echo core lab</li> <li>3. Cardiac Index <math>\geq 2.0</math></li> <li>4. Left Ventricular Ejection Fraction (LVEF) is <math>\geq 30\%</math> (within 90 days prior to subject enrollment based upon TTE)</li> <li>5. New York Heart Association (NYHA) Functional Class II, III or ambulatory IVa</li> <li>6. Prior treatment with Guideline Directed Medical Therapy (GDMT) for heart failure for at least 30 Days prior to index procedure</li> <li>7. Patient deemed a high surgical risk per MVARC definition by the site's Heart Team (as a minimum, one MV cardiac surgeon and one interventional cardiologist, and a cardiac imaging expert).</li> </ol>
<b>Exclusion Criteria</b>	<ol style="list-style-type: none"> <li>1. MR etiology that is exclusively Primary (degenerative)</li> <li>2. Echocardiographic or angiographic evidence of severe mitral annular calcification</li> <li>3. Echocardiographic evidence of EROA <math>\leq 0.3\text{cm}^2</math></li> <li>4. Untreated clinically significant coronary artery disease requiring revascularization.</li> <li>5. Hypertrophic/restrictive cardiomyopathy, constrictive pericarditis, or other structural heart disease causing heart failure other than other than cardiomyopathy of either ischemic or non-ischemic etiology</li> <li>6. Hypotension (systolic pressure <math>&lt; 90</math> mmHg)/Cardiogenic shock or other hemodynamic instability requiring the need for inotropic support or intra-aortic balloon pump or other hemodynamic support device</li> <li>7. Fixed pulmonary artery systolic pressure <math>&gt; 2/3</math> of systemic systolic blood pressure</li> <li>8. LVEDD <math>&gt; 70</math> mm</li> <li>9. Severe tricuspid regurgitation or evidence of right-sided heart failure with echocardiographic evidence of severe right ventricular dysfunction.</li> <li>10. Cardiac Anatomy deemed not suitable for the Cardiovalve Implant</li> <li>11. Elevated Creatine Kinase-MB (CK-MB)</li> <li>12. Surgical or interventional procedure planned within 30 days prior to index procedure</li> </ol>

	<ol style="list-style-type: none"> <li>13. UNOS Status 1 heart transplant or prior orthotropic heart transplantation.</li> <li>14. Life Expectancy &lt; 1 year due to non-cardiac conditions</li> <li>15. NYHA functional class IVb</li> <li>16. Chronic Kidney Disease with Creatinine clearance &lt;30 ml/min/1.73m<sup>2</sup></li> <li>17. Any prior mitral valve surgery or transcatheter mitral valve procedure</li> <li>18. Stroke or transient ischemic event within 30 Days prior to index procedure</li> <li>19. Modified Rankin Scale &gt; 4 disability</li> <li>20. Class I indication for biventricular pacing (in patient with CRT device not implanted)</li> <li>21. Implant or revision of any rhythm management device (CRT or CRT- D) or implantable cardioverter-defibrillator within one month prior to index procedure</li> <li>22. Need for cardiovascular surgery (other than MV disease)</li> <li>23. Echocardiographic evidence of intracardiac mass, thrombus, or vegetation</li> <li>24. Active endocarditis</li> <li>25. Known severe symptomatic carotid stenosis (&gt; 70 % via ultrasound)</li> <li>26. Active infections requiring current antibiotic therapy</li> <li>27. Active cancer with expected survival &lt; one year</li> <li>28. Pregnant or planning pregnancy within next 12 months.</li> <li>29. Currently participating in an investigational drug or another device study</li> <li>30. Any condition making it unlikely the patient will be able to complete all procedures</li> <li>31. Patient (or legal guardian) unable or unwilling to provide written, informed consent before study enrollment</li> <li>32. Subjects in whom transesophageal echocardiography is contraindicated</li> <li>33. Known hypersensitivity or contraindication to procedural, post procedural medication (e.g., contrast solution, heparin, anticoagulation therapy) or hypersensitivity to nickel or titanium.</li> <li>34. Aortic or pulmonic valve disease requiring surgery</li> <li>35. Venous peripheral anatomy unsuitable for implant delivery</li> <li>36. Hepatic insufficiency (MELD &gt; 10)</li> <li>37. Chronic anemia (Hgb &lt; 9)</li> </ol>
--	--

<b>Follow Up</b>	<p>Subjects shall be evaluated at 30 Days for the Primary Endpoints of safety and technical performance and will be continued to be evaluated at 3, 6, and 12 months post index procedure and annually up to 5 yrs to ensure product durability as a secondary endpoint.</p>
<b>Concomitant medications</b>	<p><b><u>ANTIBIOTIC THERAPY:</u></b></p> <p><b><u>Before Procedure</u></b></p> <p>Single dose of antibiotics in accordance with institutional standard of care for valve surgery.</p> <p><b><u>Post Procedure</u></b></p> <p>Minimum single dose of antibiotics in accordance with institutional standard of care for valve surgery.</p> <p><b><u>Follow-Up:</u></b></p> <p>Antibiotic prophylaxis for any procedures, consistent with standard of care for any bioprosthetic valve</p> <p><b><u>ANTICOAGULATE/ANTIPLATELET:</u></b></p> <p><b><u>Before Procedure</u></b></p> <p>Aspirin*: <math>\geq 75</math> mg daily for at least 7 days prior to procedure or 325 mg loading prior to procedure</p> <p>Clopidogrel (75 mg daily) may be substituted for aspirin in patients with an indication for P2Y<sub>12</sub> inhibition.</p> <p>DAPT (aspirin plus clopidogrel) is not recommended.</p> <p><b><u>During procedure</u></b></p> <p>Heparin to maintain ACT <math>\geq 250</math> seconds <b>or</b></p> <p>Bivalirudin (0.75 mg/kg IV bolus followed by 1.75 mg/kg/hour IV infusion for the duration of the procedure) in the case of Heparin allergy</p> <p><i>Discontinue Heparin/bivalirudin at the completion of procedure to facilitate access site management.</i></p> <p><b><u>Post-Procedure</u></b></p> <ul style="list-style-type: none"> <li>Heparin: Restart heparin at within 12 hours, after completion of the procedure, if no evidence of significant bleeding</li> <li>Warfarin: Initiate administration 24 hours post procedure if no significant bleeding</li> </ul> <p><i>INR Target: 3.0-3.5 for initial 6 months post procedure</i></p> <p><b><u>Subjects in normal sinus rhythm:</u></b></p>

	<ul style="list-style-type: none"> <li>low-dose aspirin (100 mg or less daily) OR clopidogrel (75 mg daily) indefinitely in patients with an indication for P2Y12 inhibition AND</li> <li>warfarin or equivalent vitamin K antagonist for at least six months</li> </ul> <p><b><u>Subjects in atrial fibrillation:</u></b></p> <ul style="list-style-type: none"> <li>low-dose aspirin (100 mg or less daily) OR clopidogrel (75 mg daily) in patients with indication for P2Y12 AND</li> <li>warfarin or equivalent vitamin K antagonist indefinitely</li> </ul> <p><b>Subjects who are within a year post-DES implantation</b> for ACS or within 6 months for stable CAD, should receive clopidogrel and no aspirin as SAPT plus warfarin for 6 months or indefinitely if in atrial fibrillation. Following the 6 months, if not in atrial fibrillation DAPT may be reinstituted as needed to complete recommended DAPT period after stenting.</p> <p><i>* Clopidogrel may be substituted for Aspirin in the case where aspirin is contradicted.</i></p>
<b>Independent Subject Screening Committee</b>	Managed by: Cardiovascular Research Foundation 1700 Broadway, NY, NY 10019 C/O Ori Ben-Yehuda, MD
<b>CEC/DMC</b>	Membership: TBD Managed by: Cardiovascular Research Group 1700 Broadway, NY, NY 10019 C/O Ori Ben-Yehuda, MD
<b>Clinical Site Management</b>	Boston Biomedical Associates 100 Crowley Drive, Suite 216 Marlborough, MA 01752 C/O Lauren Baker, PhD
<b>Echocardiographic Core Lab</b>	Baylor Scott and White Research Institute Echocardiography Core Laboratory Plano, Texas

## **2 INTRODUCTION**

### **2.1 Clinical Need**

Mitral valve (MV) disease is the most common valvular heart disease primarily with a prevalence of more than 10% in people older than 75 years of age.[1-5]The disease is characterized by mitral regurgitation (MR), defined as systolic retrograde flow from the left ventricle into the left atrium. Epidemiological data show that moderate or severe regurgitation, necessitating mitral valve surgical repair or replacement is a significant worldwide healthcare problem; it is currently the most frequent valve disease in the USA, almost twice the rate of aortic valve disease. An estimated four million people suffer from moderate to severe mitral regurgitation and 250,000 new patients are diagnosed each year in the United States.[6]Only approximately 50,000 of these patients undergo surgery annually in the United States.[7] The incidence of mitral valve regurgitation is expected to increase as the aging population grows larger.

Causes of mitral regurgitation (MR) are often classified as ischemic and non-ischemic, and may result in either organic/degenerative (or “primary”) or functional (or “secondary”) mitral regurgitation. Primary MR involves the degeneration of the mitral valve apparatus. The most common etiology of primary MR is myxomatous degeneration accounting for 50% of primary MR, rheumatic heart disease and endocarditis. Functional MR typically arises secondary to left ventricular dysfunction, where dilation of the left ventricle and papillary muscle displacement occurs due to ischemic heart disease, or non-ischemic dilated cardiomyopathy.[8]

Patients with MR may remain asymptomatic for years. Asymptomatic mitral regurgitation is a serious disease, with a five-year rate of death from any cause of 22 percent and a 33 percent incidence of adverse cardiovascular events, including death from cardiac causes, heart failure, and new atrial fibrillation.[10]

Multivariate analysis revealed that mild mitral regurgitation was independently associated with a significantly increased risk of death at 1-year (adjusted relative risk 2.31). Five year survival in another study of 303 patients with recent occurrence of MI showed that total and cardiac mortality was significantly greater in patients with mitral regurgitation than those without. Furthermore, the mortality risk was directly related to the degree of regurgitation as defined by the effective regurgitate orifice area and the regurgitate volume.[11]

### **2.2 Treatment Guidelines**

The goals of pharmacotherapy are to reduce morbidity and prevent complications. Medications are commonly used in subjects with secondary mitral regurgitation to address the underlying left ventricular dysfunction. However, conservative approaches

using medication do not specifically address the underlying valvular regurgitation. Therefore, patients with symptomatic severe mitral regurgitation have traditionally been referred to surgery as the gold standard for treatment. Surgical techniques involve either repair or replacement of the mitral valve. MV surgery for primary MR in symptomatic subjects with LVEF of 30% or greater or LVEF < 30% is a Class I or Class IIb recommendation, respectively. Similarly, MV surgery for secondary MR in symptomatic subjects has a Class IIb recommendation. While surgical repair is encouraged, surgical replacement is also routinely performed, as dictated by anatomic and hemodynamic features encountered in an individual patient. Moreover, a new recommendation in the AHA/ACC 2017 guidelines supports the use of replacement over repair for patients with secondary MR who are NHYA Class III-IV with chronic severe ischemic MR and symptomatic despite guideline directed medical therapy (GDMT).[12,13]

### **2.3 Development of Transcatheter Mitral Valve Interventions**

Minimally invasive cardiac surgical (MICS) approaches have been developed since the 1990s, to decrease the invasiveness and attendant morbidity associated with traditional sternotomy mitral valve surgery. As compared to traditional surgery, MICS has demonstrated equally good outcomes such as survival, stroke, and renal failure, as well as reduced hospital length of stay, and transfusion requirements. [16]

Building upon the MICS approaches to mitral surgery, and the success of transcatheter aortic valve implantation (TAVI), attention on transcatheter approaches to treating mitral disease have increased. Transcatheter techniques have been recognized by medical societies, including the Transcatheter Therapies for Mitral Regurgitation, published in 2014.[13] The 2014 (and 2017) AHA/ACC Guidelines for the Management of Patients with Valvular Heart Disease support the use of transcatheter mitral valve repair (recommendation Class IIb) for severely symptomatic patients with chronic severe primary MR who have a prohibitive surgical risk due to severe comorbidities (Class IIb recommendation).[15]

These interventional transcatheter methods are still largely investigational. Only one product has been approved by the FDA in the United States; the Abbott MitraClip was approved in 2013 for treatment of severe primary MR in patients who are at prohibitive surgical risk. Not surprisingly, transcatheter mitral valve intervention has anatomic considerations which differ from TAVI. Yet, the use of mitral valve replacement builds upon the concept originated by TAVI, and MV replacement has been reported using TAVI devices.[16] The continued emergence of transcatheter mitral valve therapies is expected to grow over time with several new products being investigated in the early clinical stage.[13,17-19]

Finally, the role of a multi-disciplinary heart team has been recognized as an important component when evaluating potential patients for treatment using transcatheter mitral techniques. The heart team provides valuable perspective and will remain central to aid in decision making for clinical trials which assess new mitral technologies.[13]

### **2.3.1 Cardiovalve Solution**

Cardiovalve has developed a mitral valve replacement device that is aimed at treating patients with severe mitral regurgitation that would otherwise be referred for surgical mitral valve replacement. The product is designed to be placed through a transcatheter, trans-septal approach. It is constructed of a nitinol frame with bovine pericardial valve leaflets attached. The aim of the device is to provide a functioning valve that is consistent with current surgical technology that can be placed in a minimally invasive manner for patients that are not currently ideal candidates for surgery.

### **2.3.2 The Unique Features of the Product**

The Cardiovalve System has specific differences from the other transcatheter mitral technologies currently being investigated. The Cardiovalve System utilizes transfemoral access for trans-septal delivery of a low-profile, mitral valve replacement (TMVR) which should avoid the risks of surgery.

The Cardiovalve implant has an orientation-indifferent structure for reduced procedural complexity, and a dual nitinol frame (one carrying the atrial flange, the other sustaining the ventricular leaflet-grasping legs) for enhanced radial strength and fatigue resistance. In addition, the design of the Cardiovalve implant stems from the characteristics of successful available surgical bioprosthetic valves, such as the Edwards Lifescience Perimount Magna valve. The Cardiovalve implant features three bovine pericardial leaflets with a scalloped shape design and a short frame to avoid left ventricular outflow tract obstruction.

The delivery system of the Cardiovalve was designed from inception to enable trans-septal delivery and shares many similarities with another established similar transcatheter delivery system used for mitral valve repair which bears the CE Mark (Cardioband). This is designed to provide optimal navigation, ease of positioning and successful delivery of the Cardiovalve implant.

In summary, the Cardiovalve System offers a replacement valve option that is delivered through a transcatheter approach intended to reduce the mortality and morbidity associated with surgical treatment options. In particular, Cardiovalve is designed to provide an enhanced safety profile with a transvenous femoral site access, in contrast to

the transapical approach used with other transcatheter mitral valve devices, which require a mini-thoracotomy and its attendant comorbidities such as pneumothorax. Finally, the established delivery system is expected to facilitate procedural execution which may translate into improved clinical results.

## 2.4 Cardiovalve Innovation

The Cardiovalve System has specific differences from the other products being currently investigated. Cardiovalve is a transcatheter, transseptally delivered, low-profile, mitral valve replacement (TMVR) system to avoid the risks of surgery. The Cardiovalve implant has an orientation-indifferent structure for reduced procedural complexity, and a dual nitinol frame (one carrying the atrial flange, the other sustaining the ventricular legs) for enhanced radial strength and fatigue resistance. In addition, the design of the Cardiovalve implant stems from the characteristics of successful available surgical valves, such as the Edwards Lifescience Perimount Magna valve and features three bovine pericardial leaflets with scalloped shape design, and has a short frame to avoid LVOT obstruction.



*Figure 1. The Cardiovalve Implant*

The delivery system of the Cardiovalve was designed from inception to enable trans-septal delivery and shares many similarities with the Cardioband delivery system (currently CE-Marked Mitral Valve repair system and currently in clinical trials in the US), leading to anticipate optimal navigation, ease of positioning and successfully delivery.

Therefore, the Cardiovalve offers a replacement valve delivered through a transcatheter approach intended to reduce mortality and reduce adverse event rates currently associated with surgical treatment options. In particular, Cardiovalve is expected to improve the safety due to transvenous access (as compared to transapical approach used with these other transcatheter mitral valves). In addition, the design of the delivery system is expected to facilitate procedural execution and better clinical results.

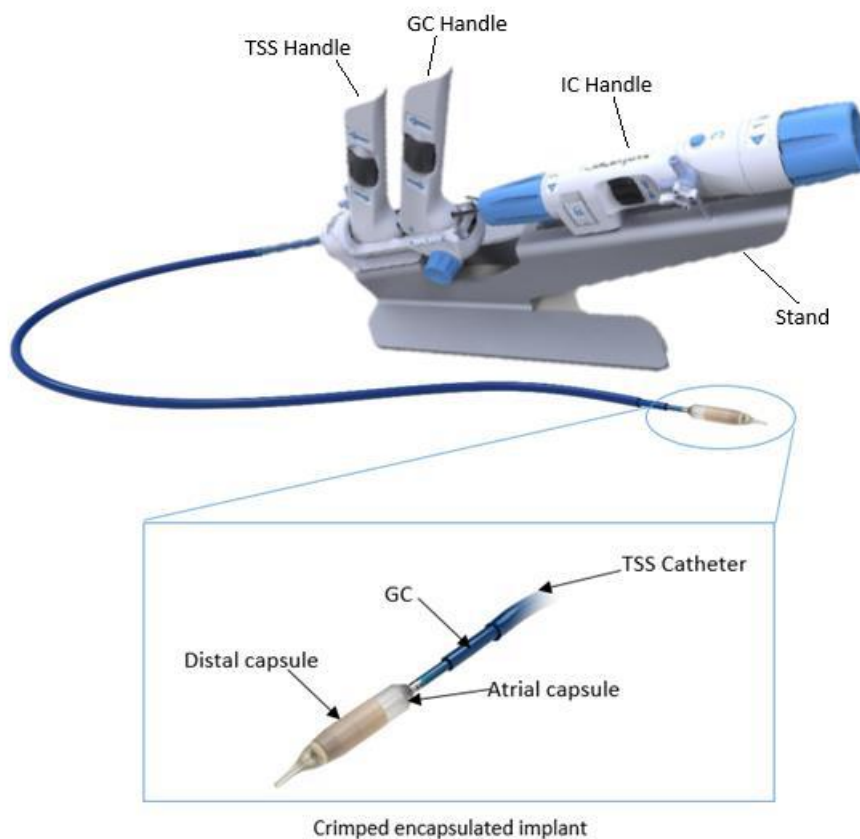
## 3 INVESTIGATIONAL DEVICE DESCRIPTION

The Cardiovalve implant is a bioprosthetic device that is placed using a minimally invasive technique. Its unique design attributes include the following product goals:

- A valve replacement implant that can be delivered using a transcatheter and trans-septal approach
- Controlled and safe delivery achieved through:
  - Trans-septal delivery
- Simplified delivery and sizing
  - Efficient sizing options to minimize complex imaging evaluations

These and other attributes are described in detail below. The Cardiovalve system is composed of:

- Cardiovalve Implant
- Cardiovalve Delivery System (DS)
- Cardiovalve Accessories



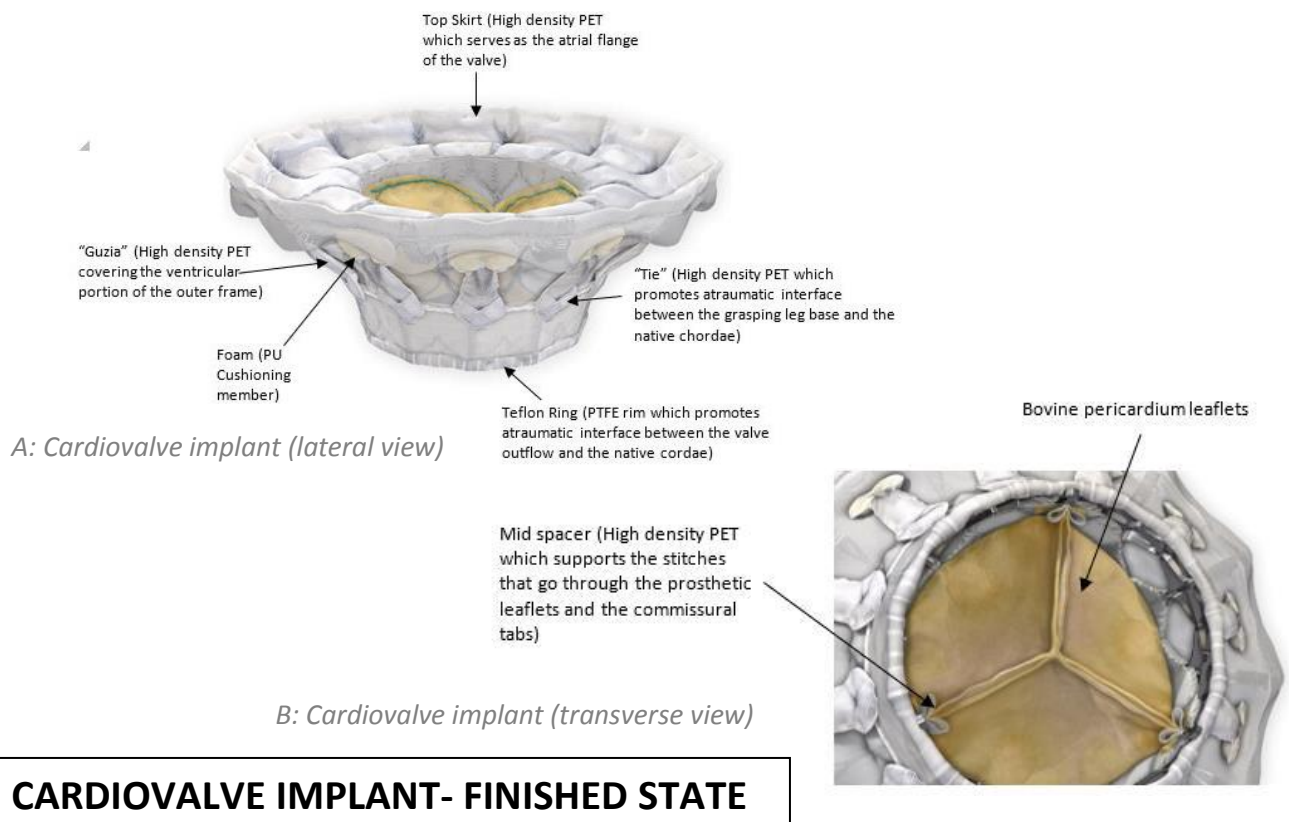
**Figure 2. Cardiovalve System**

### 3.1 The Cardiovalve Implant

The Cardiovalve implant (*Figure 3*) is based on a classic, proven design of three bovine pericardium leaflets which results in normal hemodynamic flow. The leaflets are sutured via a Dacron fabric to a dual self-expanding nitinol frame design which creates 24 grasping points that fixate the device to the native mitral annulus. The Dacron fabric is also used to cover the nitinol frame for promoting atraumatic interface with the heart tissue and enhanced sealing. The Cardiovalve implant is available in sizes medium, large and X-large.

The Cardiovalve implant undergoes a series of chemical treatments, including anti-calcification, bioburden reduction and sterilization. It is stored in a hermetically closed jar containing glutaraldehyde-based solution, and is rinsed prior to clinical use with sterile saline to remove residual storage solution.

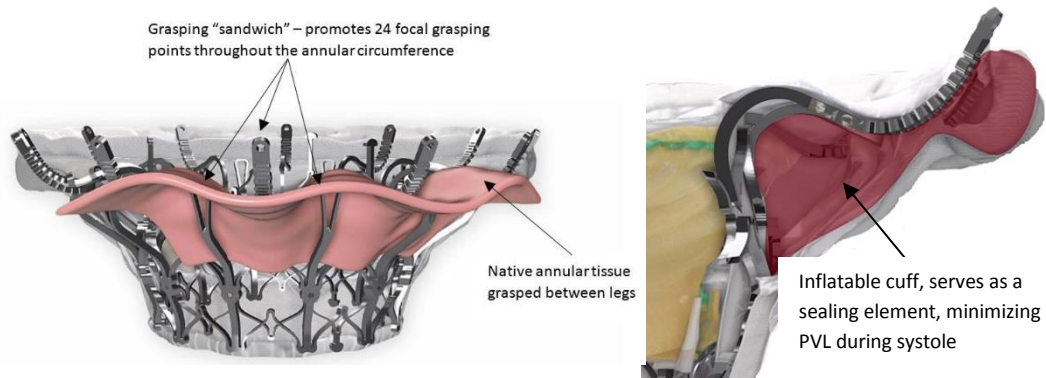
The implant is loaded onto the delivery system as part of the procedure preparation, and approved for a maximum of 2 sequential crimping cycles. The implant is deployed in three main procedural steps: (1) Exposure of the grasping legs in the in the left atrium, introducing the device into the left ventricle and grasping the native leaflets by pulling the device proximally (2) exposure of the atrial flange (3) full opening of the frame and valve and completion of the implantation.



**Figure 3. Cardiovalve Implant; A: Lateral View and B: Transverse View – depicts critical components including**

*bovine pericardial leaflets, High Density PET covering Dual Nitinol Frame and PU foam cushioning member*

The implant has flexible legs that facilitate grasping of native tissue. It utilizes 24 focal grasping locations that allow for the native annular tissue to be held securely in place (*Figure 4*).



**Figure 4. Cardiovalve implant, grasping the native annular tissue**

### **3.2 The Cardiovalve Delivery System (DS)**

The Cardiovalve DS includes the following elements:

- Catheter Assembly

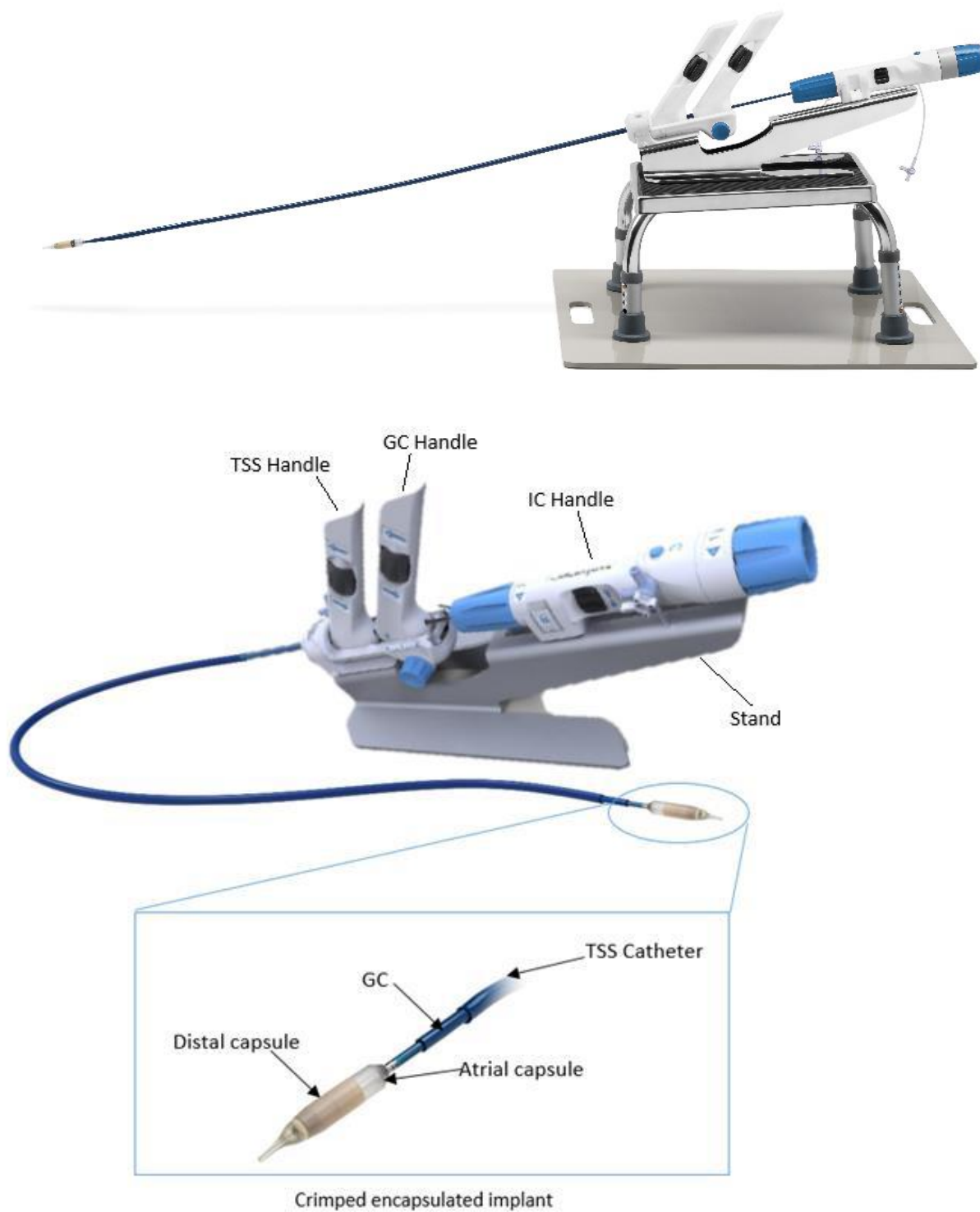
The catheter assembly is comprised of the Transseptal Steerable Sheath (TSS), Guide Catheter (GC), Capsule shaft (CS), Implant Catheter (IC) and Torque Shaft (HSS). The catheter assembly is introduced to the valve via transfemoral (venous) transseptal access. Using dual steering capability of the TSS and GC, the implant is positioned concentrically relative to the mitral native plane and co aligned with the apex to base axes. The CS and HSS control the deployment sequence of the implant, by manipulating the capsule which houses the crimped implant.

- IC Handle

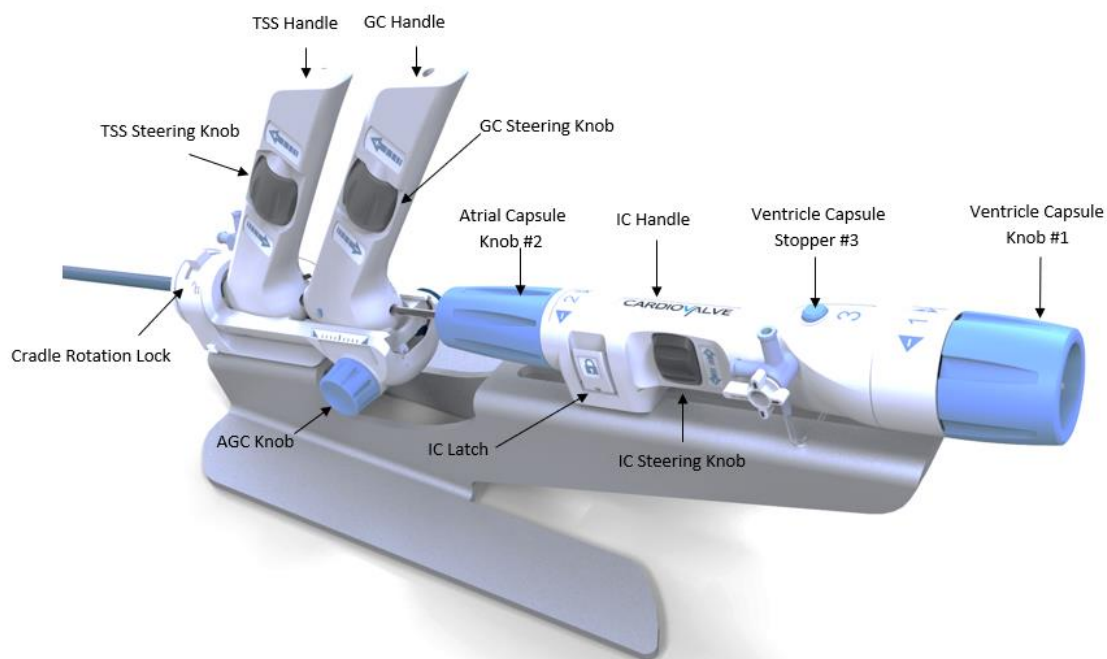
The IC handle is used for positioning and deployment of the implant

- GC and TSS Handles

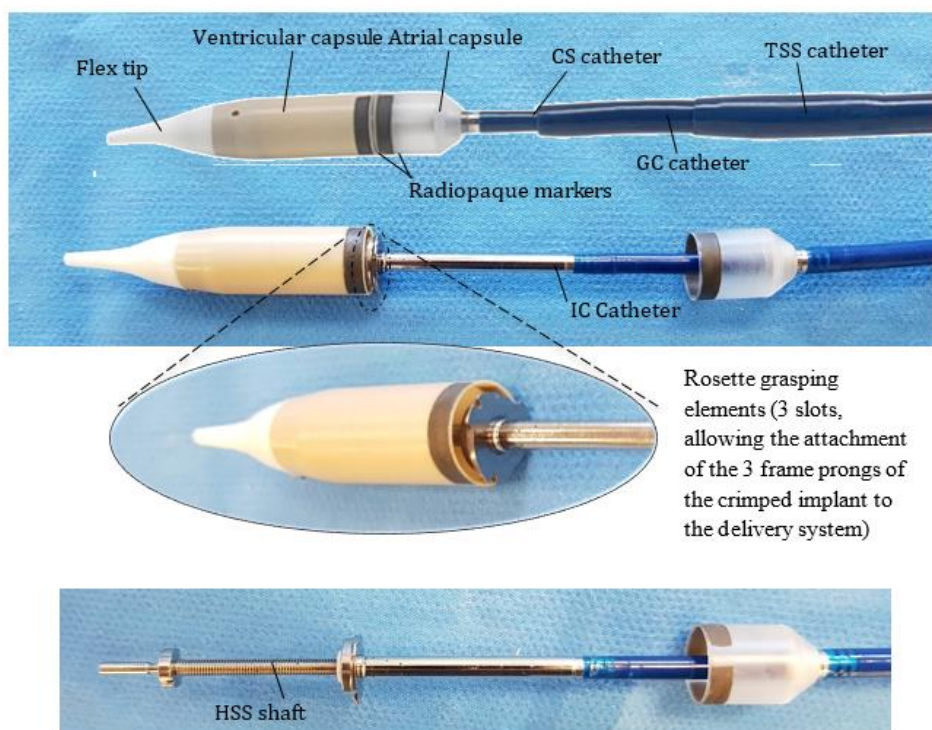
Theses handles are fixated together for steering while enabling axial movement of the GC relative to the TSS



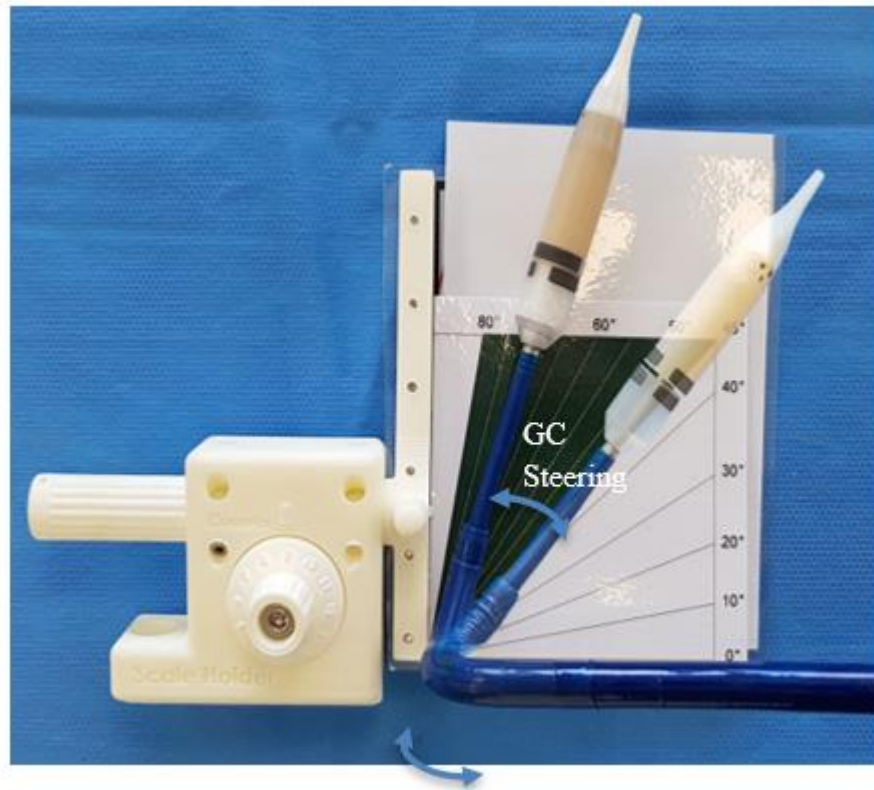
**Figure 5. The Cardiovalve Delivery System: Highlights the TSS Handle, GC Handle, IC Handle and the Delivery Catheter as a collective system**



**Figure 6. The Cardiovalve Delivery System: IC Handle Configuration on Stand**



**Figure 7. The Cardiovalve Delivery System: Catheter Distal Unit**



**Figure 8. The Cardiovalve Delivery System: Guiding Catheter Handle With Display of Functional Feature**

### 3.3 The Cardiovalve Accessories

The Cardiovalve accessories contain the support plate, booster, silicone pad, the stand, screwdriver, calibration jig, spacer, wrench kit, internal lumen washer, crimper, crimper bath, crimper mirror and dilator.

- The support plate is positioned on the operation table, intended to provide a stable support for the booster.
- The booster is located at the lower part of the patient's body above the support plate.
- The silicone pad is positioned on the covered booster. Improves physician's control over the stand movement.
- The stand is intended to support the delivery system during the procedure. It is positioned on the silicone pad to avoid movement.
- The screwdriver is used to secure and release the distal capsule knob in the handle during preparations in the Cath-lab.
- The calibration jig is used to verify proper alignment of the ventricle and atrial capsules during preparation of the delivery system in the cath-lab, to ensure correct deployment sequence of the implant.

- The spacer is used to maintain correct orientation between IC subassembly and GC while transferred from the preparation table to the operation table.
- The wrench kit is intended to support the ventricular capsule of the delivery system while crimping the implant.
- The internal lumen washer is used to flush the guide wire lumen.
- The crimper is used to crimp the implant into the capsule of the delivery system during the preparation in the Cath lab.
- The crimping bath houses the crimper while crimping the implant into the delivery system in a cooled saline environment.
- The crimper mirror is used to optimize vision of the implant during the crimping process
- The dilator (33Fr size) is used to dilate the femoral access site to accommodate the DS.

All accessories with exception of the support plate, booster, stand, crimper and crimp bath are single-use. The crimper, crimper bath and stand undergo cleaning and heat-steam sterilization for re-use.




*Figure 9. The Cardiovalve Accessories – Reusable And Disposable*

### 3.4 Valve Sizes

The Cardiovalve comes in three different sizes (Medium, Large and X-Large) for different mitral annulus sizes. Implant sizes, dimensions and suitability for specific native mitral annulus sizes are provided in **Table 1**.

**Table 1. Cardiovalve implant dimensions**

Implant Size			
Dimensions (mm)	Medium	Large	X-Large
<b>A</b> (Valve inlet)	27	29	29
<b>B</b> (Ventricular)	45	50	55
<b>C</b> (Atrial flange)	56	61	64
			

**Table 2. Cardiovalve implant sizing**

Intra-commissural (by CT)			
Implant size	Native MV annulus 36-43 mm	Native MV annulus 42-48 mm	Native MV annulus 47-53 mm
<b>Medium</b>	X		
<b>Large</b>		X	
<b>X-Large</b>			X

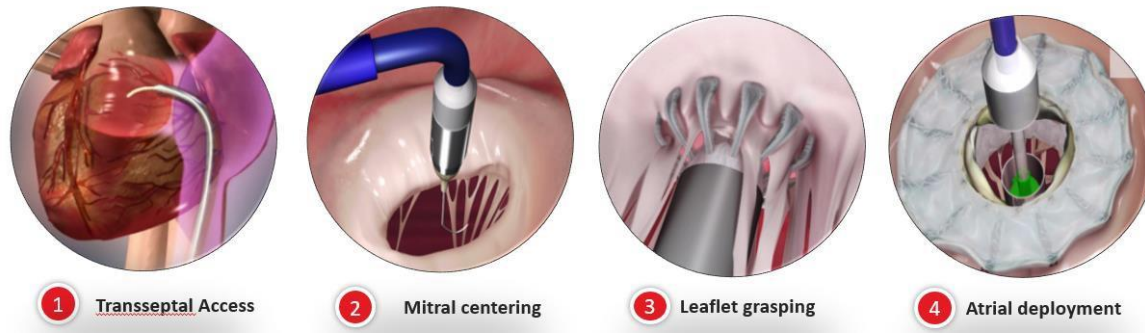
### 3.5 Device Materials

The Cardiovalve System is manufactured using bio-compatible materials with a long history of medical use. Implanted materials include, nitinol, Dacron, bovine pericardium, Teflon, polyester sutures and PTFE. Delivery system materials include medical-grade silicon, Pebax, nitinol, polycarbonate, PTFE, PET and radiopaque ink to facilitate visualization.

### 3.6 Implant Procedure

Subjects will be implanted with the Cardiovalve System via a transfemoral approach. The procedure is restricted to those physicians who have undergone dedicated training on use

of the device. The delivery system is navigated to the right atrium and the left atrium is reached using a trans-septal procedure (puncture of the inter-atrial septum). The Cardiovalve is deployed and fixated to the native annulus of the mitral valve under fluoroscopy and echocardiography guidance. The four essential steps of the implantation are shown below. For additional details, refer to the product Instructions for Use.

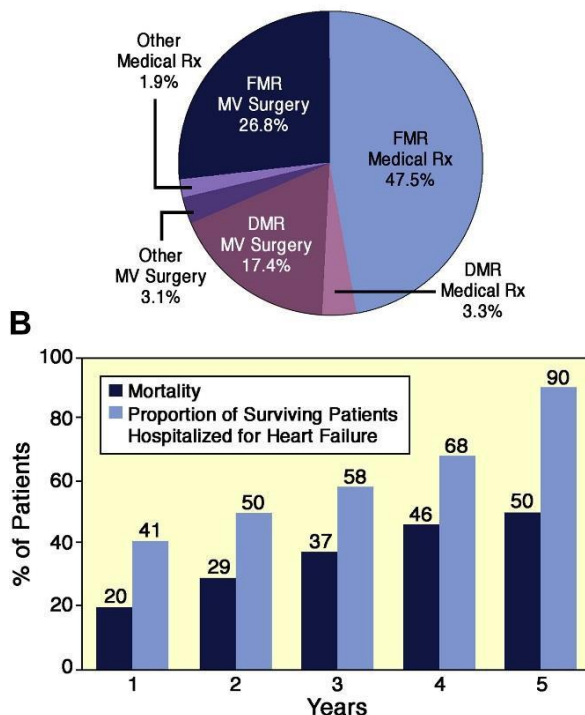


**Figure 10: Four Essential Steps of the Implantation Procedure**

## **4 RISK BENEFIT ANALYSIS**

### **4.1 Anticipated clinical benefits**

The standard treatment of MR in patients with high surgical risk is based on Guideline Directed Medical Therapy associated with significant morbidity and mortality. It is estimated that in up to 50% of patients with severe MR, surgical treatment is not performed owing to increased risk related to comorbidities and LV dysfunction (17). Goel et al. analyzed the mortality rate of unoperated patients with severe MR showing that the overall 1-Year mortality is 20% and increases to 50% at 5 years follow-up (*Figure 11*). Thus, there is an increasing need for non-surgical treatments of MR. This can partially resolved utilizing catheter based repair techniques. However, catheter based mitral valve repair techniques are only applicable for specific indications and do not completely resolve MR or suffer from MR recurrence.

**A Medically treated patients with severe MR**


**Figure 11. Prevalence and Outcomes of Unoperated Patients With Severe Symptomatic MR and Heart Failure**

(A) Pie chart showing mechanism and management of 1,095 patients with severe symptomatic MR. (B) Mortality and rates of hospitalization for heart failure in unoperated patients with severe MR. DMR ¼ degenerative mitral regurgitation; FMR ¼ functional mitral regurgitation; MR ¼ mitral regurgitation; MV ¼ mitral valve. Figure by Craig Skaggs.

Source: Goel S. et al. Prevalence and outcomes of unoperated patients with severe symptomatic mitral regurgitation and heart failure: comprehensive analysis to determine the potential role of MitraClip for this unmet need. *J Am Coll Cardiol.* 2014 Jan 21;63(2):185-6

The Cardiovalve System offers the possibility for MR treatment without the need for open heart surgery and cardiopulmonary bypass which carries several risks, such as neurologic deficits, bleeding, embolism, renal failure, acute respiratory distress and others. Cardiovalve is implanted with a transfemoral approach equivalent to transcatheter aortic valve replacement that have now become a standard of care for high risk patients with aortic stenosis. These approaches have been efficient in reducing potential adverse events and similarly, a favorable risk profile is anticipated with the Cardiovalve technology targeting the resolution of mitral valve disease. Mitral valve replacement with the Cardiovalve may result in one or more of the following benefits for patients at elevated risk for surgical MVR: decrease in mitral regurgitation, alleviation of symptoms related to mitral insufficiency, increased functional capacity and better quality of life. It is reasonable to expect that the medical benefits of the Cardiovalve will outweigh the potential adverse events but this need to be proven and the present study will collect clinical information to further confirm a favorable risk-benefit ratio.

## 4.2 Anticipated or Potential Adverse Events

The potential adverse events are those that are expected to occur during the study because they are associated with the device, transcatheter procedure, stress-induced tests (e.g. TEE, TTE, MSCT scan, exercise tolerance, etc.), or the heart failure population over time. It is anticipated that patients may require temporary medical and/or mechanical hemodynamic support in the peri- and/or early post-op period; these are therefore not considered adverse events. *Table 3* below provides a listing of the anticipated or potential adverse events. In addition to the list present in *Table 3*, contains a list of specific device-related technical failure issues in mitral replacement according to MVARC that also apply to the Cardiovalve System.

**Table 3. List of anticipated or potential Adverse Events**

<ul style="list-style-type: none"> <li>• Allergic Reaction (Contrast agent, Nickel or Chromium, Heparin)</li> <li>• Anesthesia Reactions (delirium, disorientation, etc.)</li> <li>• Anaphylactic or Cardiogenic Shock</li> <li>• Anemia or other Abnormal Laboratory Values</li> <li>• Angina</li> <li>• Aortic Valve Injury</li> <li>• Arrhythmia</li> <li>• Atrial Septal Defect requiring intervention</li> <li>• Atrioventricular Block</li> <li>• Bleeding</li> <li>• Cardiac arrest</li> <li>• Cardiac Tamponade</li> <li>• The risks of conversion to emergent/elective cardiac surgery based on a technical/clinical failure</li> <li>• Death</li> <li>• Deep Venous Thrombus (DVT)</li> <li>• Detachment/Dislodgment (Partial or Full) of the Device</li> <li>• Device Thrombosis</li> <li>• Dizziness/Syncope</li> <li>• Dyskinesia</li> <li>• Inflammation</li> <li>• Low Cardiac Output</li> <li>• Malfunction of The Device</li> <li>• Migration or Malposition of the device requiring intervention</li> <li>• Mitral Valve Stenosis</li> <li>• Multi- System Organ Failure</li> <li>• Myocardial Infarction</li> <li>• Nausea/Vomiting</li> <li>• Nerve Injury</li> <li>• Pain</li> </ul>	<ul style="list-style-type: none"> <li>• Perforation or Damage of Vessels or Tissue, Myocardium or Valvular Structure</li> <li>• Cardiac Perforation</li> <li>• Hemothorax</li> <li>• Pericardial Effusion/Cardiac Tamponade</li> <li>• Peripheral Ischemia</li> <li>• Pneumonia</li> <li>• Pneumothorax</li> <li>• Pulmonary Embolism</li> <li>• Progression of Valvular Heart Disease</li> <li>• Dyspnea</li> <li>• Edema</li> <li>• Emboli (Thrombus, Air, Cardiovalve Device)</li> <li>• Esophageal Irritation or Perforation</li> <li>• Fever</li> <li>• Hematoma</li> <li>• Heart Block</li> <li>• Hemolysis</li> <li>• Hemorrhage</li> <li>• Hypertension/Hypotension</li> <li>• Groin Infection</li> <li>• Infection Including Endocarditis and Septicemia</li> <li>• Renal Insufficiency or failure/AKI</li> <li>• Respiratory Failure</li> <li>• Stroke/Transient Ischemic Attack</li> <li>• Structural Device Degeneration</li> <li>• Thrombocytopenia</li> <li>• Vascular Injury (including A-V fistula, dissection, or pseudo-aneurysm)</li> <li>• Vessel Spasm</li> <li>• Worsening Heart Failure</li> <li>• Worsening Mitral Regurgitation</li> <li>• Wound Dehiscence</li> </ul>
---	--

Possible outcomes of the potential adverse events include reoperation, explant of the valve, permanent disability or death. There may be other potential adverse events that are unknown at this time. All safety events will be collected and reviewed throughout the entire study and follow-up period. The Investigators will be notified of any additional potential adverse events identified that could affect the health, safety or welfare of the study patients.

### 4.3 Potential Adverse Events in Transcatheter Mitral Regurgitation Trials

The major potential adverse events in transcatheter mitral regurgitation trials (according to MVARC guideline, Part 1, table 10) include major bleeding or vascular complications, pulmonary complications, stroke and other cerebrovascular events, myocardial infarction, acute kidney injury, new onset atrial fibrillation, conversion to open surgery, requirement for an insertion of an ICD or biventricular pacemaker, and device failure resulting in the inability to achieve successful MV treatment. In addition, a comprehensive list of specific device-related technical failure issues in mitral replacement is reported in MVARC Part 2, Table 11, shown in Table 4 below. These potential adverse events are applicable to the Cardiovalve System.

**Table 4. Specific Device-Related Technical Failure Issues and Complications according to MVARC**

Specific Device-Related Technical Failure Issues and Complications	
<b>I. Device failure</b>	
<input type="checkbox"/>	Device failure, defined as the absence of device success (Table 10), is subclassified as:
<input type="checkbox"/>	Delivery failure (i.e., technical failure)
<input type="checkbox"/>	Structural failure: the device does not perform as intended due to a complication related to the device (e.g., fracture, migration or embolization, frozen leaflet, device detachment, and so on)
<input type="checkbox"/>	Functional failure: the device performs as intended without complication but does not adequately reduce the degree of MR (MR > moderate, or fails to relieve or creates new mitral stenosis [EROA <1.5 cm <sup>2</sup> or transmitral gradient ≥5 mm Hg]).
<b>II. Specific device-related technical failure issues and complications</b>	
<input type="checkbox"/>	Paravalvular leak <ul style="list-style-type: none"> <li>Major: moderate or severe (2+, 3+, or 4+), or associated with hemolysis, or requiring intervention or surgery</li> <li>Minor: trace or mild (1+), without hemolysis</li> </ul>
<input type="checkbox"/>	Iatrogenic atrial septal defect <ul style="list-style-type: none"> <li>Major: significant left-to-right shunt (Qp:Qs ≥2:1) or symptomatic requiring the need for closure</li> <li>Minor: nonsignificant shunt that is still present at ≥6 months</li> </ul>
<input type="checkbox"/>	Coronary vessel compression or obstruction <ul style="list-style-type: none"> <li>Angiographic evidence of any reduction in coronary artery luminal diameter or coronary sinus diameter due to either external compression, thrombosis, embolism, dissection, or other cause, subclassified as: <ul style="list-style-type: none"> <li>Major (≥50% diameter stenosis) or minor (&lt;50%)</li> <li>Symptomatic or not</li> </ul> </li> </ul>

- Requiring treatment or not
- Transient (intraprocedural only, resolved at procedure end) or persistent
- Pericardial effusion
  - Major: leading to cardiac tamponade or requiring intervention
  - Minor: not leading to cardiac tamponade and not requiring intervention
- Conversion to open mitral valve surgery during a transcatheter procedure, subclassified as
  - Secondary to mitral valve apparatus damage or dysfunction, requiring surgical valve repair or replacement, or
  - Secondary to procedural complications (such as cardiac perforation, removal of an embolized device, and so on)
- Device malpositioning
  - Ectopic device placement: permanent deployment of a device in a location other than intended
  - Device migration: after initial correct positioning, the device moves within its initial position but not leading to device embolization
  - Device embolization: the device moves during or after deployment such that it loses contact with its initial position
- Device detachment
  - Partial: detachment of part of the device from the initial position without embolization
  - Complete: detachment leading to device embolization or ectopic device placement
- Device fracture
  - Major: a break, tear, perforation, or other structural defect in the device (stent, housing, leaflet, arm, and so on) resulting in device failure, resulting in recurrent symptoms, or requiring reintervention, or
  - Minor: a break, tear, perforation, or other structural defect in the device (stent, housing, leaflet, arm, and so on) not resulting in device failure, not resulting in recurrent symptoms, and not requiring reintervention
- Damage to the native mitral valve apparatus
  - Chords
  - Papillary muscles
  - Leaflets
  - Mitral annulus
- Interaction with non-mitral valve intracardiac structures
  - Left ventricular outflow tract obstruction (gradient increase  $\geq 10$  mm Hg from baseline)
  - Aortic valve regurgitation ( $\geq$  moderate or 2+)
  - Other
- Device thrombosis, defined as any thrombus attached to or near an implanted valve, subclassified as:
  - Major: occludes part of the blood flow path, interferes with valve function (e.g., immobility of 1 or more leaflets), is symptomatic, or is sufficiently large to warrant treatment, or
  - Minor: incidental finding on echocardiography or other imaging test that is not major
- Endocarditis
  - Any 1 of the following:
    - Fulfillment of the modified Duke endocarditis criteria (61), or
    - Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during an operation or autopsy.
  - Should be further subclassified by organism, and early (<1 yr) vs. late (>1 yr)
- Hemolysis
  - The presence of a paravalvular leak on transesophageal or transthoracic echocardiography plus anemia

requiring transfusion plus increased haptoglobin and/or LDH levels; should be confirmed by a hematologist □ Other device-specific endpoints <ul style="list-style-type: none"> <li>○ The number of devices (e.g., clips, neochords) used by intent to achieve the desired reduction in MR</li> </ul>
<b>Specific Device-Related Technical Failure Issues and Complications</b>
<ul style="list-style-type: none"> <li>○ The need for unplanned use of additional devices (e.g., valves, clips, neochords) as a result of failed device delivery, device detachment, device fracture, or other device system failure</li> <li>○ If surgery is required, inability to perform mitral valve repair because of the presence of or anatomic changes from the device</li> </ul>
<i>LDH= lactate dehydrogenase; Qp = pulmonary blood flow; Qs = systemic blood flow.</i>

#### 4.4 Risk Analysis and Risk Mitigation

The potential adverse events associated with this investigational device have been identified and been minimized through appropriate design control, and by bench testing, pre-clinical and animal testing. Mitigations for these potential adverse events for the patients include (but not limited to):

- The Cardiovalve System is designed, intended and distributed for single use only.
- A site qualification will be conducted to ensure the investigators and the site staff are adequately experienced, a heart team is in place and the necessary infrastructure is available
- Every study site needs to be able to perform an emergency open heart surgery in case of a fatal intra- or post-procedural failure
- Every investigator performing the procedure is required to undergo Cardiovalve simulator training. A sponsor's proctor will be present during the initial procedures for assistance.
- Clearly defined inclusion/exclusion criteria that ensure only appropriate high risk patients are enrolled.
- An independent Subject Screening Committee designated by the sponsor, and including an expert in computed tomography (CT), and expert in echocardiography and a medical expert with in-depth knowledge of the Cardiovalve, will confirm subject clinical and anatomical suitability for the procedure.
- Safety review processes, with continuous and ongoing meetings convened based on pre- determined trigger thresholds.
- Warning and precautions in the instructions for use including reference to

sterility issues. All adverse events will be thoroughly reviewed by the study sponsor, and independent oversight committees (Clinical Events Committee (CEC) and Data Monitoring Committee (DMC)). The rate of anticipated adverse events will be evaluated on a continuous basis during the study. If rates exceed medical expectations, the independent committees will evaluate the findings and provide recommendations to the Sponsor on any corrective and preventive measures. In the event of unforeseen or increased potential adverse events to patients, suspension or termination of the clinical investigation may be recommended.

#### **4.5 Risk To Benefit Rationale**

Cardiovalve proposes a less invasive, controllable, transcatheter replacement for mitral regurgitation. The evidence presented above indicates that Cardiovalve targets an unmet clinical need, in that the device is:

- Targets patients under high surgical risk that have no or poor treatment options
- Might improve safety due to the transfemoral delivery by:
  - o Delivery on the beating heart thus avoids the use of Cardio Pulmonary Bypass
  - o Avoiding a trans-apical access as used for other mitral valves and therefore no mini-thoracotomy and piercing a large bore hole in the ventricular wall of already impaired myocardial tissue is needed
- Might improve technical success:
  - o Sutureless, thereby may enhance the ease of the replacement operation.
  - o Has three sizes for which patients are pre-chosen based on a comprehensive CT screening.
  - o The valve is deployed under echocardiographic guidance, on beating and fully inflated heart, and thus may improve the technical success as compared to sizing and procedures performed with a flaccid heart under bypass.

The Cardiovalve System is expected to allow treatment of patients that would otherwise not undergo mitral valve replacement due to the invasiveness of current surgical techniques. Given these potential benefits, there is ample justification for a prospective investigation focusing on safety and clinical performance of the Cardiovalve System.

## **5 OBJECTIVES OF THE CLINICAL INVESTIGATION**

The purpose of this study is to evaluate the safety and technical performance of the Cardiovalve System to successfully treat patients with severe mitral regurgitation.

### **5.1 Primary Performance Endpoint**

The primary performance endpoint is Cardiovalve technical success, which is defined as:

- Successful access, delivery and retrieval of the delivery system; and
- Successful deployment and correct positioning of the first intended implant; and
- Freedom from emergency surgery or reintervention related to the device or access procedure

Without procedural mortality, stroke, and device dysfunction (Central MR grade > 1 or paravalvular leak moderate or severe, mean mitral gradient > 6 mm, LVOT obstruction (gradient increase  $\geq$  10 mm Hg)) at 30 day follow up.

### **5.2 Primary Safety Endpoint**

The primary safety endpoint is the ability of the Cardiovalve to be implanted without Major Device Related Adverse Events through 30 Days including:

- Death (Cardiovascular mortality vs non-cardiovascular);
- Reintervention (operative or transcatheter) due to progressive or recurrent MR or device related complications;
- Disabling Stroke;
- Myocardial infarction (MVARC definition);
- Major access site and vascular complications
- Fatal or Life-threatening bleeding (MVARC Type III- V)
- Arrhythmia and conduction disorder requiring permanent pacing;
- Renal Failure requiring dialysis;
- Cardiac tamponade

All other SAE's and device/procedure-related AE's will be summarized throughout the follow- up duration.

### **5.3 Secondary Performance Endpoints**

Secondary performance endpoints include (Consistent with MVARC):

- MR severity

- Change in LV end diastolic volume index (LVEDVI)
- Change in LV end systolic volume index (LVESVI)
- Changes in NYHA functional class
- 6-minute walk test distance
- Kansas City Cardiomyopathy Questionnaire score
- Clinical Frailty Score

## 6 STUDY DESIGN

This study is a prospective, multicenter, open label first in human clinical study aimed at demonstrating safety and technical performance of the Cardiovalve device to minimize mitral regurgitation. Safety will be assessed by evaluating the rate of adverse events and adverse device effects occurred throughout the study period. The study is designed according to the Mitral Valve Academic Research Consortium (MVARC) (see References: '*Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement. Part 1: clinical trial design principles*', and '*Part 2: endpoint definitions*').

Up to five (5) centers will be involved in the study to treat a maximum of 15 subjects. The primary safety end point will be achieved when the final study subject has completed 1 month follow up. Additional follow-up will be performed after 3, 6, and 12 months and annually for a total of 5 years post index. It is anticipated that it will require approximately 12 months to complete enrollment.

### 6.1 Study Duration

The duration of each subject's involvement with the study is expected to be approximately 5 years from the time of enrollment and signing of the informed consent document. Each participant will come for treatment/follow-up visits at screening/baseline, procedure, discharge (or 7- days), 30 days, 3 months, 6 months, 12 months and then yearly for a total of 5 years after the index procedure. Unscheduled visits may be scheduled if required for medical reasons.

<b>Study Enrollment Start Date:</b>	<b>Q4 2018</b>
<b>Estimated Study Enrollment End Date:</b>	<b>Q4 2019</b>
<b>Estimated Study Follow Up Completion:</b>	<b>Q4 2024</b>

### 6.2 Study Population

A maximum of 15 mITT subjects will be enrolled in this feasibility study. Target patients are symptomatic subjects (NYHA Class  $\geq$  II-IV) with severe mitral regurgitation requiring mitral valve replacement or repair who are at elevated risk for open chest surgery according to the Heart Team decision and approved by the Subject

Screening Committee.

Medicare subjects that meet the study eligibility requirements will be enrolled in this study. The results of this study are expected to be highly generalizable to the Medicare population as MV disease is prevalent in more than 10% of people older than 75 years of age.[1-5]

### **6.2.1 Inclusion Criteria**

Candidates for participation in the study must meet all of the following inclusion criteria: Major Inclusion Criteria

1.  $85 \geq \text{Age} \geq 18$  years
2. Symptomatic severe MR confirmed by the echo core lab
3. Cardiac Index  $> 2.0$
4. Left Ventricular Ejection Fraction (LVEF) is  $\geq 30\%$  (within 90 days prior to subject enrollment based upon TTE)
5. New York Heart Association (NYHA) Functional Class II, III or ambulatory IVa
6. Prior treatment with Guideline Directed Medical Therapy (GDMT) for heart failure for at least 30 days prior to index procedure
7. Patient deemed a high surgical risk per MVARC definition by the site's Heart Team (as a minimum, one MV cardiac surgeon and one interventional cardiologist, and a cardiac imaging expert).

### **6.2.2 Exclusion Criteria**

Candidates for participation will be ineligible for the study if any of the following conditions apply:

1. MR etiology that is exclusively Primary (degenerative)
2. Echocardiographic or angiographic evidence of severe mitral annular calcification
3. Echocardiographic evidence of EROA  $\leq 0.3\text{cm}^2$
4. Untreated clinically significant coronary artery disease requiring revascularization.
5. Hypertrophic/restrictive cardiomyopathy, constrictive pericarditis, or other structural heart disease causing heart failure other than other than cardiomyopathy of either ischemic or non-ischemic etiology
6. Hypotension (systolic pressure  $< 90$  mm Hg)/Cardiogenic shock or other hemodynamic instability requiring the need for inotropic support or intra-aortic balloon pump or other hemodynamic support device
7. Fixed pulmonary artery systolic pressure  $> 2/3$  of systemic systolic blood pressure
8. LVEDD  $> 70$  mm
9. Severe tricuspid regurgitation or physical evidence of right-sided heart failure with echocardiographic evidence of severe right ventricular dysfunction.

10. Cardiac Anatomy deemed not suitable for the Cardiovalve Implant
11. Elevated Creatine Kinase-MB (CK-MB)
12. Surgical or interventional procedure planned within 30 days prior to index procedure
13. UNOS Status 1 heart transplant or prior orthotropic heart transplantation.
14. Life Expectancy < 1 year due to non-cardiac conditions
15. NYHA functional class IVb
16. Chronic Kidney Disease with Creatinine clearance <30 ml/min/1.73m<sup>2</sup>
17. Any prior mitral valve surgery or transcatheter mitral valve procedure
18. Stroke or transient ischemic event within 30 Days prior to index procedure
19. Modified Rankin Scale > 4 disability
20. Class I indication for biventricular pacing (in patient with CRT device not implanted)
21. Implant or revision of any rhythm management device (CRT or CRT-D) or implantable cardioverter-defibrillator within one month prior to index procedure
22. Need for cardiovascular surgery (other than MV disease)
23. Echocardiographic evidence of intracardiac mass, thrombus, or vegetation
24. Active endocarditis
25. Known severe symptomatic carotid stenosis (> 70 % via ultrasound)
26. Active infections requiring current antibiotic therapy
27. Active cancer with expected survival < one year
28. Pregnant or planning pregnancy within next 12 months.
29. Currently participating in an investigational drug or another device study
30. Any condition making it unlikely the patient will be able to complete all procedures
31. Patient (or legal guardian) unable or unwilling to provide written, informed consent before study enrollment
32. Subjects in whom transesophageal echocardiography is contraindicated
33. Known hypersensitivity or contraindication to procedural, post procedural medication (e.g., contrast solution, heparin, anticoagulation therapy) or hypersensitivity to nickel or titanium.
34. Aortic or pulmonic valve disease requiring surgery
35. Venous peripheral anatomy unsuitable for implant delivery
36. Hepatic insufficiency (MELD > 10)
37. Chronic anemia (Hgb < 9)

## **7 PROCEDURES AND METHODS**

### **7.1 Training of Investigational Center Personnel**

Study Investigator(s), study personnel, and study center clinical staff will be trained by Cardiovalve on the use of the Cardiovalve System, the clinical protocol, and CRFs. Specific instructions for use (IFU) explanatory forms and training session were designed in order to ensure a clear understanding of the product and procedure.

The Cardiovalve simulator used for physician training, mimics the cardiovascular anatomy from the femoral vein access point through the Fossa Ovalis to the Mitral Valve, and is based on human CT scans of patients with MR. The simulator is filled with deionized water at  $37\pm 2^{\circ}\text{C}$  (temperature control) and its vessels are made from silicone with friction reduction coating to simulate the actual friction of the vessels. The simulation can be guided by water proof micro cameras. The simulator is pulsatile, with heartbeats generated by a pump; the pressure operates the mitral leaflets in order to mimic the grasping maneuver of the Cardiovalve during delivery and mitral replacement. Physicians will also be assisted by Cardiovalve proctors in all the procedures.

### **7.2 Subject Screening**

An Independent Subject Screening Committee (SSC) will be established by the Sponsor/Sponsor representative. The role of the SSC is to review key information on subjects and establish their final eligibility for participation in the study. SSC review shall occur after the Heart Team at the investigational site has established initial eligibility of a subject and appropriate core laboratory information is available on each potential subject.

### **7.3 Subject Enrolment**

All subjects who meet eligibility requirements will be asked to participate. Subjects will be considered enrolled into the study after:

1. A signed Informed Consent has been obtained.
2. The subject has met all of the eligibility criteria.
3. The screening assessments results have been approved by Heart Team.
4. The Subject Screening Committee (SSC) has confirmed eligibility.

A Screening/Enrolment Log will be maintained to document selected information about candidates who fail to meet the entry criteria. Subjects meeting all eligibility requirements will be eligible to advance in the study. If the subject does not meet all of the eligibility requirements, the subject's participation is terminated.

Assessments used for screening/baseline tests must be completed no more than 30 days before informed consent.

Subjects shall be hospitalized at least 24 hours prior to index procedure to ensure hemodynamic stability and is in optimal condition to undergo the interventional procedure. During this hospitalization a TTE should be obtained to confirm hemodynamic stability.

#### **7.4 Elevated Risk for Open-Heart Surgery Criteria**

In order to be eligible for enrollment, a subject must be deemed a high surgical risk per MVARC definition by the site's Heart Team (as a minimum, one MV cardiac surgeon and one interventional cardiologist, and a cardiac imaging expert).

In addition, an independent Subject Screening Committee (SSC), will confirm subject clinical and anatomical suitability for the procedure.

### **8 MEDICATION AND STUDY VISITS**

#### **Antibiotic Therapy**

- **Before Procedure**

Single dose of antibiotics in accordance with institutional standard of care for valve surgery.

- **Post Procedure**

Minimum single dose of antibiotics in accordance with institutional standard of care for valve surgery

- **Follow-Up:**

Antibiotic prophylaxis for any procedures, consistent with standard of care for any bioprosthetic heart valve

#### **Recommended Anticoagulant/Antiplatelet:**

Subjects should continue all heart failure medications started prior to enrollment unless otherwise directed by their site investigator

- **Before procedure:**

- Aspirin\*:  $\geq 75$ mg daily for at least 7 days prior to procedure or 325 mg

- loading prior to procedure
- Clopidogrel: 75 mg daily may be substituted for aspirin in patients with an indication for P2Y<sub>12</sub> inhibition.
- DAPT (aspirin plus clopidogrel) is ***not recommended***
- **During procedure:**
  - Heparin to maintain an ACT  $\square$  250 seconds or
  - Bivalirudin (0.75 mg/kg IV bolus followed by 1.75 mg/kg/hour IV infusion for the duration of the procedure), in the case of Heparin allergy.

*Discontinue heparin/bivalirudin at the completion of procedure to facilitate access site management.*

- **Post-procedure:**
  - Heparin: Restart heparin at within 12 hours, after completion of the procedure, if no evidence of significant bleeding
  - Warfarin: Initiate administration 24 hours post procedure if no significant bleeding

*INR Target: 3.0-3.5 for initial 6 months post procedure*

- **Subjects in normal sinus rhythm:**
  - low-dose aspirin (100 mg or less daily) OR clopidogrel (75 mg daily) in patients with an indication for P2Y<sub>12</sub> inhibition AND
  - warfarin or equivalent vitamin K antagonist for at least six months
- **Subjects in atrial fibrillation (for initial six months):**
  - low-dose aspirin (100 mg or less daily) OR clopidogrel (75 mg daily) in patients with indication for P2Y<sub>12</sub> AND
  - warfarin or equivalent vitamin K antagonist indefinitely
- **Subjects who are within a year post-DES implantation** for ACS or within 6 months for stable CAD
  - should receive clopidogrel and no aspirin as SAPT plus warfarin for 6 months or indefinitely if in atrial fibrillation. Following the 6 months, if not in atrial fibrillation DAPT may be reinstituted as needed to complete recommended DAPT period after stenting.

## 8.1 Guideline Directed HF Therapy

Guideline directed medical therapy based on AHA/ACC or national guidelines should be given post-procedure with particular attention to heart failure and concomitant CAD and hyperlipidemia. Subjects should receive antibiotic prophylaxis for endocarditis per the recommendations of the AHA for heart valve recipients.

## 8.2 Screening/Baseline Evaluation (Day -45 to 0)

The screening/baseline data can be collected from 45 days prior to procedure up to the day of procedure. Obtaining documented Informed Consent is mandatory before any study related procedure is performed. The following data shall be collected:

- Demographics and medical history
- Physical assessment includes weight, height, BMI, and vital signs
- Laboratory blood tests: chemistry panel, CBC, cardiac enzymes, plasma-free Hemoglobin, INR (Up to 72 hours prior procedure)
  - Serum creatinine, Hemoglobin, CK-MB must be collected for screening and must be collected no more than 30 days before informed consent.
- BNP or NT-proBNP (Up to 72 hours prior procedure)
- Lipid Panel (Up to 72 hours prior procedure)
- Neurological assessment/modified Rankin Scale (mRS)
- STS Risk score
- Pregnancy test (females of childbearing age only) (Up to 72 hours prior procedure)
- 12-Lead Electrocardiogram (ECG/EKG)
- Coronary angiogram for assessing coronary arteries status\* (optional, if clinically indicated)
- Transesophageal Echocardiogram (TEE)\* (if TTE suboptimal)
- Transthoracic Echocardiogram (TTE)\*
- New York Heart Association (NYHA) classification
- 6MWT
- Quality of Life Questionnaires (KCCQ)
- 4DCT Scan\*
- Clinical Frailty Score
- MELD Score
- Concomitant medications (Cardiac and anticoagulant/antiplatelet medications)
- Protocol Deviations
- Adverse events collected once the subject is enrolled

\*Coronary Angiogram, 4DCT scan, TEE and TTE may be done within 3 months of informed consent; TTE shall be repeated during the 24 hours prior to the index procedure to assure subject is hemodynamically and clinically stable to undergo the interventional procedure. If available SOC 4DCT scan does not include an Access Scan (venous phase CT abdomen/pelvis), a doppler ultrasound of the groin should be obtained to demonstrate access. The 4DCT does not need to be repeated only to obtain access scan.

### 8.3 Implant Procedure

For detailed instructions refer to Cardiovalve instructions for use. The study procedure includes the following steps:

1. Heparinize the patient. Activated Clotting Time (ACT) should be at a level of at least
2. 250 seconds throughout the whole procedure.
3. The subject is prepared as per institution's standard practice for trans- septal catheterization.
4. Cardiovalve implant size is selected according to the mitral annulus size measured preoperatively with appropriate imaging methods.  
Left atrium (LA) access is performed using standard trans-venous, trans- septal equipment, and technique.
5. An exchange length extra stiff GW (260cm) is introduced to the LA
6. Perform dilatation of the fossa ovalis using a 10mm or 12 mm balloon.
7. The femoral vein is dilated using standard femoral dilators setup to 26Fr) and finalized with Cardiovalve 33Fr dilator (supplied with the system).
8. The Cardiovalve transfemoral delivery system is introduced over the guide wire to the
9. LA until the distal capsule has crossed the fossa ovalis.
10. Using delivery system maneuverability (biplane steering of the tip of the catheter), position the Cardiovalve capsule in coaxial and concentric position relative to the mitral valve, while keeping the RO marker of the distal capsule above the mitral plane.
11. Rotate the **Ventricle capsule knob ("1")** clockwise (CW) in order to open the ventricle capsule to expose the grasping legs while verifying on echocardiography and fluoroscopy views. Continue doing so until reaching a mechanical hard stop of the delivery system.
12. Advance the IC handle in order to introduce the grasping legs into the LV.
13. Verify on echocardiographic view that the grasping legs have reached slightly beneath to the native leaflets.
14. Gently pull back the IC handle till engaging the posterior and anterior leaflets.
15. Verify by echo in at least 3 planes, A1-P3, A2-P2, A3-P1, that leaflets are grasped throughout.
16. If not, repeat steps 5-15 for adequate leaflets grasping.
17. Once leaflets grasping is verified, gently pull back the IC handle in order to secure the grasping and then lock the **IC latch** in place.
18. Rotate the **atrial capsule knob ("2")** CW in order to open the atrial capsule and unsheath the atrial flange, once verified on fluoroscopy.
19. Press down the **Ventricle capsule stopper ("3")** continuously while rotating the **ventricle capsule knob ("1")** CW until the Cardiovalve device is completely deployed and released from the delivery system.

20. Gently rotate the **Atrial capsule knob (“2”)** CCW to advance the Atrial capsule to the left ventricle. Under fluoroscopy, verify that the atrial capsule marker has passed through the deployed device and is in the LV. Press down the Ventricle capsule stopper (“3”), rotate the Ventricle capsule knob (“1”) CCW and close the ventricle capsule until the radiopaque marker is reaching the radiopaque marker of the atrial capsule.
21. Release all the steering of the delivery system and carefully retract the entire system through the deployed device and the fossa ovalis using the support of the guidewire till full retrieval of the system from the venous access.
22. Careful evaluation of the ASD shall be performed. It is strongly recommended that the iatrogenic ASD be considered for closure, especially if the opening is  $\geq 8$  mm and/or significant flow across ASD
23. Access sites (arterial as well as venous) shall be carefully managed with careful consideration of surgical repair. Ultrasound evaluation of access sites is recommended.

## 8.4 Follow-up Evaluation

The patient tests and procedures that will be performed are listed below and are presented in the Table of Assessments according to the following parameters.

- Post procedure (within 48 hours)
- Discharge (or 7 days whichever is earliest)
- 30 days (+7 days) post procedure
- 3 months ( $\pm 7$  days) post procedure
- 6 Months ( $\pm 30$  days) post procedure
- 12 months ( $\pm 60$  days) post procedure
- every year annually for a total of 5 years ( $\pm 60$  days) post procedure

The subject will come to the clinic and the following data will be obtained and documented.

### 8.4.1 *Post-procedure follow-up*

Subjects shall be admitted to the Intensive Care Unit and monitored for a minimum of 2 days (48 hours) post procedure. Invasive hemodynamic monitoring shall be used to ensure subject is stable for the 48 hours post procedure prior to discharge or transfer to a standard hospital ward. Further evaluations shall include:

- Laboratory tests: serum creatinine, cardiac enzymes, INR
- 12-Lead ECG/EKG
- Adverse events / device deficiencies / protocol deviations

#### **8.4.2 Discharge**

The following assessments will be performed at discharge or within 7 days post-procedure, whichever comes first.

- Physical assessment and vital signs
- Laboratory tests: Chemistry panel, CBC, INR
- TTE
- mRS scale (optional)
- National Institutes of Health Stroke Scale (NIHSS, optional)
- Clinical Frailty Score
- Concomitant medications
- Adverse events / device deficiencies / protocol deviations

Study subjects will receive an implant card after the implant procedure containing the implant details and investigator contacts allowing communication with the investigator during and after the study. The patient will be advised to carry the implant card at all times.

#### **8.4.3 30 Days, 3-Months, 6-Months Post-Procedure**

- Plasma-free Hemoglobin

#### **8.4.4 30 Days, 12-Months Post-Procedure**

- Laboratory Tests: CBC

#### **8.4.5 30 Days, 6-Months, 12 Months Post-Procedure, Annually for a total of 5 years Post-Procedure**

- 12-Lead ECG/EKG
- MELD Score

#### **8.4.6 6-Months, 12 Months Post-Procedure, Annually for a total of 5 years Post- Procedure**

- Clinical Frailty Scale

#### **8.4.7 30 Days, 3-Months, 6-Months, 12 Months Post-Procedure, Annually for a total of 5 years Post-Procedure**

The following assessments will take place 30 days, 3-months, 6-months, 12-months post-procedure, and then annually thereafter for a total of 5 years post-procedure:

- Physical Assessment and vital signs
- Laboratory Tests: Chemistry panel, INR, and BNP or NT-proBNP
- Laboratory Tests: Cardiac Enzymes (at 30 days only)

- TTE
- 4D CT Scan (at 30 days only)
- mRS Scale (optional)
- NIHSS (optional)
- NYHA Classification
- Quality of Life Questionnaires (KCCQ)
- 6MWT (optional at 30 D post procedure)
- Concomitant medications and changes thereof
- Adverse events / device deficiencies / protocol deviations

## 8.5 Schedules of Treatments and Assessments

**Table 5: Schedule of Treatments and Assessments**

Assessments/ Procedures	Screening/ Baseline <sup>7</sup>	Procedure	Post procedure	Discharge or 7 days	30-Day	3 Months	6 Months	12 months	Annually for 5 years post-index
<i>Visit Window</i>	<i>See footnotes</i>		<i>Within 48 hrs.</i>		<i>+7 days</i>	<i>±7 days</i>	<i>±30 days</i>	<i>±60 days</i>	<i>±60 days</i>
<b>CLINICAL ASSESSMENTS</b>									
Informed consent	X								
Inclusion /exclusion criteria	X								
Demographic & Medical History	X								
STS Score	X								
Clinical Frailty Score	X			X			X	X	X
MELD Score	X				X	X	X	X	X
Physical Exam and Vital Signs	X <sup>8</sup>			X	X	X	X	X	X
Medications (Cardiac and Antiplatelet/Anticoagulants) <sup>2</sup>	X	X		X	X	X	X	X	X
NYHA Classification	X				X	X	X	X	X
Neurological exam (NIHSS and mRS if there is a neurologic event)	X			Optional <sup>3</sup>	Optional <sup>3</sup>	Optional <sup>3</sup>	Optional <sup>3</sup>	Optional <sup>3</sup>	Optional <sup>3</sup>
Quality of Life (KCCQ)	X				X	X	X	X	X
6-Minute Walk Test (6MWT)	X				Optional <sup>3</sup>	X	X	X	X
<b>EXAMS AND TESTS</b>									
Coronary Angiogram <sup>4</sup>	Optional								
12-Lead ECG/EKG	X	X	X		X		X	X	X
TTE <sup>4</sup>	X			X	X	X	X	X	X
TEE <sup>4</sup>	X <sup>6</sup>	X							
4D CT Scan <sup>1</sup>	X <sup>9</sup>				X				
Fluoroscopy/Angiography		X							
<b>LABORATORY EXAMS<sup>1</sup></b>									
Pregnancy Test <sup>5</sup>	X								
Chemistry Panel (BUN, CO <sub>2</sub> , Serum Creatinine, Cl, K, NA, AST (GOT), serum Total Protein, Albumin, ALT (GPT), Uric Acid, LDH, Haptoglobin)	X		Serum Creatinine	X	X	X	X	X	X

Assessments/ Procedures	Screening/ Baseline <sup>7</sup>	Procedure	Post procedure	Discharge or 7 days	30-Day	3 Months	6 Months	12 months	Annually for 5 years post-index
<b>Visit Window</b>	<b>See footnotes</b>		<b>Within 48 hrs.</b>		<b>+7 days</b>	<b>±7 days</b>	<b>±30 days</b>	<b>±60 days</b>	<b>±60 days</b>
Cardiac Enzymes: CK-MB and TnT or TnI	X		X		X				
Complete Blood Count (WBC, RBC, HCT, Hgb, platelet count)	X	X		X	X			X	
BNP or NT-proBNP	X				X	X	X	X	X
Lipid Panel (Total Cholesterol, LDL, HDL, Triglycerides)	X								
Plasma-free Hemoglobin	X				X	X	X		
INR	X		X	X	X	X	X	X	X
Activated Clotting Time (ACT)		X							
<b>SAFETY/COMPLIANCE</b>									
Adverse events	X	X	X	X	X	X	X	X	X
Device Deficiencies/Failures		X	X	X	X	X	X	X	X
Protocol Deviations	X	X	X	X	X	X	X	X	X
<sup>1</sup> Laboratory tests maybe completed up to 72 hours prior to the procedure with the exception of CK-MB, serum Creatinine and Hemoglobin. These must be collected no more than 30 days before informed consent. CT scan must be completed no more than 3 months before the procedure unless there have been changes to cardiovascular health within that timeframe or if requested by the CSC. Other screening/baseline tests must be completed no more than 30 days before informed consent. <sup>2</sup> Patients on anticoagulants (warfarin, dabigatran, apixaban and rivaroxaban). Anticoagulation is recommended for a minimum of 6 months following Cardiovalve implantation <sup>3</sup> To be done when clinically indicated dependent on institution standard of care and if there is a suspected neurologic event <sup>4</sup> Coronary Angiogram, TEE and TTE May have done within 3 months, unless have been changes to cardiovascular health within timeframe or if requested by the CSC. <sup>5</sup> Urine or blood test if subject of child-bearing potential <sup>6</sup> Screening TEE only if screening TTE is suboptimal <sup>7</sup> Baseline data can be collected from 45 days prior to the procedure up to the day of procedure <sup>8</sup> Height only required at screening/baseline									

## 9 ADVERSE EVENTS

Subjects 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 in the study. The investigator will classify the AEs based on the definitions as follows.

### 9.1 General Adverse Event Definitions

**Adverse event:** is defined as any undesirable clinical occurrence or change from patient's baseline (or pre-device procedure) condition, whether it is considered device related or not.

Adverse Event Identification: a condition that is one of the following:

- 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

#### ***Serious Adverse Events:***

A serious adverse event (SAE) is any untoward medical occurrence that: Adverse event that

- Led to death,
- Led to serious deterioration in the health of the subject, that either resulted in
  - A life-threatening illness or injury, or
  - A permanent impairment of a body structure or a body function, or
  - In-patient or prolonged hospitalization, or
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

#### ***Unanticipated Serious Adverse Device Effect***

An Unanticipated Serious Adverse Device Effect (USADE) is a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report / labeling.

Study sponsor, or their designee, in cooperation with the Investigator, will assess all serious adverse events considered device-related for potential reportability to the FDA as an Unanticipated Serious Adverse Device Effect (USADE).

## 9.2 Adverse Event Classification

Adverse events will be assigned an attribution according to the Investigator's believed primary cause. Events will be categorized by relationship to the investigational device, index procedure, concomitant medications, pre-existing condition, intercurrent condition, intercurrent intervention, or other.

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

*Non-Investigational Device:* It is reasonable to believe that the event is associated with an accessory device used during the study procedure and is not specific to the investigational device use

*Procedure Related Adverse Event:* An adverse event which, in the judgment of the Investigator, results as a consequence of the index (i.e. Cardiovalve implant) procedure or any associated procedures.

*Medication-Related Adverse Event:* an adverse event is considered to be medication related when, in the judgment of the Investigator, it is reasonable to believe that the event is associated with any medications used.

*Pre-Existing Condition-Related Adverse Event:* an adverse event is considered to be related to a pre-existing condition when, in the judgment of the Investigator, it is reasonable to believe that the event is associated with the subject's pre-existing condition and is not specific to the investigational device or index procedure or medication to address heart failure. Pre-existing conditions that are aggravated or become more severe during or after the index procedure should be evaluated on a case-by-case basis to determine if the event may be more appropriately classified as device- or index procedure-related.

*Intercurrent Condition:* It is reasonable to believe that the event is directly associated with an intercurrent condition/co-morbidity.

*Intercurrent Intervention:* It is reasonable to believe that the event is directly associated with an intercurrent intervention which was performed for reasons other than to address a device- or index procedure-related complication.

*Observation/Incidental Finding:* Abnormal or non-specific findings or observations that may be associated with study activities but no identifiable clinical correlation and suggests no specific pathophysiological process (such as painful access or tired). Such an event will not be considered an adverse event unless associated with clinical sequelae or requires specific intervention. When clinical sequelae occur or when the intervention required exceeds standard response for similar symptom/event, it will be reported as an adverse event

*Unknown:* The adverse reaction cannot be judged because information is insufficient or contradictory, and cannot be supplemented or verified.

### 9.3 Adverse Event Severity

The severity of adverse events will be rated according to the following scale:

**Mild:** asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; event does not generally interfere with usual activities of daily living.

**Moderate:** minimal, local, or noninvasive intervention may be indicated; event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.

**Severe:** medically significant but not necessarily immediately life-threatening; hospitalization or prolongation of hospitalization indicated and may require intensive therapeutic intervention to resolve.

### 9.4 Events Expected to Occur with Cardiovalve 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 subjects 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 following procedure, even if requiring correction.
- Pre - Planned future Surgical Procedures.
- Low grade temperature increase ( $\leq 101^{\circ}\text{F}$  or  $38.5^{\circ}\text{C}$ ).
- 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.

- Post-operative hematocrit decrease from baseline, not associated with hemodynamic changes, remaining above 25% and requiring < 2 units PRBC's.
- Minor, localized tenderness, swelling, induration, oozing, etc. at surgical site.
- Sinus bradycardia/tachycardia that does not require treatment or intervention
- Systolic or diastolic blood pressure changes that do not require treatment or intervention.
- Thrombocytopenia: does not become an AE until treatment is administered.
- Hyperglycemia/Hypoglycemia: The use of insulin in the post op period does not constitute hyperglycemia if during the same hospitalization. An elevated blood sugar of less than 250 mg/dl during the first 48 hours post op does not constitute hyperglycemia.
- Increased INR > 4.0 during the initial 7 days post procedure

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.

## **9.5 Adverse Event Reporting Requirements**

### **9.5.1 General Reporting Requirements (Non-Serious 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 should be recorded on the Device Observations eCRF, with the exception of those adverse events identified in **Section 9.5**. 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.

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

- Completion of separate Adverse Event forms to document each event
- Completion of separate Device Observation forms for each device observation/deficiency
- The forms must be electronically signed by the Investigator, and
- Supplying to the Sponsor, upon Sponsor's request, with any additional information related to the safety reporting of a particular event
- 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 are included in the Study Reference Manual.

### **9.5.2 Reporting Requirements (Serious Adverse Events)**

All serious adverse events (including SADE and USADE) should be reported by the Investigator (or designee) by submitting the Adverse Event Electronic Case Report Form to the Sponsor, within 24 hours of learning of the adverse event.

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)<sup>1</sup>. 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 effect. Thereafter the Sponsor shall submit such additional reports concerning the effect as FDA requests.

Any unanticipated adverse events: must also be reported to the FDA, all reviewing IRB's/EC's and participating investigators within ten (10) days of receiving notice of the serious adverse event or death, (or per local IRB/EC requirements), and documentation of the report sent to Sponsor or their designee.

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

---

<sup>1</sup> 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 subjects.

## 9.6 Subject Death

Subject death during the investigation should be reported with written documentation to Sponsor or designee within 24 hours of Investigator's knowledge of the death. The Adverse Event that resulted in death should be entered in the database within 24 hours and include a brief description of the relevant details of the death. The electronic Adverse Event Form must be electronically signed by the Investigator. A copy of the death records, death certificate and an autopsy report (if performed) are required to be sent to the Sponsor or designee within 10 days following the death. In addition, subject death must be reported to the IRB/EC in accordance with IRB/EC requirements.

## 9.7 Treatment Failures & Device Malfunctions

All reported device observations, malfunctions or failures (i.e. Device Deficiencies) for the Cardiovalve System are required to be documented on the Procedure/ Device Observation Case Report Form. In the event of a suspected observation or device problem, the device shall be returned to the Sponsor to the extent possible for analysis. Instructions for returning the investigational device are included in the Study Reference Manual.

## 9.8 Sponsor Reporting

All 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 ISO 14155 and regulatory requirements, as applicable.

# 10 STATISTICAL CONSIDERATIONS

## 10.1 Statistical Overview

This is a feasibility study designed to primarily assess the safety and performance of the Cardiovalve to treat mitral regurgitation in patients at elevated risk for surgery. Given the severity of the condition treated and the potential adverse events involved, a large sample of patients would not be appropriate for the initial clinical application of the device. A sample of 15 patients treated at up to 5 different expert centers is expected to provide meaningful data for the design of a larger trial.

## 10.2 Analysis Population

All subjects that sign an Informed Consent will be tracked and if not deemed eligible during the screening process, a complete summary of the reason for screen failure shall be documented and

summarized in all study reports. If the subject has an attempted procedure but the Cardiovalve System does not enter the body, the subject shall be followed through 30 days and will be summarized for safety only. The primary analysis population (summary of all study endpoints) will include all subjects that sign the ICF and have the Cardiovalve System enter the body. These subjects will constitute the study population as outlined in the EFS IDE approval.

### **10.3 Interim and Final Analyses**

All final study analyses will be performed when all subjects have completed the 30-day follow-up visit. Interim safety reports will be performed and submitted to FDA for review for every 5 patients for the first 15 patients when the 5th, 10th, and 15th patients reach 30 days post implant. be performed to support regulatory submissions or other purposes.

### **10.4 Treatment of Missing or Spurious Data**

Reasonable efforts will be made to obtain complete data for all subjects; however, missing observations will occur due to subjects lost to follow-up or noncompliance with required assessments. Any missing data on study endpoints will be described. Study endpoints will be analyzed using all available data. Due to the nature of the study, missing data will not be imputed.

## **11 DATA HANDLING AND RECORD KEEPING**

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6 section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a manufacturer-sponsored study, each site will permit authorized representatives of the Sponsor(s), the Sponsor's designee, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

Source data are all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the trial.

The Investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

### **11.1 Data Management Procedures**

Electronic Case Report Forms (eCRFs) will be used to collect all subject data during the course of the study, which are part of a database that meets 21 CFR Part 11 requirements. eCRFs must be fully completed for each subject and electronically signed by the Investigator when complete. Federal Regulations and Good Clinical Practice Guidelines require that Investigators maintain information in the study subject's medical records that corroborate data collected on the eCRFs. In order to comply with these regulatory requirements, the following information should be maintained:

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

### **11.2 Data Retention**

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in the United States and until there are no pending or contemplated marketing applications in the United States or until at least 2 years have elapsed since the formal discontinuation of clinical development of the product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

### **11.3 Investigator Records**

Investigators will maintain complete, accurate and current study records. Records shall be maintained during the clinical study and for two years after the later of the

date on which the study is terminated or completed, or the date the records are no longer required to support approval of the device. Investigator records shall include the following materials:

- ***Correspondence:*** Documentation of all verbal and written correspondence with FDA, Sponsor, Sponsor Clinical Representative, the Clinical Monitor, the CEC, DMC, and other investigators regarding this clinical study or any patient enrolled therein.
- ***Subject Records:*** Signed informed consent forms, copies of all completed Case Report Forms and supporting documents (laboratory reports, reports of diagnostic tests, medical records, etc.) and records of exposure of each subject to the device. Informed consent must comply with FDA regulations (21 CFR, part 50).
- ***Investigational Device Accountability:*** Access to investigational devices shall be controlled and the investigational devices shall be used only in the clinical investigation and according to the Clinical Investigational Plan/Protocol. The Sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal. The Principal Investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include:
  - the date of receipt,
  - identification of each investigational device (batch number/serial number or unique code),
  - the expiry date,
  - the date or dates of use,
  - subject identification,
  - date on which the investigational device was returned, if applicable, and
  - the date of return of unused, expired or malfunctioning investigational devices, if applicable.

- **Clinical Investigational Plan/Protocol:** A current copy of the Clinical Study Protocol including IFU of the Cardiovalve device and blank case report forms.
- **Institutional Review Board (IRB) Information:** All information pertaining to IRB review and approval of this clinical study including a copy of the IRB letter approving the clinical study, a blank informed consent form approved by the IRB, and certification from the IRB Chairman that the IRB complies with FDA regulations (21CFR, Part 56)/regulatory body regulations, and that the IRB approved the clinical study protocol.
- **Investigator Agreements:** Copies of signed Investigator and Sub-Investigator Agreements with accompanying curriculum vitae.

**Other:** Any other records that may be required by applicable state or federal laws.

## 12 INVESTIGATOR REPORTS

The Investigator will prepare and submit the following reports:

**Table 6. Responsibilities for Preparing and Submitting Reports**

Type of Report	Prepared by Investigator for	Time of Notification
Enrollment Notification eCRF	Sponsor	Within 24 hours of Informed Consent
Completion of eCRFs	Sponsor	Within 10 working days
Serious/ Unanticipated Adverse Device Event eCRF	Sponsor and IRB (as required)	Within 24 hours of knowledge or as required by IRB
Subject Death	Sponsor and IRB (as required)	Within 24 hours of knowledge
Withdrawal of IRB or FDA Approval	Sponsor	Within 24 hours of knowledge
Informed Consent Not Obtained	Sponsor and IRB (as required)	Within 24 hours of knowledge or as required by IRB
Progress report	Sponsor and IRB	Annually
Final summary report	Sponsor and IRB and FDA	Within 6 months of study completion
Other reports	Sponsor and IRB and FDA	As needed

## 13 QUALITY CONTROL AND ASSURANCE

### 13.1 Site and Investigator Selection

The Sponsor selects qualified investigators with appropriate experience at health care facilities with adequate resources to participate in this study. Investigational sites will be selected using combined current assessments of site and investigator qualifications.

### 13.2 Investigator Responsibilities

Prior to participation in the Study, the appointed Principal Investigator at the Investigational Site must obtain written approval from his/her IRB. This approval must be in the Principal Investigator's name and a copy sent to the Sponsor/Sponsor Clinical Representative along with the IRB approved Informed Consent Form, and the signed Clinical Study Agreement, prior to first shipment of the investigational device.

The Principal Investigator must also:

- Conduct the study in accordance with the study protocol, the signed Clinical Study Agreement, applicable regulations (including 21 CFR Parts 11, 50, 54, 56 and 812), the Declaration of Helsinki, Good Clinical Practices, any conditions of approval from the IRB or FDA/Regulatory Authority, and ISO 14155;
- Agree to participate in a device training program prior to study initiation, as applicable;
- Provide a copy of a Financial Disclosure form that summarizes financial interest in the Sponsor. In addition, the Sponsor will be notified if disclosed financial information changes at any time during the clinical investigation or up to one year following the closure of the study;
- Provide the Sponsor with curriculum vitae, information regarding previous clinical investigation experiences (including investigations or research that was terminated);
- Assure that the study is not commenced until IRB approval has been obtained;
- Assure that informed consent is obtained from each subject prior to enrollment, using the IRB and Sponsor approved forms;
- Ensure that investigational devices are only used by approved, trained investigators in subjects who meet study inclusion/exclusion criteria;
- Supervise all testing of the device involving human subjects;
- Complete all eCRFs and study documentation and relevant imaging assessments, and promptly forward to the Sponsor or its authorized representative for data management;

- Report all adverse events, non-medical complaints and non-compliance to Sponsor according to the protocol and regulatory requirements;
- Provide all required data and agree to source document verification of study data with patient's medical records;
- Allow staff of the Sponsor and its authorized representatives, as well as representatives from regulatory bodies, to review, inspect and copy any documents pertaining to this clinical investigation; and,
- Oversee retention of required records and documents related to the investigation.

The Principal Investigator may delegate one or more of the above functions to an associate or Sub-Investigator. However, the Principal Investigator retains overall responsibility for proper conduct of the study, including obtaining and documenting patient informed consent, compliance with the study protocol, and collection of all required data. Delegated tasks must be documented on a Delegation Log.

### 13.3 Protocol Deviations

An investigator is not allowed to deviate from the Protocol if the deviation affects subject's rights, safety and wellbeing, or the scientific integrity of the clinical investigation. Under emergency circumstances, deviations from the Protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Sponsor and the IRB. Such deviations shall be documented and reported to the Sponsor and the IRB as soon as possible.

A protocol deviation is a failure to comply with the requirements specified within this clinical study protocol. Examples of protocol deviations may include enrollment of a study patient who does not meet all of the inclusion/exclusion criteria specified in the protocol and missed study visits without documentation. Each investigator shall conduct this clinical study in accordance with this clinical study protocol, regulatory body regulations, ISO guidelines, Good Clinical Practices, and any conditions of approval imposed by their IRB.

The protocol deviations for this protocol consist of, but not limited to the following:

- Failure to obtain patient's informed consent prior to any study-related activities;
- Failure to conduct protocol required clinical follow-ups;
- Failure to conduct protocol required clinical follow-ups within time windows; and,
- Failure to report serious adverse events according to protocol requirements.

In the event of any deviation from the protocol, the Investigator will be notified of the site's non-compliance. Corrective actions may be required, if necessary. Continued protocol deviations despite re-education of the study site personnel or persistent protocol deviation may result in

termination of the site's study participation. Patients enrolled at these sites will continue to be followed per the clinical protocol.

### **13.4 Protocol Deviation Process**

Investigators must report protocol deviations to the Sponsor per *Table 6* by entering data into the eCRF. Any protocol deviations that affect the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances must be reported within 24 hours to the Sponsor and IRB if required by the IRB.

### **13.5 Corrective/Preventive Action**

The Sponsor reserves the right to terminate an investigational site from the study for any of the following reasons:

1. Repeated failure to complete Electronic Case Report Forms, in a timely manner
2. Failure to attempt to obtain Informed Consent from the legally authorized representative
3. Failure to report Serious Adverse Events in a timely manner
4. Loss of or unaccountable investigational device inventory
5. Repeated protocol violations
6. Failure to enroll an adequate number of subjects

## **14 STUDY OVERSIGHT**

### **14.1 Subject Screening Committee**

An Independent Subject Screening Committee (SSC) will be established under the direction of Cardiovascular Research Foundation, an authorized designee of the Sponsor. The role of the SSC is to review key information on subjects and establish their final eligibility for participation in the study. SSC review shall occur after the Heart Team at the investigational site has established initial eligibility of a subject.

### **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 Cardiovascular Research Foundation, an authorized designee of 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 and/or heart failure medication. 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 Monitoring Committee**

The Data Monitoring Committee (DMC) will be assembled prior to subject enrollment (under the direction of Cardiovascular Research Foundation). The DMC will be comprised of leading physician practitioners and a biostatistician who are not investigators in the trial. The membership of the committee shall remain anonymous to the investigational sites to the extent possible to reduce any potential bias.

In the safety monitoring role, prior to enrollment of any subjects, the DMC will establish a charter including a mission statement, operating procedures, and proposed monitoring criteria for the study, including any required interim analysis and proposed study stopping rules. At a minimum, interim safety reports will be performed and submitted to FDA for review for every 5 patients for the first 15 patients when the 5th, 10th, and 15th patients reach 30 days post implant. be performed to support regulatory submissions or other purposes. The specific stopping rules shall remain confidential to the site and Sponsor to minimize bias. Written minutes of all meetings shall be developed after each DMC 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 Echocardiographic Core Laboratory**

Baylor Scott and White Research Institute Echocardiography Core Laboratory shall perform independent echocardiographic imaging assessments. The evaluation shall serve as an independent evaluation of the mitral valve structure to guide the potential subject enrollment as well as the product performance assessments.

## **15 ETHICS/PROTECTION OF HUMAN SUBJECTS**

### **15.1 Statements of Compliance**

This clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, International Standard Organization (ISO

14155:2011) and 21 CFR Part 812, 50, 54, 56. The clinical investigation shall not begin until the required approval/favorable opinion from the IRB or regulatory authority have been obtained, if appropriate. Any additional requirements imposed by the IRB or regulatory authority shall be followed.

## **15.2 Institutional Review Board (IRB)**

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate IRB. Any amendments to the protocol or consent materials must also be approved before they are placed into use.

## **15.3 Informed Consent Process**

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/ administering the investigational treatment. Consent forms will be IRB-approved and the subject will be asked to read and review the document. Upon reviewing the document, the Investigator will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any procedures being done specifically for the study. The subject should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

### ***15.3.1 Subject Unable to Read or Write***

Informed consent shall be obtained through a supervised oral process if a subject or legally authorized representative is unable to read or write. An independent witness shall be present throughout the process. The written informed consent form and any other information shall be read aloud and explained to the prospective subject or his/her legally authorized representative and, whenever possible, either shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent form attesting that the information was accurately explained and that informed consent was freely given.

### **15.3.2 New Information**

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the subject(s) affected in written form. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing.

### **15.4 Subject Confidentiality**

Confidentiality of data shall be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access.

The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data. The Principal Investigator or institution shall provide direct access to source data during and after the clinical investigation for monitoring, audits, IRB review and regulatory authority inspections. As required, the Principal Investigator or institution shall obtain permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical investigation.

## **16 CLINICAL INVESTIGATIONAL PLAN/PROTOCOL AMENDMENTS**

The Instructions for Use, Protocol, CRFs, ICF and other subject information, or other clinical investigation documents shall be amended as needed throughout the clinical investigation, and a justification statement shall be included with each amended section of a document. Proposed amendments to the Protocol shall be agreed upon between the Sponsor and Principal Investigator, or the coordinating investigator. The amendments to the Protocol and the subject's informed consent form shall be notified to, or approved by, the IRB and regulatory authorities, as required. For non-substantial changes [e.g. minor logistical or administrative changes, change of monitor(s), telephone numbers, renewal of insurance] not affecting the rights, safety and well-being of human subjects or not related to the clinical investigation objectives or endpoints, a simple notification to the IRB and, where appropriate, regulatory authorities can be sufficient. The version number and date of amendments shall be documented.

## **17 TERMINATION OF STUDY OR STUDY SITE PARTICIPATION**

The Sponsor may terminate the study at any time. If the study is terminated prior to the completion of expected enrollment for any reason, all participating centers will be notified within five working days. All patients already enrolled will continue to be followed for the planned course of study described in this protocol. The study shall be terminated following the final follow-up visit of the last enrolled patient.

The Sponsor reserves the right to terminate study site participation and remove appropriate study

materials at any time. Specific instances that may precipitate such termination include but are not limited to the following:

- Failure to meet minimum patient enrollment requirements
- Failure to comply with protocol specified procedures and documentation
- Failure to comply with Good Clinical Practice

The site Investigator may also discontinue study participation with suitable written notice to the Sponsor.

## 18 PUBLICATION POLICY

Boston Biomedical Associates will post results on the [clinicaltrials.gov](http://clinicaltrials.gov) registry as required by International Committee of Medical Journal Editors member journals and applicable US laws and regulations. Study results will be published regardless of the outcome.

## 19 BIBLIOGRAPHY

1. Guha K, McDonagh T. Heart failure epidemiology: European perspective. *Curr Cardiol*. Rev. May 2013;9(2):123-127.
2. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet*. Sep 16 2006;368(9540):1005-1011.
3. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med*. May 31 2001;344(22):1651-1658.
4. Rich MW. Heart failure in the 21st century: a cardiogeriatric syndrome. *J Gerontol A Biol Sci Med Sci*. Feb 2001;56(2):M88-96.
5. Writing Group M, Lloyd-Jones D, Adams RJ, et al. Heart disease and stroke statistics--2010 update: a report from the American Heart Association. *Circulation*. Feb 23 2010;121(7):e46-e215.
6. Stuart M. Percutaneous Mitral Valve Therapy: The Next Decade. *START-UP*. 2012;17(2).
7. Mitral valve repair and replacement patients: incidence of complications summary. STS National Database STS National Database [database online] 2008; <https://www.sts.org/national-database> Accessed March 9,

- 2017.
8. Griffen, Hayek. Mitral valve disease: Disease Management (Cleveland Clinic). Cleveland Clinic. July 14, 2004 2004.
9. Castillo JG, Solis J, Gonzalez-Pinto A, Adams DH. [Surgical echocardiography of the mitral valve]. Rev Esp Cardiol. Dec 2011;64(12):1169-1181.
10. Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, et al. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. N Engl J Med. Mar 3 2005;352(9):875-883.
11. Feinberg MS, Schwammenthal E, Shlizerman L, et al. Prognostic significance of mild mitral regurgitation by color Doppler echocardiography in acute myocardial infarction. Am J Cardiol. Nov 1 2000;86(9):903-907.
12. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the  
the  
2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. Jun 20 2017;135(25):e1159- e1195.
13. O'Gara PT, Calhoon JH, Moon MR, Tommaso CL. Transcatheter therapies for mitral regurgitation: a professional society overview from the American College of Cardiology, the American Association for Thoracic Surgery, Society for Cardiovascular Angiography and Interventions Foundation, and the Society of Thoracic Surgeons. J Am Coll Cardiol. Mar 4 2014;63(8):840-852.
14. Mirabel M, Iung B, Baron G, et al. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? Eur Heart J. Jun 2007;28(11):1358-1365.
15. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. Jun 10 2014;129(23):2440-2492.
16. Ramlawi B, Gammie JS. Mitral Valve Surgery: Current Minimally Invasive and Transcatheter Options. Methodist DeBakey Cardiovasc J. Jan-Mar 2016;12(1):20-26.
17. Feldman T, Young A. Percutaneous approaches to valve repair for mitral

- regurgitation. J Am Coll Cardiol. May 27 2014;63(20):2057-2068.
18. Patel A, Bapat V. Transcatheter mitral valve replacement: device landscape and early results. EuroIntervention. Sep 24 2017;13(AA):AA31-AA39.
  19. Ruiz CE, Kliger C, Perk G, et al. Transcatheter Therapies for the Treatment of Valvular and Paravalvular Regurgitation in Acquired and Congenital Valvular Heart Disease. J Am Coll Cardiol. Jul 14 2015;66(2):169-183.

## 20 APPENDIX 1: ACRONYMS

Acronym	Definition
6MWT	Six Minute Walk Test
ACC	American College of Cardiology
ACS	Acute Coronary Syndrome
AE	Adverse Event
AF	Atrial Fibrillation
AHA	American Heart Association
ASA	Acetylsalicylic Acid (Aspirin)
BNP	Brain Natriuretic Peptide
BUN	Blood Urea Nitrogen
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CBC	Complete Blood Count
CCW	Counter Clockwise
CEC	Clinical Events Committee
CI	Confidence Interval
CRF	Case Report Form
CRT	Cardiac Resynchronization Therapy
CRT-D	Cardiac Resynchronization Therapy Implantable Cardioverter Defibrillator
CS	Capsule Shaft
CT	Computed Tomography
CW	Clockwise
DCF	Data Clarification Form
DES	Drug-eluting Stent
DMC	Data Monitoring Committee
DS	Delivery System
DSMB	Data Safety Monitoring Board

Acronym	Definition
EC	Ethics Committee
ECG/EKG	Electrocardiogram
eCRF	Electronic Case Report Form
EGFR	Estimated Glomerular Filtration Rate
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analysis Set
FDA	Food and Drug Administration
GC	Guide Catheter
GCP	Good Clinical Practice
GDMT	Guideline Directed Medical Therapy
HF	Heart Failure
HSS	
IC	Implant Catheter
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFU	Instructions For Use
INR	International Normalized Ratio
IRB	Investigational Review Board
ISO	International Organization for Standardization
ITT	Intent to Treat
LVEDD	Left Ventricular End Diastolic Diameter
LVEDVI	Left Ventricular End Diastolic Volume Index
LVEF	Left Ventricular Ejection Fraction
LVESVI	Left Ventricular End Systolic Volume Index
LVOT	Left Ventricular Outflow Tract
MELD	Model for End Stage Liver Disease
MI	Myocardial Infarction
MICS	Minimally Invasive Cardiac Surgery
MR	Mitral Regurgitation
mRS	Modified Rankin Scale
MSCT	Multi-slice Computed Tomography
MV	Mitral Valve
MVARC	Mitral Valve Academic Research Consortium
NIHSS	National Institutes of Health Stroke Score
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PET	Polyethylene terephthalate
PP	Per-Protocol

Acronym	Definition
PRBC	Packed Red Blood Cells
PT	Prothrombin time
PTFE	Polytetrafluoroethylene
PTT	Partial Thromboplastin Time
PU	Polyurethane
RMA	Repeated Measures Analysis
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SSC	Subject Screening Committee
TAVI	Transcatheter Aortic Valve Implantation
TEE	Transesophageal Echocardiography
TMVR	Transcatheter Mitral Valve Replacement
TSS	Transseptal Steerable Sheath
TTE	Transthoracic Echocardiogram
UADE	Unanticipated Adverse Device Effect
UNOS	United Network for Organ Sharing
USADE	Unanticipated Serious Adverse Device Effect

## 21 APPENDIX 2: GENERAL DEFINITIONS OF ADVERSE EVENTS

### Relevant Standards And Accepted Clinical Definition Sources

ISO 14155:2011(E). Clinical investigation of medical devices for human subjects — Good clinical practice.

ISO 5840-3:2013(E). Cardiovascular implants — Cardiac valve prostheses — Part 3: Heart valve substitutes implanted by transcatheter techniques.

MVARC-2 Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions: A Consensus Document From the Mitral Valve Academic Research Consortium. Stone GW, Adams DH, Abraham WT, Kappetein AP, Généreux P, Vranckx P, Mehran R, Kuck KH, Leon MB, Piazza N, Head SJ, Filippatos G, Vahanian AS; Mitral Valve Academic Research Consortium (MVARC). J Am Coll Cardiol. 2015 Jul 21;66(3):308-21.

### Adverse Device Effect (from ISO 14155)

Adverse event related to the use of an investigational medical device.

Note 1 This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device

Note 2 This definition includes any event resulting from use error or from intentional misuse of the investigational medical device

### Adverse Event

Events that fall under the definition of Adverse Event from either ISO 14155 or ISO 5840-3: (from ISO 14155) Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

Note 1 This definition includes events related to the investigational medical device or the comparator.

Note 2 This definition includes events related to the procedures involved.

Note 3 For users or other persons, this definition is restricted to events related to investigational medical devices.

(from ISO 5840-3) Untoward medical occurrence in a study subject, which does not necessarily have to have a causal relationship with study treatment.

### Allergic Reaction

An allergic reaction characterized by exposure to contrast medium, medications or implanted materials. Symptoms may include rash, nausea, vomiting, upper respiratory congestion, urticaria, shortness-of- breath, vasovagal reaction, or general collapse (anaphylaxis).

### Anesthesia Reactions

Temporary confusion and memory loss, dizziness, difficulty passing urine, nausea and vomiting, shivering and feeling cold, throat discomfort related to breathing tube, allergic reaction and in rare cases, death

### **Anaphylactic Shock**

Acute, severe, life-threatening allergic reaction leading to a systemic response caused by the release of immune and inflammatory mediators involving least 2 organ systems

### **Anemia**

Decrease from baseline in red blood cells, hemoglobin, or total blood volume that is associated with hemodynamic changes or requires transfusion, or a drop in hematocrit to  $<21$  or Hgb  $< 7.5\%$ . Any documented anemia event requiring  $\geq 3$  units PRBCs will be considered an SAE.

### **Angina**

Chest pain due to an inadequate supply of oxygen to the heart muscle

### **Aortic Valve Injury**

Any damage to the aortic valve during the procedure requiring intervention, not excluding surgical repair

### **Arrhythmia**

An irregular heartbeat, (also called dysrhythmia). There are many types of arrhythmias, including but not limited to bradycardia, atrial fibrillation, atrial flutter, etc.

### **Arteriovenous Fistula**

A traumatic communication between an artery and vein documented by ultrasound or angiography

### **Atrial Septal Defect Requiring Intervention**

Large atrial septal defects may cause shortness of breath, especially with exercise. Additionally, increased blood in the lungs can leave one susceptible to pneumonia and bronchitis, often requiring repair with cardiac catheterization or open heart surgery.

### **Atrioventricular Block**

An interruption or delay of electrical conduction from the atria to the ventricles due to conduction system abnormalities in the AV node or the His-Purkinje system. Conduction delay or block can be physiologic if the atrial rate is abnormally fast or pathologic at normal atrial rates. AV block is generally defined based on a regular atrial rhythm.

### **Bleeding (from MVARC)**

MVARC Primary Bleeding Scale has been developed for primary definition of bleeding after MV procedures, in which fatal bleeding is more comprehensively defined and nonfatal bleeding is better characterized. The MVARC Primary Bleeding Scale is defined 5 points.

- Minor Bleeding is in which any actionable sign of hemorrhage meets  $\geq 1$  of the following:
  - Requiring nonsurgical medical intervention
  - Leading to hospitalization or increased level of care
  - Prompting evaluation
  - Requiring 1 or 2 U of blood or RBC transfusion
  - Not defined as major, extensive or life-threatening bleeding
- Major Bleeding is associated with hemoglobin drop of  $\geq 3.0$  g/dl or requiring  $\geq 3$  U of

blood or

RBC transfusion or is not defined as life-threatening or extensive bleeding.

- ☐ Extensive Bleeding is associated with hemoglobin drop of  $\geq 4$  g/dl or requiring  $\geq 4$  U of blood or RBC transfusion within any 24H period, or HB drop of  $\geq 6$  g/dl or whole blood or RBC transfusion  $\geq 4$  U (BARC type 3b) within 30 days of the procedure
- ☐ Life-threatening Bleeding is associated with hemorrhage in a critical organ necessitating surgery or intervention OR causing hypovolemic shock or hypotension or requiring significant doses of vasopressors or surgery.
- ☐ Fatal Bleeding as being a proximate cause of death (MI or cardiac arrest for example).

### **Cardiac Arrest**

Abrupt loss of heart function, often related to malignant arrhythmia

### **Cardiac Perforation**

The presence of an acquired hole in the heart. Cardiac perforation may or may not be symptomatic and or may not be self-sealing

### **Cardiogenic Shock**

Patient presents with SBP  $< 80$  mm Hg for more than 30 minutes unresponsive to fluids and / or requiring intravenous pressor agent or an intraortic balloon pump (IABP).

### **Cardiac Tamponade**

Mechanical compression of the heart by large amounts of fluid or blood within the pericardial space that limits the normal range of motion and function of the heart

### **The risks of Conversion to Emergent/elective cardiac surgery based on a technical/clinical failure**

Any and all complications related to an open cardiac surgical procedure

### **Death (from MVARC)**

**Cardiovascular mortality:** Any of the following contributing conditions:

- ☐ Heart failure (subclassified into left ventricular versus right ventricular dysfunction)
- ☐ Myocardial infarction
- ☐ Major bleeding
- ☐ Thromboembolism
- ☐ Stroke
- ☐ Arrhythmia and conduction system disturbance
- ☐ Cardiovascular infection and sepsis
- ☐ Tamponade
- ☐ Sudden, unexpected death
- ☐ Other cardiovascular
- ☐ Device failure
- ☐ Death of unknown cause

***Non-cardiovascular mortality:*** 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 non-cardiovascular

### **Deep Vein Thrombosis**

Unilateral lower extremity swelling, redness, pain with confirmation by Doppler tests of obstructed venous flow in that extremity. DVT occurring within 30 days of the surgical procedure shall be considered procedure related.

### **Detachment/Dislodgment of the Device (from MVARC)**

- ☐ Device detachment
  - Partial: detachment of part of the device from the initial position without embolization
  - Complete: detachment leading to device embolization or ectopic device placement

### **Device Deficiency (from ISO 14155)**

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunctions, use errors, and inadequate labeling.

### **Device Thrombosis (from MVARC)**

Any thrombus attached to or near an implanted valve, subclassified as:

- Major: occludes part of the blood flow path, interferes with valve function (e.g., immobility of 1 or more leaflets), is symptomatic, or is sufficiently large to warrant treatment, or
- Minor: incidental finding on echocardiography or other imaging test that is not major

### **Dissection**

Presence of angiographically evident intimal disruption (e.g., linear luminal density or luminal staining or linear intraluminal filling defect) which requires treatment.

### **Dizziness/Syncope**

Imprecise term commonly used to describe various symptoms such as faintness, giddiness, imbalance, lightheadedness, unsteadiness or vertigo (in the initial 48 hours post procedure)

### **Dyskinesia**

Impairment of voluntary movements resulting in fragmented or jerky motions

### **Dyspnea**

Difficult or labored breathing; shortness of breath

#### **Edema**

Swelling as a result of excess fluid

#### **Emboli**

A foreign substance or a blood clot that travels through the bloodstream, to an unintended and non- therapeutic location

#### **Endocarditis (from MVARC)**

- Any 1 of the following:
  - Fulfillment of the modified Duke endocarditis criteria (61), or
  - Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during an operation or autopsy.
- Should be further subclassified by organism, and early (<1 yr) vs. late (>1 yr)

#### **Esophageal Irritation**

Inflammation that may damage the tissues of the esophagus

#### **Esophageal Perforation**

A hole, break, or rupture of the esophagus

#### **Fever**

A temperature > 101°F / 38.5°C not related to a culture positive infection

#### **Groin Infection**

See “Vascular Injury”

#### **Hematoma**

Development of a collection of blood > 5 cm’s under the skin

#### **Heart Block**

See AV Block

#### **Hemolysis (from MVARC)**

The presence of a paravalvular leak on transesophageal or transthoracic echocardiography plus anemia requiring transfusion plus increased haptoglobin and/or LDH levels; should be confirmed by a haematologist

#### **Hemothorax**

The accumulation of blood between the membranes lining the lungs. Depending upon the cause, the blood may originate from the lungs, the heart, the chest wall, or the large blood vessels present in the chest

#### **Hemorrhage (from MVARC)**

MVARC Primary Bleeding Scale has been developed for primary definition of bleeding after MV procedures, in which fatal bleeding is more comprehensively defined and nonfatal bleeding is better characterized. The MVARC Primary Bleeding Scale is defined 5 points.

- Minor Bleeding is in which any actionable sign of hemorrhage meets  $\geq 1$  of the following:
  - Requiring nonsurgical medical intervention
  - Leading to hospitalization or increased level of care
  - Prompting evaluation
  - Requiring 1 or 2 U of blood or RBC transfusion
  - Not defined as major, extensive or life-threatening bleeding
- Major Bleeding is associated with hemoglobin drop of  $\geq 3.0$  g/dl or requiring  $\geq 3$  U of blood or RBC transfusion or is not defined as life-threatening or extensive bleeding.
- Extensive Bleeding is associated with hemoglobin drop of  $\geq 4$  g/dl or requiring  $\geq 4$  U of blood or RBC transfusion within any 24H period, or HB drop of  $\geq 6$  g/dl or whole blood or RBC transfusion  $\geq 4$  U (BARC type 3b) within 30 days of the procedure
- Life-threatening Bleeding is associated with hemorrhage in a critical organ necessitating surgery or intervention OR causing hypovolemic shock or hypotension or requiring significant doses of vasopressors or surgery.
- Fatal Bleeding as being a proximate cause of death (MI or cardiac arrest for example).

#### **Hypertension**

Having either a systolic blood pressure of 130mm Hg or greater or a diastolic blood pressure of 80mm HG or greater.

#### **Hypotension**

Having either a systolic blood pressure of 90mm Hg or lower or a diastolic blood pressure of 60mm Hg or lower.

#### **Inflammation**

Local response to cellular injury that is marked by capillary dilatation, leukocytic infiltration, redness, heat, pain, swelling, and often loss of function.

#### **Low Cardiac Output**

An imbalance between oxygen delivery and oxygen consumption caused by a transient decrease in systemic perfusion secondary to myocardial dysfunction.

#### **Migration/Malposition of the Device Requiring Intervention (from MVARC)**

Malposition: permanent deployment of a device in a location other than intended.

Device migration: after initial correct positioning, the device moves within its initial position but not leading to device embolization.

#### **Mitral Valve Stenosis**

Narrowing of the mitral valve resulting in a blocking of blood flow

#### **Multi-System Organ Failure**

Altered organ function in an acutely ill patient requiring medical intervention to achieve homeostasis

#### **Myocardial Infarction (from MVARC)**

### ***Periprocedural MI (≤48 hours after the index procedure)***

- In patients with normal baseline CK-MB (or cTn): The peak CK-MB measured within 48 h of the procedure rises to  $\geq 10\times$  the local laboratory ULN plus new ST-segment elevation or depression of  $\geq 1$  mm in  $\geq 2$  contiguous leads (measured 80 ms after the J-point), or to  $\geq 5\times$  ULN with new pathological Q waves in  $\geq 2$  contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the PCI rises to  $\geq 70\times$  the local laboratory ULN plus new ST-segment elevation or depression of  $\geq 1$  mm in  $\geq 2$  contiguous leads (measured 80 ms after the J-point), or  $\geq 35\times$  ULN with new pathological Q waves in  $\geq 2$  contiguous leads or new persistent LBBB.
- In patients with elevated baseline CK-MB (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.

### ***Spontaneous MI (> 48 hours after the index procedure)***

Detection of rise and/or fall of cardiac biomarkers (preferably cTn) with at least 1 value above the 99<sup>th</sup>

percentile URL (or ULN in the absence of URL) together with at least 1 of the following:

- A. Symptoms of ischaemia
- B. ECG changes indicative of new ischaemia (new ST-segment or T-wave changes or new LBBB) or new pathological Q waves in  $\geq 2$  contiguous leads
- C. Imaging evidence of a new loss of viable myocardium or new wall motion abnormality

### ***MI associated with sudden, unexpected cardiac death***

Sudden cardiac death or cardiac arrest, often with symptoms suggestive of myocardial ischaemia, 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.

#### **Nausea**

Stomach distress with an urge to vomit

#### **Nerve Injury**

Damage to either the peripheral or central nervous system

#### **Pain**

An unpleasant sensation occurring in varying degrees of severity as a consequence of injury, disease, or emotional disorder

#### **Perforation or Damage of Vessels or Tissue, Myocardium or Valvular Structure**

Any damage occurring during the procedure requiring intervention, not excluding surgical repair

#### **Pericardial Effusion**

Accumulation of fluid in the pericardial space evidenced by x-ray, echocardiography, CT Scan or

other appropriate diagnostic technique and which requires drainage. See Appendix 3 “Specific device-related technical failure issues and complications”

### **Peripheral Ischemia**

A lack of blood flow to tissues resulting in shortage of oxygen

### **Pneumonia**

An inflammation of the lungs caused by an infection, often accompanied by a fever. This condition must be confirmed by radiological evidence, positive sputum culture, or significant improvement of the condition following antibiotic treatment

### **Progression of Valvular Heart Disease**

Worsening from valvular heart disease baseline condition

### **Pseudoaneurysm**

Compartmentalized blood contiguous with arterial lumen

### **Pulmonary Embolism**

An obstruction of a blood vessel in the lungs, usually due to a blood clot, which blocks a pulmonary artery

### **Renal Insufficiency or failure/Acute Kidney Injury (from MVARC)**

**Definition:** maximal change in sCr from Baseline to 7 days post-procedure

Stage 1: Increase in sCr to 150%–199% (1.50–1.99x increase vs. baseline), increase of  $\geq 0.3$  mg/dl ( $\geq 26.4$  mmol/l) within 48 h, or urine output  $< 0.5$  ml/kg/h for  $\geq 6$  h but  $< 12$  h

Stage 2: Increase in sCr to 200%–299% (2.00–2.99x increase vs. baseline) or urine output  $< 0.5$  ml/kg/h for  $\geq 12$  h but  $< 24$  h

Stage 3: Increase in sCr to  $\geq 300\%$  ( $> 3.0$ x increase vs. baseline), sCr of  $\geq 4.0$  mg/dl ( $\geq 354$  mmol/l) with an acute increase of  $\geq 0.5$  mg/dl (44 mmol/l), urine output  $< 0.3$  ml/kg/h for  $\geq 24$  h, or anuria for  $\geq 12$  h; patients receiving renal replacement therapy are considered stage 3 irrespective of other criteria

### **Respiratory Failure**

Need for mechanical ventilation beyond 48 hours of completion of surgical procedure(s), or the need for re-intubation and ventilator support occurring at any time within 30 days of the surgical procedure, outside the setting of an additional operation

### **Septicemia**

Invasion of the bloodstream by virulent microorganisms (as bacteria, viruses, or fungi) from a focus of infection that is accompanied by acute systemic illness confirmed by positive blood cultures

### **Serious Adverse Device Effect (SADE) (from ISO 14155)**

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

### **Serious Adverse Event (from ISO 14155)**

#### Adverse event that

- a) Led to death,
- b) Led to serious deterioration in the health of the subject, that either resulted in
  - 1) A life-threatening illness or injury, or
  - 2) A permanent impairment of a body structure or a body function, or
  - 3) In-patient or prolonged hospitalization, or
  - 4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the study protocol, without serious deterioration in health, is not considered a serious adverse event.

#### **Stroke/Transient Ischemic Attack (from MVARC)**

##### Diagnostic criteria:

- ☐ Acute episode of a focal or global neurological deficit with at least one of the following:
  - change in the 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.
- ☐ In addition, there is no other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumour, trauma, infection, hypoglycaemia, peripheral lesion, pharmacological influences) as determined by or in conjunction with the designated neurologist

##### The neurological event type classification:

- ☐ Stroke: Duration of a focal or global neurological deficit  $\geq 24$  hours; OR  $< 24$  hours if available neuroimaging documents a new intracranial or subarachnoid hemorrhage (hemorrhagic stroke) or central nervous system infarction (ischemic stroke) OR the neurological deficit results in death.
- ☐ TIA: Duration of a focal or global neurological deficit  $< 24$  hours, any neuroimaging does not demonstrate a new hemorrhage or infarct.

##### Confirmation of the diagnosis of stroke or TIA requires at least 1 of the following:

- ☐ Neurologist or neurosurgical specialist, or
- ☐ Neuroimaging procedure (CT scan or brain MRI)

##### Stroke/TIA timing classification:

- ☐ Periprocedural if it occurs within 30 days of the intervention, or if beyond 30 days in the patient not yet discharged. A periprocedural stroke/TIA may be further considered immediate if it occurs within 24 h of the procedure or within

24 h of awakening from general anaesthesia if beyond 24 h.

- ☐ Nonperiprocedural if it occurs beyond 30 days after the intervention and after the patient has been discharged.

Stroke/TIA aetiology classification:

- ☐ Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue
- ☐ Haemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid haemorrhage
- ☐ Undetermined: if there is insufficient information to allow categorization as ischaemic or haemorrhagic

Stroke severity is further classified as:

- ☐ Disabling Stroke: A modified Rankin Scale (mRS) score  $\geq 2$  at 90 days plus  $\geq 1$  mRS category from the pre-stroke baseline
- ☐ Non-disabling Stroke: An mRS score of  $< 2$  at 90 days or without an increase  $\geq 1$  mRS category from the pre-stroke baseline.

**Structural Device Degeneration (from MVARC)**

Major: a break, tear, perforation, or other structural defect in the device (stent, housing, leaflet, arm, and so on) resulting in device failure, resulting in recurrent symptoms, or requiring reintervention, or

Minor: a break, tear, perforation, or other structural defect in the device (stent, housing, leaflet, arm, and so on) not resulting in device failure, not resulting in recurrent symptoms, and not requiring reintervention

**Thrombocytopenia**

Deficiency of platelets in the blood falling below 50,000/ml

**Unanticipated Serious Adverse Device Effect (USADE) (from ISO 14155)**

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

**Vascular Injury**

Vascular injury at an access site utilized for vascular access and/or device deployment, observed on imaging study or direct visualization, and requires intervention (other than compression), for infection, hospital admission, or packed red blood cell transfusion to address condition

**Vessel Spasm**

A temporary tightening (constriction) of the muscles in the wall of one of the arteries that supplies blood flow to heart muscle, which may lead to angina and myocardial infarction

**Vomit**

Forceful expulsion of the contents of the stomach

**Worsening Heart Failure**

A decline in heart failure condition from baseline

**Worsening Mitral Regurgitation**

An increase in mitral regurgitation from baseline

**Wound Dehiscence**

A surgical complication in which a wound ruptures along a surgical incision

## 22 APPENDIX 3: DEFINITIONS OF ADVERSE EVENT ACCORDING TO MVARC

### Normative and Scientific Sources

MVARC-2 Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions: A Consensus Document From the Mitral Valve Academic Research Consortium. Stone GW, Adams DH, Abraham WT, Kappetein AP, G  n  reux P, Vranckx P, Mehran R, Kuck KH, Leon MB, Piazza N, Head SJ, Filippatos G, Vahanian AS; Mitral Valve Academic Research Consortium (MVARC). J Am Coll Cardiol. 2015 Jul 21;66(3):308-21.

Specific Device-Related Technical Failure Issues and Complications	
<b>I. Device failure</b>	
<input type="checkbox"/>	Device failure, defined as the absence of device success (Table 10), is subclassified as:
<input type="checkbox"/>	Delivery failure (i.e., technical failure)
<input type="checkbox"/>	Structural failure: the device does not perform as intended due to a complication related to the device (e.g., fracture, migration or embolization, frozen leaflet, device detachment, and so on)
<input type="checkbox"/>	Functional failure: the device performs as intended without complication but does not adequately reduce the degree of MR (MR > moderate, or fails to relieve or creates new mitral stenosis [EROA <1.5 cm <sup>2</sup> or transmitral gradient ≥5 mm Hg]).
<b>II. Specific device-related technical failure issues and complications</b>	
<input type="checkbox"/>	Paravalvular leak <ul style="list-style-type: none"> <li>○ Major: moderate or severe (2+, 3+, or 4+), or associated with hemolysis, or requiring intervention or surgery</li> <li>○ Minor: trace or mild (1+), without hemolysis</li> </ul>
<input type="checkbox"/>	Iatrogenic atrial septal defect <ul style="list-style-type: none"> <li>○ Major: significant left-to-right shunt (Qp:Qs ≥2:1) or symptomatic requiring the need for closure</li> <li>○ Minor: nonsignificant shunt that is still present at ≥6 months</li> </ul>
<input type="checkbox"/>	Coronary vessel compression or obstruction <ul style="list-style-type: none"> <li>○ Angiographic evidence of any reduction in coronary artery luminal diameter or coronary sinus diameter due to either external compression, thrombosis, embolism, dissection, or other cause, subclassified as:               <ul style="list-style-type: none"> <li>- Major (≥50% diameter stenosis) or minor (&lt;50%)</li> <li>- Symptomatic or not</li> <li>- Requiring treatment or not</li> <li>- Transient (intraprocedural only, resolved at procedure end) or persistent</li> </ul> </li> </ul>
<input type="checkbox"/>	Pericardial effusion

- Major: leading to cardiac tamponade or requiring intervention
- Minor: not leading to cardiac tamponade and not requiring intervention
- Conversion to open mitral valve surgery during a transcatheter procedure, subclassified as
  - Secondary to mitral valve apparatus damage or dysfunction, requiring surgical valve repair or replacement, or
  - Secondary to procedural complications (such as cardiac perforation, removal of an embolized device, and so on)
- Device malpositioning
  - Ectopic device placement: permanent deployment of a device in a location other than intended
  - Device migration: after initial correct positioning, the device moves within its initial position but not leading to device embolization
  - Device embolization: the device moves during or after deployment such that it loses contact with its initial position
- Device detachment
  - Partial: detachment of part of the device from the initial position without embolization
    - Complete: detachment leading to device embolization or ectopic device placement
- Device fracture
  - Major: a break, tear, perforation, or other structural defect in the device (stent, housing, leaflet, arm, and so on) resulting in device failure, resulting in recurrent symptoms, or requiring reintervention, or
  - Minor: a break, tear, perforation, or other structural defect in the device (stent, housing, leaflet, arm, and so on) not resulting in device failure, not resulting in recurrent symptoms, and not requiring reintervention
- Damage to the native mitral valve apparatus
  - Chords
  - Papillary muscles
  - Leaflets
  - Mitral annulus
- Interaction with non-mitral valve intracardiac structures
  - Left ventricular outflow tract obstruction (gradient increase  $\geq 10$  mm Hg from baseline)
  - Aortic valve regurgitation ( $\geq$  moderate or 2+)
  - Other
- Device thrombosis, defined as any thrombus attached to or near an implanted valve, subclassified as:
  - Major: occludes part of the blood flow path, interferes with valve function (e.g., immobility of 1 or more leaflets), is symptomatic, or is sufficiently large to warrant treatment, or
  - Minor: incidental finding on echocardiography or other imaging test that is not major
- Endocarditis
  - Any 1 of the following:
    - Fulfillment of the modified Duke endocarditis criteria (61), or
    - Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during an operation or autopsy.
  - Should be further subclassified by organism, and early ( $<1$  yr) vs. late ( $>1$  yr)
- Hemolysis
  - The presence of a paravalvular leak on transesophageal or transthoracic echocardiography plus anemia requiring transfusion plus increased haptoglobin and/or LDH levels; should be confirmed by a hematologist
- Other device-specific endpoints
  - The number of devices (e.g., clips, neochoords) used by intent to achieve the desired reduction in MR
  - The need for unplanned use of additional devices (e.g., valves, clips, neochoords) as a result of failed device delivery, device detachment, device fracture, or other device system failure
  - If surgery is required, inability to perform mitral valve repair because of the presence of or

anatomic changes from the device
LDH= lactate dehydrogenase; Qp = pulmonary blood flow; Qs = systemic blood flow.

## Access site and vascular complications (from MVARC-2)

### Vascular complication

- Major access site vascular complications, including:
  - Aortic dissection or aortic rupture, or
  - Access site-related arterial or venous injury (dissection, stenosis, ischaemia, arterial, or venous thrombosis including pulmonary emboli, perforation, rupture, arteriovenous fistula, pseudoaneurysm, haematoma, retroperitoneal haematoma, atrial septal defect), irreversible nerve injury, or compartment syndrome resulting in death; hemodynamic compromise; life-threatening, extensive, or major bleeding (MVARC bleeding scale); visceral ischaemia; or neurological impairment, or
  - Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage, or
  - Unplanned endovascular or surgical interventions resulting in death; life-threatening, extensive, or major bleeding (MVARC bleeding scale); visceral ischaemia; or neurological impairment
- Minor access site vascular complications, including:
  - Access site arterial or venous injury (dissection, stenosis, arterial, or venous thrombosis including pulmonary emboli, ischaemia, perforation, rupture, arterio-venous fistula, pseudoaneurysm, haematoma, retroperitoneal haematoma, atrial septal defect) not resulting in death; life-threatening, extensive, or major bleeding (MVARC scale); visceral ischaemia; or neurological impairment, or
  - Distal embolization treated with embolectomy and/or thrombectomy not resulting in amputation or irreversible end-organ damage, or
  - Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication, or
  - Vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)

### Cardiac structural complications due to access-related issues:

- Major cardiac structural complications, including:

- Cardiac perforation or pseudoaneurysm resulting in death, life-threatening bleeding, hemodynamic compromise, or tamponade, or requiring unplanned surgical or percutaneous intervention
- Minor cardiac structural complications, including:
  - Cardiac perforation or pseudoaneurysm not meeting major criteria

### **Acute Kidney Injury, Definitions and Stages (from MVARC-2)**

**Definition:** maximal change in sCr from Baseline to 7 days post-procedure

Stage 1: Increase in sCr to 150%–199% (1.50–1.99x increase vs. baseline), increase of  $\geq 0.3$  mg/dl ( $\geq 26.4$

mmol/l) within 48 h, or urine output  $< 0.5$  ml/kg/h for  $\geq 6$  h but  $< 12$  h

Stage 2: Increase in sCr to 200%–299% (2.00–2.99x increase vs. baseline) or urine output  $< 0.5$  ml/kg/h

for  $\geq 12$  h but  $< 24$  h

Stage 3: Increase in sCr to  $\geq 300\%$  ( $> 3.0$ x increase vs. baseline), sCr of  $\geq 4.0$  mg/dl ( $\geq 354$  mmol/l) with an acute increase of  $\geq 0.5$  mg/dl (44 mmol/l), urine output  $< 0.3$  ml/kg/h for  $\geq 24$  h, or anuria for

$\geq 12$  h; patients receiving renal replacement therapy are considered stage 3 irrespective of other criteria

### **Bleeding (From MVARC-2)**

MVARC Primary Bleeding Scale has been developed for primary definition of bleeding after MV procedures, in which fatal bleeding is more comprehensively defined and nonfatal bleeding is better characterized. The MVARC Primary Bleeding Scale is defined 5 points.

- Minor Bleeding is in which any actionable sign of hemorrhage meets  $\geq 1$  of the following:
  - Requiring nonsurgical medical intervention
  - Leading to hospitalization or increased level of care
  - Prompting evaluation
  - Requiring 1 or 2 U of blood or RBC transfusion
  - Not defined as major, extensive or life-threatening bleeding
- Major Bleeding is associated with hemoglobin drop of  $\geq 3.0$  g/dl or requiring  $\geq 3$  U of blood or RBC transfusion or is not defined as life-threatening or extensive bleeding.
- Extensive Bleeding is associated with hemoglobin drop of  $\geq 4$  g/dl or requiring  $\geq 4$  U of blood or RBC transfusion within any 24H period, or HB drop of  $\geq 6$  g/dl or whole blood or RBC transfusion  $\geq 4$  U (BARC type 3b) within 30 days of the procedure
- Life-threatening Bleeding is associated with hemorrhage in a critical organ necessitating surgery or intervention OR causing hypovolemic shock or hypotension or requiring significant doses of vasopressors or surgery.
- Fatal Bleeding as being a proximate cause of death (MI or cardiac arrest for example).

### **Cardiovascular vs. Non-Cardiovascular Death (from MVARC-2)**

**Cardiovascular mortality:** Any of the following contributing conditions:

- ☐ Heart failure (subclassified into left ventricular versus right ventricular dysfunction)
- ☐ Myocardial infarction
- ☐ Major bleeding
- ☐ Thromboembolism
- ☐ Stroke
- ☐ Arrhythmia and conduction system disturbance
- ☐ Cardiovascular infection and sepsis
- ☐ Tamponade
- ☐ Sudden, unexpected death
- ☐ Other cardiovascular
- ☐ Device failure
- ☐ Death of unknown cause

**Non-cardiovascular mortality:** 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 non-cardiovascular

### **Hospitalization (from MVARC-2)**

**Definition:** Hospitalization is defined as admission to an inpatient unit or ward in the hospital for  $\geq 24$  hours, including an emergency department stay. Hospitalizations planned for pre-existing conditions are excluded unless there is worsening of the baseline condition.

Hospitalization is further subclassified as:

- ☐ 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 subclassified as:

- IA. Primary (cardiac related) heart failure hospitalization
- IB. Secondary (non-cardiac related) heart failure hospitalization
- ☐ Other cardiovascular hospitalization: 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: not due to heart failure or other cardiovascular causes, as defined above

## **Myocardial Infarction (from MVARC-2)**

### ***Periprocedural MI (≤48 hours after the index procedure)***

- In patients with normal baseline CK-MB (or cTn): The peak CK-MB measured within 48 h of the procedure rises to  $\geq 10$ x the local laboratory ULN plus new ST-segment elevation or depression of  $\geq 1$  mm in  $\geq 2$  contiguous leads (measured 80 ms after the J-point), or to  $\geq 5$ x ULN with new pathological Q waves in  $\geq 2$  contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the PCI rises to  $\geq 70$ x the local laboratory ULN plus new ST-segment elevation or depression of  $\geq 1$  mm in  $\geq 2$  contiguous leads (measured 80 ms after the J-point), or  $\geq 35$ x ULN with new pathological Q waves in  $\geq 2$  contiguous leads or new persistent LBBB.
- In patients with elevated baseline CK-MB (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.

### ***Spontaneous MI (> 48 hours after the index procedure)***

Detection of rise and/or fall of cardiac biomarkers (preferably cTn) with at least 1 value above the 99<sup>th</sup> percentile URL (or ULN in the absence of URL) together with at least 1 of the following:

- A. Symptoms of ischaemia
- B. ECG changes indicative of new ischaemia (new ST-segment or T-wave changes or new LBBB) or new pathological Q waves in  $\geq 2$  contiguous leads
- C. Imaging evidence of a new loss of viable myocardium or new wall motion abnormality

### ***MI associated with sudden, unexpected cardiac death***

Sudden cardiac death or cardiac arrest, often with symptoms suggestive of myocardial ischaemia, 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.

## **MVARC events (from MVARC-2)**

MVARC events are defined as:

- Mortality (all-cause, cardiovascular vs. non cardiovascular, periprocedural vs. nonperiprocedural and device relatedness)
- Hospitalization (heart failure related vs. other cardiovascular causes vs. non-cardiovascular causes)
- Neurological events (stroke vs. transient ischemic attack, ischemic vs. hemorrhagic vs. undetermined, disabling vs. nondisabling, periprocedural vs. nonprocedure related)
- Myocardial infarction (periprocedural vs. nonprocedural related)
- Access and vascular complications (arterial, venous and cardiac)
- Bleeding complications (modified VARC and BARC scale)
- Acute kidney injury (modified AKIN definition)
- Arrhythmias and conduction system disturbances (atrial fibrillation and other

atrial arrhythmias, ventricular tachycardia and other ventricular arrhythmias, heart block)

- Specific device-related technical failure issues and complications.

### **Stroke and TIA (from MVARC-2)**

#### Diagnostic criteria:

- Acute episode of a focal or global neurological deficit with at least one of the following:
  - change in the 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.
- In addition, there is no other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumour, trauma, infection, hypoglycaemia, peripheral lesion, pharmacological influences) as determined by or in conjunction with the designated neurologist

#### The neurological event type classification:

- Stroke: Duration of a focal or global neurological deficit  $\geq 24$  hours; OR  $< 24$  hours if available neuroimaging documents a new intracranial or subarachnoid hemorrhage (hemorrhagic stroke) or central nervous system infarction (ischemic stroke) OR the neurological deficit results in death.
- TIA: Duration of a focal or global neurological deficit  $< 24$  hours, any neuroimaging does not demonstrate a new hemorrhage or infarct.

#### Confirmation of the diagnosis of stroke or TIA requires at least 1 of the following:

- Neurologist or neurosurgical specialist, or
- Neuroimaging procedure (CT scan or brain MRI) Stroke/TIA timing classification:
- Periprocedural if it occurs within 30 days of the intervention, or if beyond 30 days in the patient not yet discharged. A periprocedural stroke/TIA may be further considered immediate if it occurs within 24 h of the procedure or within 24 h of awakening from general anaesthesia if beyond 24 h.
- Nonperiprocedural if it occurs beyond 30 days after the intervention and after the patient has been discharged.

#### Stroke/TIA aetiology classification:

- Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue
- Haemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid haemorrhage
- Undetermined: if there is insufficient information to allow categorization as ischaemic or haemorrhagic

#### Stroke severity is further classified as:

- Disabling Stroke: A modified Rankin Scale (mRS) score  $\geq 2$  at 90 days plus  $\geq 1$  mRS category from the pre-stroke baseline

- Non-disabling Stroke: An mRS score of <2 at 90 days or without an increase  $\geq 1$  mRS category from the pre-stroke baseline.

## 23 APPENDIX 4: GUIDELINES FOR SURGICAL RISK ASSESSMENT IN MR

In Accordance with MVARC Part 1 (Table 8) the assessment of operative risk by a multidisciplinary heart team should supersede any single risk score in determining patient eligibility for surgery. Team decision-making should integrate clinical risk scores with other variables that are not captured in these scores. These other factors should be considered when deciding whether a patient is at excessive risk for surgery, including frailty, major organ system compromise (e.g., cirrhosis), and procedure-specific impediments known prognostic variables, including assessment of frailty. The risk assessment criteria recommended by MVARC are summarized in the table below (reproduced from MVARC).

<b>TABLE 8 Risk Assessment in Valvular Heart Disease, Combining Society of Thoracic Surgery Risk Estimates, Frailty, Major Organ System Dysfunction, and Procedure-Specific Impediments for Intervention</b>				
	<b>Low Risk</b> (ALL Criteria in This Column Must Be Present)	<b>Intermediate Risk</b> (At Least 1 Criterion in This Column Must Be Present)	<b>High Risk</b> (At Least 1 Criterion in This Column Must Be Present)	<b>Prohibitive Risk</b> (Any 1 Criterion in This Column Must Be Present)
STS PROM*	<4%	4%–8%	>8%	Predicted risk with surgery of death or major morbidity (all-cause)
Frailty†	None	1 index (mild)	$\geq 2$ indexes (moderate to severe)	>50% at 1 yr
Major organ system compromise not to be improved post-operatively‡	None	1 organ system	No more than 2 organ systems	$\geq 3$ organ systems
Procedure-specific impediment§	None	Possible procedure-specific impediment	Possible procedure-specific impediment	Severe procedure-specific impediment

\*Use of the STS predicted risk of mortality (PROM) to predict risk in a given institution with reasonable reliability is appropriate only if institutional outcomes are within 1 SD of STS average observed/expected ratio for the procedure in question. †Seven frailty indexes: Katz Activities of Daily Living (independence in feeding, bathing, dressing, transferring, toileting and urinary continence) and independence in ambulation (no walking aid or assist required for 5-m walk in <6 s). Other scoring systems can be applied to calculate no, mild, or moderate-to-severe frailty.

‡Examples of major organ system compromise:

Cardiac: severe LV systolic or diastolic dysfunction or RV dysfunction, or fixed pulmonary hypertension; CKD stage 3 or worse; pulmonary dysfunction with FEV1 <50% or DLCO2 <50% of predicted; CNS dysfunction: dementia, Alzheimer's disease, Parkinson's disease, or CVA with persistent physical limitation; GI dysfunction: Crohn's disease, ulcerative colitis, nutritional impairment, or serum albumin <3.0; Cancer: active malignancy; and liver: any history of cirrhosis, variceal bleeding, or elevated INR in the absence of VKA therapy.

§Examples: tracheostomy present, heavily calcified ascending aorta, chest malformation, arterial coronary graft adherent to posterior chest wall, or radiation damage. Adapted with permission from Nishimura et al. CKD ¼ chronic kidney disease; CNS ¼ central nervous system; CVA ¼ cerebrovascular accident (stroke); DLCO2 ¼ diffusion capacity for carbon

dioxide; FEV1 ¼ forced expiratory volume in 1 s; GI ¼ gastrointestinal; INR ¼ international normalized ratio; LV ¼ left ventricular; PROM ¼ predicted risk of mortality; RV ¼ right ventricular; STS ¼ Society of Thoracic Surgeons; VKA ¼ vitamin K antagonist