INVESTIGATIONAL PLAN

The REDUCE FMR Trial:

Safety and Efficacy of the CARILLON Mitral Contour System® in Reducing Functional Mitral Regurgitation (FMR) Associated with Heart Failure

CVP-1627-01, Revision AD
12 November 2015
NCT: 02325830

Product Name:
CARILLON Mitral Contour System® (XE2)

Sponsor:
Cardiac Dimensions Pty Ltd
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PROTOCOL SIGNATURE PAGE

The signatures below constitute the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of this protocol including, without limitation, all statements regarding confidentiality, ISO 14155, Declaration of Helsinki, MEDDEV 2.7/ 3, Standards of Good Clinical Practice, as defined by the International Conference on Harmonization and all applicable regulatory requirements.

Protocol Title: The REDUCE FMR Trial: Safety and Efficacy of the CARILLON Mitral Contour System® in Reducing Functional Mitral Regurgitation (FMR) Associated with Heart Failure

Protocol Number: CVP-1627-01

Version: AD

Date: 12 November 2015

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Clinical Site Name

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Site Principal Investigator Printed Name

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Site Principal Investigator Signature Date

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CDI Representative Printed Name and Title

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CDI Representative Signature Date

Table of Contents

Protocol Synopsis

Title:	The REDUCE FMR Trial: Safety and Efficacy of the CARILLON Mitral Contour System® in Reducing Functional Mitral Regurgitation (FMR) Associated with Heart Failure
Protocol Number:	CVP-1627-01, Revision AD –12 November, 2015
Device:	CARILLON Mitral Contour System® (CMCS) - Model XE2 The CMCS received CE-Mark on 3 August 2011. In Australia/New Zealand the CMCS is "For Clinical Trial Use Only"
Study Objective:	The objective of this prospective, multi-center, randomized, double-blind trial is to assess the safety and efficacy of the CARILLON Mitral Contour System in treating functional mitral regurgitation (FMR) associated with heart failure, compared to a randomized Control group which is medically managed according to heart failure guidelines.
Number of Centers:	Up to 25 centers in Australia/New Zealand and Europe
Patient Population:	Patients with moderate heart failure and functional mitral regurgitation
Study Population:	Consent up to 180 subjects suffering from heart failure and presenting with functional mitral regurgitation in order to randomize up to 120 subjects
Study Duration:	Twenty (20) months (enrollment phase), with long-term subject follow-up of one (1) year, for a total of 32 months
Study Design:	The REDUCE FMR Trial is a prospective, multi-center, randomized, double-blind clinical trial. Subjects will be randomized between the Treatment Group and a Control Group. Subjects will be randomized in a 3:1 ratio (Treatment : Control group). The Treatment group will be implanted with the CARILLON device. The Control group will be medically managed according to current heart failure guidelines [i,ii]. As this is a double-blinded study, both the patients (Treatment and Control groups) and the assessors of key endpoints will be blinded for 12 months.

[i] Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure. *J Am Coll Cardiol*. 2013;62(16):e147-e239.

[ii] McMurray JV, Adamopoulos S, Anker SD, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. European Heart Journal (2012) 33, 1787–1847.

Subjects randomized to the Control or Treatment group will have safety and efficacy assessments performed at baseline, one (1), six (6), and twelve (12) months after randomization.

Subjects randomized to the Control group may be offered the CARILLON device once they have completed the protocol defined follow-up period (Cross-Over Registry).

Inclusion Criteria:

1. Diagnosis of dilated ischemic or non-ischemic cardiomyopathy
2. Functional Mitral Regurgitation:
   - 2+ (Moderate), 3+ (Moderate/Severe), or 4+ (Severe)
3. NYHA II, III, or IV (refer to Appendix D for NYHA Classification)
4. Six Minute Walk distance of at least 150 meters and no farther than 450 meters
5. Subject meets anatomic screening criteria as determined by angiographic screening at the time of the index procedure to ensure that implant can be sized and placed in accordance with the Instructions for Use
6. Left Ventricular Ejection Fraction ≤ 50%
   NOTE: Subjects with LVEF of 41- 50% can only be included if baseline NYHA is class III/IV **AND** MR grade is 3+/4+ (moderately-severe/severe)
7. LV end diastolic dimension (LVEDD) >55mm or LVEDD/BSA > 3.0cm/m^2
8. Stable heart failure medication regimen for at least three (3) months (refer to Appendix G for definition of stable heart failure regimen)
9. Age ≥ 18 years old and ≤ 85 years old
10. The subject has read the informed consent, agrees to comply with the requirements, and has signed the informed consent to participate in the study
11. Female subjects of child-bearing potential must have a negative serum βHCG test

Exclusion Criteria:

1. Hospitalization in past three (3) months due to myocardial infarction, coronary artery bypass graft surgery, and/or unstable angina
2. Hospitalization in the past 30 days for coronary angioplasty or stent placement
3. Subjects expected to require any cardiac surgery, including surgery for coronary artery disease (unprotected left main stenosis greater than or equal to 50% or, greater than or equal to 70% stenosis in at least three (3) epicardial coronary arteries in the absence of prior bypass surgery), or for pulmonic, aortic, or tricuspid valve disease within one (1) year

4. Subjects with echocardiographic documentation of non-compaction cardiomyopathy with associated hypercontractility of the cardiac structures supporting the mitral annulus
5. Subjects expected to require any percutaneous coronary intervention within 30 days of enrollment
6. Recipient of intravenous positive-inotrope infusion or intra- aortic balloon pump support within the past 30 days
7. Presence of a mechanical mitral heart valve, mitral bio-prosthetic valve or mitral annuloplasty ring
8. Pre-existing device (e.g., pacing lead) in coronary sinus (CS) / great cardiac vein (GCV), or anticipated need for cardiac resynchronization therapy (CRT) within twelve (12) months
9. Presence of a coronary artery stent under the CS / GCV in the implant target zone
10. Significant organic mitral valve pathology (e.g., moderate or severe myxomatous degeneration, with or without mitral leaflet prolapse, rheumatic disease, full or partial chordal rupture)
11. Presence of severe mitral annular calcification
12. Presence of left atrial appendage (LAA) clot. Patients with a current/ongoing (documented within the last 12 months) history of atrial fibrillation must undergo a trans-esophageal echo prior to the procedure to rule-out left atrial appendage clot to minimize the risk of thrombo-embolism caused by the tissue plication
13. Cerebral vascular event within the past three (3) months
14. Presence of primary renal dysfunction or significantly compromised renal function as reflected by a serum creatinine > 2.2 mg/dL (194.5 μmol/L) OR estimated Glomerular Filtration Rate (eGFR) < 30 ml/min
15. Allergy to contrast dye that cannot be pre-medicated
16. Inability to undertake a six-minute walk test due to physical restrictions/limitations
17. Chronic severe pathology limiting survival to less than 12-months
18. Anticipated need of left ventricular assist device within twelve (12) months
19. Currently participating in an investigational study that clinically interferes with the current study endpoints.

Primary Endpoint:

The primary efficacy endpoint is to demonstrate a statistically significant improvement in regurgitant volume associated with the CARILLON device at twelve (12) months, relative to the Control population.

Secondary Endpoints:

Safety: The following secondary safety endpoints will measure the effect of the CARILLON Mitral Contour System on clinical safety parameters of interest, relative to the Control population

- To document the difference in the rate of major adverse events between randomized groups, at 1 and 12-months post randomization.

  Major Adverse Events are defined as a composite of the following:

  – Death
  – Myocardial Infarction
  – Device Embolization
  – Vessel Erosion, requiring percutaneous or surgical intervention
  – Cardiac Perforation, requiring percutaneous or surgical intervention
  – Occurrence of cardiac surgery or percutaneous coronary intervention associated with device failure

- To assess the rate of heart failure hospitalizations (number of admissions, and total associated days in the hospital), from the time of the index procedure through twelve months of follow-up.

Efficacy: The following secondary efficacy endpoints will assess the effect of the CARILLON Mitral Contour System on clinical parameters of interest, relative to the Control population:

- To assess the change from baseline to twelve months for six-minute walk distance
- To assess the change from baseline to twelve months in left ventricular volumes (end diastolic and end systolic)

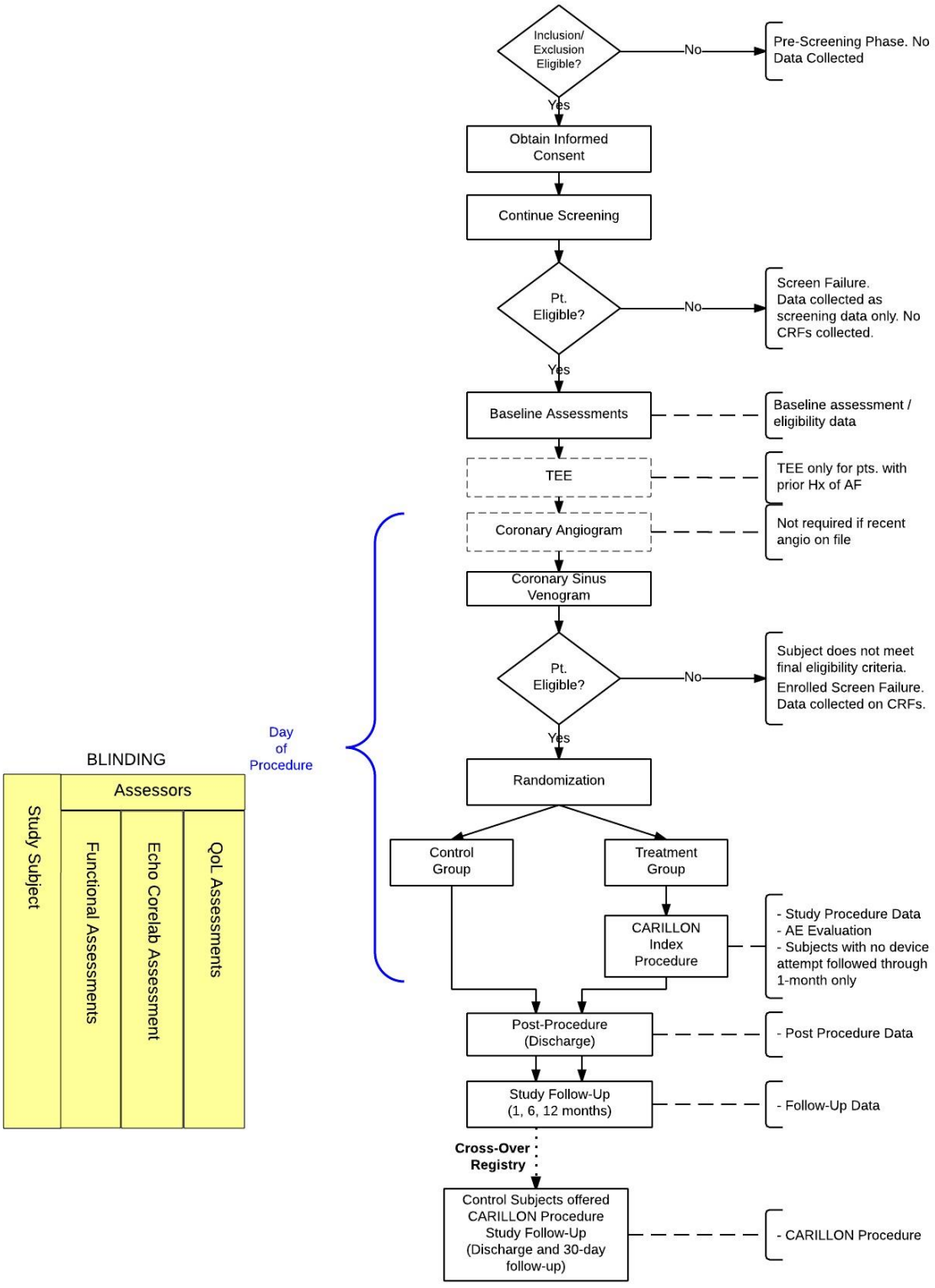
Observational Data:

- Long-term safety will be evaluated as the comparison of the following safety events between the Control and Treatment groups:
  – Mortality through six (6) and twelve (12) months
  – Serious adverse events through six (6) and twelve (12) months
- NYHA Classification
- Left ventricular hemodynamics[iii]:
  – LV end diastolic (LVEDD) and end systolic (LVESD) dimensions
  – Ejection fraction (LVEF)
  – Forward cardiac output (CO)
- Functional Mitral Regurgitation echocardiographic assessments[iii]:

[iii] Left ventricular hemodynamics and FMR assessments will also be assessed during exercise in randomized patients at a subset of study sites who have supine bicycle ergometry and echosonographers experienced in imaging acquisition during exercise.

  - Vena Contracta (VC)
  - Effective regurgitant orifice area (EROA)
  - MR Jet area / Left atrial area (MRJA/LAA)
  - MR grade
- Left atrial size
- Mitral annular diameter and area
- Diuretic dose change between baseline and 6 / 12 month follow-up
- Pulmonary Artery Systolic Pressure (echo derived at rest & during exercise[iii])
- NT-BNP
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Quality-of-Life Assessment (SF-12)

Study Design & Flow



Randomization & Study Blinding:

Randomization will only occur after the following eligibility parameters are assessed at the time of the procedure.

Eligibility Coronary Angiography: Angiography will be performed immediately prior to randomization to confirm that the subject will not require percutaneous coronary intervention within 30 days from the time of randomization (Exclusion criterion #5). At the Investigator's discretion, if the subject has:

- non-ischemic dilated cardiomyopathy - an arteriogram performed within twelve (12) months prior to eligibility assessment may be used to satisfy these criteria.
- ischemic dilated cardiomyopathy - an arteriogram performed within three (3) months prior to eligibility assessment may be used to satisfy these criteria.

If the Investigator determines that an eligibility coronary angiography is not required on the day of the index procedure, the subject will minimally undergo femoral artery cannulation prior to randomization to obtain hemodynamic data and ensure that subject is blinded to the treatment assignment. **Note**: All patients randomized to the Treatment group will undergo coronary angiography as part of the CARILLON Mitral Contour System procedure.

Eligibility Coronary Sinus Venogram: A coronary sinus venogram will be performed immediately prior to randomization in order to assess eligibility for the study (Inclusion Criterion #5).

If the eligibility arteriogram reveals the need for revascularization, or if the study subject does not meet all eligibility criteria, the subject is an enrolled screen failure. Randomization does not occur and the subject is followed through discharge only. The tests and evaluations conducted up to this point will be recorded as screening tests.

Randomization: If eligibility criteria are met, the subject can then be randomized to either the Treatment or the Control group. The Treatment group will undergo CARILLON device implant, while the Control group will not.

Subject Blinding (details in Section 4: Blinding): The trial will be double-blinded to reduce the effect of potential bias. Consequently, the overall time in the lab and perceived interventions (e.g., intra-procedure ECG, echo assessments, etc…) should be kept similar to ensure that subjects remain blinded to their randomization group.

If conscious sedation is to be used during the procedure, then the subjects should be blindfolded and earplugs provided so that they are not aware of any discussions that may reveal their randomization group. Rigorous efforts on the part of the implanting physicians, heart failure physicians, and supportive personnel will be implemented during and after the

procedure to ensure that the study subjects remain blinded to treatment assignment.

Assessor Blinding: The assessors of the NYHA Class, six-minute walk test, echo corelab assessors, and Quality of Life Questionnaires (Kansas City Cardiomyopathy Questionnaire and SF-12) will not be aware of the treatment assignment.

Cross-Over Registry:

Study subjects randomized to the Control group will be offered the option of receiving the investigational device after completing their 1-year follow-up if they continue to meet all of the study eligibility criteria.

Cross-Over registry subjects will be followed at discharge and for 30-days post the CARILLON procedure. The discharge and 30-day-up follow-up assessments will be identical to those collected in the randomized portion of the trial. On completion of the 30-day follow-up the Cross-Over registry subjects will be exited from the study.

Schedule of assessments:

Study Task	PRIMARY STUDY (Treatment & Control pts) Screening / Baseline	Randomization	Index Procedure	Discharge	1 Month (±7 Days)	6 month (±14 Days)	12 month (±30 Days)	CROSS-OVER REGISTRY (Control pts upon primary study completion) Screening / Baseline	CARILLON Procedure	Discharge	1 month (±7 Days)
Informed Consent	X							X			
Inclusion/Exclusion Criteria	X							X			
Past Medical History & Physical Exam	X							X[11,12]			
Serum Pregnancy Test	X							X			
TEE[1]	X							X			
Coronary Angiography	X[2]		X[2]					X	X		
Coronary Sinus Venogram	X							X			
Intraprocedure Echo (TTE or TEE)			X						X		
Physical Exam				X	X	X	X			X	X
Vital Signs[3]	X		X	X	X	X	X	X	X	X	X
Coagulation Tests[4]	X							X			
Cardiac Enzymes[5]	X			X	X	X	X	X		X	X
Chemistries[6]	X			X	X	X	X	X[12]		X	X
CBC[7]	X			X	X	X	X	X[12]		X	X
12-Lead ECG	X			X	X	X	X	X[12]		X	X
Complete TTE	X				X	X	X	X[12]			X
Exercise TTE[8]	X				X	X	X	X[12]			X
Abbreviated TTE[9] (safety)				X						X	
CXR or cine fluoroscopy				X		X	X			X	
Six Minute Walk Test	X[10]				X	X	X	X[12]			X
NYHA Classification	X				X	X	X	X[12]			X
KCCQ	X				X	X	X	X[12]			X
SF-12 QoL	X				X	X	X	X[12]			X
Concomitant Medications	X		X	X	X	X	X	X	X	X	X
Adverse Events	X		X	X	X	X	X	X	X	X	X

1. To rule out LAA clot - only required for subjects with a prior history of atrial fibrillation

2. The eligibility angiography may occur immediately prior to randomization, unless a recent angiogram (see section 3.4.3.2) indicating no CAD requiring intervention is available. All Treatment group subjects undergo coronary angiography as part of the CARILLON Mitral Contour System procedure.

3. Vital signs include: Blood pressure, heart rate, respiratory rate, oxygen saturation, temperature (degrees Celsius), weight, height (baseline only).

4. Coagulation Tests include: PTT and Prothrombin time.

5. Cardiac enzymes: cardiac troponin (cTn).

6. Serum chemistries: sodium, potassium, chloride, BUN, creatinine and NT-BNP.

7. CBC with differential: hemoglobin, hematocrit, platelets, and WBC.

8. Exercise TTE will be done only at pre-identified qualified sites with supine bicycle ergometry.

9. Abbreviated TTE safety assessment to rule out pericardial effusion.

10. Six-minute walk test will be undertaken for screening and baseline (reference Appendix F: Six Minute Walk Test Protocol).

11. No past medical history needed, physical exam only.

12. Data from 12-month follow-up of the primary study may be used if assessments were performed within 45 days to scheduled Cross-Over CARILLON procedure.

1 Introduction

1.1 Overview of Study

The American Heart Association (AHA) estimates that there are more than 22 million people worldwide with heart failure.[1] Functional mitral regurgitation, defined as the leakage of the mitral valve caused by global or regional changes in left ventricular geometry as well as mitral annular dilation, occurs as a consequence of heart failure. Cardiac Dimensions has developed proprietary technology designed to address functional mitral regurgitation in a minimally invasive manner.

Cardiac Dimensions plans to conduct a clinical trial of the CARILLON Mitral Contour System (XE2) in study subjects with functional mitral regurgitation. This study is a prospective, randomized parallel-group, double-blind, multi-center clinical trial designed to examine the safety and efficacy of the CARILLON Mitral Contour System in study subjects with functional mitral regurgitation. The study will consent up to 180 subjects in order to randomize up to 120 subjects at 25 investigational sites in Europe and Australia/New Zealand. Subjects will be randomized into one of two study groups using a 3:1 (Treatment group : Control group) ratio.

Study subjects who are eligible for this clinical study and have consented to participating in the study will undergo multiple assessments prior to randomization to evaluate the eligibility (inclusion/exclusion) criteria. Subjects who meet all eligibility criteria will be randomized into one of two study groups (Treatment or Control).

Study subjects randomized to the Treatment group will undergo a venous angiogram to assess the suitability of the coronary sinus/great cardiac vein (CS/GCV) for placement of the CARILLON implant. If the subject meets the anatomic requirements for device placement, the CARILLON implant procedure begins. With the distal aspect of the device anchored, incremental tension will be applied to plicate the peri-annular tissue. A transesophageal or transthoracic echocardiogram will be obtained during the procedure to evaluate the effect on functional mitral regurgitation and to evaluate left ventricular function. After the proximal anchor of the implant is locked in place, safety (including assessment of coronary arterial flow) and efficacy will be reconfirmed prior to releasing the CARILLON implant from the delivery system.

Subjects randomized to the Control group will experience an index procedure similar to the Treatment group, however, without device placement. To ensure that subjects randomized to the Control group will not be able to deduce the treatment assignment based on the type of intervention or time associated with the procedure, minimal interventional procedures, such as femoral arterial pressure monitoring and a jugular venous drip. If a recent (within the last 3 months for ischemic cardiomyopathy or 12 months for non-ischemic cardiomyopathy) coronary angiogram is available, this assessment may be precluded.

After the study subjects are discharged, the subjects' primary care specialists (cardiologist/heart failure physician) and clinical investigation site staff will coordinate

follow-up evaluations. Subjects will be evaluated at one (1), six (6), and twelve (12) months post-implant, to assess long-term safety, and functional and clinical status. (Reference Section 3.8-Study Follow-up Evaluations)

This study will provide for an independent Clinical Events Committee (CEC) and an independent Data Safety Monitoring Board (DSMB). The CEC will be responsible for adjudicating complications reported during the study that are related to study endpoints (objectives), the procedure or the device. The DSMB will review the safety data against the established criteria and in the context of other safety data accumulated to date and the continued validity of the study.

1.2 Rationale for Study

1.2.1 Rationale for the Use of the Device

The appeal of percutaneous approaches to treat functional mitral regurgitation is that they may provide a sufficient reduction in mitral regurgitation without the morbidity and mortality typically associated with surgery. In addition, for subjects who are high risk surgical candidates and in whom medical therapy is suboptimal, a percutaneous procedure provides an alternative treatment option.

Cardiac Dimensions has developed a coronary sinus-based technique that involves anchoring a device distally in the CS/GCV, plicating the mitral annular tissue through external tension, then anchoring the implant in the proximal coronary sinus so as to maintain the annular reduction. The acute and chronic efficacy of this approach has been reported in canine and ovine models of heart failure. In addition to a reduction in the degree of mitral regurgitation, increases in cardiac output, a decrease in pulmonary capillary wedge pressure, and no untoward effects on cardiac function or hemodynamics have been reported.[2,3,4,5,6,7,8,9]

1.2.2 Rationale for Subject Population Selection

The contribution of mitral regurgitation to the morbidity and mortality of patients suffering from heart failure has been well documented.[10] Patients with functional mitral regurgitation have few options available to them in the treatment of their disease. Medical management continues to inadequately address the problem of functional mitral valve regurgitation. The surgical approaches to mitral annuloplasty demonstrate improved hemodynamics; however, the high post-operative morbidity and mortality associated with surgery in this population does not warrant widespread use of this approach, especially for lesser degrees of functional mitral regurgitation. Percutaneous approaches may be able to achieve the same goal without the associated morbidity and mortality seen in the surgical approaches. Therefore, it is this population of subjects with functional mitral regurgitation that may benefit the most from the CARILLON Mitral Contour System.

1.2.3 Rationale for Device Placement

The CARILLON Mitral Contour System received CE-Mark in August 2011 and is designed to place a permanent implant in the CS/GCV and to allow the manual tensioning necessary to cause mitral annular reduction and thereby decrease mitral regurgitation. The distal end of the CARILLON implant is secured in the GCV, and the proximal end is secured in the coronary sinus. When traction is applied (manually) to the delivery system, the CARILLON implant reshapes the mitral annulus in such a way as to reduce mitral regurgitation. It is anticipated that this plication of the mitral annulus will lead to improvements in the subject's functional status and may also improve left ventricular hemodynamics.

1.3 Background

1.3.1 Heart Failure

Heart failure is defined as a clinical condition in which the heart is unable to pump a sufficient amount of blood to meet the metabolic demands of the body. This compromised myocardial contractility triggers a set of compensatory responses whereby the heart attempts to accommodate for the altered function. Included in these compensatory responses are increased preload via the Frank-Starling mechanism, activation of the neurohumoral systems, and myocardial remodeling. The enhanced preload and increased sarcomere length allow the ventricle to generate more work and eject a higher stroke volume. Although the changes in cardiac anatomy and physiology are initially able to minimize the effect of the myocardial dysfunction, the compensatory mechanisms are unable to sustain cardiac performance indefinitely, and chronic deterioration (decompensation) ensues.

The American Heart Association (AHA) estimates that there are more than 22 million people worldwide with congestive heart failure (CHF)[1], of these, 85% of subjects have a dilated cardiomyopathy. Based upon the Framingham Heart Study, about 550,000 new cases of CHF occur each year. The incidence approaches 10 per 1,000 people after age 65.[11] The estimated direct and indirect cost of heart failure in the United States for 2009 is $37.2 billion.[1]

1.3.1.1 Prevalence of Mitral Regurgitation in Heart Failure

In patients with a dilated cardiomyopathy, one of the consequences of chronic cardiac deterioration is progressive ventricular dilation. This dilation not only compromises myocardial contractility, but also compromises the efficiency of the ventricle by contributing to the development of functional mitral regurgitation (MR). Functional MR refers to leakage of the mitral valve due to dilation of the left ventricle (LV) and the annulus that surrounds and supports the mitral valve. This is in contrast to "organic" MR where an abnormality of the valve itself (e.g., myxomatous degeneration) results in the leakage. In patients with severe heart failure, functional MR increases the hemodynamic stress on the failing LV resulting in progressive LV dilation, progressive systolic dysfunction, higher filling pressures and lower cardiac output. Between 54% and 60% of patients with dilated cardiomyopathy have been reported to have functional mitral regurgitation.[12,13,14,15]

1.3.2 Morbidity and Mortality Related to Functional Mitral Regurgitation

Functional mitral regurgitation increases both the morbidity and mortality of subjects with heart failure.[10] The labile nature of functional mitral regurgitation and its effect on exercise tolerance have also been documented.[16]

If functional mitral regurgitation further strains the failing myocardium, both at rest and especially with exercise, then the impact could translate into decreased survival as well. A positive correlation between mitral regurgitation and increased mortality has in fact been delineated in a variety of recent studies. Blondheim followed 91 subjects with dilated cardiomyopathy longitudinally and found a markedly decreased survival in the group with mitral regurgitation (i.e., 22% vs. 60% at 32 months). The trend also held true for mild mitral regurgitation.[17]

1.3.3 Current Treatment of Patients with Mitral Regurgitation

1.3.3.1 Medical Treatment

Heart failure patients are routinely managed with a combination of four types of drugs: a diuretic, an angiotensin converting enzyme inhibitor (or angiotensin receptor blocker), a beta-adrenergic blocker, and an aldosterone blocker. Patients with evidence of fluid retention receive a diuretic until an euvolemic state is achieved. The diuretic is continued to prevent the recurrence of fluid retention. Even if a patient has responded favorably to the diuretic, treatment with an ACE inhibitor and a beta-blocker is initiated and maintained in patients who can tolerate them as they have been shown to favorably influence the long-term prognosis of heart failure. Therapy with digitalis may be initiated at any time to reduce symptoms and enhance exercise tolerance.[18,19]

1.3.3.2 Surgical Treatment

The efficacy of performing mitral valve repair has been thoroughly studied in subjects with organic mitral regurgitation, and the long-term results are encouraging. Although surgical options exist for treatment of organic mitral valve pathologies, surgical repair of the mitral valve to treat functional mitral regurgitation is not currently recommended for subjects with significant LV dysfunction. Surgical intervention is warranted in certain cases, however as noted in the ACC/AHA Guidelines for the Management of Patients with Valvular Heart Disease:

> Furthermore, when chronic severe secondary MR is addressed surgically, it is not clear that repair, so valuable in treating primary MR, is even preferred over MVR in chronic severe secondary MR. Small RCTs have demonstrated that mitral valve surgery reduces chamber size and improves peak oxygen consumption in chronic severe secondary MR. Deciding which patients with chronic severe secondary MR will benefit from mitral surgery awaits the results of larger RCTs. Ischemic or dilated cardiomyopathy presents different challenges for mitral repair. Regurgitation is caused by annular dilation as well as apical and lateral displacement of the papillary muscles. New techniques have facilitated mitral repair in this situation, but durability of the repair is primarily dependent on regression or progression of ventricular dilation.[20]

The paucity of clinical options available to treat functional MR in patients with dilated cardiomyopathy has led to the exploration of novel therapeutic modalities. These novel therapeutic approaches include both surgical and percutaneous techniques.

1.3.4 Novel Therapies for Functional Mitral Regurgitation

1.3.4.1 Cardiac Resynchronization

For patients with CHF and prolonged QRS duration, cardiac resynchronization therapy has been shown to improve both quality of life and exercise tolerance.[21,22] In a sub-study of 24 patients with functional mitral regurgitation and heart failure, the degree of mitral regurgitation was quantified before and after biventricular pacemaker implantation. Breithardt found that resynchronization therapy was associated with significant reduction in mitral regurgitation from moderate to mild.[23] Although this observation is promising for patients in whom intraventricular conduction delay contributes to their pathology, the technique is not applicable to patients with adequate conduction and functional mitral regurgitation.

1.3.4.2 Percutaneous Alfieri Procedure

A unique approach to mitral valve repair was developed by Alfieri whereby the anterior and posterior leaflets of the mitral valve are stitched together to reduce the degree of mitral regurgitation.[24] A percutaneous form of this therapy was developed by Evalve / Abbott where access to the mitral valve was achieved through a transeptal procedure, then a clip was positioned on the leaflets to create a double orifice mitral valve.[25,26,27,28] The MitraClip system received CE Mark approval in March 2008, and as a result of promising initial clinical experiences with this procedure, this device has been implanted as a less invasive treatment alternative to surgery in more than 10,000 patients worldwide. In the United States, the EVEREST II randomized trial was conducted and compared treatment with the MitraClip device to treatment with surgery for MR in a relatively low-risk group of patients. At 1 year, the rate of death was similar in both groups, whereas the degree of residual MR was higher with the percutaneous approach compared with surgery. However, major adverse events at 30 days were lower overall for percutaneously treated subjects. While the majority of the patients enrolled in the EVEREST II High- Surgical-Risk cohort had functional MR, it was a heterogeneous group and was not compared to the medical standard of care. The data from this cohort did demonstrate positive and consistent results for high-surgical-risk patients in terms of safety, reduction of MR, reverse left ventricular remodeling, improvement in heart failure symptoms, improvement in quality of life, and reduced rates of rehospitalization, albeit in a small number of patients.[29]

1.3.4.3 Implications of Percutaneous Therapies

The contribution of mitral regurgitation to the morbidity and mortality of patients suffering from heart failure has been well documented. Medical management continues to inadequately address the problem of functional mitral valve regurgitation. The feasibility studies performed on patients with dilated cardiomyopathy and severe mitral regurgitation documenting improved outcomes following mitral annuloplasty are encouraging. The high post-operative morbidity and mortality associated with surgery

in this patient population makes widespread acceptance of this approach uncertain. With no single treatment regimen resonating as the gold standard for treatment and correction of functional mitral regurgitation, there remains room for new therapies to yield better results in this patient population.

1.3.5 Summary of Pre-Clinical Studies

In addition to extensive bench-top safety testing, Cardiac Dimensions has conducted several pre-clinical animal studies designed to evaluate the feasibility, efficacy and safety of the CARILLON Mitral Contour System. Studies have been performed in large animal species, in healthy and diseased animals, and in acute and chronic settings. Proof of concept studies and preliminary safety studies in combination with bench-top and cadaver work have led to the current design of the CARILLON implant. The results of these studies indicate that the investigational device can be safely and reliably loaded, deployed, locked, tensioned, recaptured and removed. Pre-clinical use of the device did not result in any vein damage including perforation, thrombus or occlusion

1.3.6 Summary of Clinical Studies

1.3.6.1 Multi-Center Study of the CARILLON Mitral Contour System, Europe – The AMADEUS Trial

In 2005, Cardiac Dimensions initiated a safety study of the CARILLON Mitral Contour System in thirty (30) subjects in seven (7) clinical investigation sites in Germany, the Netherlands, and Poland. The primary objective of the "AMADEUS Trial: A Safety and Efficacy Study of the CARILLON Mitral Contour System for the Treatment of Mitral Regurgitation" was to evaluate the safety of deploying and implanting the Cardiac Dimensions CARILLON implant in the coronary sinus and great cardiac vein of subjects with functional mitral regurgitation (FMR). The secondary objectives were to determine the long-term safety of the device and the effect of the device on hemodynamics and subject function.

Patients with dilated cardiomyopathy, moderate to severe FMR, ejection fraction < 40%, and six minute walk distance between 150 and 450 meters were enrolled in the AMADEUS Trial. Echocardiographic FMR grade, exercise tolerance, New York Heart Association (NYHA) class, and quality of life (QOL) were assessed at baseline, one, and six months. Of the 48 subjects enrolled in the trial, 30 were permanently implanted with the CARILLON device. Eighteen (18) subjects did not receive a device due to access issues, insufficient acute FMR reduction, or coronary artery compromise. The major adverse event rate was 13% at 30 days. At six months, the degree of FMR reduction among five different quantitative echo measures ranged from 22 – 32%. Six minute walk distance improved from 307 ±87 meters at baseline, to 403 ±137 meters at six months ($p<0.001$). QOL, measured by the Kansas City Cardiomyopathy Questionnaire, improved from 47 ±16 points at baseline, to 69 ±15 points at six months ($p<0.001$). The results of the AMADEUS study have been published in a peer-reviewed journal – Circulation in 2009.[30] Follow-up in the study was completed in 2007.

1.3.6.2 Pilot Safety Study of the CARILLON Mitral Contour System, Europe – The TITAN Trial

The European feasibility trial of the CARILLON Mitral Contour System, named TITAN, is a multi-center, safety study for the treatment of functional mitral regurgitation. The primary objective of the study is to evaluate the safety of deploying and implanting the CARILLON device in the coronary sinus/great cardiac vein in patients with functional mitral regurgitation. The secondary objectives are to determine the long-term safety of the device, and the effect of the device on hemodynamics and patient function.

The TITAN Trial Investigational Plan was reviewed and approved by the appropriate medical ethics committees and notification was made to the Competent Authorities. The TITAN Trial was initiated in April 2008. Three (3) sites in Germany, two (2) sites in Poland, and two (2) sites in France were ultimately initiated.

Patients with dilated ischemic or non-ischemic cardiomyopathy, moderate to severe FMR, ejection fraction < 40%, and six minute walk distance between 150 and 450 meters were enrolled in the TITAN Trial. Echocardiographic FMR grade, exercise tolerance, NYHA class, and Quality-of-Life (QOL) were assessed at baseline, one, six and twelve months. Of the 65 subjects enrolled in the trial, 12 subjects did not meet the study eligibility criteria. Of the 53 subjects who underwent a procedure to implant the CARILLON device, 36 ultimately received the CARILLON device. Seventeen subjects did not receive a device due to access issues, insufficient acute FMR reduction, or coronary artery compromise.

The major adverse event rate was 1.9% at 30 days. Analysis of the TITAN study indicates that at 12 months, the degree of FMR reduction among four different quantitative echo measures ranged from 32 – 46%, with regurgitant volume showing a the greatest reduction between baseline and 12 months. NYHA grade improved by 32% from baseline to 12 months, six minute walk distance improved by over 125 meters (41% increase from baseline) and QOL, as measured by the Kansas City Cardiomyopathy Questionnaire, improved by 53% at twelve months. Left ventricular dimensions in the implanted population also showed a significant trend toward reverse remodeling, with end diastolic and systolic volumes decreasing by 9% and 12%, respectively at 12 months. The results of the TITAN study have been published in a peer-reviewed journal - European J. Heart Failure in 2012.[31]

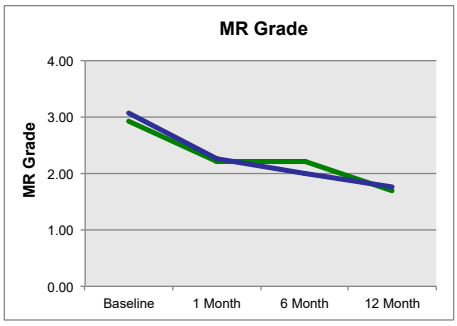
1.3.6.3 Safety Study of the CARILLON Mitral Contour System, Europe – The TITAN II Trial:

The European safety trial of the CARILLON Mitral Contour System (modified XE2), named TITAN II, is a multi-center, safety study for the treatment of functional mitral regurgitation. The primary objective of the study is to evaluate the safety of deploying and implanting the CARILLON device in the coronary sinus/great cardiac vein in patients with functional mitral regurgitation. The secondary objectives are to determine the long-term safety of the device, and the effect of the device on hemodynamics and patient function.

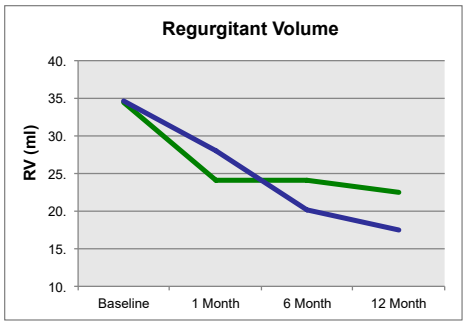
The TITAN II Trial Investigational Plan has been reviewed and approved by the appropriate medical ethics committees and notification was made to the Competent Authorities. The TITAN II Trial was initiated in July 2011. Three (3) sites in Germany, one site in Poland, and one site in France have been initiated and have enrolled patients. As of August 28, 2013, a total of 30 patients have been implanted with the CARILLON device and patient enrollment is now complete. Per the study protocol, all implanted patients were followed for 12-months post procedure.

Of the 43 subjects enrolled in the trial, seven (7) subjects did not meet the study eligibility criteria. Of the 36 subjects who underwent a procedure to implant the CARILLON device, 30 ultimately received the CARILLON device. Six (6) subjects did not receive a device due to access issues or coronary artery compromise.

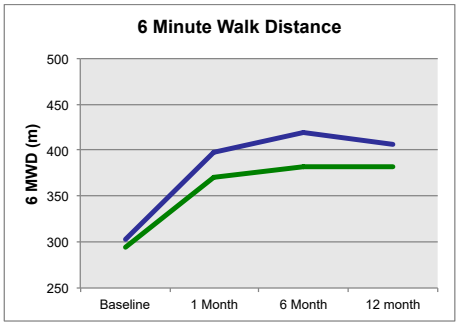
The major adverse event rate in the intent-to-treat population at 30 days (the primary endpoint for the study) was 2.8%. Although a complete analysis of the data is awaiting complete monitoring of all the follow-up information, the preliminary analysis of the mitral regurgitation (MR Grade and Regurgitant Volume) and functional parameters (six minute walk distance and NYHA class) shows improvements that are comparable to that found in the TITAN study.



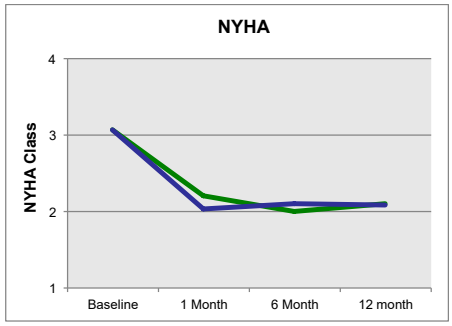
TITAN II: Baseline n=25, 1mo n=24, 6mo n=23; 12mo n=16
TITAN: Baseline n=36, 1mo n=33, 6mo n=31. 12mo n=25



TITAN II: Baseline n=24, 1mo n=22, 6mo n=18; 12mo n=14
TITAN: Baseline n=36, 1mo n=33, 6mo n=31. 12mo n=25



TITAN II: 6MWD Baseline n=29, 1mo n=25, 6mo n=18; 12mo n=19
TITAN: 6MWD Baseline n=36, 1mo n=32, 6mo n=27; 12mo n=23



TITAN II: NYHA Baseline n=30, 1mo n=29, 6mo n=23; 12mo n=21
TITAN: NYHA Baseline n=36, 1mo n=32, 6mo n=29; 12mo n=25

2 Device Overview

The CARILLON Mitral Contour System (XE2) is a Class III medical device and is manufactured by Cardiac Dimensions, Inc., in Kirkland, Washington, USA. The device received CE-Mark on 3rd August 2011. In Australia/New Zealand, the CARILLON device is intended "For Clinical Trial Use Only".

2.1 Device Components

The CARILLON Mitral Contour System (XE2) consists of the following components:

- An implant intended for permanent placement in the coronary sinus (CS)/great cardiac vein (GCV)
- A delivery system which consists of a custom 9F delivery catheter and a handle assembly.

The implant is attached to the handle assembly and is delivered through the delivery catheter to the coronary vein along the posterolateral aspect of the mitral annulus.

2.1.1 CARILLON Implant

The CARILLON implant (XE2) is made of nitinol and titanium and is manufactured in different lengths and with different anchor sizes to accommodate individual venous anatomy. The implant is composed of a distal anchor (positioned in the GCV), proximal anchor (positioned in the CS), ribbon connector (joining the anchors), proximal crimp tube and distal crimp tube. The implant is designed to be deployed, tensioned, and locked in the coronary vein in order to reshape the mitral annulus and thus reduce mitral annular dilation and mitral regurgitation.

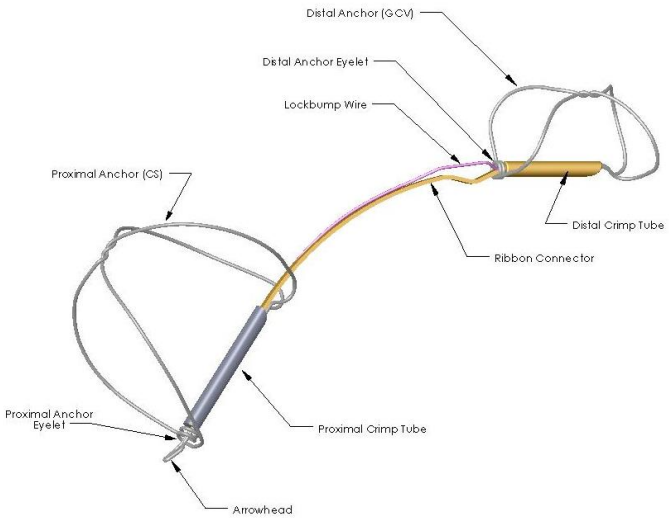


Figure 2.1 CARILLON Implant (XE2)

2.1.2 Delivery System

2.1.2.1 Delivery Catheter

The delivery catheter is curved at its distal end and has a 9F (3.0 mm) outer diameter and 70 cm effective length. The inside diameter is 2.5 mm and will accept a 0.035" (0.89 mm) guidewire or a 7F (2.3 mm) outer diameter diagnostic or deflectable catheter.

The delivery catheter is used to introduce a graded measuring device (e.g., marker catheter), to inject radiopaque contrast for venograms, to connect to the cartridge of the handle assembly to help deliver the implant, to engage the locking mechanism of the distal anchor, and to recapture the implant. The straight port allows for advancement and removal of a measuring device and introduction of the implant. The side port may be used for injection of radiopaque contrast medium.

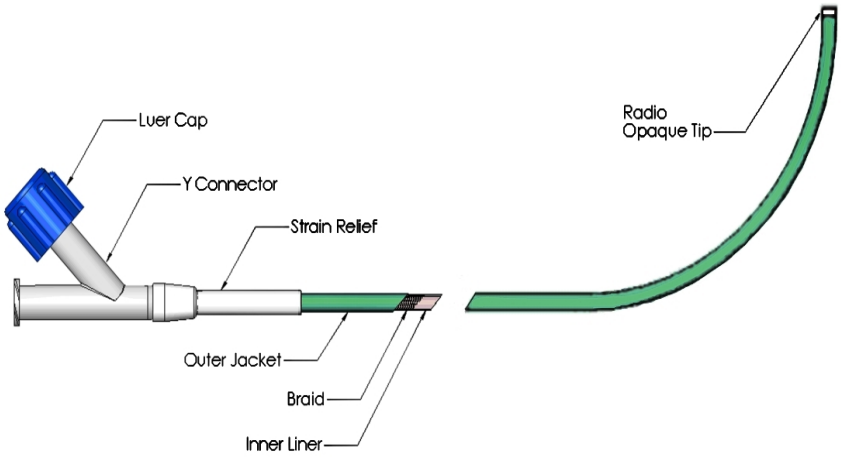


Figure 2.2 CARILLON 9F Delivery Catheter

2.1.2.2 Handle Assembly

The handle assembly is composed of a cartridge, a sheath/pusher assembly and a handle assembly with cartridge window, rotating knobs, and release safety.

The cartridge contains the implant, which is folded in the unlocked position within the cartridge lumen. During delivery, the implant is manually advanced from the cartridge into the delivery catheter. The handle facilitates deployment, locking, decoupling and recapture of the implant. This is accomplished by rotating knobs that enable controlled movements of the delivery catheter, the implant, the sheath/pusher and the decoupling mechanism. The release safety must be removed prior to decoupling the implant from the handle assembly.

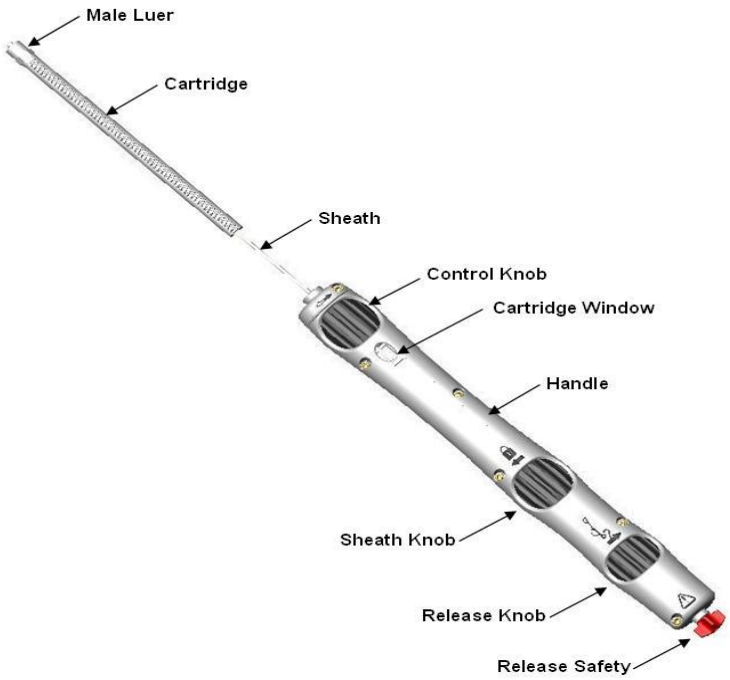


Figure 2.3 Handle Assembly

2.2 Principles of Operation

The CARILLON implant is implanted through transvenous placement (jugular cannulation) under fluoroscopy following standard percutaneous cannulation/ catheterization procedures.

After catheterization of the coronary venous system, an assessment of the size of the CS/GCV is made to determine the proper sizing of the CARILLON implant. This is accomplished by performing a venogram to assist in measurement of vein diameter and length. An angiogram is also performed to determine the location of the coronary arteries in relation to the CS/GCV.

The CARILLON implant is comprised of distal and proximal anchors joined with a ribbon connector. The design of the distal portion of the implant (described as the "distal anchor") enables it to be anchored in the distal portion of the GCV. This is accomplished by expanding the anchor in the vein and locking it in place with the tip of the delivery catheter. The pressure applied on the vein wall by the expanded and locked anchor enables secure anchoring of the CARILLON implant. The delivery catheter is then withdrawn proximally to expose the ribbon connector.

Tension is applied manually to the delivery system, pulling the proximal portion of the CARILLON implant (described as the "proximal anchor") toward the CS ostium. Fluoroscopy and echocardiography guide the tensioning process. The proximal anchor is deployed and locked in the CS by advancing the sheath component of the delivery system, thus reshaping the mitral annulus. After determining that no coronary artery flow is compromised (assessed by coronary angiography), that there is some reduction

in the mitral regurgitation characteristics (assessed by echocardiography) and ensuring that the proximal anchor is locked (assessed by fluoroscopic imaging), the operator may then decouple the handle assembly from the implant and remove the catheter.

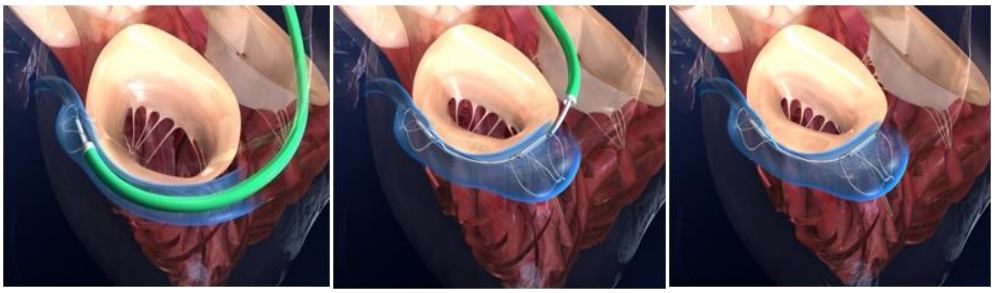


Figure 2.4 Deployment of the CARILLON Implant and Plication of the Mitral Valve Annulus

The CARILLON Mitral Contour System is designed to enable acute recapture during the implantation procedure (prior to decoupling) if for any reason the implant cannot be successfully deployed, or for other clinical or safety reasons. The implant is recaptured by advancing the sheath to the proximal anchor arrowhead. The delivery catheter is then advanced over both the proximal and distal anchors by turning the control knob. Both anchors will be completely recaptured into the delivery catheter

2.3 Indications for Use

The CARILLON Mitral Contour System is indicated for use in patients with secondary (functional) mitral regurgitation.

2.4 Contraindications

The CMCS is contraindicated for use in:

- Patients with existing devices in the CS/GCV
- Patients who have had a mitral valve replacement or a mitral annuloplasty ring implant

3 Clinical Study Design

3.1 Study Executive Committee

The REDUCE FMR study has an Executive Committee which provides oversight for the overall direction and strategy of this clinical trial. The Executive Committee will contribute to the design of the study, increase information exchange at an early stage of trial development, increase the efficiency of clinical trial collaboration and contribute to the publication of the study data.

The Executive Committee consists of the following individuals:

- Prof. Ian Meredith, Prof. Horst Sievert and Prof. David Kaye – overall REDUCE FMR Study Principal Investigators
- Dr. Steve Goldberg – Medical Monitor for the REDUCE FMR study
- Prof. Tomasz Siminiak and Dr. Janusz Lipiecki – site Principal Investigators

3.2 Study Objectives

3.2.1 Primary Endpoint

The primary efficacy endpoint is to demonstrate a statistically significant improvement in regurgitant volume associated with the CARILLON device at twelve (12) months, relative to the Control population.

3.2.2 Secondary Endpoints

The secondary objectives of the REDUCE FMR Trial are to determine the procedural safety of the device and the effect of the CARILLON implant on hemodynamics, subject function and long-term safety, further defined as follows.

3.2.2.1 Safety

The following secondary safety endpoints will measure the effect of the CARILLON Mitral Contour System on clinical safety parameters of interest, relative to the Control population

- To document the difference in the rate of major adverse events between randomized groups, at 1 and 12-months post randomization.

  Major Adverse Events are defined as a composite of the following:
  - Death
  - Myocardial Infarction
  - Device Embolization
  - Vessel Erosion, requiring percutaneous or surgical intervention
  - Cardiac Perforation, requiring percutaneous or surgical intervention
  - Occurrence of cardiac surgery or percutaneous coronary intervention associated with device failure

- To assess the rate of heart failure hospitalizations (number of admissions, and total associated days in the hospital), from the time of the index procedure through twelve months of follow-up.

3.2.2.2 Efficacy

The following secondary endpoints will measure the effect of the CARILLON Mitral Contour System on clinical parameters of interest, relative to the Control population:

- To assess the change from baseline to twelve months for six-minute walk distance
- To assess the change from baseline to twelve months in left ventricular volumes (end diastolic and end systolic)

3.2.3 Observational Data

The following observational data will provide additional safety, clinical and/or mechanistic data:

- Long-term safety will be evaluated as the comparison of the following safety events between the Control and Treatment groups:
  - Mortality at six (6) and twelve (12) months
  - Serious adverse events at six (6) and twelve (12) months
- NYHA Classification
- Left ventricular hemodynamics[iv]:
  - LV end diastolic (LVEDD) and end systolic (LVESD) dimensions
  - Ejection fraction (LVEF)
  - Forward cardiac output (CO)
- Functional Mitral Regurgitation echocardiographic assessments[iv]:
  - Vena Contracta (VC)
  - Effective regurgitant orifice area (EROA),
  - MR Jet area / Left atrial area (MRJA/LAA)
  - MR grade
- Left atrial size
- Mitral annular diameter and area
- Diuretic dose change between baseline and 6 / 12 month follow-up
- Pulmonary Artery Systolic Pressure (echo derived at rest & during exercise[iv])
- NT-BNP

[iv] Left ventricular hemodynamics, FMR assessments and pulmonary artery pressure (echo derived) will also be assessed during exercise in randomized patients at a subset of study sites who have supine bicycle ergometry and echosonographers experienced in imaging acquisition during exercise.

- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Quality-of-Life Assessment (SF-12)

3.2.4 Subject Follow Up Duration

Subjects will be followed for 12 months from the time of randomization to meet primary and secondary endpoints in accordance with the follow-up periods as defined in this *Investigational Plan* and the Subject Study Calendar (reference Appendix C).

3.3 Subject Eligibility

This study intends to enroll patients with moderate heart failure and functional mitral regurgitation. All evaluations assessing eligibility criteria for this study must be performed within 45 days prior to randomization and the index procedure, unless otherwise noted.

All subjects will require informed consent for enrollment in this clinical study.

Many of the evaluations at eligibility will have been collected as part of a subject's standard chronic heart failure treatment regimen, prior to the subject being consented for the study. If these tests or examinations were completed as standard of care for the subject, and timing of the test or exam is within 45 days prior to randomization and the index procedure, the results are acceptable for use as satisfying eligibility requirements.

In cases when key evaluations have occurred more than 45 days prior to randomization, the subject must undergo new assessments for qualifying the subject for the clinical study.

3.3.1 Inclusion Criteria

The subject must meet **all** of the following criteria at the time of eligibility for randomization and the index procedure:

1. Diagnosis of dilated ischemic or non-ischemic cardiomyopathy
2. Functional Mitral Regurgitation:

   2+ (Moderate), 3+ (Moderate/Severe), or 4+ (Severe)
3. NYHA II, III, or IV (refer to Appendix D for NYHA Classification)
4. Six Minute Walk distance of at least 150 meters and no farther than 450 meters
5. Subject meets anatomic screening criteria as determined by angiographic screening at the time of the index procedure to ensure that implant can be sized and placed in accordance with the Instructions for Use
6. Left Ventricular Ejection Fraction ≤ 50%
   NOTE: Subjects with LVEF of 41- 50% can only be included if baseline NYHA is class III/IV **AND** MR grade is 3+/4+ (moderately-severe/severe)

7. LV end diastolic dimension (LVEDD) >55mm or LVEDD/BSA > 3.0cm/m^2
8. Stable heart failure medication regimen for at least three (3) months (refer to Appendix G for definition of stable heart failure regimen)
9. Age ≥ 18 years old and ≤ 85 years old
10. The subject has read the informed consent, agrees to comply with the requirements, and has signed the informed consent to participate in the study
11. Female subjects of child-bearing potential must have a negative serum βHCG test

3.3.2 Exclusion Criteria

The following must **NOT** be present at the time of eligibility for randomization and the index procedure:

1. Hospitalization in past three (3) months due to myocardial infarction, coronary artery bypass graft surgery, and/or unstable angina
2. Hospitalization in the past 30 days for coronary angioplasty or stent placement
3. Subjects expected to require any cardiac surgery, including surgery for coronary artery disease (unprotected left main stenosis greater than or equal to 50% or, greater than or equal to 70% stenosis in at least three (3) epicardial coronary arteries in the absence of prior bypass surgery), or for pulmonic, aortic, or tricuspid valve disease within one (1) year
4. Subjects with echocardiographic documentation of non-compaction cardiomyopathy with associated hypercontractility of the cardiac structures supporting the mitral annulus
5. Subjects expected to require any percutaneous coronary intervention within 30 days of enrollment
6. Recipient of intravenous positive-inotrope infusion or intra- aortic balloon pump support within the past 30 days
7. Presence of a mechanical mitral heart valve, mitral bio-prosthetic valve or mitral annuloplasty ring
8. Pre-existing device (e.g., pacing lead) in coronary sinus (CS) / great cardiac vein (GCV), or anticipated need for cardiac resynchronization therapy (CRT) within twelve (12) months
9. Presence of a coronary artery stent under the CS / GCV in the implant target zone
10. Significant organic mitral valve pathology (e.g., moderate or severe myxomatous degeneration, with or without mitral leaflet prolapse, rheumatic disease, full or partial chordal rupture)
11. Presence of severe mitral annular calcification
12. Presence of left atrial appendage (LAA) clot. Patients with a current/ongoing (documented within the last 12 months) history of atrial fibrillation must undergo a

trans-esophageal echo prior to the procedure to rule-out left atrial appendage clot to minimize the risk of thrombo-embolism caused by the tissue plication

13. Cerebral vascular event within the past three (3) months
14. Presence of primary renal dysfunction or significantly compromised renal function as reflected by a serum creatinine > 2.2 mg/dL (194.5 µmol/L) OR estimated Glomerular Filtration Rate (eGFR) < 30 ml/min
15. Allergy to contrast dye that cannot be pre-medicated
16. Inability to undertake a six-minute walk test due to physical restrictions/limitations
17. Chronic severe pathology limiting survival to less than 12-months
18. Anticipated need of left ventricular assist device within twelve (12) months
19. Currently participating in an investigational study that clinically interferes with the current study endpoints.

3.4 Informed Consent and Study Enrollment

3.4.1 Informed Consent

To protect the rights and welfare of subjects, this clinical study will be conducted in conformance with ISO 14155:2011 Section 4 – Ethical Considerations.

The subject will be provided with ample time to read, ask questions as needed, be provided with all appropriate answers, and to understand the study before making decision to participate in the study or not.

For additional details on the Informed Consent process, please see section 7.1 – Informed Consent.

3.4.2 Enrollment and Eligibility

Once the subject has provided their consent, the subject is enrolled in the study.

Once the subject has completed the required baseline assessments and met all eligibility criteria (with the exception of the final anatomic eligibility), the subject can then be scheduled for angiographic/venogram to assess final eligibility prior to randomization.

Recruitment will continue in a consecutive manner until enrollment for the study is complete. In order to provide traceability for each subject enrolled in this study, unique study numbers will be assigned according to Cardiac Dimensions standard operating procedures, including study sites, study number, and a unique subject number.

3.5 Screening/Baseline Assessments

The following examinations and tests will be completed according to the schedule as shown. These will be completed prior to randomization and the index procedure for

those study subjects who continue to be eligible. This set of examinations and tests will be considered the study subject's baseline evaluations.

3.5.1 Not More than 45 Days Prior to Randomization

The following evaluations must be performed within 45 days prior to the index procedure. Subjects who continue to meet all of the inclusion and none of the exclusion criteria will be scheduled for randomization and the index procedure. Subjects who are found ineligible will be categorized as screen failures.

- Complete past medical history, physical exam (history to include details of original diagnosis and review of current and prior heart failure treatment)
- Transthoracic echocardiogram (TTE)
  ***Note**: Study sites that have experience and necessary equipment may undertake exercise echocardiography in addition to the standard resting echocardiographic assessment required by the protocol.*
- Functional assessments:
  - NYHA Classification (reference Appendix D: NYHA Classification)
  - Six minute walk test. To minimize any training effect, the screening and baseline tests must be two separate assessments at least two hours apart (reference Appendix F: Six Minute Walk Test Protocol)
  - Kansas City Cardiomyopathy Questionnaire (KCCQ)
  - SF-12 Quality-of-Life Assessment Questionnaire
- Electrocardiogram (12-lead ECG)
- Serum chemistries: sodium, potassium, chloride, glucose, BUN, creatinine, and NT-BNP
- CBC with hemoglobin, hematocrit, platelets, and WBC
- Serum pregnancy test (if subject is a female of child-bearing potential)
- Other information to be recorded between eligibility and the study procedure:
  - Current medications
  - Adverse events including newly diagnosed infections, organ dysfunction, etc.

3.5.2 Not More than Three (3) Days Prior to Randomization

The following safety evaluations must be performed within three (3) days prior to the index procedure to ensure that subjects continue to be eligible for randomization and the index procedure:

- Vital signs: blood pressure, heart rate, respiratory rate, oxygen saturation, temperature, weight and height
- PTT and PT
- Cardiac enzymes: cardiac troponin (cTn)

- Serum creatinine
- Transesophageal echocardiogram (TEE) - to rule out left atrial appendage clot

  ***Note**: only required in subjects with existing atrial fibrillation.*

  ***Note**: if TEE is done on the day of the study procedure and an LAA clot is identified (subject is ineligible), no study discharge evaluations are necessary. These subjects are regarded as screen failures.*

3.5.3 Study Procedure - Prior to Randomization

3.5.3.1 Cardiac Catheterization Requirements

All subjects brought into the catheterization lab on the day of the index procedure will be pre-medicated according to institutional procedures for cardiac catheterization. Additionally, subjects will be heparinized prior to the angiographic procedure according to institutional policies. Anti-platelet therapy is not required in the trial, however, individual Investigators may prescribe such medications in accordance with their institution's standard of care or as necessary to treat other concurrent cardiac conditions. The use of anti-platelet therapy will be noted on the case report forms.

3.5.3.2 Eligibility Coronary Angiography

Coronary angiography will be performed immediately prior to randomization to confirm that the subject will not require percutaneous coronary intervention within 30 days from the time of randomization (Exclusion Criteria #5). At the Investigator's discretion, if the subject has:

- non-ischemic dilated cardiomyopathy - an arteriogram performed within twelve (12) months prior to eligibility assessment may be used to satisfy these criteria.
- ischemic dilated cardiomyopathy - an arteriogram performed within three (3) months prior to eligibility assessment may be used to satisfy these criteria.

If the Investigator determines that the eligibility angiography is not required on the day of the index procedure, the subject will minimally undergo femoral artery cannulation prior to randomization to obtain hemodynamic data and ensure that subject is blinded to the treatment assignment.

If the eligibility angiography reveals the need for revascularization, or if the study subject does not meet all eligibility criteria, the subject is an enrolled screen failure. Randomization does not occur and the subject is followed through discharge only.

3.5.3.3 Eligibility Venogram

A coronary sinus venogram will be performed immediately prior to randomization in order to assess eligibility for the study (Inclusion Criteria #5).

If the study subject does not meet the final venogram eligibility criteria, the subject is an enrolled screen failure. Randomization does not occur and the subject is followed through discharge only.

3.5.3.4 Fully Eligible Subjects

If the study subject meets all eligibility criteria, then the subject will be randomized. The test and evaluation results captured to date will become the study subject's baseline measurements.

3.6 Randomization

Randomization will occur in a 3:1 allocation to the Treatment (CARILLON) or Control group. Randomization will be stratified according to investigational center in a randomized permuted blocks design.

The study statistician will generate randomization schedules (independent of the Sponsor) and the randomization will be identified either through a web-based portal or by randomization envelopes provided for each center.

3.7 Study Procedure – Post Randomization

3.7.1 Index Procedure

3.7.1.1 Sponsor Support of Procedure

Cardiac Dimensions will provide a trained field clinical technician to support the investigational team during the procedure. Cardiac Dimensions may additionally provide a physician proctor, as needed.

3.7.1.2 Treatment Group

For subjects randomized to the Treatment group, the CARILLON Mitral Contour System procedure will be performed. The implant procedure is described in Appendix A: Instructions For Use.

Pre-medication will be according to institutional procedures for cardiac catheterization. Additionally, subjects will be heparinized prior to the angiographic procedure according to institutional policies. Anti-platelet therapy is not required in the REDUCE FMR Trial, however, individual Investigators may prescribe such medications in accordance with their institution's standard of care or as necessary to treat other concurrent cardiac conditions. The use of anti-platelet therapy will be noted on the case report forms.

Either Transesophageal Echocardiogram (TEE) or Transthoracic Echocardiogram (TTE) may be used during the implant procedure to evaluate the safety and effectiveness of device placement. If TEE is used during the index procedure, the assessment of the left atrial appendage clot exclusion criteria (required for subjects with existing atrial

fibrillation) may be made immediately prior to randomization and the index procedure (i.e., a separate TEE is not required.)

All subjects randomized to the Treatment group will have coronary angiography performed prior to the CARILLON implant attempt. This is in order to establish the baseline flow characteristics of the coronary arterial vessels in the same location (AV groove) as the coronary sinus/great cardiac vein. If coronary artery flow compromise is noted during the CARILLON implant procedure, the CARILLON device can be recaptured. At the investigator and proctor's discretion, another CARILLON device attempt can occur if the device can be placed in a portion of the coronary sinus/great cardiac vein where coronary flow is not compromised.

However, if there is **clinically significant** coronary artery compromise, mitral stenosis, systolic anterior motion or other safety issues, the CARILLON implant will be recaptured and the procedure ended.

If the patient becomes hemodynamically unstable and/or no CARILLON device implant is attempted, the subject will be classified as a Procedural Screen Failure in the Treatment group and will be followed through 1-month with a safety assessment only (full 1-month follow-up assessments are not necessary), then exited from the study.

If CARILLON device implant attempt(s) occur but the CARILLON device is ultimately recaptured and no implant takes place, the subject is classified as Non-implanted in the Treatment group and will be followed through the 12-month primary endpoint.

3.7.1.3 Control Group

Since eligibility angiography (if indicated, see section 3.5.3.2 - Eligibility Coronary Angiography) and venography will be performed in all subjects prior to randomization, subjects ultimately randomized to the Control group will experience a procedure similar to the Treatment group to ensure that they will not be able to deduce their treatment assignment. In addition to the femoral arterial (for the eligibility angiography) and jugular venous punctures (for the eligibility venogram), subjects will undergo electrocardiographic and echocardiographic examinations similar to those performed during the CARILLON implant procedure. These subjects **will not** undergo placement of the CARILLON implant.

3.7.2 Study Subject Follow-up Categories

SCREEN-FAILURE → Subject consented but did not meet baseline eligibility criteria (including TEE, if applicable). No study discharge evaluations are necessary.

ENROLLED SCREEN-FAILURE → Subject consented, met all baseline eligibility criteria, but did not meet final angiographic eligibility. Implant was <u>not</u> attempted. Limited study discharge evaluations are necessary, but no follow-up visits are required.

PROCEDURAL SCREEN-FAILURE → Randomized to treatment group, but procedure discontinued before an implant attempt. Full study discharge evaluations are required and the subject is followed through 1-month.

NON-IMPLANTED → Randomized to treatment group, implant attempted, but not successful. Full study discharge evaluations are required and the subject is followed through 12-months.

IMPLANTED → Randomized to treatment group, device successfully implanted. Full study discharge evaluations are required and the subject is followed through 12-months.

CONTROL → Randomized to control group, implant not attempted. Full study discharge evaluations are required and the subject is followed through 12-months.

3.7.3 Discharge Evaluations

3.7.3.1 Randomized Subjects

Immediately following the index procedure, all randomized subjects will be observed overnight for complications related to the final eligibility assessments and/or procedure. This includes Procedural Screen Failures, Treatment subjects (non-implanted and implanted) and Control subjects.

Prior to hospital discharge, the following assessments will be performed:

- Physical examination
- Vital signs
- Abbreviated Echocardiogram (TTE) safety assessment
- Chest X-ray (PA and lateral) or cine fluoroscopy (for assessment of pulmonary congestion and assessment of implant integrity in implanted subjects)
- ECG (12-lead)
- Serum creatinine
- NT-BNP
- Cardiac enzymes: cardiac troponin (cTn)
  Cardiac enzymes will be monitored 6-8 hours post procedure (or the following morning if procedure time was late in the day). If a clinically significant elevation in cardiac enzymes is noted then a repeat measurement should be undertaken for confirmation.
- CBC with differential, includes hemoglobin, hematocrit, platelets, and WBC
- Clinical assessments by the physician and other information to be evaluated and recorded as they occur including:
  - Concomitant medications
  - Adverse events

If the index procedure was discontinued before a CARILLON implant was attempted in a Treatment group subject, they are considered a Procedural Screen Failure and are followed through discharge and 1-month (safety assessment only), then exited from the study.

3.7.3.2 Enrolled Screen Failures

The following safety evaluations will be performed prior to discharge for subjects who were brought into the catheterization lab but **do not** meet final eligibility criteria or for any other reason device implant is not attempted:

- Vital signs
- ECG (12-lead)
- Serum creatinine
- Cardiac enzymes: cardiac troponin (cTn)

Enrolled screen failure subjects are followed through discharge and then exited from the study.

3.8 Study Follow-up Evaluations

Randomized subjects (Treatment and Control groups) will be required to complete all scheduled follow-up visits as outlined below:

- 1, 6 and 12 months

Subjects randomized to the Control group may be offered the CARILLON device once they have completed the 1-year protocol defined follow-up period (reference Section 3.8.7: Cross-Over Registry).

Reference Appendix E: Echocardiogram Protocol and Appendix F: Six Minute Walk Test for all study follow-up visits.

3.8.1 Follow-Up Schedule – One (1) Month

One (1) month (30 days ± seven (7) days) after the index procedure, the study subject will return to the study site for follow-up evaluations. The evaluations at this visit will include:

- Physical examination
- Vital signs
- Echocardiogram (TTE)
  ***Note**: Study sites that have experience and necessary equipment may undertake exercise echocardiography in addition to the standard echocardiographic assessment required by the protocol.*
- ECG (12-lead)
- Serum chemistries: sodium, potassium, chloride, glucose, BUN, creatinine, and NT-BNP
- Cardiac enzymes: cardiac troponin (cTn)
- CBC with differential, includes hemoglobin, hematocrit, platelets, and WBC
- Quality of Life questionnaires:

  - KCCQ
  - SF-12
- NYHA Classification assessment
- Functional assessment:
  - Six minute walk test
- Clinical assessments by the physician and other information to be evaluated and recorded as they occur including:
  - Concomitant medications
  - Adverse events

If the index procedure was discontinued before a CARILLON implant was attempted in a Treatment group subject, they are considered a Procedural Screen Failure and are followed through 1-month, then exited from the study.

3.8.2 Follow-up Schedule – Six (6) Months

Six (6) months (180 days ± 14 days) after the index procedure, the study subject will return to the study site for follow-up evaluations. The evaluations at this visit will include:

- Physical examination
- Vital signs
- Echocardiogram (TTE)
  ***Note**: Study sites that have experience and necessary equipment may undertake exercise echocardiography in addition to the standard echocardiographic assessment required by the protocol.*
- Chest X-ray (PA and lateral) or cine fluoroscopy (with device integrity assessment for implanted subjects)
- ECG (12-lead)
- Serum chemistries: sodium, potassium, chloride, glucose, BUN, creatinine, and NT-BNP
- CBC with differential, includes hemoglobin, hematocrit, platelets, and WBC
- Quality of Life questionnaires:
  - KCCQ
  - SF-12
- NYHA Classification assessment
- Functional assessment:
  - Six minute walk test
- Clinical assessments by the physician and other information to be evaluated and recorded as they occur including:

- Concomitant medications
- Adverse events

3.8.3 Follow-Up Schedule – Twelve (12) Months

Twelve (12) months (365 days ± 30 days) after the index procedure, the study subject will return to the study site for follow-up evaluations. The evaluations at this visit will include:

- Physical examination
- Vital signs
- Echocardiogram (TTE)
  ***Note**: Study sites that have experience and necessary equipment may undertake exercise echocardiography in addition to the standard echocardiographic assessment required by the protocol.*
- Chest X-ray (PA and lateral) or cine fluoroscopy (with device integrity assessment for implanted subjects)
- ECG (12-lead)
- Serum chemistries: sodium, potassium, chloride, glucose, BUN, creatinine, and NT-BNP
- CBC with differential, includes hemoglobin, hematocrit, platelets, and WBC
- Quality of Life questionnaires:
  - KCCQ
  - SF-12
- NYHA Classification assessment
- Functional assessment:
  - Six minute walk test
- Clinical assessments by the physician and other information to be evaluated and recorded as they occur including:
  - Concomitant medications
  - Adverse events

3.8.4 Unscheduled Follow-Up Procedures and Data Requirements

In some circumstances, Investigators may need to see a subject in advance of the normal study schedule or a subject may return to the investigational site to report new or unresolved signs or symptoms. Such visits will be documented as unscheduled follow-up visits. No specific study evaluations are required to be performed at unscheduled visits, but adverse events will be documented and reported.

3.8.5 Study Exit

Upon completing the protocol defined follow-up, the subject will be exited from the study. Upon study completion, the study investigator should contact the patient's heart failure doctor to discuss their involvement in this study and ongoing medical treatment.

3.8.6 Subject Withdrawal

3.8.6.1 When and How to Withdraw Subjects

A subject may be withdrawn early from the study prior to study completion for several reasons, including but not limited to:

- Loss to follow-up
- Subject consent withdrawal
- Heart transplantation or other confounding intervention
- Physician discretion (for patient health reasons)

If a subject is withdrawn early from the study for any reason, the Cardiac Dimensions clinical study monitor must be notified by telephone, facsimile or e-mail. The Investigator or designee must document the reason for the termination of enrollment and advise Cardiac Dimension of situations that are not resolved.

A subject should not be considered lost to follow-up until three or more attempts have been made to contact the subject and all attempts have failed. One of these attempts should be a letter sent using certified mail with signature confirmation.

If a subject is withdrawn from the study early, the study investigator should contact the patient's heart failure doctor to discuss their involvement in this study and the ongoing medical treatment plan for the subject.

3.8.6.2 Procedures for Reporting Subjects Missing Follow-Up

As soon as it has been determined that a subject has missed a scheduled follow-up examination, the Cardiac Dimensions clinical study monitor must be notified by telephone, e-mail, or facsimile. The study coordinator should attempt to contact the subject at least three times after each missed visit and one of these attempts should be by certified mail with signature confirmation. The subject should not be considered lost-to-follow-up until all attempts to contact the subject have failed.

3.8.6.3 Data Collection and Follow-up for Withdrawn Subjects

If a subject withdraws consent to participate in the study, attempts should be made to obtain permission to record survival data through the 1-year follow-up period.

3.8.7 Cross-Over Registry

Study subjects randomized to the Control group will be offered the option of receiving the investigational device after completing their 1-year follow-up if they continue to meet all of the study eligibility criteria.

Cross-Over registry subjects will be followed at discharge and for 30-days post the CARILLON procedure. The discharge and 30-day-up assessments will be identical to those collected in the randomized portion of the trial (see Sections 3.7.3.1 and 0). On completion of the 30-day follow-up the Cross-Over registry subjects will be exited from the study.

4 Blinding

4.1 Double-Blind Study

This will be a double-blind study in order to reduce the effect of bias and potential placebo effect on specific primary and/or secondary endpoint assessments. A double-blind is a type of masking in which two or more parties involved with the clinical trial do not know which participants have been assigned which interventions. All study subjects and any study personnel responsible for primary efficacy and/or select secondary endpoint assessments (reference section 4.1.1) will be blinded as to whether subjects are in the Treatment group or the Control group. Blinding will be maintained through the 12 month follow-up. All study personnel will be trained to follow study blinding procedures to ensure maintenance of the study blind. Subjects will be continually reminded that adhering to the blinding procedures is a critical part of their involvement in the study.

4.1.1 Blinded Assessments

The following study-related assessments require the assessor to be blinded to the treatment assignment:

- Six minute walk test (6MWT)
  - 6MWT administrator
- All echocardiographic mitral regurgitation and LV hemodynamic parameters
  - Echo corelab assessor
- New York Heart Association (NYHA) classification
  - NYHA assessor
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
  - KCCQ administrator
- SF-12 QoL Questionnaire (SF-12)
  - SF-12 administrator

4.1.2 Subject Training

Study subjects will initially learn about the blinding procedures and the importance of maintaining the blind during the informed consent process. Subjects will be reminded at each follow-up visit that blinding is an essential part of their involvement in the study to maintain the scientific integrity and value of their participation.

Since subjects may visit non-study related physicians during the course of their participation in this study e.g., for emergency or standard care, each subject will be given a study participant card with instructions to present the card to healthcare providers at any non-study related visit. The subject participant card will alert non-study

medical personnel that the subject is in a blinded clinical study and request that they maintain the study blind whenever possible.

The study subject will be questioned at every follow-up to ask if they have become unblinded, and if so, the reason associated with becoming unblinded. The study site personnel will remind the patient that even if they know their group assignment, it is imperative that they do not reveal this to any of the study assessors.

4.1.3 Site Personnel Training

Detailed training specific to each study position will be provided to study site personnel to ensure that the blinding procedure is fully understood (reference Section 4.2: Blinding Procedures).

4.1.4 Randomization

After all pre-randomization assessments have been completed, each subject will be assigned sequentially to one of the two study groups (Treatment or Control), by means of a computer-generated random number scheme created by the Sponsor (reference Section 3.6: Randomization). The study coordinator and limited study personnel (e.g., implanting physician) will also have knowledge of the treatment assignment.

4.2 Blinding Procedures

4.2.1 Index Procedure through Discharge

All subjects will experience similar procedures to ensure that they will not be able to deduce the treatment assignment based on the type of intervention or time associated with the index procedure. If general anesthesia is not used, subjects will wear earbuds while in the catheterization lab to ensure that they cannot hear study personnel discussing randomization or the procedure, and their vision masked (either with a blindfold or with sterile drapes appropriately positioned) so as to ensure they are unable to see any of the catheterization lab monitors.

Catheterization lab personnel will be trained to the importance of maintaining the study blind and to ensure that study subjects are treated similarly during and after the procedure. Recovery room and floor nursing staff will receive training on continued maintenance of the study blind during the recovery period.

4.2.2 Study Follow-Up Visits

Rigorous efforts on the part of the subjects, implanting physicians, heart failure physicians, and supportive personnel will be implemented to ensure that endpoint assessors remain blinded through the 12-month follow-up.

4.2.2.1 Echocardiographic Assessments

The site echosonographer will conduct intra-procedure echocardiographic assessments and cannot be blinded to the subject's treatment assignment. In order to ensure that

study subjects remain blinded during scheduled follow-up echocardiograms, sonographers at each participating site will be instructed on preserving blinding prior to study start. Specific blinding procedures which will be followed by site sonographers, include:

- Keeping the echo screen faced away from the subject during the procedure
- Not discussing any details of the echo results with a study subject
- Not discussing the treatment assignment of a study subject, especially with the blinded study personnel or any non-study hospital staff

All baseline and follow-up echocardiographic analysis will be performed by an independent echocardiography corelab. A designated member of the corelab staff will remove all subject identifying information (including the date and visit interval) and digitally mask the coronary sinus/great cardiac vein (location of device). This will be done for all views required to assess the echocardiographic endpoints related to mitral regurgitation and left ventricular hemodynamics. This will ensure that the designated corelab assessor will always remain blinded.

For those parameters that are unavoidably affected by digital masking (e.g., mitral annular dimensions), an unblinded assessor will be used to gather the most accurate information without hindrance of the digital masking.

Echocardiographic analysis will be done in batches, with multiple subjects (Treatment and Control) at different visit intervals analyzed within the same batch, at the same time, for both consistency and blinding purposes. (Reference Appendix E: Echocardiogram Protocol.)

4.2.2.2 Functional and QOL Assessments

The assessors/administrators of the NYHA classification, six minute walk test and QoL questionnaires (KCCQ and SF12) will not be aware of the subject's group assignment. Other study personnel will be trained to ensure that these assessors are not included in study communications to ensure that they remain blinded.

If a functional assessor/administrator becomes unblinded, a back-up functional assessor is to be used for all future assessments for that subject. Likewise, if a study subject becomes unblinded, steps will be taken to ensure the continued blinding of the assessors.

4.3 Unblinding

The treatment assignment for a subject will be unblinded only in the following circumstances:

1) In the event of medical emergency where it is medically necessary to know if the subject received an implant.
2) After a randomized study subject has completed their 12-month visit, the treatment assignment for that subject can be unblinded.

The DSMB and/or CEC, upon request, may be provided with the randomization assignment of a particular subject(s) or to assess safety trends between study groups. This can be provided by the study statistician and does not require unblinding of critical site and study personnel.

5 Adverse Events and Risk Analysis

5.1 Adverse Events

The primary measures of safety are based on reported adverse events. Adverse events shall be assessed and documented from the time of consent and through the last study follow-up visit. An underlying disease that was present at the time of enrollment is not reported as an adverse event (AE), but any increase in the severity of the underlying disease during the course of the study shall be reported as an AE. The Investigator shall provide source documentation as requested by the Sponsor, DSMB, and CEC to facilitate adjudication of the adverse event.

5.1.1 Adverse Event Definitions

5.1.1.1 Adverse Event

An adverse event is defined as 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.
Notes:
1. This definition includes events related to the investigational medical device or the comparator.
2. This definition includes events related to the procedures involved.
3. For users or other persons, this definition is restricted to events related to investigational medical devices.

5.1.1.2 Device Deficiency

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

5.1.1.3 Malfunction

Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP.

5.1.1.4 Use Error

Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.
Notes:
1. Use error includes slips, lapses, and mistakes.
2. An unexpected physiological response of the subject does not in itself constitute a use error.

5.1.1.5 Serious Adverse Event

An adverse event is considered serious if it:

a) results in 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 foetal distress, foetal death or a congenital abnormality or birth defect.

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

5.1.1.6 Adverse Device Effect (ADE)

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

Notes:

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

5.1.1.7 Serious Adverse Device Effect (SADE)

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

5.1.1.8 Unanticipated Serious Adverse Device Effect (USADE)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current study documentation.

Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

5.1.1.9 Anticipated Adverse Events

Table 5.1 below provides the list of anticipated adverse events for this study. Anticipated adverse events are those that are expected to occur in this trial because they are associated with:

- The CARILLON Mitral Contour System device or procedure
- Invasive or stress-inducing tests (cardiac catheterization, transesophageal echocardiography, exercise)
- A heart failure population over time

Reference Section 9.2: Definitions of Terms for the specific definitions of these adverse events.

Table 5.1 Adverse Event Listing

Anticipated Adverse Events	
Angina pectoris (stable or unstable)	Hypotension / Hypertension
Allergic reaction	Infection, generalized
Aneurysm (pseudoaneurysm)	Infection / Inflammatory response at the catheter insertion sites requiring treatment
Anuria	Leukopenia
Aortic Stenosis	Mitral Stenosis
Arrhythmias	Mitral valve injury
Arterio-venous fistula	Myocardial Infarction
Asthenia	Myocardial Ischemia
Bleeding	Nausea / Vomiting
Cardiac tamponade	Pain
Carotid artery trauma	Perforation (arterial, venous or cardiac)
Chronic nerve damage	Pericardial effusion
Coagulopathy	Pericarditis
Deep vein thrombosis	Peripheral ischemia
Dental injury	Pharyngeal and/or laryngeal trauma
Denudation (arterial or venous)	Physical injury
Depression	Pneumonia
Device embolization	Pneumothorax
Device malfunction or failure	Radiation dermatitis
Dissection (arterial or venous)	Renal failure
Dyspnea	Renal insufficiency
Electromechanical dissociation / Pulseless electrical activity	Respiratory distress
Embolism (air, tissue, or thrombus)	Septicemia / Sepsis
Endocarditis	Stroke
Esophageal Injury	Transient ischemic attack
Fatigue	Urinary tract infection
Headache	Vasovagal reaction
Heart failure	Vessel erosion
Heart failure hospitalization	Vessel occlusion (arterial or venous)
Hematoma	Vessel spasm or stenosis (arterial or venous)
Hemolysis	

5.1.2 Recording Adverse Events

All adverse events and device deficiencies occurring during the study, up to and including the study subject's final scheduled visit that are observed by study personnel or reported by the subject will be recorded on the appropriate CRFs, whether or not the event is considered related to the device and/or the index procedure. Reporting will include the event name, onset and resolution date, severity, and assessment of relatedness to placement and use of the CARILLON Mitral Contour System or other suspected cause. Adequate documentation must be supplied with all case reports forms to determine if the adverse event is related to the device or the index procedure.

5.1.3 Description of AE Severity

Mild: awareness of a sign or symptom that does not interfere with the patient's usual activity or is transient, resolved without treatment and with no sequelae.
Moderate: interferes with the patient's usual activity and/or requires symptomatic treatment
Severe: symptom(s) causing severe discomfort and significant impact on the patient's usual activity and requires treatment.

5.1.4 Description of AE Causal Relationship

The causal relationship should be rated as follows:
No = Unrelated: the event is definitely not associated with the investigational device use or procedures
Possible = the temporal sequence between the investigational device use or procedures and the event is such that the relationship is likely or patient's condition or concomitant therapy could have caused the AE
Yes = Definite: the temporal sequence is relevant and the event abates upon investigational device use or procedures completion/removal (dechallenge) or reappearance of the event on repeated device use or procedure (rechallenge).

5.1.5 Reporting SAEs

All serious adverse events and device deficiencies that could have led to a serious adverse device effect (SADE) a) if either suitable action had not been taken, b) if intervention had not been made, or c) if circumstances had been less fortunate must be reported to the study monitor or Cardiac Dimensions within 24 hours of the investigator's first knowledge of the event. The Investigator must forward information about the event promptly and complete the SAE report form provided by the Sponsor, even if the information is incomplete or it is obvious that more data will be needed to form any conclusions.

Additional information regarding the event may be recorded on a follow-up SAE report form and forwarded to the sponsor/monitor. Site personnel will submit follow-up information and the complete event forms to Cardiac Dimensions as the event continues and/or resolves.

It is the responsibility of each Investigator to report all Serious Adverse Events and/or Serious Adverse Device Effects to the Ethics Committee. According to national regulations and Ethics Committee requirements, this reporting requirement can be under the sponsor's responsibility. Upon review of SAE CRFs, Cardiac Dimensions may require the site to provide additional information and source documentation as soon as possible, including, physician notes, lab reports, discharge summaries, other appropriate hospital/ patient records, etc. Source documentation must be supplied as requested by the Sponsor to allow adequate evaluation of the event and its relationship to the study device and procedure.

The sponsor will report all reportable Events to the National Competent Authority in accordance with Medical Devices directives and all applicable official guidelines and national regulations.

5.1.6 Vigilance reporting (EU sites)

At EU sites, vigilance requirements should apply and the site will have to report incidents and complaints to the manufacturer as per their institution's normal procedure.

5.1.7 Data Safety Monitoring Board

In this study, intense and continuous monitoring will occur. A Data Safety Monitoring Board (DSMB), independent of the Sponsor and Investigators, will be convened to assess the progress of the clinical study, including safety data adverse events adjudication and the critical study and subject endpoints at intervals, and to recommend to the Sponsor whether to continue, modify or stop the study.

The DSMB will consist of at least three (3) independent medical professionals who are experts in the fields of cardiology, interventional cardiology, heart failure, or biostatistics, and who are not Investigators.

5.1.8 Clinical Events Committee

A Clinical Events Committee (CEC) will be responsible for adjudicating MAEs, and device (incl. USADEs) and procedural adverse events. The CEC members will be independent medical professionals with expertise in the fields of cardiology, interventional cardiology (including cardiac surgery), or heart failure and without conflict of interest. The CEC will adjudicate to determine if the event is:

- considered a major adverse event
- related to the device (implant and/or catheter)
- related to the procedure
- an anticipated or unanticipated adverse event.

In addition, the CEC will adjudicate events resulting in death to determine whether the death is considered cardiac, non-cardiac, or operative mortality. Members will be provided event data from the clinical study without site or Investigator identification.

5.2 Risk Analysis

Cardiac Dimensions has conducted an analysis of the benefits and risks of the CARILLON Mitral Contour System procedure and the study design for the REDUCE FMR Trial.

5.2.1 Benefits

The major benefit of percutaneous treatment with the CARILLON Mitral Contour System is a potential reduction in mitral regurgitation through a minimally invasive

treatment method, where no current minimally invasive treatment option exists for these subjects. The major potential benefits include:

- Clinical reduction in mitral regurgitation with a non-surgical treatment method
- Improvements in overall function including potential reduction of symptoms associated with dilated cardiomyopathy/mitral regurgitation.

5.2.2 Risks

Risks associated with the CARILLON Mitral Contour System include those risks associated with routine coronary angiography as well as those risks predominantly associated with the delivery and permanent placement of the CARILLON implant. These risks are provided in the CARILLON Mitral Contour System Instructions for Use (reference Appendix A).

5.2.3 Efforts for Risk Minimization

Efforts to minimize risk include the following:

- Clearly defining the subject inclusion/exclusion criteria
- Selecting only qualified, experienced Investigators who have participated in an extensive training program to assure thorough knowledge of the Investigational Plan and proper technique for implantation of the CARILLON implant
- Monitoring angiographic, electrocardiographic and hemodynamic parameters during placement of the implant to evaluate for compromised coronary flow and preclude clinically significant coronary artery compression
- Attending to coronary venous access technique to minimize the trauma to vascular structures
- Ensuring that treatment and follow-up of subjects is consistent with standard and current medical practice
- Providing proctor and/or field clinical technician to offer device related guidance during the implant procedure

If the Investigator and/or the Medical Monitor determine that an adverse event is sufficiently severe to remove the subject from the study, a termination assessment will be performed. The subject will then be given appropriate treatment under medical supervision.

5.2.4 Conclusion

Cardiac Dimensions, its Chief Medical Officer, and the Investigators have determined that this research study is justified because the overall potential benefit to the population outweighs its attendant risks.

6 Statistical Plan

6.1 Study Populations

This is a randomized parallel-group, double-blind, multi-center trial to evaluate the safety and efficacy of the CARILLON Mitral Contour System in treating functional mitral regurgitation (FMR) associated with heart failure. Following successful completion of the cardiac catheterization screening procedures, subjects will be randomized in a 3 : 1 allocation to Treatment or Control. All assessors conducting endpoint assessments will be blinded to randomization assignment.

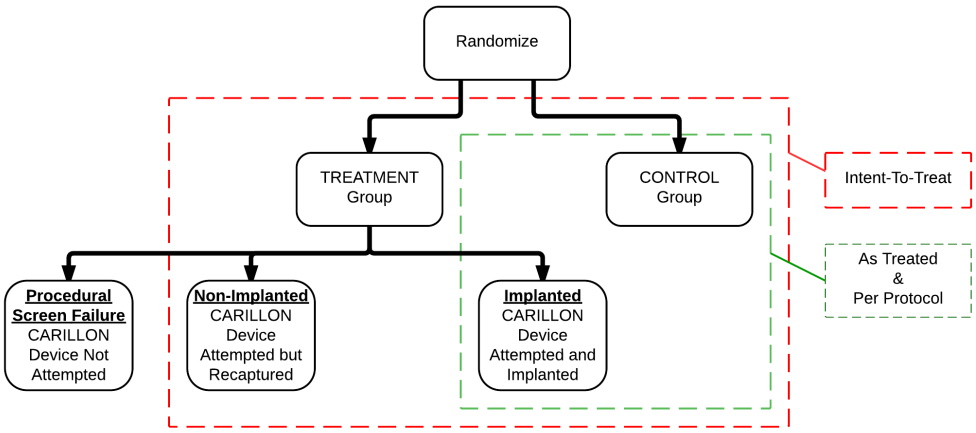
6.2 Study Analyses

The primary analyses will be conducted according to the principles of intent-to-treat. All subjects will be analyzed according to randomized group assignment, and subjects randomized to the Treatment group but who do not receive a permanent implant will be included. If any subject does not have endpoint data available (12-month data), the primary analysis will assume that data as missing and that subject's data will not be included in the primary analysis.

In addition, a series of supportive, sensitivity analyses will be performed to assess the robustness of the primary analysis results, including imputing the last value observed (last value carried forward) for all missing endpoint evaluations.

Additional subgroup analyses will be conducted for all primary and secondary endpoints on as-treated and per-protocol cohorts defined as:

- **As-treated**: All subjects who left clinic with the randomized therapy administered (i.e., randomized to Treatment group and received a permanent implant, or randomized to Control group)
- **Per-protocol**: All subjects who received randomized therapy, assessors remained blinded, and who did not receive alternative or confounding therapies (e.g., CRT therapy, transplant, stenting, etc.) through the primary endpoint timeframe of the study



6.3 Study Objectives

6.3.1 Primary Endpoint

The primary efficacy endpoint is to demonstrate a statistically significant improvement in regurgitant volume associated with the CARILLON device at twelve (12) months, relative to the Control population.

6.3.2 Secondary Endpoints

The secondary endpoints of the REDUCE FMR Trial are to determine the procedural safety of the device and the effect of the CARILLON implant on hemodynamics, subject function and long-term safety, further defined as follows.

6.3.2.1 Safety

The following secondary safety endpoints will measure the effect of the CARILLON Mitral Contour System on clinical safety parameters of interest, relative to the Control population

- To document the difference in the rate of major adverse events between randomized groups, at 1 and 12-months post randomization.

  Major Adverse Events are defined as a composite of the following:

  – Death
  – Myocardial Infarction
  – Device Embolization
  – Vessel Erosion, requiring percutaneous or surgical intervention
  – Cardiac Perforation, requiring percutaneous or surgical intervention
  – Occurrence of cardiac surgery or percutaneous coronary intervention associated with device failure

- To assess the rate of heart failure hospitalizations (number of admissions, and total associated days in the hospital), from the time of the index procedure through twelve months of follow-up

6.3.2.2 Efficacy

The following secondary endpoints will measure the effect of the CARILLON Mitral Contour System on clinical parameters of interest, relative to the Control population:

- To assess the change from baseline to twelve months for six-minute walk distance
- To assess the change from baseline to twelve months in left ventricular volumes (end diastolic and end systolic)

6.3.3 Observational Data

The following observational data will provide additional safety, clinical and/or mechanistic data:

- Long-term safety will be evaluated as the comparison of the following safety events between the Control and Treatment groups:
  - Mortality at six (6) and twelve (12) months
  - Serious adverse events at six (6) and twelve (12) months
- NYHA Classification
- Left ventricular hemodynamics[v]:
  - LV end diastolic (LVEDD) and end systolic (LVESD) dimensions
  - Ejection fraction (LVEF)
  - Forward cardiac output (CO)
- Functional Mitral Regurgitation echocardiographic assessments[v]:
  - Vena Contracta (VC)
  - Effective regurgitant orifice area (EROA),
  - MR Jet area / Left atrial area (MRJA/LAA)
  - MR grade
- Left atrial size
- Mitral annular diameter and area
- Diuretic dose change between baseline and 6 / 12 month follow-up
- Pulmonary Artery Systolic Pressure (echo derived at rest & during exercise[v])
- NT-BNP
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Quality-of-Life Assessment (SF-12)

6.4 Randomization

Randomization will occur in a 3:1 allocation to the Treatment or Control group. Randomization will be stratified according to investigational center in a randomized permuted blocks design.

The study statistician will generate randomization schedules (independent of the Sponsor) and the randomization will be identified either through a web-based portal or by randomization envelopes provided for each center.

[v] Left ventricular hemodynamics, FMR assessments and pulmonary artery pressure (echo derived) will also be assessed during exercise in randomized patients at a subset of study sites who have supine bicycle ergometry and echosonographers experienced in imaging acquisition during exercise.

6.5 Unblinding

The treatment assignment for a subject will be unblinded only in the following circumstances:

1) In the event of medical emergency where it is medically necessary to know if the subject received an implant.
2) After a randomized study subject has completed their 12-month visit, the treatment assignment for that subject can be unblinded.

The DSMB and/or CEC, upon request, may be provided with the randomization assignment of a particular subject(s) or to assess safety trends between study groups. This can be provided by the study statistician and does not require unblinding of critical site and study personnel.

6.6 Primary Endpoint Evaluation & Sample Size Assumptions

The primary endpoint of the study is to demonstrate a significantly greater improvement from baseline in Regurgitant Volume (assessed by echo corelab) associated with the CARILLON Mitral Contour System at 12-months, relative to the Control group.

Parameter of Interest

The parameter of interest for each treatment group is the mean change from baseline in regurgitant volume, in milliliters, at 12-months.

Hypotheses

H_0: $\mu_{CARILLON} = \mu_{CTL}$

H_a: $\mu_{CARILLON} \neq \mu_{CTL,}$

where $\mu_{CARILLON}$ is the mean change in regurgitant volume for those randomized to the Treatment group, and μ_{CTL} is the mean change in regurgitant volume for those randomized to the Control group.

Sample Size Estimation

Sample size is calculated using a comparison of means (Student's t test). The minimum required sample size was calculated under the following assumptions:

- Significance level two-sided 0.05
- Statistical power to detect design alternative hypothesis is 80%
- Hypothesized mean regurgitant volume change (baseline to 12-month) in the Control group = -2.4 ml
- Hypothesized mean regurgitant volume change (baseline to 12-month) in the Treatment group = -12.4 ml
- Hypothesized standard deviation:

- Treatment group = 13 ml,
- Control group = 13 ml

- 3:1 randomization allocation

Under the assumptions outlined above, the estimated minimum required sample size is 76 subjects (57 Treatment, 19 Control).

Justification for Sample Size Assumptions

Assumptions for sample size calculations are derived from a two previous studies of subjects implanted with the CARILLON Mitral Contour System in a similar patient population – the TITAN and TITAN II studies. The hypothesized mean change (baseline to 12 months) for the Control group is conservatively assumed to be approximately -2.4 ml. The hypothesized mean change for the Treatment group, and the standard deviations for both groups, is expected to be similar to that observed in the TITAN and TITAN II study cohorts 12 months after implantation. In these studies, the observed change in regurgitant volume at 12 months was -14.1 ml. The observed mean difference between the populations is adjusted to account for as many as 15% of the Treatment group subjects not receiving a permanent implant (Non-Implanted Treatment group patients) but still counted in the intent to treat analysis, thus yielding regurgitant volume results similar to the Control group, without compromising the power of the study. This study assumes a -10 ml mean difference in regurgitant volume between the study populations.

The clinical relevance of this magnitude of a difference is supported by other trials evaluating the clinical impact of functional mitral regurgitation. For example, Amigoni showed in the VALIANT trial database that a 1% increase in FMR was associated with an increased risk of heart failure hospitalization, and an increased risk of death or heart failure hospitalization.[32] Extending the clinical significance to mortality, Grigioni showed in a group of patients with Q-wave MI that those patients with a regurgitant volume >30 ml demonstrated higher mortality than those regurgitant volume <30 ml (RR 1.13 per 10 ml RVol increase).[33] In CRT candidate patients with at least mild MR and an average LVEF 25 ±7%, Madaric showed that CRT decreased the regurgitant volume from 36 ±19 ml to 25 ±11 ml, but he also showed that even an increase in regurgitant volume from 25 ±11 ml at rest to 29 ±12 ml with exercise was statistically significant to $p<0.001$.[34] Lastly, Bursi noted in their study of heart failure after myocardial infarction that patients with MR had worse outcomes, which exhibited a graded 'dose-response' relationship with the severity of MR, a pattern that supports causality.[35] These data taken together suggest that a small change in FMR (e.g., 1%) can be clinically significant, and the 10 ml difference between populations proposed in this study is similar to the magnitude of change seen in other trials, and is clinically relevant.

Data Analysis

The mean improvement in regurgitant volume for each treatment group, from baseline to twelve months, will be compared in a two-sided, two-sample t-test. The 95% confidence interval on the between-group difference will also be calculated and presented. If assumptions of normality are violated, the nonparametric Mann-Whitney test will be used to assess statistical significance, and the 95% confidence interval on the

difference between groups will be calculated using the Hodges-Lehmann estimate and distribution-free confidence interval based on a Wilcoxon Rank Sum test. The primary analysis will be conducted on the intent-to-treat population, and supportive analyses will be performed on the previously defined per-protocol and as-treated populations (reference Section 6.2: Study Analyses). Further supportive analyses will be conducted which characterize the longitudinal effect of treatment on regurgitant volume in a repeated measures regression model.

6.7 Size and Duration of Trial

An estimated minimum of 76 randomized, evaluable subjects is required to have 80% power to detect a reduction in the change in regurgitant volume between CARILLON device and Control groups. A total of 120 subjects at up to 25 centers will be randomized, allowing for approximately 30% attrition (mortality, missing data and loss to follow-up) in the first 12 months of follow-up.

6.8 Secondary Endpoint & Observational Data Assessment

The secondary endpoints and observational data will be analyzed and the results will be reported with descriptive statistics to provide supportive evidence of the safety and efficacy of the CARILLON Mitral Contour System.

6.9 Supportive Analyses & Missing Data Imputation

The following supportive analyses will also be undertaken.

- Assessment of treatment efficacy in subjects receiving a permanent implant through the primary endpoint – "as-treated" analysis
- Assessment of treatment efficacy in subjects receiving a permanent implant and who did not receive alternative or confounding therapies (e.g., CRT therapy, transplant, stenting, etc.) through the primary endpoint – "per protocol" analysis
- Assessment of treatment efficacy according to etiology of cardiomyopathy (ischemic vs. non-ischemic) through the primary endpoint
- Assessment of treatment efficacy according to baseline LV ejection fraction (≤40% vs. 41-50%) through the primary endpoint

Missing data will be imputed using a last observation carried forward (LOCF) methodology and be reported separately for:

- the primary and secondary endpoint parameters
- the observational parameters
- the primary (intent to treat) and supportive analyses noted above.

7 Ethical, Regulatory, and Administrative Considerations

This study will be conducted in accordance with the International Standard ISO 14155:2011, recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions, Good Clinical Practice: Consolidated Guidance (ICH E-6) and any regional or national regulations, as appropriate.

Only centers willing and able to comply with these practices will be included in the study.

7.1 Informed Consent

To protect the rights and welfare of subjects, this clinical study will be conducted in conformance to the International Standard ISO 14155: 2011, Section 4.7: Informed Consent.

Informed consent must be obtained from each subject prior to participation in this clinical study. Subjects who elect to enroll in the study must be informed of the risks and potential benefits of the CARILLON Mitral Contour System, as well as the risks and benefits of the associated medical procedures. Alternative modes of treatment must be explained to the subject as well. Such information is provided in the Subject Informed Consent. The information that is given shall be in a language that the subject understands. No informed consent, whether oral or written, may include any exculpatory language through which the subject is made to waive or appear to waive any of their legal rights, or releases or appears to release Cardiac Dimensions, the institution, or its agents from liability for negligence.

The subject must be able to comprehend the informed consent and must sign the document prior to enrollment in the study. The subject will receive a copy of the respective signed consent form.

The original signed consent, as approved by the respective site Medical Ethics Committee (MEC) or Human Research Ethics Committee (HREC), is retained in the subject's study records. The subject will receive a copy of the signed consent form. A sample of the informed consent is provided in Appendix B.

Alternative consent materials, if used, must be approved by Cardiac Dimensions and the study center MEC/HREC prior to use, and must contain the elements of the sample informed consent. Documentation of subject informed consent **for each subject** must be provided to Cardiac Dimensions.

7.2 Institutional Review

No clinical studies will begin without documented approval of the clinical investigation by the MEC/HREC affiliated with the study center. The Sponsor or the Principal Investigator will obtain approval for the study from the study site's MEC/HREC. Prior to submission to the MEC/HREC, Cardiac Dimensions must review and approve the consent form from the study site. The Principal Investigator will provide Cardiac Dimensions with a copy of the communication from the MEC/HREC indicating approval of the *Investigational Plan* and consent form prior to initiation of the study.

The Principal Investigator will be responsible for obtaining annual MEC/HREC renewal through the duration of the study as appropriate, or more frequently if required by the MEC/HREC. Copies of the Principal Investigator's report and copies of the MEC/HREC's continuance of approval must be maintained in the regulatory binder located at the study site. The Principal Investigator shall report to Cardiac Dimensions within five (5) working days, any withdrawal of approval by the reviewing MEC/HREC.

7.3 Site Requirements

The Principal Investigator selected will be responsible for fulfilling the clinical study requirements that are outlined in this *Investigational Plan*. The investigational site must have the necessary resources so that the investigators can adhere to all clinical study requirements. The following criteria will be used to select sites and Principal Investigators for participation in this clinical study:

- The Principal Investigator must have expertise in clinical areas relevant to the clinical study. This includes an extensive background in interventional cardiology, catheterization procedures, management of subjects with heart failure and mitral valve regurgitation, and clinical research.
- Appropriate and sufficient personnel must be available to obtain and report data as required by the *Investigational Plan*. There will be a team at each center (or affiliated with the center) consisting of investigators with expertise in interventional cardiology, management of patients with heart failure and echocardiography; and a study center coordinator to manage and organize the routine activities of the clinical study (i.e., assure that informed consent has been obtained, case report forms have been completed, and subject follow-up examinations have been scheduled).
- Appropriate and sufficient personnel must be available to meet the implant schedule requirements for the CARILLON Mitral Contour System.
- Personnel must be willing to comply with all aspects of the clinical study as described in the *Investigational Plan*. This includes collection of complete and accurate data in a timely manner according to the prescribed subject follow-up schedule. In addition, Principal Investigators must be accessible to their support staff and Cardiac Dimensions personnel.

- Investigators (Principal and sub-Investigators) must be willing to comply with all aspects of the Investigator's Agreement as described in the *Investigational Plan*, including disclosure of financial information.
- Investigators must have access to a hospital and/or clinic having the equipment necessary to perform the clinical study.

7.3.1 Individual Responsibilities

Individuals engaged in the conduct of or responsible for the supervision of this clinical study must have the necessary education, training and experience to enable them to perform the assigned functions. The responsibilities of key clinical personnel who will be involved in the conduct of this clinical study are described in the following sections.

7.3.2 Sponsor Responsibilities

Sponsor assumes all responsibilities per ISO 14155: 2011, Section 8, including but not limited to:

- Selecting qualified Principal Investigators and investigational centers and providing them with the information they need to conduct the investigation properly
- Ensuring proper monitoring of the investigation
- Ensuring that MEC/HREC review and approval are obtained
- Notifying the applicable National Competent Authority (NCA)
- Ensuring that any reviewing MEC/HREC and NCA are promptly informed of significant new information about an investigation
- Obtaining NCA approval for the study
- Ensuring that study specific insurance is contracted where required by national/local regulations
- Securing compliance with this Investigational Plan, Investigator agreement, and federal, state and local regulations as outlined in Section 7.3.3
- Conducting evaluations of unanticipated serious adverse device effects
- Controlling the device(s) under investigation
- Promptly informing the clinical investigator(s), when a clinical investigation is prematurely terminated or suspended, and, where applicable, informing the regulatory authority(ies) and ethics committee(s) of the termination or suspension and the reason(s) for the termination or suspension
- Maintaining records and reports as outlined in Section 7.9
- Analyzing and reporting data as outlined in Section 7.9

7.3.3 Investigator Responsibilities

The study investigators are responsible for the management of subjects involved in this clinical study as well as for the clinical use of the CARILLON Mitral Contour System at the selected site. The Principal Investigators will assume overall responsibility and accountability for the research team and for the clinical data obtained from subjects participating in the study. Principal Investigator assumes all responsibilities per ISO 14155: 2011, Section 9, including but not limited to:

- Ensure MEC/HREC approval and notifying Competent Authority for this Investigational Plan when required by national and/or local regulations
- Ensuring that the clinical study is conducted according to this Investigational Plan, federal, state and local regulations, and the signed agreement
- Providing financial disclosure according to federal regulations
- Protecting the rights, safety and welfare of the subjects
- Controlling any study device(s) stored at their site, including supervision and disposal of devices
- Obtaining informed consent
- Providing any pertinent new information regarding device safety to study subjects
- Inform the Sponsor about all adverse events and adverse device effects in a timely manner
- Maintaining records and reports as outlined in Section 7.9
- Reviewing and signing (or assigning to an appropriate designee) all case report forms for subjects enrolled in the clinical study under the Principal Investigator's care

7.3.4 Study Center Coordinator Responsibilities

The study (center) coordinator is under the supervision of the Principal Investigator. The study center coordinator is responsible for:

- Tracking all subjects involved in the clinical study
- Scheduling required follow-up evaluations
- Maintaining all records defined in the Investigational Plan
- Collecting all clinical data from subjects involved in the clinical study
- Ensuring that complete data obtained in accordance with the Investigational Plan are provided to Cardiac Dimensions in a timely manner
- Ensuring that all case report forms are returned to Cardiac Dimensions in their entirety
- Maintaining control over any Cardiac Dimensions product (i.e., procedure manual and device) received and maintained at the site

- Meeting routinely with the Principal Investigator to discuss study progress and issues
- Assisting the Sponsor in monitoring the integrity of the site records

7.4 Investigational Plan Compliance

The Principal Investigator is required to conduct the study in accordance with this *Investigational Plan*. The Principal Investigator will carefully review the procedures defined in the *Investigational Plan* and in the CRFs with his/her staff prior to the time of study initiation to ensure appropriate interpretation and implementation. The Principal Investigator must document any deviation to the *Investigational Plan* on the appropriate case report form together with the reason for the deviation. The Sponsor will classify all deviations in accordance with approved procedures.

Deviations from the *Investigational Plan* to protect the life or physical well-being of a subject in an emergency should be reported by the Principal Investigator to the MEC/HREC and Sponsor no later than five (5) working days after the emergency. Except in such an emergency, prior approval by the Sponsor is required for any change in or deviation from the plan, and if the change or deviation could affect the rights, safety or welfare of human subjects or the scientific soundness of the plan, MEC/HREC approval is also required.

7.5 Investigational Plan Amendments

Investigational Plan amendments will be reviewed by the study's Executive Committee. All changes must be documented in the format of an amendment with justification statements. All amendments must be submitted to the MEC/HREC and regulatory authority for review and approval. Following approval, the protocol amendment will be distributed to all protocol recipients at the study site.

7.6 Data Completion and Study Monitoring

Cardiac Dimensions is the Sponsor of the clinical study. Monitors are selected and monitoring will be performed in accordance with the Sponsor's approved procedures or third-party procedures approved by the Sponsor.

Cardiac Dimensions Vice President of Clinical Programs will have overall management responsibility for the clinical study. A Clinical Affairs Manager will have administrative management responsibility for the study. This responsibility may include serving as a clinical study monitor. Additional personnel, as assigned by the Sponsor may serve as clinical monitors, study administrators, and/or be responsible for data review and data integrity. Sponsor contact information is provided in Section 8: Sponsor Personnel and Contacts.

Monitors may change periodically; however Cardiac Dimensions does not consider this a significant change to the *Investigational Plan*. All monitors will be qualified to perform their assigned responsibilities.

7.6.1 Study Monitoring

Monitoring of the clinical study will be a continuous process to ensure that high-quality data are obtained through compliance with the *Investigational Plan* and will be conducted in accordance with ISO 14155:2011 Section 8.2.4, and Cardiac Dimensions approved procedures or the operating procedures of the Contract Research Organization (CRO) designated by Cardiac Dimensions.

Case report forms will be reviewed for completeness, conformity with requirements, and safety monitoring of adverse events. Frequent communication will be maintained with each site to keep both the study site and Cardiac Dimensions up-to-date and aware of the progress of the clinical study.

On-site monitoring of all study sites will be frequent enough (at least annually) to assure continued acceptability of the data by assessing compliance of the center to the *Investigational Plan*, adherence to the data collection procedures, and maintenance of study records. Accuracy of data reported on the case report forms will be verified by comparison to the subject's source documents, when applicable. If necessary, appropriate corrective action will be taken to ensure adherence to the *Investigational Plan*.

The scheduled site visits and/or audits will include, but not be limited to the following.

7.6.1.1 Pre-Study Qualification

The Sponsor will assure that the Principal Investigator and their staff understand and accept the obligation to conduct the clinical investigation in accordance with the *Investigational Plan*, Cardiac Dimensions approved procedures for conducting clinical investigations, applicable federal regulations, and Good Clinical Practices.

7.6.1.2 Site Initiation Visit

Site initiation visits will be conducted by Cardiac Dimensions (and/or a designated CRO) to train the Principal Investigator and supporting study staff on the objectives, study subject timelines, device accountability, and case report form completion guidelines specific to the *Investigational Plan*.

The site initiation visit will occur after the study site has received written MEC/HREC approval to conduct the *Investigational Plan* and all site related requirements (such as clinical trial agreements and budget negotiations) have been completed. The site may not enroll study subjects into the clinical trial until the site initiation visit is completed.

7.6.1.3 Interim Site Visits and Audit

On-site monitoring visits will assess the progress of the clinical study and identify any concerns that result from device performance or review of the site's study records, study management documents, and subject informed consent documents. This includes adherence to the *Investigational Plan*, MEC/HREC review of the clinical study and its progress, and maintenance of records and reports.

To assure the integrity of the clinical study data, 100% of individual subject records and other supporting documents will be compared to the case report forms and reports prepared by the study center coordinator and/or site investigators for submission to Cardiac Dimensions. During monitoring visits or audits, the monitor will compare subject records and other supporting documents with reports from the site investigators to determine that:

- The facilities used by the investigators continue to be acceptable for the purposes of the clinical study
- The *Investigational Plan* is being followed, and that only eligible subjects are being enrolled in the study
- Deviations to the *Investigational Plan* have been reported to Cardiac Dimensions and the MEC/HREC, as applicable
- The Principal Investigator is carrying out the agreed-upon activities and has not delegated them to inappropriate personnel
- Adverse events are promptly being reported
- Informed consent has been obtained and documented
- Device accountability is being maintained, if applicable
- The information recorded in the reports and/or case report forms is complete, accurate and legible
- There are no omissions in the reports and/or case report forms of specific data elements
- Missed follow-up visits are noted in the reports
- Subjects failing to complete the clinical study and the reason for failure are recorded

Study investigators not complying with the *Investigational Plan* and regulations will be terminated from the study and shall be required to return all unused devices and/or associated study materials and procedure manuals.

7.6.1.4 Closeout Site Visit

A closeout site visit to the study center may be made by the monitor, if necessary. Any ongoing responsibilities will be discussed with the Principal Investigator and the study center coordinator.

7.6.2 Completion of Case Report Forms (CRFs)

The Principal Investigator or his designee will be responsible for completing, in a timely manner, a case report form (CRF) for each subject who is registered to participate in this study. An electronic (eCRF) system will be utilized for this study and instructions and specific training for their completion will be provided to the study staff. eCRFs will be completed as information becomes available. If errors or omissions are found in the course of a CRF audit, data edit sheets will be generated and the errors, omissions or clarifications will be corrected on these sheets.

The Principal Investigator or designate will sign and date the indicated places on the eCRF. This signature will indicate that a thorough inspection of the audited data therein has been made and will thereby certify the contents of the form.

7.6.3 Central Database

All study data will be collected and compiled in a central database by the Sponsor or delegate. Appropriate quality control measures will be established to ensure secured, accurate and complete transfer of information from the study documentation to the central database. Procedures used for data review, database cleaning, and issuing and resolving data queries and procedures for verification, validation and securing of electronic clinical data systems are detailed in the Data Management Plan.

7.7 Study Training

Cardiac Dimensions will provide in-depth training for the Principal Investigators and study staff either at the individual sites or at a common location. Cardiac Dimensions clinical research personnel, or their designees, will conduct and document this training in accordance with appropriate procedures.

Topics to be covered at this visit include:

- Anatomy
- Disease states
- The CARILLON Mitral Contour System
- Study procedures
- Overview of the study
- Investigational Plan
- Regulatory requirements and compliance
- Issues that might arise in regard to clinical study site management and case report forms

7.7.1 CARILLON Mitral Contour System Procedure Training

Cardiac Dimensions will schedule training sessions with the study investigators to provide training in the techniques and procedures required for implanting the

CARILLON implant. The training plan for individual study investigators will be tailored to the investigator's previous experience using the investigational device. Cardiac Dimensions staff, including the Chief Medical Officer or consultant interventional cardiologists, will conduct the sessions.

7.8 Subject Recruitment

Appropriate recruitment materials, if needed, will be provided by Cardiac Dimensions following review and approval by the MEC/HREC. Recruitment will continue in a consecutive manner until enrollment for the study is complete.

7.9 Maintenance of Study Records

It is the responsibility of the Principal Investigator and study staff to maintain a comprehensive and centralized filing system of all study-related documentation. This filing system must be suitable for inspection at any time by the Clinical Research Associate (CRA) or Quality Assurance (QA) designee of Cardiac Dimensions, the MEC/HREC, or other regulatory body.

At all times throughout the clinical investigation confidentiality shall be observed by all parties involved. All data shall be secured against unauthorized access.

Privacy and confidentiality of information about each subject shall be preserved in the reports and any publication of the clinical investigation data.

Lists of subjects' names and identifying information should, wherever possible, be maintained separately from case report forms.

Study record elements should include:

Subject Files

Contains the completed subject CRFs (as necessary), supporting source documentation, and a signed and dated Informed Consent. Study subject files will be maintained on all enrolled subjects. Documents for subjects who are screened but not enrolled will be maintained in the patient's medical file.

Regulatory Binder

Contains the *Investigational Plan* with all amendments, MEC/HREC approvals and communications, current MEC/HREC approved Consent Form, study site logs, accountability records and laboratory documents (i.e., certification, norms/ranges, etc.).

Reference Documents

Contains the resource list; responsibilities of the Principal Investigator, Sponsor, and MEC/HREC; regulatory, adverse event, and informed consent guidelines; study aids and core/central laboratory instructions.

7.9.1 Records and Reporting

7.9.1.1 Investigator Records

Records may be subject to regulatory inspection and will be retained for a period of two years following (1) the date the investigation is completed or terminated, or (2) the records are no longer required to support a regulatory submission, whichever is longer. The Principal Investigator is responsible for the records cited below:

- All correspondence which pertains to the investigation
- Records of persons authorized to conduct the study
- Records of receipt, use or disposition of the device, if applicable
- Subject medical records and completed case report forms and supporting documentation
- Informed consent documentation (including copy of an approved, blank informed consent form)
- Adverse events and unanticipated adverse device effects
- Investigational Plan (including certification of approval) and reasons for deviations from the Investigational Plan
- Signed Investigator Agreement and curriculum vitae of study investigators participating in the study

Investigator records cannot be discarded without written consent from Cardiac Dimensions.

Data recorded on the echocardiographic reports and patient questionnaires (Kansas City Cardiomyopathy Questionnaire and SF-12 questionnaire) are considered to be source data, and are not derived from hospital records. The data collected on those forms must be as accurate, complete and secure as possible to assure data integrity.

7.9.1.2 Investigator Reports

The Principal Investigator is responsible for the preparation (review and/or signature) and submission of the reports cited in the table below. These reports are also subject to regulatory inspection and record retention requirements described above for Investigator Records.

Table 7.1 Principal Investigator Reporting Requirements

Report Title	Submit to	Requirements
All serious adverse events (SAE) and device deficiencies that could have led to a serious adverse device effect (SADE) a) if either suitable action had not been taken, b) if intervention had not been made, or c) if circumstances had been less fortunate (see section 5 - Adverse Events and Risk Analysis)	Sponsor, MEC/HREC (if required by national/local regulations)	Report of event must be submitted within 24 hours after the investigator first learns of the event (see section 5).
Withdrawal of MEC/HREC Approval	Sponsor	Report must be submitted without delay after the investigator learns of the withdrawal.
Progress Report/ Continuing Review	Sponsor/Monitor and MEC/HREC	Report must be submitted annually, or as required per individual MEC/HREC policies, for the duration of the clinical investigation. Alternatively, the Sponsor may prepare the report.
Deviations from the *Investigational Plan* • Anticipated • Without Prior Notification	Sponsor and MEC/HREC If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects, the deviation must be approved by the Sponsor, NCA (if applicable), and the MEC/HREC. If the deviation does not affect these issues then only the Sponsor must approve it.	 Changes must be approved before implementation. Notification must be made no later than 5 working days after the event if the deviation was to protect the life or physical well-being of a subject, and there was inadequate time to obtain prior approval from the Sponsor.
Failure to Obtain Informed Consent	Sponsor and MEC/HREC	Notification must be made within 5 working days of the device use. The report will include a brief description of the circumstances justifying failure.
Final Report Submission	Sponsor and MEC/HREC	Report must be submitted per the national/local regulations.
Subject Case Report Forms	Sponsor	Forms must be completed and ready for submission in a timely manner.

7.9.1.3 Sponsor Records

Cardiac Dimensions will maintain records for each investigational site for a period of at least two (2) years following (1) the date the investigation is completed or terminated, or (2) the records are no longer required to support a regulatory submission, whichever is longer. Cardiac Dimensions will maintain the following records:

- All correspondence which pertains to the investigation
- Records of device shipment, receipt and disposition
- Study Site qualification records, including:
  - *Curriculum vita*e (and as applicable statements of relevant experience) of the investigators
  - A signed Investigator Agreement and related clinical study agreements (including financial disclosure)
  - Documentation of NCA and MEC/HREC approval
  - Informed consent form (if different than Sponsor draft)
- Copies of completed case report forms and specific source documents (e.g., X-rays, echo reports)
- Adverse device effects and adverse events

7.9.1.4 Sponsor Reports

Cardiac Dimensions (or an authorized designate) is responsible for the reports cited in the table below. These reports are also subject to record retention and inspection regulations. Records will be maintained in accordance with Cardiac Dimensions approved procedures.

Table 7.2 Cardiac Dimensions Reporting Requirements

Report Title	Submit to	Requirements
All serious adverse events (SAE) and device deficiencies that could have led to a serious adverse device effect (SADE) a) if either suitable action had not been taken, b) if intervention had not been made, or c) if circumstances had been less fortunate (see section 5 - Adverse Events and Risk Analysis)	Principal Investigator NCA (per national/local regulations)	Report of event must be submitted immediately, but not later than 7 calendar days after initial notification of the event. Report must be submitted immediately, but not later than 2 calendar days after initial notification if an event indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients, or a new finding to it.
Withdrawal of MEC/HREC Approval	NCA (if necessary)	Report must be submitted within 5 working days receipt of withdrawal.
Withdrawal of NCA Approval	Principal Investigator/ MEC/HREC	Report must be submitted without delay after receipt of notice.
Progress Reports	All MEC/HREC NCA (if necessary)	Reports must be submitted per NCA and MEC/HREC requirements.
Recall and Device Disposition	MEC/HREC NCA (if necessary)	Notification must be made within 30 working days.
Final Report	NCA (notification and report, if necessary) Principal Investigators/ MEC/HREC (report only)	Per NCA and MEC/HREC requirements.
Failure to Obtain Informed Consent	NCA (if necessary)	Reports will be submitted within 10 working days of receipt of notice of use.

7.10 Product Handling & Accountability

The Principal Investigator should take adequate precautions, including storage of the products, to prevent theft or diversion of the products into unauthorized channels of distribution. Should a product not be used, the Principal Investigator or appropriate designee will return or dispose of the device as per the Sponsor's instructions.

7.10.1 Investigational Product Accountability and Supply

The Principal Investigator or responsible designee will record the receipt and dispensation of the CARILLON Mitral Contour System in the Device Accountability Log. Cardiac Dimensions will monitor these forms on an ongoing basis. At the end of the study, the originals will be returned to the Sponsor and a copy kept in the regulatory records binder at the study site.

Principal Investigators will be provided with the material necessary to prepare the application for MEC/HREC review, including the *Investigational Plan* (with informed consent materials, case report forms, etc.). The materials will include a summary of the results of prior pre-clinical and clinical studies.

At site initiation, study center coordinators will be provided with an Investigator file containing the *Investigational Plan*, and supporting study management materials. Sufficient subject files containing the case report forms will be provided to initiate the study. Additional subject files will be supplied as Cardiac Dimensions is notified of CARILLON implant procedures.

7.10.2 Device Accountability

Only institutions participating in the clinical study will be eligible to receive the CARILLON Mitral Contour System and accessories. Devices may be sent to the study site upon receipt by Cardiac Dimensions of the following:

- *Curriculum vitae* of the Investigator(s)
- A signed Investigator's Agreement
- Documented NCA and MEC/HREC approvals
- An MEC/HREC approved informed consent form

The Sponsor will supply devices to the sites as described in the clinical study procedures for this study. Sites may be allowed to store controlled inventory when qualified.

Study sites are responsible for maintaining control over any associated product received and maintained at the investigational site. These devices must be segregated, and provided only to investigators participating in the study.

7.11 Confidentiality and Data Protection

Information about study subjects will be kept confidential and managed according to the requirements of ISO 14155: 2011, Section 6.7.

At all times throughout the clinical investigation confidentiality shall be observed by all parties involved. All data shall be secured against unauthorized access.

Privacy and confidentiality of information about each subject shall be preserved in the reports and any publication of the clinical investigation data.

Lists of subjects' names and identifying information should, wherever possible, be maintained separately from case report forms.

7.12 Study Termination For Cause

Cardiac Dimensions retains the right to terminate a Principal Investigator or an investigational site's participation in this study for any cause, suspending subject enrollment and removing all investigational products and related study materials from the study site at any time. Specific instances that may precipitate such termination are:

- Consistent deviation from Investigational Plan requirements
- Inaccurate and/or incomplete data recording on a recurrent basis
- Unauthorized use of investigational products in any laboratory study or administration to any subject not enrolled as part of this Investigational Plan
- Delinquent fulfillment of obligation on the part of the Principal Investigator with regard to adverse event reporting, unacceptable subject enrollment, or other responsibilities as outlined in this Investigational Plan

Disclosure of study termination by the Sponsor will be made immediately to the MEC/HREC.

If a study site is terminated, the treatment assignment for the patients enrolled and randomized at that site will be divulged to the Principal Investigator so that study subjects can be appropriately followed up.

7.13 Authority to Execute

The Principal Investigator warrants that he/she is permitted to conduct this study and that the terms of the *Investigational Plan* are not in conflict with any employment agreement the Principal Investigator may hold with another party or any other contractual arrangement to which the Principal Investigator or institution is a party.

7.14 Publication Plan

As specified in the Clinical Trial Agreement, neither the complete nor any part of the results of the study carried out under this *Investigational Plan,* nor any of the information provided by the Sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study Sponsor. Any Investigator involved with this study is obligated to provide the Sponsor with complete test results and all data derived from the study. The first publication of the results of the study will be made by the Principal Investigator, in conjunction with the presentation of the results of the multi-center study with the Investigators and institutions from all sites contributing data, analyses and comments.

8 Sponsor Personnel and Contacts

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9 Definitions of Terms, Abbreviations and Acronyms

This section provides definitions for terms and abbreviations used in this *Investigational Plan*.

9.1 Definitions of Abbreviations and Acronyms

6MWT / 6MWD
Six minute walk test / Six minute walk distance

21 CFR
Title 21, Code of Federal Regulations (various applicable parts and subparts referenced)

ACE
Angiotensin converting enzyme

AE
Adverse event

AHA
American Heart Association

AIV
Anterior interventricular vein

ARB
Angiotensin receptor blocker

AV
AtrioVentricular

BP
Blood pressure

BUN
Blood urea nitrogen

CABG
Coronary artery bypass graft

CBC
Complete blood count

CEC
Clinical Events Committee

CHF
Congestive heart failure

Cr
Creatinine

CRA
Clinical research associate

CRO
Contract research organization

CRF
Case report form

CS
Coronary Sinus

cTn
Cardiac Troponin

CXR
Chest x-ray (PA and lateral) or cinefluoroscopy

DSMB
Data Safety Monitoring Board

ECG/EKG
Electrocardiogram, usually 12-lead

ECHO
Echocardiogram

EF
Ejection fraction

ETT
Exercise treadmill test (modified Naughton)

FMR
Functional mitral regurgitation

GCV
Great Cardiac Vein

HREC
Human Research Ethics Committee

ICD
Implantable cardioverter defibrillator

IFU
Instructions for Use

KCCQ
Kansas City Cardiomyopathy Questionnaire

LA
Left atrium

LAA
Left atrial appendage

LV
Left ventricle

LVAD
Left ventricular assist device

LVEDd
Left ventricular end diastolic dimension

LVESd
Left ventricular end systolic dimension

LVEF
Left ventricular ejection fraction

MAE
Major adverse event

MEC
Medical Ethics Committee

MI
Myocardial infarction (heart attack)

MR
Mitral regurgitation

MRJA/LAA
Mean regurgitant jet area to left atrial area

MV
Mitral valve

NT-BNP
N-terminal B-type natriuretic peptide

NYHA
New York Heart Association

PISA
Proximal iso-velocity surface area

QOL
Quality of life

QRS
Complex of cardiac rhythm representing ventricular depolarization

SAE
Serious adverse event

SAM
Systolic anterior motion of the mitral valve leaflet

TEE
Transesophageal echocardiogram

TIA
Transient ischemic attack

TIMI
Thrombolysis in Myocardial Infarction

TTE
Transthoracic echocardiogram

URL
Upper reference limit

USADE
Unanticipated serious adverse device effect

WBC
White blood count

9.2 Definitions of Terms

ANTERIOR INTERVENTRICULAR VEIN
The coronary vein located in the anterior interventricular groove.

ADVERSE EVENT
An adverse event is defined as 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.
Notes:

1. This definition includes events related to the investigational medical device or the comparator.
2. This definition includes events related to the procedures involved.
3. For users or other persons, this definition is restricted to events related to investigational medical devices.

ALLERGIC REACTION

Hypersensitivity to a particular contrast agent, device, medication, or transfusion product given to the subject for completion of a study related procedure (e.g., cardiac catheterization, CARILLON implant) that may or may not require treatment.

ANCHORING

The proprietary mechanism by which the CARILLON implant is fixed in position within the coronary sinus/great cardiac vein.

ANEURYSM (pseudoaneurysm)

Any abnormal dilation of a vessel, including pseudoaneurysm or dissection, requiring medical or surgical intervention, or resulting in death, that occurs as a result of the subject's index procedure at any of the catheter insertion sites.

ANGINA PECTORIS (stable or unstable)

A deep, poorly localized chest, arm, or jaw discomfort caused by inadequate flow to the heart muscle. These events may occur at any time throughout a subject's participation in the study.

Stable angina

Angina without change in frequency or pattern associated with physical exertion or emotional stress and relieved promptly (e.g., less than 5 minutes) by rest or sublingual nitroglycerin.

Unstable angina

A more frequent or severe form of angina, which can occur at rest. This is an acute process of myocardial ischemia that is not of sufficient severity and duration to result in permanent myocardial damage. This episode does not present with ST-segment elevation on the ECG and does not release biomarkers indicative of myocardial necrosis into the blood.

ANGIOGRAM/ANGIOGRAPHY

A radiographic record of the size, shape and location of the heart and blood vessels, after introduction of a radiopaque contrast medium.

ANNULOPLASTY

Plication ("tightening") of tissue around the heart valve annulus.

ANURIA

Absence of urine formation, which requires treatment.

AORTIC STENOSIS

A narrowing of the aorta or its orifice, obstructing free flow of blood from the left ventricle to the aorta, which requires treatment. This may occur at any time throughout a subject's participation in the study.

ARRHYTHMIA

Documented dysrhythmia by ECG or other rhythm monitoring device (e.g., portable heart monitor, pacemaker) that results in the signs and symptoms of vital organ hypoperfusion (e.g., dizziness, lightheadedness, or syncope) and requires treatment. This may occur at any time throughout a subject's participation in the study.

ARTERIOGRAM

Angiography of an artery.

ARTERIO VENOUS FISTULA

An abnormal channel or passage between the artery and vein that disrupts the normal blood flow pattern and requires surgical intervention.

ARTIFICIAL HEART

A mechanical pump used to replace the function of a damaged heart, either temporarily or as a permanent internal prosthesis.

ASTHENIA

General weakness or loss of strength, which requires treatment. Asthenia may occur at any time throughout a subject's participation in the study.

BLEEDING COMPLICATIONS

Major Bleeding

Major bleeding events involve episodes of intra-cranial, pericardial, or retroperitoneal bleeding or a procedure-related hemorrhagic event that requires transfusion (two units or greater) or surgical intervention, or results in a greater than five (5) gram decrease in hemoglobin.

Minor Bleeding

Minor bleeding events involve all other episodes of blood loss that do not meet the definition of Major Bleeding.

CARDIAC ARREST

Defined as the absence of pulse and respirations occurring in the post-operative period and resulting from ventricular tachycardia, ventricular fibrillation, electromechanical dissociation, or asystole.

CARDIAC SURGERY OR PERCUTANEOUS CORONARY INTERVENTION FOR NON-CARILLON IMPLANT FAILURE

Defined as surgery or percutaneous coronary intervention performed for the treatment of cardiovascular disease, including coronary artery bypass surgery, valvular disease unrelated to the mitral valve, and other cardiovascular surgical

procedures not related to cardiac surgery performed for failure of the CARILLON implant. The priority of surgery is defined as:

1. Elective: Surgery not requiring immediate attention and performed at the subject's convenience.
2. Urgent: Subject must have surgery within 24 hours.
3. Emergency: Immediate need for surgery to preserve life.

CARDIAC SURGERY OR PERCUTANEOUS CORONARY INTERVENTION FOR CARILLON IMPLANT FAILURE

Defined as cardiac surgery or percutaneous coronary intervention performed for failure of the CARILLON implant, including implant detachment, migration, or other CARILLON implant malfunction that may result in cardiac injury to the annulus. The priority of surgery is defined as:

1. Elective: Surgery not requiring immediate attention and performed at the subject's convenience.
2. Urgent: Subject must have surgery within 24 hours.
3. Emergency: Immediate need for surgery to preserve life.

CARDIAC TAMPONADE

Fluid in the pericardial space, documented by echocardiography or other methods, that results in systemic hypotension requiring percutaneous or open surgical intervention. This may occur at any time throughout a subject's participation in the study.

CARILLON MITRAL CONTOUR SYSTEM

The CARILLON Mitral Contour System is the investigational device that is the subject of this clinical study. It is composed of a proprietary implant intended for permanent implantation in the Coronary Sinus (CS)/Great Cardiac Vein (GCV) and a proprietary, catheter-based delivery system through which the implant is deployed, anchored, and locked in the CS/GCV. The delivery system can also be used to recapture and remove the implant, if necessary, prior to decoupling.

CAROTID ARTERY TRAUMA

Trauma to a subject's carotid artery during the index procedure that prolongs the hospitalization and/or requires percutaneous or surgical intervention.

CHRONIC NERVE DAMAGE

Damage to a nerve during the index procedure or other study related procedure causing permanent nerve impairment.

COAGULOPATHY

A defect in the blood-clotting mechanisms that occurs at any time throughout a subject's participation in the study.

CORONARY SINUS

A vessel or passage that receives the blood flow from the cardiac veins and opens into the right atrium.

DEATH

Death is divided into two categories and will be reported at any time in a subject's participation in the study:

Cardiac death is defined as death due to any of the following:

- Acute Myocardial Infraction
- Cardiac perforation/pericardial tamponade
- Arrhythmia or conduction abnormality
- Stroke within 30 days of the procedure or stroke suspected of being related to the procedure
- Death due to complication of the index procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery
- Any death for which a cardiac cause cannot be excluded

Non-cardiac death is defined as death not due to cardiac causes (as defined above).

Operative mortality is defined as death from any cause that occurs during the hospitalization in which the operation was performed or through 30 days postoperatively if the subject was discharged.

All deaths will be adjudicated by the Clinical Events Committee.

DEEP VEIN THROMBOSIS

A condition where there is a blood clot in a deep vein, occurring at any time throughout a subject's study participation, that may or may not require treatment.

DELIVERY CATHETER

The CARILLON Mitral Contour System delivery catheter facilitates percutaneous entry of the marker catheter, attachment of the cartridge which houses the CARILLON implant, and enables placement and recapture of the implant.

DENTAL INJURY

Injury to the teeth or oral cavity related to a transesophageal echocardiogram performed during the subject's participation in the study, which requires treatment.

DENUDATION (ARTERIAL OR VENOUS)

Removal of layer(s) of a blood vessel wall.

DEPLOYMENT

Deployment is the procedure of delivering and locking the CARILLON implant anchors within the CS/GCV.

DEPRESSION

Psychological distress, depression, or anxiety, which requires treatment.

DEVICE EMBOLIZATION

The movement of the CARILLON implant (distal anchor, proximal anchor and/or ribbon connector) to a location out of the coronary sinus/great cardiac vein that creates an obstruction to a cardiac chamber or a blood vessel and requires percutaneous or surgical intervention.

DEVICE MALFUNCTION OR FAILURE

Device malfunction

The failure of a device to meet any of its performance specifications or otherwise perform as intended. Performance specifications are claims made in the labeling of the device.

Device failure

A device that is used in accordance with the Instructions for Use, but does not perform according to the Instructions for Use and negatively impacts the treatment.

A device malfunction or failure may occur at any time throughout a subject's participation in the study. A device malfunction or failure is an adverse event only if it causes an untoward event in the subject.

DEVICE MIGRATION

The physical movement of the complete CARILLON implant (the distal anchor, proximal anchor and ribbon connector), from its deployed location (after decoupling of the CARILLON implant from the delivery system has occurred).

DISSECTION (ARTERIAL OR VENOUS)

A tear of the layers in the blood vessel that causes blood to flow between the layers of the wall of the blood vessel and that results in residual contrast staining of the vessel wall after contrast has cleared the vessel lumen.

DILATED CARDIOMYOPATHY

Left ventricular end diastolic dimensions (LVEDd) > 55 millimeters (mm) or LVEDd/BSA > 3.0 cm / m^2.

DOUBLE BLIND

A type of masking in which two or more parties involved with the clinical trial do not know which participants have been assigned which interventions.

DYSPNEA

Shortness of breath, resulting in labored or difficult breathing, which requires treatment.

ECHOCARDIOGRAM

Cardiac ultrasound including color flow Doppler.

ELECTROCARDIOGRAM

Twelve (12) lead electrocardiogram and monitoring electrocardiogram used in a cardiac catheterization laboratory.

ELECTROMECHANICAL DISSOCIATION / PULSELESS ELECTRICAL ACTIVITY

Persistence of electrical activity in the heart without an associated mechanical contraction or pulse.

EMBOLISM (AIR, TISSUE, OR THROMBUS)

Sudden obstruction of a blood vessel (arterial or venous, including the coronary sinus) or cardiac chamber by foreign or biological substances brought to its site of lodgment by the cardiovascular system, which may cause symptoms such as dyspnea, hypotension, sharp chest pains and decreased level of consciousness, and which requires treatment. This may occur at any time throughout a subject's participation in the study.

EMERGENCY CARDIAC SURGERY

The requirement for a subject to have non-planned, emergent interventional procedure or surgery for the treatment of a new or worsening cardiovascular condition (e.g., coronary artery stenosis, mitral valve dysfunction), occurring at any time throughout a subject's participation in the study.

ENDOCARDITIS

Any infective endocarditis associated with the CARILLON implant or implant procedure as defined by the Duke Scale[36] and assessed by echocardiographic findings, clinical criteria including positive cultures, clinical signs (fever, new or altered cardiac murmurs, splenomegaly, systemic emboli, or immunopathological lesions) and/or histologic confirmation of endocarditis at biopsy or autopsy. This may occur at any time during a subject participation in the study. A full course of antibiotic therapy is defined as seven (7) days or longer.

ESOPHAGEAL INJURY

Esophageal perforation

An opening or hole through the esophagus, requiring treatment. This may be related to the transesophageal echocardiogram (TEE) performed during the index procedure or anytime during the trial should this test become necessary.

Esophageal stricture

An abnormal narrowing of the esophagus acquired from trauma (e.g., TEE) or infection that may result in mechanical or chemical irritation, muscular spasm, or pressure from adjacent structure or tumors, and which requires treatment. This event may occur at any time throughout a subject's participation in the study and may be temporary or permanent.

FATIGUE

A feeling of tiredness or weariness resulting from continued activity or as a side effect of prolonged radiation exposure or psychotropic drug.

FEVER

A fever above 101 degrees Fahrenheit that results in medical intervention. This may occur at any time throughout a subject's participation in the study.

GREAT CARDIAC VEIN

The vein in the transverse groove between the left cardiac atrium and ventricle that drains into the coronary sinus.

HEADACHE

An acute or chronic, diffuse pain in different portions of the head, not confined to any nerve distribution area. It may be frontal, temporal, or occipital, and may be confined either to one side of the head or to the region immediately over one eye. Headaches requiring treatment will be documented as adverse events.

HEART FAILURE

A chronic syndrome resulting from failure of the heart to maintain adequate circulation of blood. Symptoms resulting from decompensation of the heart or exacerbation of heart failure symptoms, which occur during the study and require treatment, will be documented as adverse events.

HEART FAILURE HOSPITALIZATION

A diagnosis of acute decompensated heart failure hospitalization (ADHF) requires an in-hospital stay that includes at least one calendar date change and requires intravenous or mechanical heart failure treatment. The length of hospital stay will be calculated from admission to discharge to home or other disposition.

The diagnosis of ADHF will be based on:

- Symptoms of worsening heart failure such as increased shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, fatigue, decreased exercise tolerance or history of weight gain;
- Physical examination evidence such as neck vein distention, the presence of a third heart sound, bilateral pulmonary rales, worsening ascites or pedal edema, hypotension or signs of worsening end-organ perfusion; and/or
- Laboratory evidence, which may include pulmonary congestion on chest x-ray, elevated natriuretic peptide level, worsening oxygenation or respiratory acidosis.

Examples of intravenous heart failure therapy would include:

- IV bolus or infusion of loop diuretics, vasodilators such as nitrates, nitroprusside, nesiritide, vasopressors including dobutamine or dopamine, and inotropic agents such as milrinone.
- Also included would be other invasive or mechanical heart failure treatments such as ultrafiltration, or hemodynamic assist devices such as intra-aortic balloon pumps or LVADs.

Notes:

1. Treatment with IV antiarrhythmic medication, electrical cardioversion and/or ablation in the absence of other intravenous or invasive heart failure treatments would **not** *per se* constitute an ADHF event.

2. Heart failure exacerbation that can be managed solely by augmentation of oral heart failure therapies does not meet criteria for heart failure hospitalization.

3. ADHF that develops secondary to another diagnosis such as a non-cardiac diagnosis (e.g., pneumonia/bronchitis, limb fracture, renal failure), an acute MI complicated by ADHF, acute onset of atrial fibrillation with rapid ventricular response or a rupture chordae would **not** be counted as ADHF events.

HEART TRANSPLANT

Replacement of a native heart with a donor heart.

HEMATOMA

A swelling or mass of blood (usually clot), six (6) centimeters or longer, that causes bruising or bleeding of the body tissue at the catheter insertion site. This event may occur after the index procedure and may or may not require treatment.

HEMOLYSIS

A new onset of anemia associated with laboratory evidence of red cell destruction. This is diagnosed as plasma free hemoglobin that is greater than 40 mg/dL on two (2) measures within 24 hours or on one measure if the intervention is initiated based upon other clinical symptoms.

HYPOTENSION/HYPERTENSION

Hypotension

A decrease of the systolic and diastolic blood pressure to below normal for the subject, which requires treatment. This may occur as a result of infection, fever, hemorrhage, shock, or anemia. It may occur anytime throughout a subject's participation in the study.

Hypertension

A higher than normal blood pressure that requires treatment. This may occur at any time throughout a subject's participation in the study.

INDEX PROCEDURE

The index procedure takes place immediately following randomization and is the starting point for timing of all follow-up evaluations and data analyses.

INFECTION, GENERALIZED

The presence and growth of microorganisms that produces tissue damage, usually accompanied by inflammation. Infection requiring treatment will be documented as an adverse event.

INFECTION AT THE CATHETER INSERTION SITES

An infection or inflammatory response that occurs at one or more catheter insertion sites in relationship to the index procedure and that requires treatment.

INFORMED CONSENT

Informed consent is a process by which a subject voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the investigation that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.

INVESTIGATOR

A person responsible for the conduct of the clinical investigation at an investigation site. If an investigation is conducted by a team of individuals at an investigation site, the Investigator is the responsible leader of the team and may be called the Principal Investigator. The Investigator is responsible for assuring the investigation is conducted in accordance with all applicable regulations including those protecting human subjects.

INVESTIGATIONAL PRODUCT

Investigational product is defined as the investigational device, its accessories, and accompanying labeling.

LEFT VENTRICULAR EJECTION FRACTION

The percentage of the blood emptied from the ventricle during systole.

LEUKOPENIA

Decrease in white blood count to below the lower limit of normal. Leukopenia may be caused by prolonged radiation exposure.

MAJOR ADVERSE EVENT (MAE)

Defined as one of the following: (1) Death; (2) Myocardial Infarction; (3) Device embolization; (4) Vessel erosion requiring percutaneous or surgical intervention; (5) Cardiac perforation requiring percutaneous or surgical intervention; or (6) Occurrence of cardiac surgery or percutaneous coronary intervention associated with device failure.

MARKER CATHETER

An angiographic catheter used to measure the coronary sinus/great cardiac vein.

MEDICAL ETHICS COMMITTEE

The medical ethics committee, according to Directive 2001/20/EC, is an independent body in a member state of the European Union, consisting of healthcare professionals and non-medical members, whose responsibility it is to protect the rights, safety and well being of human subjects involved in a clinical trial and to provide public assurance of that protection, by, among other things, expressing an opinion on the clinical trial protocol, the suitability of the investigators involved in the trial and the adequacy of facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent.

MITRAL ANNULOPLASTY RING

A prosthetic ring sutured into the mitral valve annulus during open heart surgery.

MITRAL REGURGITATION

The backward flow of blood across the mitral valve from the left ventricle to the left atrium that results from imperfect closure of the mitral valve. Mitral valve regurgitation may be classified in several ways including echocardiographically, fluoroscopically, and clinically.

Primary cardiomyopathy with secondary mitral regurgitation will be distinguished by the presence of left ventricular dilation, left ventricular dysfunction, and 2+ - 4+ mitral regurgitation and the absence of significant mitral valve pathology where mitral valve pathology includes mitral valve prolapse, flail leaflet, or evidence of degenerative or rheumatic mitral valve disease. Primary mitral regurgitation with secondary dysfunction implies that structural valve pathology exists (e.g., prolapse, flail leaflet, degenerative or rheumatic mitral valve disease) and has caused the left ventricular dilation and dysfunction. Thus, subjects with significant organic mitral valve pathology and left ventricular dysfunction will be considered to have primary mitral regurgitation and secondary dysfunction.

Mitral regurgitation may occur at any time throughout a subject's participation in the study. An acute, hemodynamically significant increase in MR will be documented as an adverse event.

MITRAL STENOSIS

A narrowing of the mitral orifice, obstructing free flow of blood from the left atrium to the left ventricle. This may occur at any time throughout a subject's participation in the study.

This study will define mitral stenosis as being present if both of the following criteria are met:

1. Either peak E wave velocity > 1.5 m/s (corresponding to a peak gradient ≥ 10 mmHg), or mean pressure gradient > 5 mmHg, and
2. Either, one of the following:
   a. Mitral valve area calculated by PHT is < 2.0 cm^2 (i.e., PHT > 110 msec), or
   b. 2D mitral valve planimetry (or alternatively a mitral inflow color PISA, if present) reveals a mitral valve area of < 2.0 cm^2.

MITRAL VALVE

The cardiac valve between the left atrium and left ventricle.

MITRAL VALVE INJURY

Injury or trauma to the mitral valve that requires observation or intervention throughout a subject's participation in the study.

MYOCARDIAL INFARCTION

Myocardial infarction (MI) is defined for events that occur ≤ 24 hours and for events that occur > 24 hours after the index procedure or any percutaneous cardiac intervention that may be required during the subject's participation in the study.

Less than or equal to 24 hours post-intervention

In patients undergoing PCI with normal (≤99th percentile URL) baseline cTn concentrations, elevations of cTn >5 x 99th percentile URL occurring within 48 hours of the procedure—plus either:

(i) evidence of prolonged ischemia (≥20 min) as demonstrated by prolonged chest pain, or

(ii) ischemic ST changes or new pathological Q waves, or

(iii) angiographic evidence of a flow limiting complication, such as of loss of patency of a side branch, persistent slow-flow or no-reflow, embolization, or

(iv) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

is defined as PCI-related MI (type 4a).

Note: When a cTn value is ≤5 x 99th percentile URL after PCI and the cTn value was normal before the PCI—or when the cTn value is >5 x 99th percentile URL in the absence of ischemic, angiographic or imaging findings—the term 'myocardial injury' should be used.

More than 24 hours post-intervention

Myocardial infarctions more than 24 hours after percutaneous cardiac intervention will be defined according to the ESC/ACCF/AHA/WHF Expert Consensus Universal Definition of MI[37] and will be adjudicated by an independent Clinical Events Committee.

MYOCARDIAL ISCHEMIA

Inadequate circulation of blood to the heart muscle due to obstructions of coronary arteries as documented by electrocardiography and/or imaging modalities. This may occur at any time throughout a subject's participation in the study.

NAUSEA/VOMITING

Nausea is an uneasiness of the stomach that often accompanies the urge to vomit, but doesn't always lead to vomiting. Vomiting is the forcible voluntary or involuntary emptying ("throwing up") of stomach contents through the mouth. Nausea or vomiting requiring treatment will be documented as adverse events.

NEW YORK HEART ASSOCIATION CLASSIFICATION (NYHA)

Classification system for defining cardiac disease and related functional limitations into four broad categorizations. NYHA Classification assessment will be made by independent examiner at all study time-points. Refer to Appendix D for specific definitions.

NITINOL

A super-elastic shape-memory Nickel-Titanium alloy used commonly in cardiac, dental, and orthopedic implants as well as in other non-implant medical devices.

NON-PYROGENIC

The term applies to a biocompatibility test of the device materials to assure that no foreign proteins are produced by the interaction of the device with the myocardial tissue that would cause a fever.

PAIN

An unpleasant sensory and emotional experience arising from actual or potential tissue damage, which requires treatment.

PERFORATION (arterial, venous or cardiac)

Perforation associated with puncture and/or rupture of a cardiac structure, or of a arterial or venous access vessel.

A perforation during the index procedure will be classified as a major adverse event only if it is associated with puncture or rupture of a cardiac structure (heart, coronary artery, and/or coronary vein) leading to hemopericardium and requiring percutaneous or surgical intervention.

PERFUSION

Passage of blood into the surrounding tissue

PERICARDIAL EFFUSION

Fluid in the pericardial space documented by echocardiography or other methods.

PERICARDITIS

Inflammation of the pericardium or development of an unexplained pericardial effusion. Pericarditis will be diagnosed by the presence of at least two of the following clinical features: 1) chest pain, 2) pericardial friction rub on exam, 3) characteristic ECG changes (new widespread ST elevation or PR depression), and 4) pericardial effusion.

PERIPHERAL ISCHEMIA

Inadequate flow of blood to the arteries or veins of the extremities that may result in pain or injury to the blood vessel. This event may or may not require intervention and can occur at any time throughout a subject's participation in the study.

PHARYNGEAL / LARYNGEAL TRAUMA

Injury to the pharynx or larynx (e.g., dysphagia, vocal cord disorder, throat pain), which requires treatment and is related to a transesophageal echocardiogram performed during the subject's participation in the study.

PHYSICAL INJURY

Trauma or damage to a part of the body, which requires treatment and is related to functional tests (e.g., exercise treadmill) performed during the subject's participation in the study.

PLICATION

The creation of folds or tucks in tissue (e.g., vein) to shorten its length.

PNEUMONIA

An inflammation of the alveoli, interstitial tissue, and bronchioles of the lungs due to infection by bacteria, virus, or other pathogenic organisms, or to irritation by chemical or other agents.

PNEUMOTHORAX

A collection of air in the pleural cavity that requires intervention. This may be a result of injury, bleb, or superficial lung abscess and may occur at any time throughout a subject's participation in the study.

RADIATION DERMATITIS

Skin burns ranging from erythema to blistering/ulceration, and caused by prolonged radiation exposure.

RECAPTURE

The mechanism of retrieving the CARILLON implant from its anchored position within the coronary sinus/great cardiac vein. This is achieved by using the delivery catheter to collapse the device into the catheter for removal from the subject. The CARILLON Mitral Contour System is designed to enable acute recapturing (i.e., prior to decoupling from the delivery system) if the implant cannot be placed safely in its intended location.

REINTERVENTION

Any unscheduled visit to the operating room or catheterization laboratory for reintervention related to the CARILLON investigational procedure or study device.

RENAL FAILURE

Renal insufficiency resulting in an increase in serum creatinine that requires dialysis. This event may occur as a result of any study procedures that require the use of contrast media.

RENAL INSUFFICIENCY

Any clinically significant increase in creatinine above baseline requiring treatment (excluding dialysis).

RESPIRATORY DISTRESS

Severe and sustained impairment of respiratory function, which is related to study procedures and requires treatment.

SEPTICEMIA/SEPSIS

A serious, systemic, rapidly progressive, life-threatening infection caused by pathogenic organisms or their toxins, that may or may not be associated with a positive blood culture, and requiring hospitalization and treatment with antibiotics. A full course of antibiotic therapy is defined as seven (7) days or longer.

SERIOUS ADVERSE EVENT

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 foetal distress, foetal death or a congenital abnormality or birth defect

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

SIGNIFICANT ORGANIC MITRAL VALVE PATHOLOGY

Moderate or severe myxomatous degeneration, with or without mitral leaflet prolapse, rheumatic disease, full or partial chordal rupture.

STROKE

A neurological deficit lasting 24 hours or longer, or lasting less than 24 hours with a brain imaging study showing infarction. This may occur at any time throughout a subject's participation in the study and may or may not require treatment.

SYSTOLIC ANTERIOR MOTION

Anterior displacement of the anterior mitral valve leaflet during systole causing left ventricular outflow tract obstruction.

TENSIONING

With the CARILLON implant deployed, tensioning is the process of applying translational movement (by pulling) of the delivery system to cause the coronary sinus/great cardiac vein tissue to plicate.

TIMI CLASSIFICATION

Thrombolysis in Myocardial Infarction has four classifications:

***TIMI 0*:** No perfusion.

***TIMI 1*:** Penetration with minimal perfusion. Contrast fails to opacify the entire bed distal to the stenosis for the duration of the cine run.

***TIMI 2*:** Partial perfusion. Contrast opacifies the entire coronary bed distal to the stenosis. However, the rate of entry and/or clearance is slower in the coronary bed distal to the obstruction than in comparable areas not perfused by the dilated vessel.

TIMI 3: Complete perfusion. Filling and clearance of contrast equally rapid in the coronary bed distal to stenosis as in other coronary beds.

TISSUE NECROSIS

Tissue death within the external or internal layers of the blood vessel(s) (arterial or venous), heart structures, or myocardium caused by the CARILLON implant, which requires treatment. This may occur at any time throughout a subject's participation in the study.

TISSUE PENETRATION

Outward radial movement of the CARILLON implant (e.g., the anchor wireforms) from the lumen of the vein into the adjacent tissue, with no compromise to the

integrity of the tissue. The relative position of the device with respect to its intended position within the vein is unchanged.

TRANSIENT ISCHEMIC ATTACK (TIA)

A neurological deficit lasting less than 24 hours and, if an imaging study is performed, shows no evidence of infarction. This may occur at any time throughout a subject's participation in the study and may or may not require treatment.

UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE)

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

URINARY TRACT INFECTION

Infection of the urinary tract with microorganisms, which requires treatment.

VASOVAGAL REACTION

Hypotension, pallor, sweating, hyperventilation, bradycardia, and/or syncope produced by stimulation of the vagus nerve during study-related procedures. A vasovagal reaction requiring treatment will be documented as an adverse event.

VENOGRAM

Angiography of the vein.

VENTRICULAR ASSIST DEVICE

A mechanical pump that assists the heart by pumping blood through the body.

VESSEL EROSION

A physical or inflammatory process adjacent to the CARILLON implant causing loss of tissue integrity of the blood vessels (arterial or venous), heart structures, or myocardium. Vessel erosion will be classified as a major adverse event only if percutaneous or surgical intervention is required.

VESSEL OCCLUSION (arterial or venous)

Complete blockage of a blood vessel preventing the flow of blood and resulting in cardiac symptoms and requiring treatment.

VESSEL SPASM OR STENOSIS (ARTERIAL OR VENOUS)

Vessel Spasm

Temporary abrupt contraction of the muscles in the wall of a blood vessel resulting in reduced blood flow. A spasm that results in myocardial ischemia or requiring treatment will be considered an adverse event.

Vessel Stenosis

Narrowing of a blood vessel that requires treatment.

Appendix A – Instructions for Use

This appendix provides a copy of the Instructions for Use for the CARILLON Mitral Contour System.

Appendix B – Sample of Informed Consent

This appendix provides a copy of the sample informed consent for the REDUCE FMR Trial.

Appendix C – Subject Study Calendar

Schedule of assessments:

PRIMARY STUDY
(Treatment & Control pts)

CROSS-OVER REGISTRY
(Control pts upon primary study completion)

Study Task	Screening / Baseline		Index Procedure	Discharge	1 Month (±7 Days)	6 month (±14 Days)	12 month (±30 Days)	Screening / Baseline	CARILLON Procedure	Discharge	1 month (±7 Days)
Informed Consent	X							X			
Inclusion/Exclusion Criteria	X							X			
Past Medical History & Physical Exam	X							X[11,12]			
Serum Pregnancy Test	X							X			
TEE[1]	X							X			
Coronary Angiography	X[2]		X[2]					X	X		
Coronary Sinus Venogram	X							X			
Intraprocedure Echo (TTE or TEE)			X						X		
Physical Exam				X	X	X	X			X	X
Vital Signs[3]	X		X	X	X	X	X	X	X	X	X
Coagulation Tests[4]	X	Randomization						X			
Cardiac Enzymes[5]	X			X	X	X	X	X		X	X
Chemistries[6]	X			X	X	X	X	X[12]		X	X
CBC[7]	X			X	X	X	X	X[12]		X	X
12-Lead ECG	X			X	X	X	X	X[12]		X	X
Complete TTE	X				X	X	X	X[12]			X
Exercise TTE[8]	X				X	X	X	X[12]			X
Abbreviated TTE[9] (safety)				X						X	
CXR or cine fluoroscopy				X		X	X			X	
Six Minute Walk Test	X[10]				X	X	X	X[12]			X
NYHA Classification	X				X	X	X	X[12]			X
KCCQ	X				X	X	X	X[12]			X
SF-12 QoL	X				X	X	X	X[12]			X
Concomitant Medications	X		X	X	X	X	X	X	X	X	X
Adverse Events	X		X	X	X	X	X	X	X	X	X

1. To rule out LAA clot - only required for subjects with a prior history of atrial fibrillation

2. The eligibility angiography may occur immediately prior to randomization, unless a recent angiogram (see section 3.4.3.2) indicating no CAD requiring intervention is available. All Treatment group subjects undergo coronary angiography as part of the CARILLON Mitral Contour System procedure.

3. Vital signs include: Blood pressure, heart rate, respiratory rate, oxygen saturation, temperature (degrees Celsius), weight, height (baseline only).

4. Coagulation Tests include: PTT and Prothrombin time.

5. Cardiac enzymes: cardiac troponin (cTn).

6. Serum chemistries: sodium, potassium, chloride, BUN, creatinine and NT-BNP.

7. CBC with differential: hemoglobin, hematocrit, platelets, and WBC.

8. Exercise TTE will be done only at pre-identified qualified sites with supine bicycle ergometry.

9. Abbreviated TTE safety assessment to rule out pericardial effusion.

10. Six-minute walk test will be undertaken for screening and baseline (reference Appendix F: Six Minute Walk Test Protocol).

11. No past medical history needed, physical exam only.

12. Data from 12-mo follow-up of the primary study may be used if assessments were performed within 45 days to scheduled Cross-Over CARILLON procedure.

Appendix D – NYHA Classification of Patients with Diseases of the Heart

Functional Classification

Class I	Patient with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

(New York Heart Association Criteria Committee: Diseases of the Heart and Blood Vessels: Nomenclature and Criteria for Diagnosis, 6th ed. Boston, Little, Brown, & Co. 1964)

Appendix E – Echocardiogram Protocol

This appendix provides a copy of the Echocardiogram Protocol for the baseline, procedure, discharge, and follow-up echocardiograms for the REDUCE FMR Trial.

Appendix F – Six Minute Walk Test Protocol

All study subjects will perform a Six Minute Walk Test (6MWT) at screening, baseline and at each scheduled follow-up visit. To minimize any training effect, the screening and baseline tests should be two distinct assessments. Site personnel who administer the 6MWT will be blinded to the study subject's randomization assignment.

The test will be supervised by the Investigator or designee who will be responsible for the quality of patient preparation, reports and data collection.

- Prior to the start of each exercise test, make sure that the subject has not had any unstable cardiac symptoms and that there is no contraindication for proceeding with a stress test.
- Select a low-traffic corridor that is at least 25 meters in length. This corridor must not have any doors or obstructions that would open into the course and interfere with the subject's ability to walk. Mark off sections that are five (5) meters apart.
- Have a chair available for the study subject to rest in if needed.

Six Minute Walk Test Procedure

1 Study Subject Instructions

Instruct the study subject to walk as far as they can for six minutes. If they need to stop for fatigue or other medical reasons, they may do so, but should start walking as soon as they are able or are instructed to stop. Inform the subject to turn around when they reach the 25 meter mark and walk back to the starting point. They are to repeat this process as many times as they are able until they are instructed to stop. Answer any questions the subject has regarding the 6MWT prior to starting the test.

2 Exercise

As soon as the study subject starts walking, start the stop watch and monitor the distance covered. During the test, DO NOT speak with the subject unless there is an emergent reason.

3 Immediate Post Exercise

At six minutes, instruct the subject to stop and stand in that spot. Bring the chair to the subject and ask him or her to rest. Calculate the total distance walked during the six minutes to the nearest meter.

Appendix G – Definition of Stable Heart Failure Regimen

All study subjects must be on a stable heart failure medical regimen. A stable regimen is defined as the following:

- On an adjustable diuretic dose for three (3) months
- On ACE inhibitor or angiotensin receptor blocker for three (3) months with stable dosage for two (2) months (or documented intolerance to the medication)
- On a beta-blocker for three (3) months with stable dosage for two (2) months (or documented intolerance to the medication)

Patients must meet all three of the medication criteria unless intolerance to the medications is documented.

Appendix H – Exercise Echocardiography Protocol Synopsis

Only study centers with the necessary exercise equipment and echosonographers experienced in obtaining echo imaging during exercise will be allowed to undertake exercise TTE assessments.

Study subjects who are physically capable of exercising on a supine bicycle ergometer and who consent to undergoing exercise echocardiography will undertake these assessments at baseline and at each scheduled follow-up visit.

The assessment will be supervised by the Investigator or qualified designee who will be responsible for the safety of the subject during the exercise protocol, quality of patient preparation, reports and data collection.

- Prior to the start of each exercise test, make sure that the subject has not had any unstable cardiac symptoms and that there is no contraindication for proceeding with the exercise test.

Exercise Methodology

Resting echo measurements will be obtained as part of the complete TTE assessment undertaken in the primary study protocol. Subjects will then undergo a graded exercise test on a supine bicycle ergometer with workloads being increased by 25W every 3 minutes until patient/symptom limitation.

Single-lead electrocardiograms and blood pressure will be recorded every minute. Subjects will be asked to declare their perceived exertion according to a Borg scale during the test.

Criteria to halt the test will be chest pain, severe dyspnea, severe fatigue, sustained hypotension, sustained ventricular tachycardia, short runs of three or more ventricular premature contractions, pallor, or dizziness.

Echocardiographic Acquisition Methodology

All echocardiographic images will be obtained in the last 90 seconds of each 3-minute workload level. Imaging should be acquired during a breath hold at the end of expiration. The averages of three consecutive beats during exercise will be used for each parameter.

Imaging views to assess the following parameters will be acquired:

- Effective Regurgitant Orifice Area
- Mitral Annular diameter/area measurements
- Pulmonary artery systolic pressure (from TR velocity)

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