Protocol with Statistical Analysis Plan Cover Page:

Official Title:	NHLBI DIR Transcatheter Mitral Cerclage Annuloplasty early feasibility study
NCT number:	NCT03929913
Document Type:	Protocol with Statistical Analysis Plan (SAP)
Document Date:	06-14-2021

PROTOCOL TITLE:

NHLBI DIR Transcatheter Mitral Cerclage Annuloplasty early feasibility study

SHORT TITLE:

Cerclage EFS study

INVESTIGATIONAL DEVICE EXEMPTION (IDE)

G190005

NHLBI PROTOCOL NUMBER

19-H-0088

VERSION HISTORY

2018-08-27	NHLBI Cardiovascular Branch Review
2019-02-06	Interactive FDA IDE review
2019-02-27	Change to single IRB of record
2019-05-12	Amendment A: *MitraClip* Arm, increase in sample size, other study clarifications
2019-06-27	Amendment B: Clarifications of, secondary endpoint, ADE, reporting, consent
2019-09-06	Amendment C: Additional CT scan, remove NIH as enrolling site
2019-10-21	Amendment D: Screening consent, minor cleanup
2020-02-18	Amendment E: Additional sites and optional non-invasive tests
2020-07-09	Amendment F: Change selection criteria
2021-06-14	Amendment G: Add long term FU adverse event recording and reporting criteria; Additional CT scan

SPONSOR INFORMATION:

Sponsor	NHLBI Office of Clinical Director
Sponsor Representative	Robert J. Lederman, MD, Senior Investigator, NHLBI Division of Intramural Research

KEY ROLES

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CT core lab	Marcus Chen, MD	NHLBI DIR	
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Independent Clinical Events Adjudication Committee	Hector Garcia-Garcia, MD (Chair)	Medstar Heart and Vascular Institute, NHLBI Contractor	
Data Safety Monitoring Board	Jamieson M. Bourque, MD, MHS (Chair)	NHLBI	
Study Statistician	Xin Tian, PhD	NHLBI Office of Biostatistics Research	
Institutional Review Board (IRB) of Record	—	Advarra	00023875

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* No subject enrollment

ESTIMATED DURATION OF STUDY:

[6 years]

ESTIMATED COMPLETION DATE OF STUDY:

December 31, 2024

SUBJECTS OF STUDY AND SITES:

Subjects	Sex	Age range	Sites
60 screened 30 enrolled	Men & Women	≥21 years	Up to 6

DISCLOSURES

RJL and TR are co-inventors on patents, assigned to NIH, on the test article. They may be required to receive royalty payments should the test article advance to commercialization.

The non-NIH site Principal Investigators have the following conflicts of interest:

ABG serves as a proctor for Edwards Lifesciences, Medtronic, and Abbott Vascular, and is a shareholder in Transmural Systems, the manufacturer of the test article.

VCB is a consultant for Edwards Lifesciences and for Abbott Vascular, and his employer has research contracts from Edwards Lifesciences, Abbott Vascular, Medtronic, and Boston Scientific.

TR serves as a proctor for Edwards Lifesciences and Medtronic and is a consultant for Medtronic.

DD serves as a proctor for Edwards Lifesciences, and receives payments from Teleflex for a medical device for interventional procedures not tested in this protocol.

CS serves as a proctor and consultant for Edwards Lifesciences and Medtronic, and is a consultant for Abbott Vascular, Boston Scientific, and Abiomed. NHLBI and Transmural Systems, the manufacturer of the cerclage device system, have a collaborative research and development agreement on different cardiovascular devices. NHLBI has awarded a Small Business Innovation Research contract to Transmural Systems to support the early clinical development of this device system.

ABBREVIATIONS

ADE	Adverse Device Effect
CIED	Cardiac implanted electronic device
CMR	Cardiovascular magnetic resonance imaging
CMS	Centers for Medicare and Medicaid Services
CRT	Cardiac resynchronization therapy
CT	Computed tomography
CTP	CMS Clinical Trial Policy (CTP).
DIR	Division of intramural research
EFS	FDA Early Feasibility Study under Investigational Device Exemption license
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
ICD	Implanted cardioverter defibrillator
IEC	Institutional Ethics Committee
IRB	Institutional Review Board
MVARC	Mitral valve academic research consortium (criteria)
MR	Mitral valve regurgitation
MS	Mitral valve stenosis
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SEC	Study eligibility committee
TEE	Transesophageal echocardiography
TMCA	Transcatheter Mitral Cerclage Annuloplasty
TTE	Transthoracic echocardiography
UADE	Unanticipated Adverse Device Effect
UP	Unanticipated Problem

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0.0 PUBLIC PRÉCIS

This research protocol tests a new technique and devices that we have developed to treat functional mitral valve regurgitation, called transcatheter mitral valve cerclage annuloplasty, otherwise known as "cerclage." Functional mitral valve regurgitation is a condition caused by damaged heart muscle involving the left ventricle which results in mitral valve leakage. This leakage causes heart failure (breathlessness and lack of energy especially when walking or exercising, and hospital admissions for fluid buildup).

This is an early feasibility study (EFS) evaluation of special devices, permanently implanted in the heart, to perform mitral cerclage annuloplasty. Mitral cerclage annuloplasty is a catheter procedure performed under X-ray and ultrasound guidance without surgery. The cerclage devices compress the mitral valve like a purse-string. The cerclage device has a special feature that prevents a coronary artery from getting squeezed as part of this purse-string.

The protocol has been changed to allow patients who have mitral valve regurgitation despite prior *Mitra-Clip* treatment. The protocol has been changed to allow patients who have symptomatic heart failure and mild mitral regurgitation.

1.0 OBJECTIVE

The original objective of this protocol is to evaluate the feasibility and safety of Transcatheter Mitral Cerclage Annuloplasty to treat severe functional mitral valve regurgitation in patients with NYHA class II, III or IV heart failure symptoms despite optimal medical therapy.

In Amendment F, the objective of this protocol is changed to evaluate the feasibility and safety of Transcatheter Mitral Cerclage Annuloplasty to treat symptomatic heart failure accompanied by mitral valve regurgitation despite optimal medical therapy. New subjects may have less severe mitral valve regurgitation compared with the first 10 subjects.

2.0 BACKGROUND

Functional mitral regurgitation (also known as secondary mitral regurgitation) is a common manifestation of left ventricular dysfunction. Ventricular dysfunction leads to dilation, which in turn leads to mitral annular dilation and leaflet traction. This causes a failure of coaptation of the otherwise intact leaflets of the mitral valve, leading to regurgitation through a central orifice between the mal-coapting leaflet tips. Functional mitral regurgitation contributes to heart failure symptoms.

Annular and/or ventricular restraint are investigational mechanical approaches to mitigate symptoms of cardiac dysfunction, that may act by reducing heart failure manifestations during exertion and that may induce favorable "negative" chamber remodeling. Transcatheter Mitral Cerclage Annuloplasty is one such annular and/or ventricular restraint device strategy.

3.0 CLINICAL AND SCIENTIFIC JUSTIFICATION

There is precedent to support the safety of devices that reside in the coronary sinus to treat mitral valve regurgitation. But, these so-called 'partial' annuloplasty devices and approaches have had mixed results with regards to effectiveness. These shortcomings include compression in the commissural more than septal-lateral dimensions of the dilated annulus, compression of entrapped circumflex coronary arteries inducing myocardial ischemia or infarction predicted in up to two thirds of patient candidates, and compression applied far from the annulus when the individual patient coronary sinus anatomically runs along the far-left atrial wall. By contrast, cerclage imparts circumferential compression that reduces the septal-lateral dimension, incorporates a protection element to prevent extrinsic compression of

entrapped coronary arteries, and exhibit planar discordance that achieves annular reduction even when the coronary sinus is anatomically located along the posterior left atrial wall. Because it is an entirely right-sided procedure and device (i.e. it is not exposed to blood on the left side of the heart), we expect to have a similar safety profile to aforementioned partial annuloplasty devices.

Importantly, cerclage does not preclude other transcatheter mitral valve therapies in the future, including edge-to-edge mitral valve repair (e.g. Mitraclip), transcatheter mitral valve replacement (TMVR), or surgery. This stands in stark contrast with edge-to-edge repair, that is commonly performed outside the US for functional mitral regurgitation.

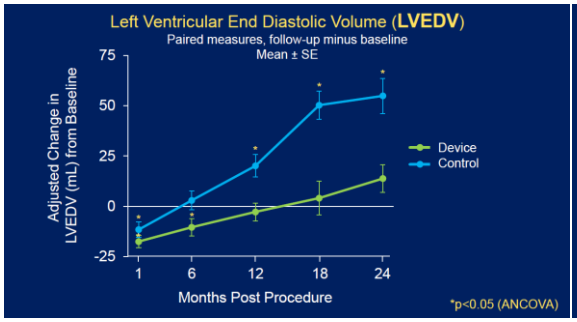
Two relevant randomized clinical trials have been published since this study was first proposed, both evaluating an alternative transcatheter treatment for functional mitral valve regurgitation.

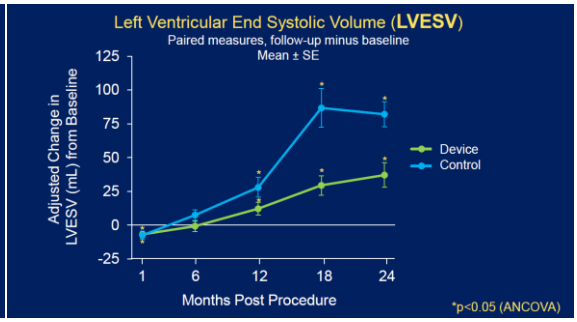
The MITRA-FR was a randomized investigator-initiated comparison of Mitra-Clip leaflet apposition or medical therapy alone [1]. At 12 months, the combined primary endpoint of death or unplanned hospitalization was 48.7% versus 47.4% for intervention versus control. The secondary endpoint of death was 24.3% versus 22.4% in the intervention and control groups respectively. This study did not support the use of *Mitra-Clip* therapy for functional mitral valve regurgitation.

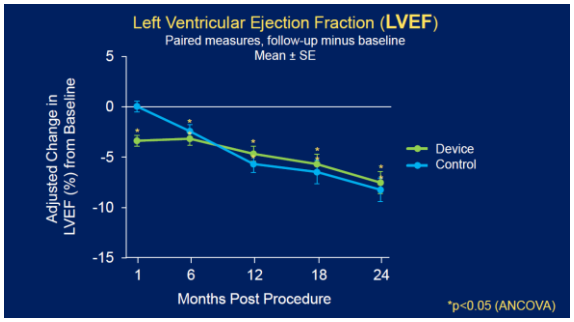
The COAPT trial was a randomized pivotal industry comparison of *Mitra-Clip* leaflet apposition or medical therapy alone [2]. At 24 months, the primary endpoint of heart failure hospitalization was 35.8% for device therapy compared with 67.9% for control (HR 0.53, CI 0.40-0.70). The secondary endpoint of death at 24 months was 29.1% for device therapy compared with 46.1% for control (HR 0.62, CI 0.46-0.82). This study strongly supported the use of *Mitra-Clip* therapy for functional mitral valve regurgitation.

These inconsistent randomized trial results are expected not to lead to a definitive (Class I) guideline recommendation in favor of *Mitra-Clip* therapy for functional mitral valve regurgitation. We therefore consider it ethically and medically acceptable to retain the current selection criteria and continue the investigational plan of open-label early feasibility evaluation of Cerclage in “all-comer” eligible subjects with functional mitral valve regurgitation.

In Amendment A, we specifically seek patients with symptomatic functional mitral valve regurgitation despite treatment with *Mitra-Clip* transcatheter edge-to-edge leaflet repair. Preliminary data from the COAPT randomized comparison of *Mitra-Clip* versus control on background heart failure therapy suggests that both arms show continued left ventricular enlargement and dysfunction.







Federico ASCH, presented at CRT 2019, Washington DC, March 2019.

We hypothesize that mitral cerclage annuloplasty will complement edge-to-edge leaflet repair and retard the progression of ventricular enlargement and dysfunction, analogous to standard surgical practice combining leaflet and annuloplasty mitral repairs.

In Amendments C and E, additional tests were added (see section 5.4).

In Amendment F, we invite candidates with NYHA Class III or greater symptoms and at least mild mitral valve regurgitation. This is based on preliminary findings in the first ten subjects that cerclage caused significant improvement in symptoms and functional status but only modest improvement in mitral valve regurgitation. This applied equally to patients with “atrial” and “ventricular” functional mitral valve regurgitation, which could be alternatively characterized as “heart failure with preserved ejection fraction, HFpEF” and “heart failure with reduced ejection fraction, HFrEF,” respectively.

4.0 TREATMENT OPTIONS

Candidates for Transcatheter Mitral Cerclage Annuloplasty currently have limited treatment options: medical therapy (including cardiac resynchronization therapy) or open surgical mitral valve repair/replacement. Because open heart surgery is an invasive procedure, it is typically reserved for the patients who are highly symptomatic with severe mitral regurgitation and who have coronary artery disease that is likely to benefit from concomitant surgical revascularization. Most patients are therefore treated medically, and many will continue to experience heart failure-related symptoms, often leading to repeat hospitalizations. *MitraClip* is a recently approved option for functional mitral valve regurgitation, with inconsistent results in two recently reported randomized controlled clinical trials (see section 3.0 above).

5.0 STUDY DESIGN

5.1 OVERVIEW OF STUDY DESIGN

This is an early feasibility study (EFS) of the Transmural Systems Transcatheter Mitral Cerclage Annuloplasty device. It is a prospective, open-label, multi-center, investigator-initiated, and independently-adjudicated investigation of the cerclage device in patients with symptomatic functional mitral valve regurgitation due to underlying cardiomyopathy.

5.2 EVALUATION OF STUDY CANDIDATES AND PREPARATION FOR THE CERCLAGE PROCEDURE

Candidates will be identified by the participating structural heart disease programs. Imaging for procedural planning will include clinically-necessary imaging studies [specifically contrast-enhanced cardiac CT, transesophageal echocardiography (TEE), transthoracic echocardiography (TTE), cardiac catheterization and angiography, and if necessary cardiac magnetic resonance imaging (CMR)]. Candidates may authorize transmission of medical records and clinical imaging examinations using a protocol-specific screening form, if required by the enrolling site.

Eligibility will be reviewed and proposed by the local multidisciplinary heart teams. Anatomic eligibility will be confirmed by the echocardiography and CT analysis Core Laboratories. Candidates will then undergo central eligibility review by the Study Eligibility Committee. If deemed eligible, candidates will be offered participation in the study. Eligible subjects will be invited to sign the research consent only afterwards.

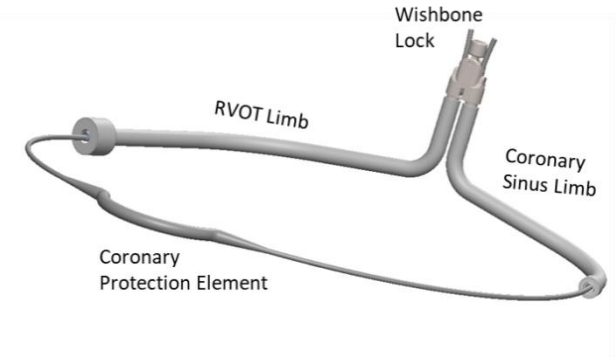
Candidates will be counseled about the importance of study compliance before enrollment. Once enrolled, subjects will undergo protocol baseline assessment. If eligible, subjects will be admitted to the hospital and undergo Transcatheter Mitral Cerclage Annuloplasty under this protocol. They will undergo follow-up testing including regular transthoracic echocardiography and CT scan before hospital discharge, 30 days, and 6 months.

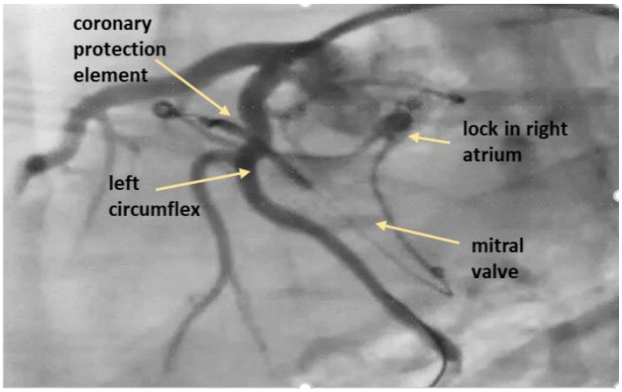
Optionally, subjects may undergo baseline cardiopulmonary exercise testing (CPEX), and/or stress (bicycle- or treadmill-) echocardiography, pending local site availability and subject willingness to participate.

5.3 TRANSCATHETER MITRAL CERCLAGE ANNULOPLASTY PROCEDURE

The Transcatheter Mitral Cerclage Annuloplasty procedure is planned from a time-resolved contrast-enhanced CT of the heart to confirm suitable coronary venous anatomy.

The final cerclage implant comprises two components, the cerclage implant with or without a coronary artery protection element, and the wishbone lock with coronary sinus and RVOT limbs.





If the subject is not undergoing therapeutic anticoagulation for another indication (such as atrial fibrillation), antiplatelet medication is administered on the day of the procedure (aspirin 162-325mg or clopidogrel or equivalent daily at the discretion of the treating physician).
The procedure is performed under general anesthesia or monitored anesthesia care at the discretion of the local heart team. The procedure is performed using fluoroscopy and echocardiography (typically transesophageal) guidance. The procedure is performed from a transjugular venous approach (preferably right side) with a single sheath. Femoral or radial arterial access is also required for selective left coronary angiography. After anticoagulation with heparin or equivalent to achieve activated clotting time (ACT) >250sec, a balloon wedge end-hole catheter is floated from the internal jugular sheath superior vena cava (SVC) to the pulmonary artery. Echocardiography and fluoroscopy are used to ensure the catheter does not undermine tricuspid valve chords or the right ventricle moderator band. A guidewire is used to exchange the balloon wedge end-hole catheter for the target capture catheter, which is then opened in the right ventricular outflow tract (RVOT). This serves as a target and as a snare to capture the septal traversal guidewire.

Using fluoroscopy, a balloon-tip guiding catheter is advanced from the same internal jugular sheath into the coronary sinus, the balloon is inflated and a coronary sinus venogram is acquired. Simultaneous selective left coronary angiography is acquired to confirm the anatomic relationship of the coronary sinus and the left circumflex artery. This serves to confirm the coronary venous anatomy identified on the pre-procedural CT scan. Coronary guidewires and coronary microcatheters are then used to navigate into a suitable coronary vein towards the target capture catheter.

Once the guidewire is confirmed through the open target capture catheter, the snare is closed to capture the guidewire tip. The target capture catheter is then withdrawn from the internal jugular sheath. The coronary sinus guidewire is advanced in tandem with the withdrawal of the target capture catheter. This creates a wire loop from the internal jugular sheath, along the coronary sinus, through the basal septum into the RVOT, through the tricuspid annulus, and back out of the internal jugular sheath.

The cerclage implant is then attached to the back end of the guidewire and pulled through the internal jugular sheath, along the coronary sinus, through the basal septum, through the tricuspid valve, and back out of the internal jugular sheath. The cerclage coronary sinus limb is shortened using a scalpel if necessary. The position of the cerclage implant is adjusted so that the coronary protection element lies directly over any underlying branch of the left coronary artery (typically the left circumflex and/or obtuse marginal branch of the circumflex).

The wishbone lock is then advanced over the two limbs of the cerclage implant and the desired tension is titrated to the degree of mitral regurgitation using echocardiography guidance. Selective coronary angiography is performed to confirm there is no coronary compression. Once the desired tension has

been achieved, the wishbone lock is locked and the two limbs of the cerclage implant are cut with a cutter catheter.

Echocardiography assessment of the mitral annulus and mitral regurgitation is again performed, along with repeat selective coronary angiography. The internal jugular sheath is then removed, and the patient convalesces in the appropriate inpatient recovery unit.

Before discharge, transthoracic echocardiography is performed. Repeat time-resolved cardiac CT is acquired if renal function allows, otherwise it is deferred to the 30-day follow up visit. If renal function does not allow contrast by the 30-day follow-up, non-contrast CT is performed for limited geometric assessment.

Anti-platelet medication is continued for 6 months, or longer at the discretion of the attending physician; anti-platelet medication is not required if the patient receives therapeutic anticoagulation.

Optionally, subjects may undergo follow-up cardiopulmonary exercise testing (CPEX), and/or stress (bicycle- or treadmill-) echocardiography, as outlined in section 5.4.

The procedure is unchanged in the presence of prior *Mitra-Clip*.

5.3.1 Pregnancy contingency

Should a subject become pregnant during the study, CT scans will be omitted but all other study-specific follow-up will be unaffected.

5.4 TIME AND EVENTS SCHEDULE

	Screening ± 6 wks	Baseline ± 6 wks	Day 0	Inpatient	30 d (±14d) FU	6 mo (± 1 mo)	12 mo (± 1 mo) (range) FU	2 yrs (± 1 mo) (range) FU	3 yrs (± 1 mo)	4 yrs (± 1 mo)	5 yrs (± 1 mo)
Research informed consent		X									
Multidisciplinary heart team eligibility determination	X										
Baseline clinical assessment		X									
6 minute walk test		X			X	X	X				
Kansas City Cardiomyopathy Questionnaire (KCCQ)-23		X			X	X	X				
NYHA Classification		X			X	X	X				
Frailty test**s:** Katz ADL, 5MW, Albumin		X									
Blood test for pregnancy (hCG)	X	X									
Blood tests (see below)		X		X	X	X	X				
Vital signs and in-person visit		X			X	X	X				
Cardiac CT contrast-enhanced gated dynamic (Baseline may be up to 6 months old)	Screening or baseline	Screening or baseline		Inpatient *	30-90d*	X	X				
Transesophageal echocardiogram. May be omitted day 0 with SEC concurrence	Screening or baseline	Screening or baseline	X								
Transcatheter Mitral Cerclage Annuloplasty			X								
Transthoracic echocardiogram (TTE). Baseline may be up to 3 months old.	Screening or baseline	Screening or baseline		X	X	X	X				
ECG		X		X	X	X	X				
Adverse event assessment			X	X	X	X	X				

	Screening ± 6 wks	Baseline ± 6 wks	Day 0	Inpatient	30 d (±14d) FU	6 mo (± 1 mo)	12 mo (± 1 mo) (range) FU	2 yrs (± 1 mo) (range) FU	3 yrs (± 1 mo)	4 yrs (± 1 mo)	5 yrs (± 1 mo)
Vital status, assessment of SAE and SADE, & clinical echo or echo report. Phone call and review of records from primary physician are acceptable								X	X	X	X
OPTIONAL: Exercise echocardiogram		X			X	X	X				
OPTIONAL: Cardiopulmonary Exercise Test (CPEX)		X			X	X	X				

* follow-up contrast-CT scans may be postponed or omitted as required by patient renal function in written coordination with the sponsor representative.

Subjects would receive continuing care from their primary physicians with consultant input as requested from the structural heart disease program.

For subjects who die, necropsy evaluation is requested to examine the heart at NIH.

In Amendment C, an additional follow-up CT was added at 30-90 days.

In Amendment F, additional 6MWT, KCCQ, and proBNP tests were added at 6 months.

In Amendment G, assessment of and reporting of SAE and SADE is required for long term follow-up.

5.4.1 Blood tests

All of the blood tests specified here are mandatory for routine medical care before, during, and after transcatheter mitral valve repair procedure. The results are recorded as research values and in surveillance for adverse events. **No other blood tests are reported as adverse events.**

The specific blood tests are enumerated below, and reported as study adverse events if change from baseline > 10% AND out-of-range:

Test	Detail	Inpatient value to record	Timepoints to collect
Blood count: hemoglobin	Marker of anemia and hemodilution.	Lowest	Baseline through 30d
Blood count: hematocrit	Marker of anemia and hemodilution.	Lowest	Baseline through 30d
Blood count: white blood cell count	Nonspecific marker of inflammation and infection.	Highest	All except 6 mo
Blood count: platelet	Nonspecific marker of coagulation and of inflammation.	Lowest	Baseline through 30d
Chemistry: Albumin	Marker of nutritional status and frailty		Baseline only
Chemistry: Creatinine	Marker of renal excretion.	Highest	All
Chemistry: Estimated glomerular filtration rate (eGFR)	Calculated from age, sex, race, and creatinine	Lowest	All
Chemistry: NT-Pro-Brain natriuretic peptide (NT-Pro-BNP)	Marker of volume overload.	Lowest	All
Chemistry: Cardiac troponin	Marker of cardiomyocyte injury, institution-specific subtype (Troponin-I or Troponin-T).	Highest	Baseline through 30 day
Chemistry: Bilirubin, total	Used to classify Childs-Pugh status, collected only if available from clinical evaluation	Highest	Baseline only

5.5 CMS CLINICAL TRIAL POLICY (CTP) ON FINANCIAL COVERAGE OF ROUTINE MEDICAL COSTS OF CARE IN THIS RESEARCH PROTOCOL.

By virtue of NHLBI sponsorship of clinical research protocols, enrolling sites qualify for Centers for Medicare and Medicaid Services (CMS) coverage of associated routine costs of medical care under the CMS Clinical Trial Policy (CTP). This policy is detailed at https://www.cms.gov/Medicare/Coverage/ClinicalTrialPolicies/index.html. According to this policy, CMS is "explicitly authorize[d to provide] payment for routine patient care costs...and costs due to medical complications associated with participation in clinical trials…
"Routine costs of a clinical trial include all items and services that are otherwise generally available to Medicare beneficiaries (i.e., there exists a benefit category, it is not statutorily excluded, and there is not a national non-coverage decision) that are provided in either the experimental or the control arms of a clinical trial except the investigational item…"

Site billing and reimbursement offices are reminded not to use the IDE number, but instead only bill for routine services using the NCT number, which is mandatory. Moreover, site billing and reimbursement offices are reminded that under the CTP pathway, the trial is not listed on any CMS web site.

6.0 ELIGIBILITY ASSESSMENT

Eligibility criteria were revised in Amendment F to allow patients with symptomatic heart failure (HFrEF and HFpEF) accompanied by mitral valve regurgitation. The original criteria are retained below (with text struck-out) to allow readers, regulators, and reviewers the opportunity to understand the selection conditions for all subjects.

6.1 REVISED SELECTION CRITERIA BEGINNING WITH AMENDMENT F

6.1.1 Inclusion Criteria

1. Adults age ≥21 years
2. Symptomatic functional mitral valve regurgitation
   a. Mild or greater mitral valve regurgitation, LVEF ≤ 0.50, and NYHA class III - IV heart failure
   b. Moderate or greater mitral valve regurgitation and NYHA II - IV heart failure, irrespective of LV systolic function
3. On optimal medical therapy for at least one month (see section 6.3)
4. Left ventricular ejection fraction ≥0.20 assessed by echocardiography, CT, or CMR
5. Suitable coronary venous anatomy for Transcatheter Mitral Cerclage Annuloplasty based on pre-procedural cardiac CT or coronary venogram
6. Concordance of the Study Eligibility Committee
7. If present, a MitraClip was implanted at least 30 days previously

6.1.2 Exclusion criteria

1. Subjects unable to consent to participate
2. Subjects unwilling to participate or unwilling to return for study follow-up activities.
3. Prior cardiac implanted electronic devices (CIED) likely to be entrapped by cerclage.
   - Candidates with coronary sinus or left ventricular pacing or defibrillation leads that are not likely to be entrapped by cerclage, evident on baseline CT or angiogram, are eligible to participate.
4. TAVR within 6 weeks

5. Intended concurrent structural heart procedure, such as aortic or tricuspid valve intervention
6. Aortic stenosis more than mild in severity
7. Single-leaflet *MitraClip* detachment, if present
8. Pregnancy or intent to become pregnant prior to completion of all protocol follow-up procedures

6.2 ORIGINAL SELECTION CRITERIA BEFORE AMENDMENT F

~~6.2.1 Inclusion Criteria~~

~~8. Adults age ≥21 years~~
~~9. Severe functional mitral valve regurgitation defined as:~~
~~a. Effective orifice area ≥20mm², AND~~
~~b. Regurgitant volume ≥30mL/beat~~
~~10. On optimal medical therapy for at least one month (see section 0)~~
~~11. NYHA class II, III or IV heart failure symptoms~~
~~12. Left ventricular ejection fraction ≥0.20 assessed by echocardiography, CT, or CMR~~
~~13. Suitable coronary venous anatomy for Transcatheter Mitral Cerclage Annuloplasty based on pre-procedural cardiac CT or coronary venogram~~
~~14. Concordance of the Study Eligibility Committee~~

~~*ADDITIONAL INCLUSION FOR MITRACLIP ARM*~~

~~15. Predominantly functional mitral regurgitation as indication for *MitraClip*~~
~~16. At least 30 days after *MitraClip* implantation, and at least 24 months after *MitraClip* implantation if enrolled in COAPT trial~~

~~6.2.2 Exclusion criteria~~

~~9. Subjects unable to consent to participate~~
~~10. Subjects unwilling to participate or unwilling to return for study follow-up activities.~~
~~11. TAVR within 6 weeks~~
~~12. Prior cardiac implanted electronic devices (CIED) likely to be entrapped by cerclage: Cardiac Resynchronization Therapy (CRT) with coronary sinus lead; Implantable Cardioverter Defibrillator (ICD) with lead likely to be entrapped based on corelab assessment of baseline CT; or, Single- or dual-chamber pacemaker with lead likely to be entrapped based on corelab assessment of baseline CT~~
~~13. Prior Cardiac Resynchronization Therapy (CRT) with biventricular pacemaker/Implantable Cardioverter Defibrillator (ICD) and coronary sinus lead~~
~~14. Intended concurrent structural heart procedure, such as aortic or tricuspid valve intervention~~
~~15. Aortic stenosis more than mild in severity~~
~~16. Pregnancy or intent to become pregnant prior to completion of all protocol follow-up procedures~~

~~*ADDITIONAL EXCLUSION FOR MITRACLIP ARM*~~

~~17. Single-leaflet detachment of *MitraClip*~~

6.3 RATIONALE FOR SELECTION CRITERIA

The protocol originally selected subjects with severe mitral regurgitation defined according to European Society of Cardiology guidelines [3], which define the intended treatment population. Beginning with Amendment F, eligibility was extended to patients with severe symptomatic cardiomyopathy (NYHA Class III or IV) and any (≥mild) functional mitral valve regurgitation based on evidence in the first ten subjects of significant functional and symptomatic benefit out of proportion to reduction in mitral valve regurgitation. At the time of the amendment, no subjects had been enrolled with MitraClip and >24 months had elapse since enrollment completed in the COAPT trial, so enrollment of subjects having MitraClip implants was consolidated into a single treatment arm. “Optimal medical therapy” refers to guideline-directed medical therapy according to contemporary ACC/AHA/HFSA [4] and/or ESC [5] guidelines. This includes pharmacotherapy of atherosclerosis with medications such as antiplatelet medications, lipid-lowering agents, anti-ischemic medications, and revascularization therapy as indicated. This also includes Guideline-Directed therapy for symptomatic left ventricular dysfunction and mitral valve regurgitation as tolerated including beta-adrenergic blockade, angiotensin converting enzyme or angiotensin receptor blocker or angiotensin receptor–neprilysin inhibitor, diuretics, and additional agents as indicated and as tolerated including aldosterone antagonists, hydralazine-nitrate, and cardiac electronic implanted device therapy. “Optimal medical therapy” is confirmed by the Study Eligibility Committee.

The selection criteria allow enrollment of the intended population with little anticipated selection bias. Planned concurrent valve procedures such as TAVR are disallowed. Subjects having pre-existing implanted devices that might be disturbed or damaged by the cerclage procedure or implant tension are disallowed from this early feasibility study (EFS). Conversely, when demonstrated by imaging that CIED follow the “outer curvature” of the coronary sinus allowing an “inner curvature” cerclage implant, such candidates are allowed to participate in the trial beginning with Amendment F.

Children are excluded because this is an early feasibility study. Pregnant women are excluded because of the research radiation.

The inclusive selection criteria and geographic extent of enrolling sites are expected to allow recruitment of a diverse economic, ethnic, and racial mix of patients that reflects the incident disease. Specifically, the results are expected to be generalizable to Medicare and Medicaid beneficiaries because of age and disease-related disability.

The Study Eligibility Committee confirms eligibility before enrollment (see section 13.8).

7.0 STRATEGIES FOR RECRUITMENT

Subjects will be recruited from the Structural Heart Disease clinical programs of the participating hospitals.

The distribution of planned enrolling sites assures accessibility of the trial to ethnically, racially, and economically diverse populations. The study will track sex, age, ethnicity, and racial background of subjects.

Once recruited, subject retention rate is expected to be high because follow-up activities are not onerous and are timed to correspond with routine follow-up medical care, without prohibitively expensive follow-up testing.

8.0 SAMPLE COLLECTION, STORAGE AND TRACKING PLAN

Imaging data (such as from angiography, fluoroscopy, CT, and echocardiography) constitute the only information to be collected. CT examinations performed for clinical evaluation prior to signing informed consent may be used as the baseline scan.

CT and fluoroscopy data will be analyzed at the NHLBI DIR Core Laboratory. These data will be transmitted on electronic media such as a DVD via carrier or using secure file transfer mechanisms abiding Federal Information Security Management Act (FISMA), Health Insurance Portability and Accountability Act of 1996 (HIPAA) and local institutional standards (such as https://dirweb.nhlbi.nih.gov/oc).

Imaging data are transmitted to a central facility (NHLBI) using secure HIPAA compliant methods and are stored in a secure Picture Archive Computer System (PACS), according to local institutional standards. This includes imaging data used for screening eligibility.

Necropsy specimens will be handled according to local institutional medical standards and will be disposed accordingly.

8.1 DATA TRANSFER TO COLLABORATORS

De-identified and de-linked data and images will be posted at the NHLBI Cardiovascular Intervention Structural Heart Image Data Repository (https://ledermanlab.nhlbi.nih.gov/repository/index.htm or equivalent). They are provided for the purpose of medical education and research. Data are de-identified and de-linked, so that patients can not readily be identified, and are therefore not considered human research subjects research data under US 45CFR§46.104(d)(2)(i).

De-identified images will also be transferred to collaborating investigators at academic and industry sites. They are provided for the purpose of medical education and research. For some, data are de-identified and de-linked, so that patients can not readily be identified, and are therefore not considered human research subjects research data under US 45CFR§46.104(d)(2)(i). For others, data are de-identified but linked, in case receiving collaborators require additional information. The table below indicates which recipients will receive de-identified but linkable data and which will only receive de-identified and de-linked data.

These recipients include all site Principal Investigators and:

Recipient	Organization	Location	Linkable
Nasser Rafiee	Transmural Systems	Andover, MA, USA	Linked
June-Hong Kim, PhD, MD	Pusan National University	Busan, Republic of Korea	Linked
Ajit Yoganathan, PhD	Georgia Institute of Technology	Atlanta, Georgia, USA	De-linked
Martijn Chatrou, PhD	3mensio Pie Medical Esaote	Bilthoven, Netherlands	De-linked

9.0 BIOSTATISTICAL AND ANALYTICAL CONSIDERATIONS

9.1 SAMPLE SIZE

This is an early feasibility study of a device not previously used in humans. An arbitrary initial sample size of 30 is proposed in coordination with the FDA Centers for Devices and Radiologic Health, which is increased from 15 in Amendment A

Up to 60 subjects will be consented until 30 subjects undergo attempted Transcatheter Mitral Cerclage Annuloplasty total in this protocol.

We will adhere to the extent possible to consensus guidelines that have been established for the analysis and reporting of transcatheter mitral valve repair investigational procedures (MVARC).[6, 7]

There are no prespecified acceptance criteria for failure rate.

9.2 STUDY ANALYSIS

Analyses will be performed using principles both of (1) intention-to-treat, defined as attempting or initiating Transcatheter Mitral Cerclage Annuloplasty, and (2) as-treated, defined as completing Transcatheter Mitral Cerclage Annuloplasty. We expect these to be the same.

Clinical events are classified by the site Principal Investigator and confirmed by the NIH Principal Investigator. The results of the study will be released within 12 months of study completion.

The study will be analyzed using descriptive statistics, including a case-by-case narrative summary of major adverse events. Representative descriptive statistics include typical demographic features (age, sex, comorbidity), symptoms (NYHA heart failure classification), ventricular geometry and function (volumes, ejection fraction), hemodynamics (chamber pressures), procedure characteristics (procedure time, contrast exposure), *etc*.

We will attempt to stratify subjects by various phenotypes (HFrEF vs HFpEF, MR severity, dimensions) and associate these with measurements (cerclage geometric shortening), and outcomes (symptom status, functional status, change in chamber volumes and regurgitation, adverse events), as allowed by the small sample size.

Afterwards, we will survey for parameters associated with an increased risk of major adverse events.

9.3 PRIMARY ENDPOINT: TECHNICAL SUCCESS

The primary endpoint is **Technical success**. This endpoint is measured at exit from the catheterization laboratory. All of the following must be present:

- Alive
- Successful deployment and correct final positioning of a single intended Transcatheter Mitral Cerclage Annuloplasty. Repositioning and recapture of the device, if needed, is not classified as failure.
- Retrieval of the cerclage delivery system
- Absence of cerclage-related coronary artery compression and absence of additional procedure such as percutaneous coronary intervention (PCI) to relieve coronary artery compression
- No additional unplanned or emergency surgery or re-intervention related to the cerclage or delivery system

The primary endpoint is classified by the NHLBI Principal Investigator and reviewed for possible reclassification by the Clinical Events Adjudication Committee.

9.4 SECONDARY ENDPOINTS

9.4.1 Procedural success

The secondary endpoint is **Procedural success** This endpoint is measured at 30 days. All of the following must be present

- Technical success
- No cerclage device-related Serious Adverse Device Effects, defined as VARC-2 life-threatening bleeding, major vascular or cardiac complications related to the cerclage requiring unplanned reintervention or surgery

Such reinterventions are directly related to the valve. Pacemaker implantation, for example, is consistent with procedural success.

The secondary endpoint is classified by the NHLBI Principal Investigator and reviewed for possible reclassification by the Clinical Events Adjudication Committee.

9.5 EXPLORATORY ENDPOINTS

Exploratory endpoints include:

- MVARC[6] 30-day Device Success
- MVARC[6] 1-year Patient Success
- Change from baseline in degree of mitral regurgitation post-procedure, at 30 days, 6-months, and 12-months
- Change from baseline in left ventricular dimensions/volumes post-procedure, at 30 days, 6-months, and 12-months
- Change in symptoms assessed by New York Heart Association heart failure classification and by Kansas City Cardiomyopathy Questionnaire
- Mortality, all-cause, cardiovascular vs non-cardiovascular, peri- vs non-periprocedural, including Transcatheter Mitral Cerclage Annuloplasty relatedness)
- Neurological events as reported by the site clinicians only
- Procedural[9] Myocardial infarction
- VARC-2[8] vascular complications
- MVARC[6] bleeding complications, which includes pericardial bleeding
- AKI acute kidney injury
- Arrhythmia and conduction disturbances
- Infection related to the cerclage
- Device related technical failure: Device Failure, Pericardial effusion, Conversion to open surgery, Device mal-positioning or migration or detachment, Device fracture, Unintended damage to native mitral valve or tricuspid valve apparatus
- Device thrombosis

- Change in optional exercise endpoints including mitral regurgitation severity, pulmonary artery pressure estimated from tricuspid regurgitation jet velocity, and gas exchange, when available.

Procedural myocardial infarction will rely on the updated Fourth Universal Definition Type II (supply-demand mismatch) within 48 hours of cerclage. This definition most closely applies to the presumed etiology of myocardial infarction theoretically attributable to cerclage. Application of this definition requires rise and fall of cardiac troponin above the 99th upper limit of normal, combined with any of: symptoms of acute myocardial ischemia; new ischemic ECG changes; development of pathologic Q waves, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology [9].

9.6 INDEPENDENT CLINICAL EVENTS ADJUDICATION

An independent Clinical Events Adjudication Committee will review all of the following that occur in the first year:

- Deaths
- Technical success (primary endpoint)
- Procedure success (secondary endpoint)

The CEAC will classify relatedness of the above events to the Transcatheter Mitral Cerclage Annuloplasty procedure and to the cerclage device.

9.7 CORE LABORATORIES

The NHLBI CT and Echocardiography Core Laboratories will analyze all imaging and compare post-procedure imaging with baseline (pre-procedure) imaging. Analysis will include but will not be limited to the following:

- Assessment of baseline eligibility
    - Likelihood of entrapment of Cardiac Implanted Electronic Devices (CIED) by the cerclage system
    - Suitability of coronary venous anatomy for the cerclage procedure
    - Geometry of likely cerclage trajectory

- Assessment of cerclage device post-implantation characteristics
    - Cerclage position
    - Cerclage integrity
    - Cerclage-related compression of underlying coronary arteries
    - Cerclage-related tricuspid valve dysfunction

- Assessment of impact of cerclage on heart function

    - Cardiac chamber size and function
    - Severity of mitral valve regurgitation
    - Impact of cerclage on function of non-target valve function (tricuspid and aortic)

9.8 DATA SAFETY MONITORING

A Data Safety and Monitoring Board (DSMB) appointed by the NHLBI Division of Intramural Research will monitor the safety of subjects in the study as described in the investigational plan, as required for interventional studies at NHLBI Division of Intramural Research. All members of the DSMB are unaffiliated

to the study. The NHLBI DSMB will review the protocol progress report at six-month intervals. The DSMB may recommend early termination of the study for considerations of safety and efficacy, using proposed Stopping Rules (section 9.9) as a guidance. Unanticipated Adverse Device Effects (UADEs) will be submitted to the DSMB following the same timelines as the IRB (See section 9.2.4).

In all cases of death or serious UADE, the sponsor and the NIH Principal Investigator will make a determination whether the event presents an unreasonable risk to the participating subjects. If this determination is affirmative, the clinical trial will be terminated within 5 working days after making that determination and not later than 15 working days after the sponsor first receives notice of the effect. [21 CFR 812.46]. All clinical sites will be notified of this action.

The IRB will review all Unanticipated Adverse Device Effects, and Unanticipated Problems, and may choose to suspend or terminate the protocol based on those findings. We believe this will protect subject safety. The IRB will review Serious Adverse Events and Serious Adverse Device Effects during continuing review.

9.9 STOPPING RULES

The study will be monitored to ensure that the mortality within 30-days after the procedure does not substantially exceed an anticipated rate. We anticipate the rate of 30-day mortality is 10% or less and determine the stopping rule by a Bayesian approach [10]. The stopping boundary is reached if the posterior probability that the 30-day mortality rate exceeds 10% is at least 85%. We take our prior distribution to be a beta distribution so that our prior clinical opinion is worth 20% of the weight we will place on the new data. This gives the prior parameters $a = 0.6, b = 5.4$. Hence when we make decisions about stopping the study, the data from the study will dominate over the prior opinion.

The following table summarizes the threshold numbers for the stop rule boundary, which may lead to a recommendation to stop the study due to the excess 30-day mortality.

Number of subjects	Stop if the number of deaths within 30 days reaches
2-5	2
6-12	3
13-20	4
21-28	5
28-30	6

We investigated the performance of the above stopping rule by a simulation study. In each simulation run, we generated a study with 15 independent Bernoulli trials, each with a true certain 30-day mortality, and compared these outcomes with the above stopping boundary to determine whether the study was stopped. We repeated the simulation 100,000 times and computed the proportion of stopped studies using the above stopping rule. The following table summarizes the performance of this stopping rule:

True 30-day mortality rate	2.5%	5%	10%	15%	20%	25%	30%	35%
Proportion of Stopped Studies (%)	1	4	24	52	76	90	97	99
Average number of subjects (n)	29.8	29.1	25.8	21	16.1	12.2	9.4	7.4
Average number of 30-day mortality (n)	0.7	1.5	2.6	3.2	3.2	3.1	2.8	2.6

These simulation results suggest that our stopping rule has a low probability of stopping a study when the true 30-day mortality rate is 10% or less, and the probability of stopping a study is high when the true 30-

day mortality rate exceeds 10%. There, we believe that our stopping rule for 30-day mortality has satisfactory statistical properties.

9.10 OFF STUDY CRITERIA

- Completion of the 5-year follow-up
- The subject voluntarily withdraws
- The cerclage procedure fails and no implant is left behind, after the first 30 day assessment
- Significant subject non-compliance with follow-up visits, despite repeated site Principal Investigator effort to assure compliance including telephone encouragement and registered letter reminders if necessary.
- Death

Confirmation of survival will be sought from all subjects, even after they voluntarily withdraw, by contacting their physicians, the social security death index, and the subjects themselves.

10.0 ADVERSE EVENT REPORTING

10.1 DEFINITIONS

Adverse events: Any untoward medical occurrence in a human subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

This will include:

- Expected events related to the subject's disease process during active enrollment in the research protocol and do not directly result from use of the investigational device or study.
- Procedural events directly related to the cardiac catheterization procedure and recovery from the procedure and do not directly result from use of the investigational device.

Serious Adverse Event (SAE): A serious adverse event that results in any of the following and NOT directly related to the device. This includes any event that

- Results in death
- Is life-threatening (places the subject at immediate risk of death from the event as it occurs);
- results in in-patient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant incapacity;
- results in a congenital anomaly/birth defect (not relevant to this study); or
- based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Adverse Device Effect (ADE): Any untoward or unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device or any event that is a result of user error.

During this clinical investigation an event should be considered related to the device when it is the result of:

- Transcatheter Mitral Cerclage Annuloplasty procedure
- Transcatheter Mitral Cerclage Annuloplasty device

An event will be considered NOT related to the Transcatheter Mitral Cerclage Annuloplasty procedure when it is the result of a pre-existing medical condition.

Anticipated Adverse Device Effects (AADEs): An AADE is an adverse event with a reasonable possibility that the device or procedure caused or contributed to the event. The following AADEs are considered anticipated based on judgement and clinical experience:

- Death
- Cardiac arrhythmia including ventricular tachycardia, ventricular fibrillation, supraventricular tachycardia, and atrial fibrillation and including cardiac arrest
- Cardiopulmonary resuscitation (CPR) in response to cardiac arrhythmia, cardiac arrest, or cardiogenic shock
- Anaphylactic or toxic reaction to anesthesia, medications, or contrast media, or device materials
- Hypersensitivity or immune reaction to the test article(s) or their components
- Complications of vascular access including bleeding (hemorrhage), fistula, dissection, pseudoaneurysm, retroperitoneal hematoma, pneumothorax, hemothorax, site hematoma or bruising and requiring transcatheter or surgical repair or further medical evaluation or management.
- Conduction system injury including atrio-ventricular conduction block, high-degree atrio-ventricular block, partial and complete bundle branch block, requiring CPR or temporary or permanent pacemaker. At present we believe there is a high chance of needing a pacemaker after the cerclage procedure.
- Coronary artery compression which may cause angina, myocardial ischemia, myocardial infarction, or ventricular arrhythmia, caused either by the cerclage device or by coronary arteriography during or after implantation, and that may require percutaneous or surgical intervention
- Embolization of air, thrombus, or debris to coronary arteries, brain, limbs, or viscera causing myocardial infarction, stroke, transient ischemic attack, etc
- Transcatheter Mitral Cerclage Annuloplasty device failure including failure to traverse, to deliver, to position, or to lock catheters or guidewires
- Malposition, embolization, dislocation, migration, or deployment in an unintended location of the cerclage device or its components, or surgical retrieval
- Myocardial or coronary vein perforation during the implantation procedure causing pericardial effusion or tamponade, including requiring percutaneous or surgical intervention.
- Bleeding (hemorrhage) caused by the cerclage implantation procedure apart from vascular access complications, including blood transfusion
- Bleeding (hemorrhage) caused by vascular access for the cerclage implantation procedure, including causing low blood pressure and requiring vasopressor support or requiring blood transfusion
- Anemia requiring blood transfusion, such as from procedural blood loss
- Coronary vein dissection or thrombosis caused by the cerclage implantation procedure
- Mechanical injury to the myocardium or heart valves that may cause elevation of myocardial biomarkers (Troponin) other than myocardial infarction
- Mechanical injury to, or decline in function of, tricuspid or aortic heart valves or subvalvular apparatus causing valve regurgitation including requiring mechanical intervention
- Chest pain
- Cardiogenic shock or hypotension caused by valvular, subvalvular, or myocardial injury during or after cerclage implantation procedure requiring vasopressor support or mechanical circulatory support or other mechanical or surgical intervention

- Myocardial erosion which may cause myocardial perforation, intracardiac shunt, pericardial effusion or tamponade and which may require surgical or transcatheter intervention
- Renal injury or failure, including contrast-induced nephropathy, requiring temporary or permanent hemodialysis or medical treatment
- Volume overload, congestive heart failure, dyspnea, pulmonary edema, or pleural or pericardial effusion from procedure-related volume perturbations
- Congestive heart failure, cardiomyopathy, cardiogenic shock, respiratory failure, BNP elevation
- Narrowing the mitral valve too much, causing a condition called mitral valve stenosis. This can result in lung congestion causing shortness of breath, similar to symptoms of leaky (regurgitant) mitral valve.
- Respiratory failure requiring oxygen or mechanical support or mechanical ventilation
- Endocarditis or endarteritis or sepsis related to the cerclage device
- Venous thrombosis or thromboembolism including deep vein thrombosis, and pulmonary thromboembolism
- Ecchymoses or gastric bleeding related to anti-platelet medications.
- Other infection related to access site or procedure including urinary or pulmonary or sepsis
- Pain including back pain and access site pain and generalized pain
- Low or high blood pressure values, or low or high heart rate values, whether related to anesthesia or not
- Abnormal blood cell tests including hemoglobin, hematocrit, platelets and white blood cells
- Abnormal blood chemistries including creatinine, troponin, and NT-pro-BNP
- Radiation injury including intractable skin injury
- Emergency cardiovascular surgery

Serious Adverse Device Effect (SADE): An adverse effect that may have been or is attributed to the use of the device and produce an injury or illness that is life-threatening, results in permanent impairment or damage to the body, or requires medical or surgical intervention to prevent permanent harm to the body.

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

Unanticipated Problem (Up): An unanticipated problem is any incident, experience, or outcome that meets ALL of the following criteria:

- Unexpected in terms of nature, severity, or frequency in relation to:

a. the research risks that are described in the IRB-approved research protocol and informed consent document, Investigator's Brochure or other study documents, and

b. the characteristics of the subject population being studied, and

- Related or possibly related to participation in the research, and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or expected.

Unanticipated Problem that is not an Adverse Event: An unanticipated problem that does not fit the definition of an adverse event, but which may, in the opinion of the NIH and site Principal Investigators,

involves risk to the subject, affect others in the research study, or significantly impact the integrity of research data. For example, report occurrences of breaches of confidentiality, or accidental destruction of study records.

Protocol Deviation: A protocol deviation is any change, divergence, or departure from IRB-approved research protocol.

> *Major Deviations* - Deviations from the IRB approved protocol that have, or may have the potential to, negatively impact, the rights, welfare or safety of the subject, or to substantially negatively impact the scientific integrity or validity of the study.
>
> *Minor Deviations* - Deviations that do not have the potential to negatively impact the rights, safety, or welfare of subjects or others, or the scientific integrity or validity of the study.

Non-compliance: Failure of investigator(s) to follow the applicable laws, regulations, or institutional policies governing the protection of human subjects in research, or the requirements or determinations of the IRB, whether intentional or not.

> Serious non-compliance: Non-compliance, whether intentional or not, that results in harm or otherwise materially compromises the rights, welfare and/or safety of the subject. Non-compliance that materially effects the scientific integrity or validity of the research may be considered serious non-compliance, even if it does not result in direct harm to research subjects.
>
> Continuing non-compliance: A pattern of recurring non-compliance that either has resulted, or, if continued, may result in harm to subjects or otherwise materially compromise the rights, welfare and/or safety of subjects, affect the scientific integrity of the study or validity of the results. The pattern may comprise repetition of the same non-compliant action(s), or different noncompliant events. Such non-compliance may be unintentional (e.g. due to lack of understanding, knowledge, or commitment), or intentional (e.g. due to deliberate choice to ignore or compromise the requirements of any applicable regulation, organizational policy, or determination of the IRB).

10.2 ADVERSE EVENT MANAGEMENT:

The following adverse event management guidelines are intended to ensure the safety of each subject while on the study. Adverse events and adverse device effects will be attributed to study procedure and graded by severity according to the following tables:

10.2.1 Grading of adverse events and adverse device effects

Category	Description
Mild	Awareness of symptom. Not expected to have a clinically significant effect on the subject's condition. Not surpassing the expected standard medical intervention.
Moderate	Condition creates a level of discomfort that interferes with the subject's usual activity or affects clinical status. May require medical intervention.
Severe	Incapacitating and significantly affects the subject's clinical status. Likely requires medical intervention and prolonged hospitalization.

10.2.2 Attribution of adverse events to the research protocol

The relatedness of adverse events will be classified as:

Classification	Description
Definite	The event is clearly related to the research protocol.
Probable	The event is likely related to the research protocol. The event has a reasonable temporal relationship to the research device or research procedure and alternative causes, such as underlying disease, concomitant medications, or concomitant treatment-can be excluded.
Possible	The event may be related to the research protocol. The event has a reasonable temporal relationship to the research device or research procedure, and attribution of the event to the device or procedure cannot be excluded. However, alternative causes—such as underlying disease, concomitant medications, or concomitant treatments—are presumably responsible.
Unlikely	It is doubtful the event is related to the research protocol. The event can reasonably be explained by other factures, including underlying disease, concomitant medications, or concomitant treatments.
Unrelated	The event is clearly not related to the research protocol. There either is no temporal association with the research device or procedure, or the event is readily explained by other factures, including underlying disease, concomitant medications, or concomitant treatments.

10.2.3 Adverse Event Reporting

Adverse event recording will start on Day (0) of the Transcatheter Mitral Cerclage Annuloplasty procedure and will continue through the 12 month Follow Up. Assessment, recording and reporting of serious adverse events (SAE) and serious adverse device effects (SADE) will continue at annual visits thereafter.

New events or conditions present at baseline that increase in severity will be recorded and evaluated and reported on the case report form. Once the subject has completed the 30 day follow up, only serious adverse events (SAE), serious adverse device effects (SADE), unanticipated device effects (UADE) and unanticipated problems (UP) will be reported to the Sponsor . It is the responsibility of the site Principal Investigator to report adverse events and adverse device effects to the IRB of record, to the study sponsor, and to other regulatory bodies according to their reporting requirements. Monitoring visits will be conducted by the Sponsor to review source documentation, and accuracy and completion of the adverse event case report forms.

Section 5.4.1 enumerates blood tests that are monitored for adverse events. No other blood test are reported as adverse events.

10.2.4 Adverse event reporting timeframes

The tabular summaries are provided below to aid investigators and staff. Further detail is provided below

Reporting obligations of site Principal Investigator

Submission or event	**Reporting Time Frame**	**Recipient**
Deviations from the investigational plan (emergency)	Immediately, but no later than 3 working days	Sponsor
Unanticipated Adverse Device Effects (UADE)	Immediately, but no later than 10 working days	Sponsor
Serious Anticipated Adverse Device Effect (SADE)	Within 3 working days	Sponsor
Anticipated Adverse Device effect (ADE)	Within 7 working days	Sponsor
Serious Adverse Events (SAE-not directly related to the device)	Within 5 working days	Sponsor
Adverse Events (AE)	Within 7 working days	Sponsor
Death	Immediately but within 3 working days	Sponsor
Serious Unanticipated Problems (UP)	Within 3 working days	Sponsor
Unanticipated Problems, non-serious (UP)	Within 3 working days	Sponsor
Protocol Deviations (PD), serious	Within 3 working days	Sponsor
Protocol Deviations, non-serious (PD)	Within 7 working days	Sponsor
Non-compliance, Serious	Within 3 working days	Sponsor
Non-compliance, Continuing	Within 7 days	Sponsor
Non-compliance, Non-serious	Within 7 days	Sponsor

Reporting obligations of NIH Principal Investigator

Submission or event	**Reporting Time Frame**	**Regulatory Body**
Current Investigator list	Every 6 months	FDA
IDE Progress Report or Continuing Review	Annual	FDA; IRB
Deviations from the investigational plan (emergency)	Within 5 working days	IRB; FDA
Unanticipated Adverse Device Effects (UADE)	As soon as possible but within 10 working days. Within 7 days (CD)	FDA; IRB; CD
Anticipated Adverse Device effect (ADE)	Annual summary	FDA; IRB
Serious Adverse Events (SAE-not directly related to the device)	Annual progress report; Within 14 days (CD)	IRB; FDA CD;
Adverse Events	Annual summary	IRB; CD; FDA
Death	Possibly related to research: within 24 hours of ascertainment otherwise within 7 days (CD) Annual Progress Report	CD; IRB; FDA
Unanticipated Problems (UP) involving subject risk	Within 7 days (CD) otherwise 10 days	IRB; CD
Major Protocol Deviations (PD)	Annual progress report Within 7 days (CD)	FDA; IRB; CD
Minor Protocol Deviations (PD)	Annual progress report; Within 14 days(CD)	FDA; IRB; CD;

Serious or Continuing Non-compliance	Within 10 days Within 7 days (CD)	IRB; CD
Informed consent (use of a device without obtaining informed consent)	Within 5 working days	FDA
Withdrawal of IRB approval	Within 5 working days	FDA; IRB; All PIs
Withdrawal of FDA approval	Within 5 working days	All PIs; IRB
New information that might affect willingness of subjects to enroll or continue participation	Within 7 days	CD
Recall and Device disposition	Within 30 working days	All PIs; IRB; FDA
Sponsor suspend or terminate protocol	If UADE increases risk to subjects, 5 days after determination and ≤ 15 working days after sponsor first notified	All PIs; IRB; FDA
Final Report (enrollment complete & termination)	Within 30 working days (termination) Within 6 months (final report)	FDA;

Abbreviations: CD = NHLBI Clinical Director. FDA = United States Food and Drug Administration; IRB = Institutional Review Board; PI = Principal Investigator

All other adverse events are reported collectively at time of IRB continuing review.

10.2.5 Interim reporting to FDA CDRH for Early Feasibility Study

For each sequential cohort of 5 subjects, we will summarize and transmit the 30-day data to FDA CDRH.

10.3 MONITORING FOR SPECIFIC ADVERSE EVENTS

Because non-clinical tests of complement activation have not been completed on the cerclage delivery system, there is a remote possibility of complement activation-mediated immune reactions such as angioedema and anaphylaxis. We will therefore observe subjects for manifestations of immune-mediated reactions such as angioedema and anaphylaxis after the procedure and before hospital discharge.

11.0 HUMAN SUBJECT PROTECTION

11.1 RATIONALE FOR SUBJECT SELECTION

11.1.1 Study population:

Subjects are selected for being adults who are determined otherwise likely to benefit from Transcatheter Mitral Cerclage. The determination will be made by the local institutional multidisciplinary Heart Team . No patient will be excluded from participation based on gender, race or ethnicity.

11.2 RISKS AND DISCOMFORTS

The enumeration of risks has been harmonized to match the list of anticipated adverse device effects, except for the risks below identified with [SR] to denote subject risk that would not be adverse device effect.

A formal risk analysis is provided in Appendix A: Risk Analysis.

- Death
- Cardiac arrhythmia including ventricular tachycardia, ventricular fibrillation, supraventricular tachycardia, and atrial fibrillation and including cardiac arrest

- Cardiopulmonary resuscitation (CPR) in response to cardiac arrhythmia, cardiac arrest, or cardiogenic shock
- Anaphylactic or toxic reaction to anesthesia, medications, or contrast media, or device materials
- Hypersensitivity or immune reaction to the test article(s) or their components
- Complications of vascular access including bleeding (hemorrhage), fistula, dissection, pseudoaneurysm, retroperitoneal hematoma, pneumothorax, hemothorax, site hematoma or bruising and requiring transcatheter or surgical repair or further medical evaluation or management.
- Conduction system injury including atrio-ventricular conduction block, high-degree atrio-ventricular block, partial and complete bundle branch block, requiring CPR or temporary or permanent pacemaker. At present we believe there is a high chance of needing a pacemaker after the cerclage procedure.
- Coronary artery compression which may cause angina, myocardial ischemia, myocardial infarction, or ventricular arrhythmia, caused either by the cerclage device or by coronary arteriography during or after implantation, and that may require percutaneous or surgical intervention
- Embolization of air, thrombus, or debris to coronary arteries, brain, limbs, or viscera causing myocardial infarction, stroke, transient ischemic attack, etc
- Transcatheter Mitral Cerclage Annuloplasty device failure including failure to traverse, to deliver, to position, or to lock catheters or guidewires
- Malposition, embolization, dislocation, migration, or deployment in an unintended location of the cerclage device or its components, or surgical retrieval
- Myocardial or coronary vein perforation during the implantation procedure causing pericardial effusion or tamponade, including requiring percutaneous or surgical intervention.
- Bleeding (hemorrhage) caused by the cerclage implantation procedure apart from vascular access complications, including blood transfusion
- Bleeding (hemorrhage) caused by vascular access for the cerclage implantation procedure, including causing low blood pressure and requiring vasopressor support or requiring blood transfusion
- Anemia requiring blood transfusion, such as from procedural blood loss
- Coronary vein dissection or thrombosis caused by the cerclage implantation procedure
- Mechanical injury to the myocardium or heart valves that may cause elevation of myocardial biomarkers (Troponin) other than myocardial infarction
- Mechanical injury to, or decline in function of, tricuspid or aortic heart valves or subvalvular apparatus causing valve regurgitation including requiring mechanical intervention
- Chest pain
- Cardiogenic shock or hypotension caused by valvular, subvalvular, or myocardial injury during or after cerclage implantation procedure requiring vasopressor support or mechanical circulatory support or other mechanical or surgical intervention
- Myocardial erosion which may cause myocardial perforation, intracardiac shunt, pericardial effusion or tamponade and which may require surgical or transcatheter intervention
- Renal injury or failure, including contrast-induced nephropathy, requiring temporary or permanent hemodialysis or medical treatment
- Volume overload, congestive heart failure, dyspnea, pulmonary edema, or pleural or pericardial effusion from procedure-related volume perturbations
- Congestive heart failure, cardiomyopathy, cardiogenic shock, respiratory failure, BNP elevation
- Narrowing the mitral valve too much, causing a condition called mitral valve stenosis. This can result in lung congestion causing shortness of breath, similar to symptoms of leaky (regurgitant) mitral valve.

- Respiratory failure requiring oxygen or mechanical support or mechanical ventilation
- Endocarditis or endarteritis or sepsis related to the cerclage device
- Venous thrombosis or thromboembolism including deep vein thrombosis, and pulmonary thromboembolism
- Ecchymoses or gastric bleeding related to anti-platelet medications.
- Other infection related to access site or procedure including urinary or pulmonary or sepsis
- Pain including back pain and access site pain and generalized pain
- Low or high blood pressure values, or low or high heart rate values, whether related to anesthesia or not
- Abnormal blood cell tests including hemoglobin, hematocrit, platelets and white blood cells
- Abnormal blood chemistries including creatinine, troponin, and NT-pro-BNP
- Radiation injury including intractable skin injury
- Emergency cardiovascular surgery

Risks Related to Radiation

In this research protocol, subjects will be exposed to radiation from 4 research CT scans (increase from 3 CT scans in Amendment G). The CT scans are performed for surveillance of transcatheter heart valve dysfunction. It is estimated that the amount of research radiation that a subject will be exposed to during participation in this research protocol will be approximately 3.2 Rem from the three CT scans, and 36mSv[11] from approximately 30-50 minutes of fluoroscopy during performance of Transcatheter Mitral Cerclage Annuloplasty. This is equivalent to 900 chest X-rays.

The dosimetry per full-function cardiac CT scan was reduced in Amendment G from 1.8 Rem per scan to 0.79 Rem per full-function exam based on continued evolution of scanners used. Therefore the estimated total CT-related radiation was reduced from 5.4 to 3.2 Rem. The number of chest X-ray equivalents was left unchanged, in order to be conservative.We believe the total fluoroscopy exposure to be justifiable in this setting, given the seriousness of their cardiovascular disease and limited options. We estimate the benefit to the research subjects for these procedures to outweigh the risks.

11.2.1 Personal Identifiable Information

Clinical data from subjects participating in this trial will retain personally identifiable information. This includes CT scans, echocardiograms, fluoroscopy, and medical records.

Abstracted data will be coded and de-identified for transmission to participating subcontracting investigators, such as core imaging laboratories, clinical events adjudication committee, and statistician.

DICOM data will be stored in a secured NIH research PACS system for analysis, including personally identifiable information.

See also section 13.3 (“subject confidentiality”).

11.3 INFORMED CONSENT PROCESS:

Candidates may authorize transmission of medical records and clinical imaging examinations using a protocol-specific screening form, if required by the enrolling site. After the study has been fully explained, written informed consent will be obtained from the subject prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

Subjects who are UNABLE to provide consent may NOT be enrolled. The use of a legally authorized representative, or telephone consent for any subject enrolling in this study is not acceptable to the Sponsor.

Subjects participating at covered entities will provide written Privacy Rule Authorization (aka "HIPAA Authorization") to use and disclose individually identifiable health information for this protocol. Subjects will be counseled about privacy and confidentiality protections and provisions as part of the informed consent process.

11.3.1 Informed consent for non-English speaking subjects.

Translation of the full consent document will occur per institutional guidelines and standards of practice.

Enrolling sites will follow Advarra processes for short form consent of non-English speaking research participants. This includes use of Advarra-approved short form consent templates posted by Advarra CIRBI system, which require no additional IRB approval. If no Advarra short form consent is pre-approved in the candidate's native language, or if a different short form consent is used, the certified translation from Advarra must be submitted for IRB review. The IRB approved long form English consent is used as the written summary of what the investigator presents orally.

12.0 TEST ARTICLES AND INDICATIONS FOR USE

12.1 DEVICE DESCRIPTION

The Transmural Systems Mitral Cerclage Annuloplasty system is designed to treat heart failure symptoms including with secondary mitral regurgitation. It is fully retrievable during the implant procedure and post deployment.

The Transmural Systems Mitral Cerclage Annuloplasty system consists of four main parts:

1. a guidewire capture target and snare
2. an implant which consists of radiopaque tether with or without a coronary artery protection element
3. straightening catheter
4. wishbone lock
5. tether cutter

12.1.1 Guidewire capture target and snare

Transmural Systems guidewire capture target and snare are used at the beginning of the procedure to capture the guidewire after it has traversed the interventricular septum and consist of an adjustable and retrievable braided Nickel Titanium (NiTi) basket attached to a flexible inner push rod with a guidewire lumen. The basket is housed inside of a 10F delivery catheter and can be deployed and positioned in the RVOT to serve as a target for the septal traversal guidewire. The combination of both push rod and braided structure allows for adjustability and manipulation of the capture basket shape and profile which can better adapt to the variable shapes of the RVOT anatomy.

This is intended to prevent trabecular or sub-valvar entrapment of the traversal guidewire. Once the traversal guidewire advances into the capture basket, the capture basket can be collapsed into the delivery catheter and externalized to the venous access site. Now, the implant can be connected to the guidewire and exchanged.

The primary features of the guidewire capture target and snare are:

a) Radiopaque braided structure is visible and provides a target for traversal guidewire
b) Adjustable braided basket conforms to various RVOT anatomies

c) Helps to prevent implant from interacting with or entrapping tricuspid subvalvular structures

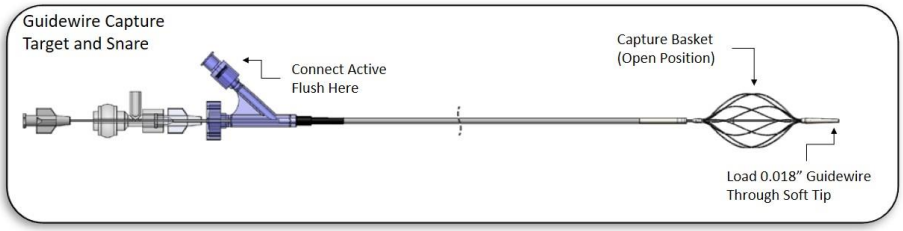


Figure 1. Transmural Systems Guidewire capture target and snare

12.1.2 Implant with or without Coronary artery protection element:

The implant consists of a braided flat radiopaque tether made of Polyester which incorporates a coronary artery protection element, where required. Loaded over the length of the implant tethers on either side of the protection element are removable polymer delivery tubes, which aid in delivery of the implant. On the end of the distal removable delivery tube is a 0.014" guidewire compatible connector, which connects the implant to the proximal end of the traversal guidewire. These features enable the exchange of the traversal guidewire for the implant. When the implant delivered to the site and positioned, the connector and the delivery tubes are removed from the implant. The radiopaque tether is long enough on both ends to exit through the Superior Vena Cava (SVC). The implant can be repositioned or completely removed at any time during the procedure, or after completion of the procedure.

In patients whose cardiac vein does not cross the coronary artery a version of the implant is available which does not utilize a coronary artery protection element. A loading tube is used to facilitate smooth delivery of the implant and protection element through the introducer sheath.

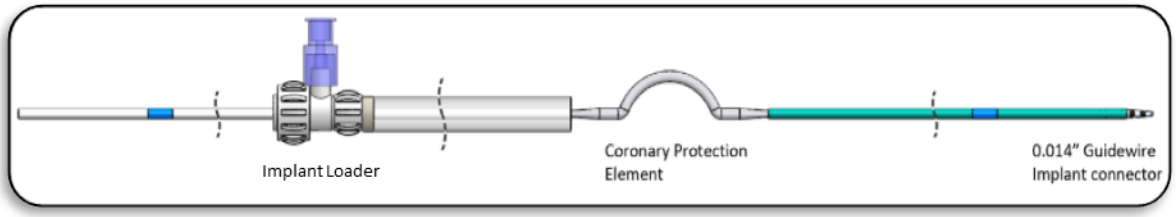


Figure 2. Transmural Systems Implant with coronary artery protection element

The primary features of the implant system are:

a) A connector feature to provide a smooth and secure connection between the traversal guidewire and the implant.
b) Removable delivery tubes to aid in the delivery of the implant.
c) A radiopaque implant tether that is designed to provide visibility and circumferential tension.
d) A coronary artery protection element which prevents the implant from causing extrinsic compression of an entrapped coronary artery. The implant is packaged with a loading tube which the covers the coronary artery protection element to facilitate insertion into the introducer sheath.

12.1.3 Straightening Catheter

The straightening catheter consists of a dual lumen polymer tube with tri-adaptor hemostasis valve. One lumen is loaded with a CS snare (white) and the other lumen is loaded with a RVOT snare (green). The tri-adaptor has a port with a one-way flush valve to allow connection to an active flush. The tip of the catheter has a radiopaque marker band to allow for visibility under fluoroscopy.

Once the delivery tubes of the implants are removed, each end of the implant tether is loaded into the corresponding snare openings and pulled through the lumen of the straightening catheter. The straightening catheter is loaded into the introducer sheath and visualized with fluoroscopy. If twists in the implant tether are visible, the straightening catheter is rotated to untwists the implant. Once all twists are removed the straightening catheter can be carefully removed from the body and the implant tethers are separated to prevented from further twisting. Parallel implant tethers allow of easy introduction of the wishbone lock and delivery system.

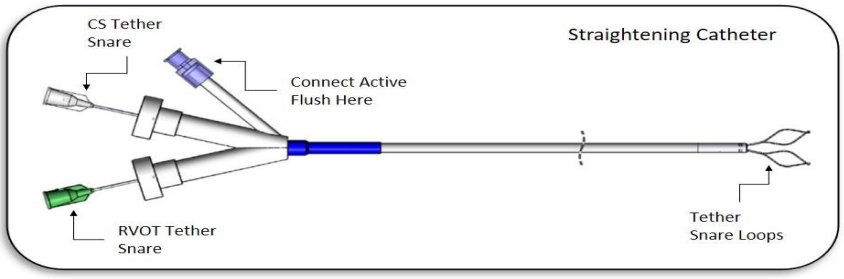


Figure 3. Transmural Systems straightening catheter

The primary features of the Straightening Catheter are:

- The snares are color coded to allow easy identification of CS and RVOT sides of the implant.
- Pre-loaded implant tether snares extending from the tri-adaptor hemostasis valve to distal end of the catheter. These snares are utilized to easily load and the implant through the straightening catheter.
- An active flush port with one-way valve.
- Radiopaque tip for ease of visualization under fluoroscopy.

12.1.4 Wishbone Lock and delivery system

The Transmural Systems lock consists of an adjustable implantable lock with an attached wishbone extension that is packaged in a peel-away delivery sheath, a delivery system with pre-loaded tether snares, and a handle to manage the tension applied to the implant tethers.

Each end of the implant tether is looped through the pre-loaded tether snares and externalized at the proximal end of the delivery system handle. The lock system is advanced over the implant tethers to a position within the right atrium. Once the lock is in place, tension can be applied and released repeatedly to one or both implant tethers as required. This allows the user to fine tune the final position of the implant as well as assess and adjust mitral annular circumferential reduction.

When the desired results are achieved, the lock can then be permanently released from the delivery system by removing the lock retaining suture and withdrawing the delivery system.

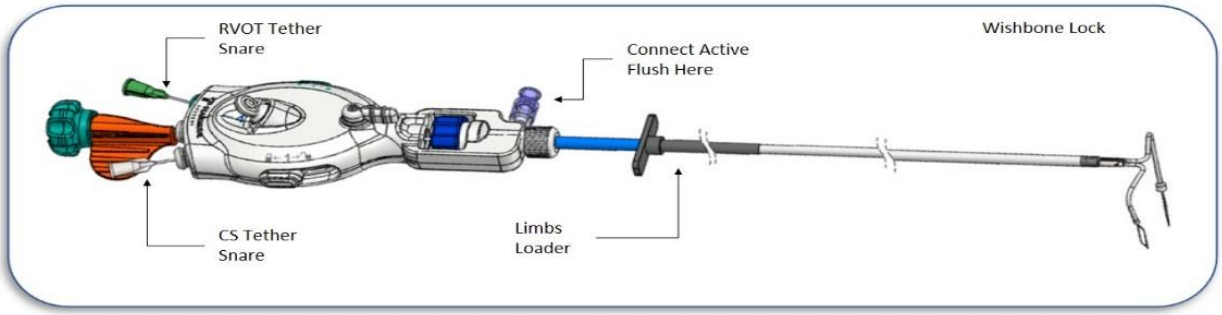


Figure 4. Transmural Systems wishbone lock and delivery system

The primary features of the wishbone lock and delivery system are:

a) An adjustable lock that allows for repositioning and is designed so that no slippage occurs after it is closed.
b) A pre-shaped wishbone is attached to the distal end of the lock. The wishbone is comprised of two Limbs which are shaped to conform to the anatomy. The Coronary Sinus Limb (CS Limb) protects the coronary sinus. The Right Ventricular Outflow Tract Limb (RVOT Limb) straddles and protects the septal tricuspid leaflet and coronary conduction system and incorporates a distal bumper to create an atraumatic interface with the RVOT wall. The wishbone lock is packaged in a peel-away sheath to aid in insertion into the introducer sheath.
c) A delivery system which is includes a lock housing for securing the wishbone lock to the delivery system, and a retention suture to ensure the lock remains secure in the housing until final deployment.
d) Pre-loaded tether snares extending from the delivery system handle through the wishbone lock. These snares are utilized to load the implant through the wishbone lock, delivery system and handle.
e) A handle attached to the delivery system to individually or collectively manage implant tether and the lock retention suture tension.

12.1.5 Tether cutter

After removing the delivery system from the lock, the back ends of the tethers are threaded through the supplied pre-loaded snare and drawn through the cutter housing. The cutter is then advanced along the length of the tethers, until it reaches a position at the proximal end of the lock. A spring-loaded actuation button on the handle is pressed, cutting the tethers. The cut end of the tethers and the cutting device are then withdrawn from the body.

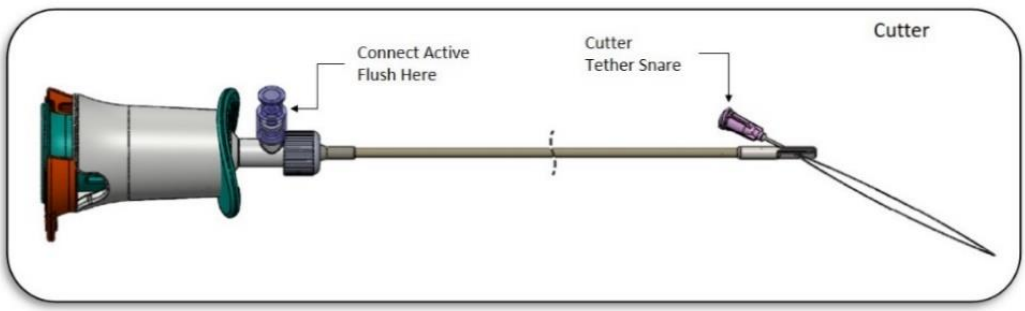


Figure 5. Transmural Systems tether cutter.

The primary features of the Tether cutter are:

a) An inner shaft is attached to a forward facing “V” shaped blade at the distal end, to facilitate cutting the radiopaque tethers.
b) A blade housing with through holes and pre-loaded snare for threading the tethers through the cutter.
c) A spring-loaded actuation handle to minimize the likelihood of inadvertently cutting the implant tether prematurely, and to retract the blade.

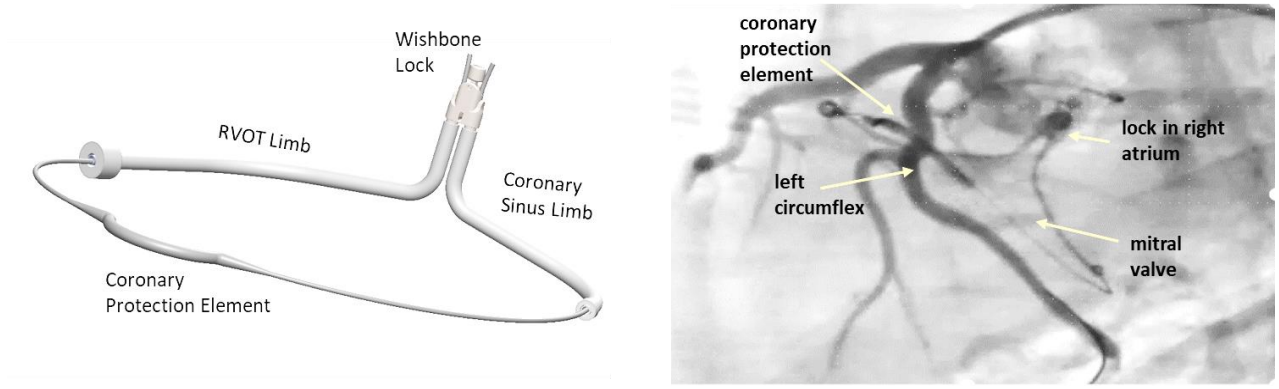


Figure 6. Transmural Systems final deployed Implant

12.2 INDICATIONS FOR USE

The Transmural Mitral Cerclage Annuloplasty is indicated to treat heart failure symptoms including with secondary mitral valve regurgitation by reducing mitral annular dimensions.

13.0 INVESTIGATOR ADMINISTRATIVE REQUIREMENTS

13.1 GOOD CLINICAL PRACTICE

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) E6 (Guideline for Good Clinical Practice), Title 21 of the Code of Federal Regulations, Parts 50 (Protection of Human Subjects), and 56 (Institutional Review Boards), and other appropriate regulatory requirement(s). The Investigators will be thoroughly familiar with the Transcatheter Mitral Cerclage Annuloplasty technique as described in the protocol and the Investigational plan. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Regulatory files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

The site Principal Investigator must sign and date the Investigator’s Agreement provided by the Sponsor to endorse the recorded data.

13.2 IRB SUBMISSIONS

The IRB/IEC and other appropriate institutional regulatory bodies will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the subjects. The study will only be conducted at sites where IRB/IEC and other appropriate institutional regulatory body approval have been obtained. The protocol, informed consent, safety updates, annual progress reports, and any

revisions to these documents will be provided to the IRB/IEC and other appropriate institutional regulatory bodies by the site Principal Investigator.

13.3 SUBJECT CONFIDENTIALITY

Clinical data from subjects participating in this trial will retain personally identifiable information. This includes CT scans, echocardiograms, fluoroscopy, and medical records.

We believe medical safety in this protocol is more important than the privacy benefits of masking patient identity in research documentation. Therefore, many subject-specific research documents will retain patient identifiers. This includes medical images and medical records retained for source documentation, case report forms, and medical communications.

Abstracted data will be coded and de-identified for transmission to participating subcontracting investigators, such as core imaging laboratories, clinical events adjudication committee, and statistician. Privacy will be protected in all public communications such as scientific presentations and manuscripts.

See also section 11.2.1 (“Personal Identifiable Information”).

13.4 DIRECT ACCESS TO SOURCE DATA

Monitoring and auditing procedures developed by the Sponsor will be followed, in order to comply with GCP guidelines.

Regulatory authorities, the IRB/IEC and other appropriate institutional regulatory bodies, and/or the Sponsor may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the site Principal Investigator, who must provide support at all times for these activities. **Monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority (ies) are provided direct access to the local electronic health record.**

The subject’s confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

13.5 CASE REPORT FORM COMPLETION

CRFs will be completed for each study subject **no more than 7 days** after procedures, visits, or events. It is the site Principal Investigator’s responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject’s CRF. Source documentation supporting the CRF data should indicate the subject’s participation in the study and should document the dates and details of study procedures, AEs, and subject status. Source documents will be provided to the Sponsor electronically according to provided Source Document Transmittal List within 7 days of subject discharge or out-patient visit.

An explanation should be given for all missing data. Accompanying source documents should be assembled and scanned and may retain subject identifiers.

The Principal Investigator must sign and date the Investigator’s Statement at the end of the CRF to endorse the recorded data.

13.6 RECORD RETENTION

The site Principal Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years following marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product

or according to applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

The Sponsor has full rights over any invention, discovery, or innovation, patentable or not, derived from performing the study.

13.7 PUBLICATION AND PRESENTATION OF STUDY FINDINGS AND USE OF INFORMATION

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. A Publications Committee comprised of the NIH Principal Investigator and Investigators participating in the study, as appropriate, will be formed to oversee the publication and presentation of the study results, which will reflect the experience of all investigational sites. No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement between NIH Principal Investigator and the non-NIH Investigator and/or the Investigator's institution.

Upon request, the primary study publication will be provided to research subjects.

13.8 STUDY ELIGIBILITY COMMITTEE

Clinical data for all research candidates are confirmed by the Study Eligibility Committee before enrollment. The Committee confirms the candidate has been adequately treated with optimal medical therapy, and that the candidate meets the study selection criteria.

The Study Eligibility Committee consists of the NIH Principal Investigator and associate investigators, the site Principal Investigators, and a NHLBI core lab representative. A quorum of the committee requires a site Principal Investigator where the candidate is not to be enrolled, as well as at least two NIH investigators. In addition, at least one member at each Eligibility meeting must be free of actual or perceived financial conflict of interest. The considerations and determination of the Study Eligibility Committee will be recorded

14.0 SPONSOR REGULATORY REQUIREMENTS

14.1 ROLE AND GENERAL DUTIES OF SPONSOR REPRESENTATIVE

Dr. Robert Lederman is the NIH Principal Investigator and sponsor representative on behalf of NHLBI and the NHLBI Office of Clinical Director. Dr. Lederman has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the appropriate regulatory bodies.

The NIH Principal Investigator’s general duties consist of submitting the appropriate regulatory applications, selecting investigators, obtaining their signed agreement, providing them with the information necessary to conduct the study, ensuring proper clinical site monitoring, and ensuring study subject informed consent is obtained.

14.2 SAFETY MONITORING

14.2.1 Principal Investigator (PI):

Accrual and safety data will be monitored by the NIH PI. The protocol will be continuously evaluated for any unusual or unpredicted complications with the aim of detecting and preventing unacceptable increase in morbidity and mortality over and above that anticipated from the procedure.

14.2.1 Institutional Ethics Committee (IEC) Submissions:

Sites will rely on a single IRB of record.

14.2.2 IRB of Record:

Accrual and safety data will be monitored and reviewed annually by the IRB of Record. Prior to implementation of this study, the protocol, and subject research consents will be reviewed and approved according to Protection of Human Subjects Research Title 45 CFR Part 46 of the Code of Federal Regulations (45 CFR 46). The IRB must approve all amendments to the protocol or informed consent, and conduct continuing annual review so long as the protocol is open to accrual or follow up of subjects.

14.2.3 DSMB:

The NHLBI Data Safety and Monitoring Board (DSMB) will review the protocol at six and twelve month intervals. A progress report will be forwarded to the DSMB at these times. The DSMB may recommend early termination of the study for considerations of safety and efficacy.

14.2.4 Independent Data Monitor:

As per ICH-GCP 5.18 and FDA 21 CFR 312.50 clinical protocols are required to be adequately monitored by the study sponsor.

The objectives of a monitoring visit will be:

1) to verify the existence of signed informed consent form and documentation of the informed consent process for each monitored subject;
2) to verify the prompt and accurate recording of all monitored data points, and prompt reporting of all SAEs;
3) to compare abstracted information with individual subjects' records and source documents (subject's charts, laboratory analyses and test results, physicians' progress notes, nurses' notes, and any other relevant original subject information); and
4) to help ensure investigators are in compliance with the protocol.

The monitors also will inspect the clinical site regulatory files to ensure that regulatory requirements (Office for Human Research Protections, OHRP), FDA and applicable guidelines (ICH-GCP) are being followed. During the monitoring visits, the site Principal Investigator (and/or designee) and other study personnel will be available to discuss the study progress and monitoring visit. The site Principal Investigator (and/or designee) will make study documents (e.g., consent forms and pertinent hospital or clinical records readily available for inspection by the IRB, the FDA, the site monitors, and the NHLBI staff for confirmation of the study findings.

On-site monitoring visits will be conducted after the first 3 subjects are treated and return for 30-day follow up. Remote monitoring visits will conducted wherever possible using remote access to electronic medical records, transmitted source documents, associated emails, and monitoring reports. Electronic data queries from the Sponsor to the study site must be resolved within 7 days of site notification.

In this study, we plan 100% source-data verification.

14.3 SITE SELECTION AND TRAINING

The NIH Principal Investigator or his designee will ensure appropriate training in the technique of Transcatheter Mitral Cerclage Annuloplasty prior to enrollment at any enrolling site.

14.3.1 Site selection:

Site selection will be based on

- Physician expression of interest and need to apply this treatment approach to patients at the site.

- Physician prior experience with transcatheter mitral valve therapies (e.g. Mitraclip edge-to-edge repair, transcatheter mitral valve replacement).
- Site prior participation in IDE protocols, especially sponsored by NHLBI DIR, evaluating a treatment of structural heart disease
- Site ability to obtain CT examinations that are satisfactory for consideration of Transcatheter Mitral Cerclage Annuloplasty.
- Record of research support team conduct in the performance of structural heart disease research protocols
- Site investigators willing and able to comply with the requirements of this protocol.

14.3.2 Site training:

Site training will consist of

- NIH Principal Investigator and NIH PI-designee didactic training about the technique, preclinical, and clinical experience to date.
- Proctored conduct of Transcatheter Mitral Cerclage Annuloplasty procedures in patients at the local site, at the sole discretion of the NIH Principal Investigator.
- Completion of training, and suitability for independent Transcatheter Mitral Cerclage Annuloplasty enrollment, will be certified by the NIH Principal Investigator.

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APPENDIX A: RISK ANALYSIS

This is a patient-centered risk analysis[12] in accordance with 21 CFR 812.25(c). It considers probable and not possible risk. This risk analysis applies to candidates for Transcatheter Mitral Cerclage Annuloplasty on optimal medical therapy and with few or no further therapeutic options.

Failure	Impact	Severity	Likelihood	Score	Available evidence to consider risk	Mitigation
Coronary artery compression	Myocardial ischemia, infarction	4	2	8	Preclinical and early clinical experience in Korea	Up to two-thirds of patients are expected to have a coronary artery run underneath the cerclage system. The cerclage system integrates a dedicated coronary protection device to prevent compression of underlying coronary artery. Coronary compression is assessed carefully during application of cerclage tension using intra-procedural selective coronary angiography.
Tricuspid valve leaflet or sub-valvular entrapment	Tricuspid regurgitation	3	3	9	Preclinical and early clinical experience in Korea	Echo assessment of tricuspid valve during procedure
Tricuspid valve leaflet or sub-valvular laceration	Tricuspid regurgitation	4	2	8	Early preclinical experience. Introduction of target-capture system through other-than-major tricuspid orifice could lead to subvalvular tricuspid chordal laceration that could cause or exacerbate tricuspid regurgitation.	Careful advancement of the balloon wedge end-hole catheter across the tricuspid major orifice before exchange for the target-capture catheter.
Atrioventricular node compression and/or injury	Heart block	3	2	6	Preclinical experience	Intra-procedural rhythm monitoring, ECGs obtained post-procedure and at follow up visits If observed during procedure, tension can be reduced, or whole device can be removed If it persists, it may require permanent pacemaker implantation

Myocardial erosion	Cardiac perforation, loss of therapeutic effect	3	1	1	Preclinical experience	Preclinical evaluation strategy to assure freedom from erosion Clinical feasibility evaluation using serial CT to assure freedom from erosion Device designed to redistribute erosive force along "thicker" prosthesis
Imperfect or missing basal septal perforator coronary vein	Aborted procedure, no permanent harm expected	2	2	4	Preclinical and early clinical experience in Korea	Target/capture system and crossing systems designed to operate from any anatomic position even if there is no suitable septal perforator vein. Has been demonstrated in pigs.
Epicardial coronary artery injury from vein-to-RV crossing	Myocardial ischemia or infarction.	5	1	5	Preclinical and early clinical experience in Korea	Use coronary arteriography during cerclage to assure vein crossing point does not threaten epicardial coronary artery (LAD)
Interference with coronary sinus leads used for cardiac resynchronization therapy	Cerclage compression leads to lead erosion and failure.	4	2	8	Theoretical	Exclude candidates from initial EFS in whom CIED leads are threatened based on core lab evaluation of CT.
Coronary sinus position is far from mitral annular plane	Reduction/loss of therapeutic effect	3	2	6	Theoretical	Abort procedure, remove implant, no permanent harm expected, or intermediate-phase failure to improve mitral valve regurgitation after otherwise successful procedure.
Procedural coronary sinus injury, dissection, perforation	Pericardial effusion, or tamponade	3	2	6	Theoretical, prior experience with coronary sinus pacing leads	Coronary sinus injury, disruption, dissection, or perforation is common in CRT lead implantation procedures and is usually benign. Pericardial effusion is uncommon and drainage, although infrequently required, is definitive.
Occluded superior vena cava, jugular vein, subclavian vein	Unable to deliver device	1	1	1	Theoretical	Abort procedure, no permanent harm expected

Excessive cerclage tension causing mitral valve stenosis	Hemodynamic compromise, heart failure symptoms, myocardial ischemia or infarction	4	1	4	Preclinical experience	Careful titration of system tension using intraprocedural echocardiography Reverse lock, reduce tension, if necessary abort procedure and remove implant, no permanent harm expected
Mitral regurgitation reduced after initial application of tension, but reappears later with exercise	Loss of therapeutic effect	2	3	6	Prior clinical experience with both surgical and transcatheter mitral valve repair techniques	Serial observation for at least 12 months after cerclage.
Failure of cerclage tension lock mechanism	Loss of therapeutic effect	3	2		Theoretical	Lock has been designed to tighten with every heartbeat, permanent implant has been bench tested to withstand much more tension than will be required in clinical practice