Protocol Title:

NHLBI DIR LAMPOON Study: Intentional laceration of the anterior mitral leaflet to prevent left ventricular outflow tract obstruction during transcatheter mitral valve implantation

Version History

2016-11-07	IDE Submission	
2016-11-14	NHLBI Branch Review	
2016-12-02	FDA IDE Submission	
2016-12-09	NHLBI Scientific Review	
2016-12-27	NHLBI IRB	Response to Stipulations for NHLBI Scientific Review
2017-03-31	Amendment A	Stopping rules, removed consent waiver for retrospective review
2017-04-26	Response	Stipulations for Amendment A
2017-08-17	Amendment B	Additional adverse device effect definitions. Additional sites
2017-10-13	Amendment C	Updated selection criteria. Additional sites, new AADE
2018-01-17	Amendment D	Update sites; consent amendment DSMB
2018-09-05	Amendment E	Add Core Lab; Section 9.1 Data Transfer to Collaborators; Reclassify additional secondary endpoints as exploratory
2019-10-17	Amendment F	Administrative amendment. Study staff changes only. No changes to protocol or consent.
2019-11-21	CR approval	2019 Continuing Review
2020-04-21	Amendment G	Update to adverse event reporting requirements as per NIH Policy 801.
2020-08-24	Amendment H	Administrative amendment. NIH study staff change only. No changes to protocol or consent.

Investigational Device Exemption

G160239 issued 2016-12-08

Sponsor-Investigator:

Robert J. Lederman, MD, Senior Investigator, NHLBI Division of Intramural Research

Key Roles

Role	Individual	Affiliation	FWA If applicable
Principal Investigator (NIH)	Robert J. Lederman, MD	NHLBI DIR	00005897
National Co-Principal Investigators	Adam B. Greenbaum, MD Vasilis C. Babaliaros, MD	Emory University Hospital Emory University Hospital	
Study Manager	Annette M. Stine, RN	NHLBI DIR	
Associate Investigators (NIH)	Jaffar M. Khan, BM BCh	NHLBI DIR	
Echocardiography core lab	Dee Dee Wang, MD	Henry Ford Hospital	
CT core lab 1	Dee Dee Wang, MD	Henry Ford Hospital	
CT core lab 2	Marcus Y. Chen, MD	NHLBI DIR	
Monitoring service		NHLBI Contractors	
Independent Clinical Events Adjudication Committee		Medstar Research Institute Inc.	
Data Safety Monitoring Board	Jamieson M. Bourque, MD, MHS	NHLBI University of Virginia	

IDE Study Sponsor	Robert J. Lederman, MD, on behalf of NHLBI	NHLBI DIR	
Data Coordinating Center	Robert J. Lederman, MD	NHLBI DIR	00005897
Study Statistician	Xin Tian, PhD	NHLBI Office of Biostatistics Research	
Site 1 PI	Marvin Eng, MD	Henry Ford Hospital, Detroit, MI	00005846
Site 2 PI	Vasilis C. Babaliaros, MD	Emory University Hospital, Atlanta, GA	00005792
Site 3 PI	Nilesh J. Goswami, MD	St. John's Hospital (enrollment), Springfield, IL; Prairie Education & Research Cooperative	00003647
Site 4 PI	Mark Reisman, MD James McCabe, MD Danny Dvir, MD	University of Washington Division of Cardiology Seattle, WA 98195	00006878 WIRB IRB
Site 5 PI	Toby Rogers, MD	Medstar Washington Hospital Center, Cardiovascular Research Program Washington, D.C. 20010	00000504
Site 6 PI	Jason Foerst, MD	Carilion Medical Center Roanoke, VA 24014	WIRB IRB
Site 7 PI	Shawn Yazdani, MD	Inova Fairfax Hospital Fairfax, VA	00000573

Study Site:	**Site Principal Investigator:**
National Heart, Lung and Blood Institute, NIH **FWA #00005897** **(Data Coordinating Center)***	Robert J. Lederman, MD, Senior Investigator National Heart Lung and Blood Institute, National Institutes of Health Building 10, Room 2c713, MSC 1538 Bethesda, MD 20892-1538 Voice: 301-402-6769 Email: lederman@nih.gov Statistician: Xin Tian, PhD NHLBI Office of Biostatistics Research * NHLBI associate investigators Jaffar M. Khan, BM BCh

Henry Ford Hospital FWA#: 00005846	Marvin Eng, MD Henry Ford Hospital, Cardiac Cath Lab K-2 2799 West Grand Blvd, Detroit, MI. 48202 Phone: (313) 916-2008 Email: meng1@hfhs.org Robert J. Lederman, MD (will participate in interventional procedures)
Emory University FWA #: 00005792	Vasilis C. Babaliaros, MD Emory University 1364 Clifton Rd. NE, Suite F606 Atlanta, GA 30322 Phone: 678-557-4514 Fax: 404-712-0884 Email: vbabali@emory.edu
St. John's Hospital (patient enrollment) **Prairie Education & Research Cooperative** FWA#: 00003647	Nilesh J. Goswami, MD Prairie Education & Research Cooperative 317 North 5th St. Springfield, IL 62701 Phone: 217-788-0706 Fax: 217-522-1206 Email: Ngoswami@prairieheart.com
University of Washington **WIRB IRB** FWA#: 00006878	Mark Reisman, MD, FACC Clinical Professor of Medicine Section Head, Interventional Cardiology Director, Cardiovascular Emerging Therapies Auth Endowed Chair in Cardiovascular Innovation University of Washington Medical Center 1959 NE Pacific St. Box 356171 Seattle, WA 98195 Email: reismanm@uw.edu Office: 206-598-5599 Fax: 206-598-8269 Cell: 425-372-8906 James McCabe, MD Division of Cardiology 1959 NE Pacific St. Box 356422 Seattle, VA 98195 Phone: 206-598-6646 Fax: 206-616-4847 Email: jmmccabe@u.washington.edu Danny Dvir, MD Division of Cardiology 1959 NE Pacific St. Box 356422 Seattle, WA 98195 Phone: 206-543-5898 Fax: 206-616-4847 Email: ddvir@cardiology.washington.edu

Medstar Washington Hospital Center FWA#: 00000504	Toby Rogers, MD Medstar Washington Hospital Center 110 Irving Street, NW Suite 4B-1 Washington, DC 20010 Phone: 202-877-5975 Fax: 202-877-2715 E-mail: toby.rogers@gmail.com
Carilion Medical Center FWA#: 00000392	Jason Foerst, MD Director of the Adult Structural Heart and Valve Fellowship Program Carilion Clinic Roanoke, VA 2001 Crystal Spring Ave, Suite 203 Roanoke, VA 24014 Phone: 540-632-9220 Fax: 540-266-6198 Email: jrfoerst@carilionclinic.org
Inova Fairfax Hospital FWA#: 00000573	Shahram Yazdani, MD Inova Medical Group - Cardiology 8100 Ashton Ave Manassas, VA 20109 phone: (703) 335-8750 E-mail: Shahram.Yazdani@inova.org

* No subject enrollment

Estimated Duration of Study:

[6 years]

Estimated Completion Date of Study:

December 31, 2023

Subjects of study and sites:

Subjects	Sex	Age range	Sites
60 screened 30 enrolled	Men & Women	≥21 years	Up to 8

DISCLOSURES

The non-NIH investigators have the following conflicts of interest:

ABG serves as a proctor for Edwards Lifesciences and St Jude Medical.

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

MEG serves as a proctor for, and receives research support from, Edwards Lifesciences.

ABBREVIATIONS

CT	Computed tomography
LAMPOON	Intentional laceration of the anterior mitral valve leaflet to prevent LVOT obstruction during TMVR
LVOT(O)	Left ventricular outflow tract (obstruction)
MVARC	Mitral valve academic research consortium (criteria)
MR	Mitral valve regurgitation
MS	Mitral valve stenosis
TAVR	Transcatheter aortic valve implantation
TEE	Transesophageal echocardiography
THV	Transcatheter heart valve
TMVR	Transcatheter mitral valve implantation

PRÉCIS

Transcatheter mitral valve replacement (TMVR) is an option to treat mitral valve failure when no surgical options exist. In as many as half of patients, TMVR can cause life-threatening blockage of the left ventricle by displacing the existing mitral valve leaflet. For these patient's the only options appear to avoid TMVR or in some to cause a focused heart attack and to wait 6 weeks. The investigators have developed and tested a technique to tear the existing mitral valve leaflet and enable TMVR in patients who have no other options. The procedure is called intentional laceration of the anterior mitral leaflet to prevent left ventricular outflow tract obstruction (LAMPOON). Although there are no dedicated TMVR devices commercially available, there has been short-term success with implanted transcatheter aortic valve devices in the mitral position for TMVR.

The purpose of this study is to perform LAMPOON and TMVR in patients who have no good options to treat their mitral valve failure, using heart valve devices designed to implant in the aortic valve position.

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1.0 Protocol Summary

Title:	NHLBI LAMPOON Study: Intentional laceration of the anterior mitral leaflet to prevent left ventricular outflow tract obstruction during transcatheter mitral valve implantation
Précis:	Transcatheter mitral valve replacement (TMVR) can cause life-threatening complications such as left ventricular outflow tract obstruction and transcatheter heart valve dysfunction, in cases of extreme septal displacement of the anterior mitral valve leaflet (AML). LAMPOON is a new catheter technique to split the AML and prevent iatrogenic left ventricular outflow tract obstruction immediately before TMVR. It mimics surgical chord-sparing AML resection. It has been used successfully in a small number of patients
Hypothesis:	LAMPOON enables transcatheter mitral valve implantation (TMVR) without life-threatening left ventricular outflow obstruction or transcatheter heart valve dysfunction
Objectives:	Technical success (defined below) of LAMPOON-TMVR Safety (Freedom from MACE to hospital discharge and 30days) of LAMPOON-TMVR
Safety Endpoints	Survival to discharge Survival to 30days Freedom from MACE (according to MVARC)
Feasibility Endpoints	Procedure technical success (TMVR with successful LAMPOON, without requiring bailout cardiac surgery or bailout septal reduction) Stratified analysis based on predicted LVOT obstruction or predicted THV dysfunction (“hanging leaflet”)
Population:	Patients with native mitral valve failure (regurgitation or stenosis) after surgical mitral annuloplasty or from native mitral annular calcification, requiring transcatheter mitral valve replacement because of prohibitive risk of mitral valve surgery

Inclusion Criteria	Undergoing TMVR for valve-in-ring, valve-in-band, or valve-in MAC: Adults age ≥ 21 years Severe symptomatic native mitral valve failure after mitral annuloplasty repair or related to mitral annular calcification. Transcatheter mitral valve replacement (TMVR) is felt indicated by the multidisciplinary institutional heart team, including at least one cardiovascular surgeon who has examined the patient High or prohibitive risk of LVOT obstruction (predicted neo-LVOT less than 200 $mm^{2)}$) or transcatheter heart valve dysfunction from long/redundant anterior mitral valve leaflet, as determined by the multidisciplinary institutional heart team. Anatomic eligibility for LAMPOON based on core lab assessment of the baseline CT and echocardiogram. Concordance of the study selection team
Exclusion Criteria	Subjects unable to consent to participate, unless the subject has a legally authorized representative Subjects unwilling to participate or unwilling to return for study follow-up activities. Predicted neo-LVOT created by the Sapien 3 skirt, after LAMPOON, less than 150 mm^2 TAVR within 6 weeks Intended concurrent structural heart procedure, such as aortic or tricuspid valve implantation Pregnancy or intent to become pregnant prior to completion of all protocol follow-up procedures
Phase:	Phase IIa

Study Procedure	NHLBI Data Coordinating Center NHLBI + Local Institutional Review Boards Sites are trained by national PIs and NHLBI investigators Subjects are identified by site investigators CT and echo are analyzed by core laboratories Subject eligibility is confirmed by local multidisciplinary heart team including cardiac surgery, and is confirmed by study eligibility committee Subjects are enrolled prospectively Baseline and follow-up echocardiography are analyzed at Henry Ford Hospital core laboratory, and baseline and follow-up CT are analyzed at the NHLBI core laboratory; hemodynamics, fluoroscopy are analyzed at NHLBI Primary analysis based on 30-day outcomes; Secondary analysis includes 12-month outcomes
Sample Size	30 subjects at up to 8 sites
Risk-benefit determination	These subjects have no therapeutic alternatives and have the potential to benefit from this procedure
Number of Sites enrolling participants:	8
Study Duration:	Six years
Participant Duration:	Five years

2.0 OBJECTIVE

The objective of this protocol is further to characterize the feasibility and safety of intentional laceration of the anterior mitral leaflet to prevent left ventricular outflow tract obstruction (LAMPOON), in patients who require transcatheter mitral valve replacement (TMVR) for native mitral valve failure, but who are at risk of left ventricular outflow tract (LVOT) obstruction.

In this protocol, we use a transcatheter heart valve (THV), marketed for implantation in the aortic or pulmonic positions, off-label. The THV device is the Sapien 3 marketed by Edwards Lifesciences.

It is important to discriminate the principal research objective, which is evaluation of the LAMPOON technique, from the off-label use of the significant risk medical device, the Edwards Sapien 3 THV, which is used in the clinical TMVR procedure.

3.0 BACKGROUND

The anterior mitral valve leaflet (AML) is a mobile structure that physically separates inflow and outflow zones of the left ventricle [1]. Preserving the anterior mitral leaflet during surgical mitral valve replacement can cause LVOT obstruction, either when the prosthesis struts protrude into the LVOT or when a long redundant anterior leaflet prolapses into the LVOT [2, 3]. In a similar manner, implantation of a transcatheter heart valve (THV) inside the native or repaired mitral valve enforces an "open position" of the anterior mitral valve leaflet that may encroach on the left ventricular outflow tract [4-7]. This septal displacement of the AML is exaggerated when the aortic and mitral annular planes are acutely angulated rather than parallel, when the interventricular septum bulges towards the LVOT, when the AML is elongated, and when the implant extends or flares into the left ventricle. In this setting TMVR may cause life-threatening LVOT obstruction [Figure]. Moreover, after TMVR an excessively long AML may prolapse anteriorly into a narrowed LVOT as in hypertrophic cardiomyopathy, or it can prolapse posteriorly and interfere with bioprosthetic heart valve opening or closing by mechanical or Bernoulli effects after surgical [3] or transcatheter mitral replacement [8]. Longer AMLs are more susceptible to these effects[9]. Although few data are available to guide decision-making, half of TMVR candidates having an intact AML in an ongoing clinical investigation [Mayra Guerrero personal communication, NCT02370511], are excluded because of the perceived risk of life-threatening LVOT obstruction.

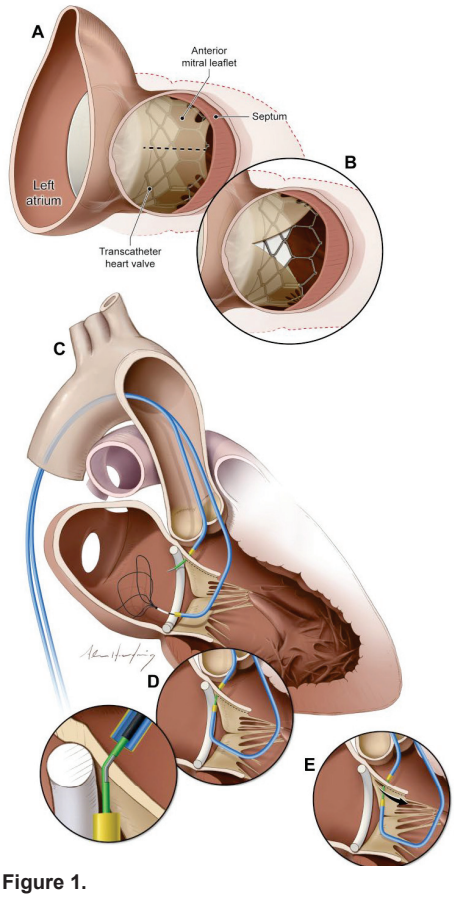


Figure 1.

One approach to prevent or treat TMVR-related LVOT obstruction is pre-emptive transcoronary alcohol septal ablation [10, 11], which sacrifices myocardium, risks conduction system injury and pacemaker-dependence in patients with cardiomyopathy, which is unsuitable in patients with thin interventricular septa, and which delays TMVR by 4-6 weeks to allow remodeling in highly symptomatic patients. Another option is surgical anterior mitral leaflet resection combined with TMVR during thoracotomy and cardiopulmonary bypass [12-14], with attendant risk and comorbidity.

4.0 CLINICAL AND SCIENTIFIC JUSTIFICATION

As an alternative, we have developed a simple transcatheter adjunct to TMVR, and described its preclinical use [15]. This technique resembles Tirone David's surgical anterior resection with chordal sparing [16] which has become widely adopted as a method of surgical mitral valve replacement. We create a longitudinal split of the middle scallop (A2) of the AML, immediately before TMVR. As a result, chordal attachments displace the split AML away from the LVOT after the cylindrical THV is implanted, and blood flows unobstructed across the THV stent struts [Figure 1].

We recently reported the initial human experience with this intentional Laceration of the Anterior Mitral leaflet to Prevent left ventricular Outflow tract Obstruction (LAMPOON) procedure [17]. Five patients with prohibitive risk of LVOT obstruction or transcatheter heart valve (THV) dysfunction from TMVR successfully underwent LAMPOON, with longitudinal splitting of the A2 scallop of the AML, prior to valve implantation. Multiplane CT modelling predicted hemodynamic collapse assuming an intact AML. However, critical LVOT gradients were not seen following LAMPOON and TMVR. Doppler blood flow was seen across THV struts that encroached the LVOT, because the AML was split. Transcatheter heart valve function was unimpeded. We concluded that this novel catheter technique, which resembles surgical chord-sparing AML resection, may enable TMVR in patients with prohibitive risk of LVOT obstruction or THV dysfunction.

Recently there have been reports of late transcatheter heart valve thrombotic dysfunction[18]. This warrants further investigation using follow-up imaging.

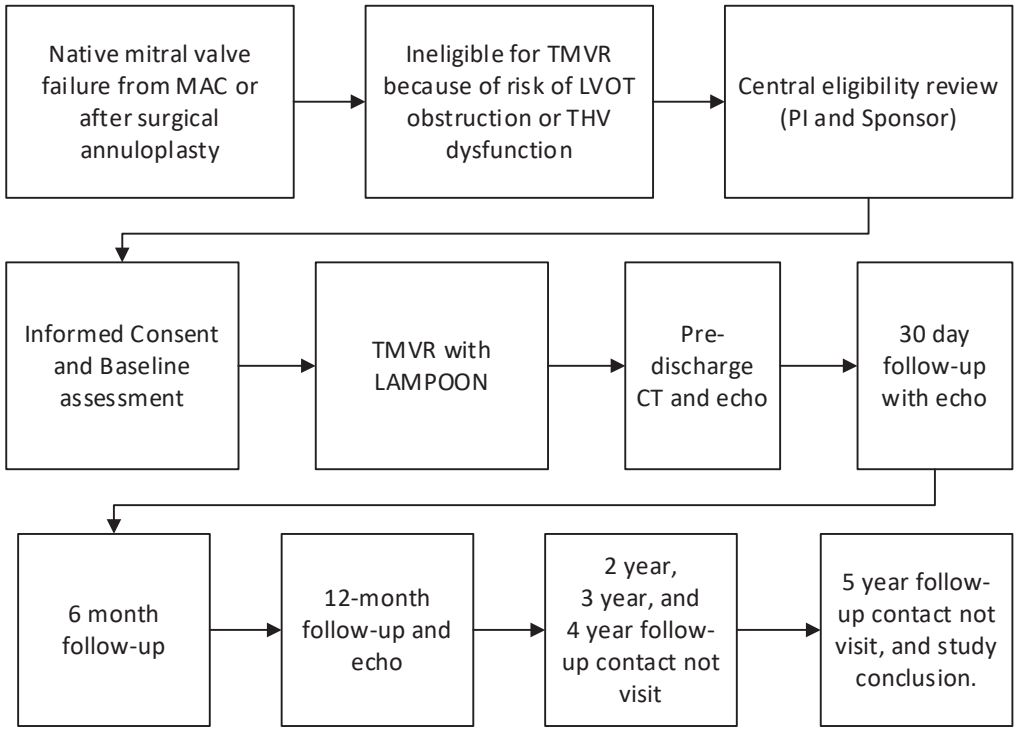
Since preparation of the clinical manuscript, there have been four patients who underwent clinical non-research TMVR with LAMPOON at Emory and Henry Ford Hospital, respectively. Three of four were technically successful, and two of four were clinically successful. One patient underwent concurrent transcarotid TAVR and LAMPOON TMVR, and unfortunately suffered dislocation of the TMVR device, causing fatal mitral regurgitation and heart failure, before it could be flared on the ventricular aspect by post-dilatation after delivery. This classifies as technically unsuccessful because the TMVR device was not correctly positioned. One patient with extreme comorbidity underwent technically successful LAMPOON TMVR but suffered a cardiac arrest overnight afterwards. This additional clinical experience teaches that LAMPOON TMVR should not be combined with other intended valve procedures such as TAVR during the same procedure, and that technically successful LAMPOON TMVR may nevertheless prove fatal in patients with extreme comorbidity.

5.0 TREATMENT OPTIONS

Candidates for TMVR with LAMPOON have no good alternative treatment options. They are not eligible for definitive treatment using surgical mitral valve repair or replacement. They are not eligible for TMVR using off-label THV devices because of the risk of LVOT obstruction. They are not deemed suitable for an alternative investigational preemptive treatment through transcoronary alcohol septal ablation/infarction/debulking because of anatomic limitations and/or the attendant hazard and myocardial injury and requisite 4-6 weeks delay in highly symptomatic patients.

6.0 STUDY DESIGN

6.1 Schematic of Study Design



6.2 Overview of Study Design

This is a prospective, open-label, single-arm, multi-center, investigator-initiated, independently-adjudicated trial of LAMPOON immediately before transcatheter antegrade transseptal TMVR in subjects otherwise ineligible for TMVR.

Candidates will be identified by the participating structural heart disease programs. In evaluation of mitral valve disease, candidates will undergo clinical evaluation including transesophageal imaging and contrast-enhanced gated cardiac CT. Eligibility will be reviewed and proposed by the local multidisciplinary heart teams. Candidates will then undergo central eligibility review by the sponsor and designated investigators. If deemed eligible, candidates will be offered participation in the study.

Once enrolled, subjects will undergo baseline assessment, which includes quality of life questionnaires, walking tests, frailty assessments, and blood tests.

Subjects will be admitted to the hospital and undergo TMVR with LAMPOON. They will undergo endpoint assessment before discharge, after 30 days, 6 months, and then 12 months.

6.3 LAMPOON TMVR Procedure

The TMVR procedure is planned from a contrast-enhanced CT of the heart to select a suitable transcatheter heart valve size, predict suitability of the mitral annular landing zone, and predict post-TMVR LVOT obstruction related to TMVR encroachment and long or redundant anterior mitral valve leaflets. The LAMPOON procedure uses the same clinical CT exam to choose a crossing point for the anterior mitral valve leaflet and to select appropriate fluoroscopic projection angles and radiographic landmarks.

The procedure is performed under general anesthesia or under moderate sedation at the discretion of the institutional heart team. The LAMPOON procedure has three steps: (1) leaflet traversal with a guidewire, followed by (2) leaflet laceration, immediately followed by (3) TMVR. These are all guided by fluoroscopy combined with TEE or intracardiac echocardiography.

First catheter access is obtained typically via three transfemoral arterial (two for LAMPOON and one for LV hemodynamics and angiography) and two transfemoral venous introducers sheaths (one for TMVR and another for temporary transvenous pacing). After anticoagulation with heparin or equivalent to achieve an activated clotting time > 300s, transvenous atrial transseptal puncture is performed under echocardiographic guidance. Atrial septostomy is performed, and a percutaneous transapical rail is established at operator discretion as needed.

Hemodynamic and echocardiography measurements are recorded at baseline including gradients across the mitral and aortic valves and LVOT, and severity of valvular regurgitation.

Two retrograde catheters are positioned, using a guidewire rail with the antegrade transseptal catheter as needed, in the LVOT and LA respectively. Catheter and echocardiographic maneuvers are performed at operator discretion to assure traversal of the major orifice of the mitral valve. Typically, these maneuvers include advancement of a large-volume inflated balloon tip catheter from the LA to the LVOT under angiographic and echocardiographic guidance to assure no entrapment. Next a snare catheter is positioned in the mitral inflow via the LA catheter. An insulated transcatheter electrosurgery catheter system (typically a rigid 0.014" guidewire inside a polymer jacket wire convertor) is positioned against the anterior mitral leaflet target at the A2 scallop, using fluoroscopic and echocardiographic guidance. Nonionic conductive flush (dextrose 5%) can be administered as needed via the guiding catheters to reduce guidewire char and thromboembolism.

Traversal is accomplished by transcatheter electrosurgery by connecting the back end of the 0.014" guidewire to an electrosurgery pencil during short bursts of "pure, cutting" radiofrequency energy at approximately 50W. The guidewire is repositioned as needed until it crosses the mitral leaflet and is snare-retrieved.

Next the polymer jacket wire convertor is withdrawn, and the traversal wire is modified at the bedside by the operator by (1) denuding a non-circumferential segment ~2mm in length, 90^{o} arc and (2) kinking the denuded segment to enforce its position at the inner curvature of the intended guidewire lacerating surface. Next the polymer jacket radiopaque marker tip is locked adjacent to the kinked denuded shaft segment. Next the ensnared guidewire is externalized to position the lacerating surface across the base of the leaflet.

Next, at operator discretion, the transcatheter heart valve may be positioned in the left atrium or across the mitral valve before or after the laceration step. If before, the operator assures no entrapment of the TMVR system with the laceration system of catheters.

Laceration is performed by positioning the laceration surface along the intended leaflet base and applying tension on both free ends of the guidewire, while simultaneously apply electrosurgery energy in short bursts, until the laceration is complete and the guidewire is free.

Hemodynamics are recorded quickly after laceration before TMVR. Then TMVR is performed using established techniques[14] typically during rapid ventricular pacing. The THV device is used outside the manufacturer instructions for use, in that it is implanted in the mitral position. The device size and inflation volumes are selected and applied at the discretion of the operator. A balloon flaring maneuver is encouraged to reduce the likelihood of THV embolization into the left atrium.

Completion hemodynamics and echocardiography are recorded. Adjunctive transcatheter procedures, including to close paravalvular leaks and to close iatrogenic atrial septal defects, are performed at operator discretion and details are recorded. Finally, percutaneous femoral artery and vein vascular hemostasis is obtained and the subject convalesces in the appropriate inpatient recovery unit.

Before discharge, follow-up transthoracic echocardiography is recorded. A single contrast-enhanced CT of the heart is obtained before discharge if renal function allows, otherwise it is deferred as long as 30-days. Blood tests are recorded for research only as obtained for medical care.

After discharge, subjects are recommended to undergo at least 3 months of warfarin anticoagulation with a target INR of 2-3, along with aspirin 81mg indefinitely. These recommendations are superseded by indications for long-term anticoagulation (such as atrial fibrillation), or P2Y12 inhibitors.

6.4 Time and Events Schedule

	Screening	Baseline	Day 0	Inpatient	30 d (±14d) FU	6 mo (± 30 Days)	12 mo (± 4 wk)	2 yrs (± 1 mo) (range)	3 yrs (± 1 mo)	4 yrs (± 1 mo)	5 yrs (± 1 mo)
Baseline informed consent:		X									
Multidisciplinary heart team eligibility determination		X									
Baseline clinical assessment		X									
6 minute walk test		X			X		X				
Kansas City Cardiomyopathy Questionnaire (KCCQ)		X			X		X				
NYHA Classification		X			X	X	X				
Frailty test**s:** Katz ADL, 5MW, Albumin		X									
Blood tests: CBC, Platelet, Haptoglobin, Liver panel, Chemistry Panel, Albumin, LDH, BNP/Pro-BNP (as clarified below)		X		X	X	X	X				
Vital signs and in-person visit		X			X	X	X				
Cardiac CT contrast-enhanced gated dynamic	Screening or baseline	Screening or baseline		Inpatient or 30D	Inpatient or 30D						
Transesophageal echocardiogram	Screening or baseline	Screening or baseline	X								
TMVR with LAMPOON			X								
Surface echocardiogram	Screening or baseline	Screening or baseline		X	X	X	X				
ECG		X		X	X	X	X				
Adverse event assessment				X	X	X	X				
Vital status and clinical echo or report								X	X	X	X

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.

6.4.1 Applicability to CMS Coverage Evaluation Determination

Requirements for a Coverage Evaluation Determination (CED) by Centers for Medicare and Medicaid Services (CMS) are reviewed here. (1) The principal purpose of the study is to test whether LAMPOON TMVR meaningfully improves health outcomes of affected beneficiaries. (2) Scientific evidence supports the study rationale. (3) The study does not unjustifiably duplicate existing knowledge. (4) The study design is methodologically appropriate and sufficiently powered to answer the research question. Even though the sample size is not statistically driven, the experience is expected to set the standard for TMVR using commercially available valves. (5) The study sponsor is capable of completing the study. (6) The study complies with applicable Federal Law and obtains meaningful informed consent regarding risks and the data disposition. (7) The study is conducted ethically. (8) There is a written study protocol that adheres to CMS standards. (9) The study does not test exclusively toxicity nor natural history, although the studied condition is lethal. (10) The study will be registered in clinicaltrials.gov. (11) The study indicates results will be released within 12 months of completing enrollment, irrespective of outcome. (12) The study protocol explicitly discusses beneficiary subpopulations affected by TMVR LAMPOON, especially medically underrepresented groups, with a recruitment and retention plan.

6.5 Visit Schedule

All activities except TMVR/LAMPOON, Consent, KCCQ, and Adverse event assessment are performed for standard clinical care.

Timing	Event
Screening (any time)	Medical, Surgical and Interventional Assessment, determination and documentation that the subject has no other options for MVR
Screening (any time)	Cardiac CT contrast enhanced, gated dynamic
Screening (any time)	Transesophageal echocardiogram
Screening (any time)	Multidisciplinary heart team eligibility determination and documentation
Baseline (within 30 days of procedure)	Research Informed Consent to include documented Inclusion and Exclusion criteria
Baseline (within 30 days of procedure)	Clinical Assessment to include: • Vital signs • Baseline symptoms • Medication Assessment • NYHA Classification • Other co-morbidities that could preclude the subject living the required 6 months post procedure • ECG • Surface echocardiogram-transthoracic

Baseline (within 30 days of procedure)	Clinical Blood tests: • CBC • Platelets • Haptoglobin • Liver Function panel • Chemistry panel • Troponin • Albumin • LDH • BNP/Pro-BNP • Pregnancy test if applicable
Baseline (within 30 days of procedure)	6-minute walk
Baseline (within 30 days of procedure)	Kansas City Cardiomyopathy Questionnaire (KCCQ)
Baseline (within 30 days of procedure)	Frailty Tests: Katz ADL, 5-meter walk, Albumin
Day 0	TMVR with Lampoon procedure
Within 48 hours of Lampoon TMVR	Blood work to include: • Troponin
Pre-discharge	Clinical Evaluation to include: • Cardiac CT scan contrast enhance, gated dynamic- if not clinically suitable then re-schedule for 30 Day follow up visit • Surface echocardiogram • ECG • Medication Assessment • Adverse Event Assessment

30-day (±14 days)	Clinic/office visit to update subject's vital status to include: • Vital signs • ECG • Medication Assessment • NYHA Classification • Surface Echocardiogram • Cardiac CT scan contrast enhance, gated dynamic- if not conducted pre-discharge for clinical reasons • 6-minute walk • Kansas City Cardiomyopathy Questionnaire • Blood work to include: CBC with platelets Haptoglobin Chemistry Panel PT INR BNP/Pro-BNP • Adverse Event Assessment
6-month (±30 days)	Clinic/office visit to update subject's vital status to include: • Vital signs • NYHA Classification • ECG • Medication Assessment • Surface Echocardiogram • Blood work to include: CBC with platelets Haptoglobin PT INR BNP/Pro-BNP Chemistry Panel • Adverse Event Assessment

12 month (±30 days)	Clinic/office visit to update subject's vital status to include: • Vital signs • ECG • Medication Assessment • NYHA Classification • Surface Echocardiogram • 6-minute walk • Kansas City Cardiomyopathy Questionnaire • Blood work to include: CBC with platelets Haptoglobin Chemistry Panel PT INR BNP/Pro-BNP • Adverse Event Assessment
Annually years 2-5 (± 30 days)	• Telephone call or local physician contact to assess vital status • Collect results or images of clinical echocardiogram

7.0 ELIGIBILITY ASSESSMENT

7.1 Inclusion Criteria

- Adults age ≥ 21 years
- Severe symptomatic native mitral valve failure after mitral annuloplasty repair or related to mitral annular calcification.
- Unacceptably high or prohibitive risk for surgical mitral valve replacement and indicated for transcatheter mitral valve replacement (TMVR) as determined by the multidisciplinary institutional heart team, including at least one cardiovascular surgeon who has examined the patient
- High or prohibitive risk of LVOT obstruction (predicted neo-LVOT less than 200 $mm^{2)}$ or transcatheter heart valve dysfunction from long/redundant anterior mitral valve leaflet, as determined by the multidisciplinary institutional heart team.
- Anatomic eligibility for LAMPOON based on core lab assessment of the baseline CT and echocardiogram.
- Concordance of the study selection team

7.2 Exclusion criteria

- Subjects unable to consent to participate, unless the subject has a legally authorized representative
- Subjects unwilling to participate or unwilling to return for study follow-up activities.
- Predicted neo-LVOT created by the Sapien 3 skirt, after LAMPOON, less than 150 mm^2

- TAVR within 6 weeks
- Intended concurrent structural heart procedure, such as aortic or tricuspid valve implantation
- Pregnancy or intent to become pregnant prior to completion of all protocol follow-up procedures

7.3 Rationale for selection criteria

The selection criteria allow enrollment of the intended population with little anticipated selection bias. Instead of functional or geometric selection criteria, the study will enroll all subjects deemed otherwise suitable for TMVR yet at risk of the problem to be addressed by LAMPOON, the investigational procedure. Planned concurrent valve procedures such as TAVR are disallowed based on a recent fatal adverse event described in section 4.0.

In Amendment C, an additional exclusion criterion was added. This considers whether the fabric-covered "skirt" of the Sapien 3 transcatheter heart valve might obstruct the left ventricular outflow tract despite successful LAMPOON. Candidates who might continue to have an obstructive "skirt neo-LVOT" are excluded. This amendment also formalizes a threshold neo-LVOT for selection.

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.

8.0 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.

One site investigator, Dr Mayra Guerrero, is the Principal Investigator of the MITRAL study (NCT02370511) of TMVR which specifically excludes subjects suitable for this study. She estimates as many as half of her study candidates fail screening because of predicted LVOT obstruction [Mayra Guerrero, MD, Personal Communication, October [2016]. Dr Guerrero will recommend referring physicians refer to sites participating in this study.

During the early clinical development of the LAMPOON procedure, 9 clinical patients were treated in approximately 5 months at two centers, which suggest the recruitment objectives will be met.

9.0 SAMPLE COLLECTION, STORAGE AND TRACKING PLAN

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

CT and Echocardiography data will be analyzed at the Henry Ford Hospital Core Laboratory as well as to the NHLBI for concurrent analysis. These data will be transmitted on electronic media such as a DVD via carrier or using secure file transfer mechanisms abiding HIPAA and local institutional standards (such as SFTP or https://secureemail.nih.gov).

Imaging data are stored according to local institutional standards.

Copies of imaging studies are transmitted to a central facility (NHLBI) using secure HIPAA compliant methods and are stored in a secure Picture Archive Computer System (PACS), known as NHLBIPACS.

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

9.1 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. They 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§46.102(f).

De-identified and de-linked images will also be transferred to collaborating investigators at academic and industry sites. They are provided for the purpose of medical education and research. They 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§46.102(f).

These recipients include all enrolling site investigators and:

Ajit Yogonathan, PhD	Georgia Institute of Technology	Atlanta, Georgia, USA
Martijn Chatrou, PhD	3mensio Pie Medical Esaote	Bilthoven, Netherlands
Nasser Rafiee	Transmural Systems	Andover, MA, USA
Bill Havel, PhD	Cook Medical	West Lafayette, IN, USA
Kanishka Ratnayaka, MD	UCSD Rady Childrens Hospital	San Diego, CA

9.2 Core Laboratories

Core laboratories are employed for centralized and systematic analysis of key imaging data, including echocardiography and CT.

Amendment E adds a core laboratory #2 for analysis of CT. Measurements from core laboratory #1 are superseded by core lab #2.

10.0 BIOSTATISTICAL AND ANALYTICAL CONSIDERATIONS

10.1 Sample Size

The sample size is not statistically derived. This is a safety and feasibility study that enables patient access to off-label use of a medical device, when these patients have no other good medical options to treat

symptomatic mitral valve failure. An arbitrary initial sample size of 30 is proposed, and will be increased if needed, until a commercial solution is found for medical care.

Up to 60 subjects will be consented until 30 subjects undergo attempted LAMPOON TMVR 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.[19, 20]

10.2 Study Analysis

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

Analyses will be stratified according to the setting for TMVR, whether valve-in-ring, valve-in-band, or valve-in-MAC.

The study will be analyzed using descriptive statistics, including a case-by-case narrative summary of major adverse events. Afterwards, we will survey for parameters associated with an increased risk of major adverse events.

Primary and secondary endpoints will also be analyzed separately among patients with- and without- mitral annular calcification as the primary indication for TMVR.

10.2.1 Primary endpoint

The primary endpoint is **Technical success ACCEPTABLE** (measured at exit from the catheterization laboratory)[19]. All of the following must be present:

- Successful LAMPOON traversal and laceration; and
- Peak LVOT gradient < 50 mm Hg; and
- Absence of procedural mortality; and
- Successful access, delivery, and retrieval of the LAMPOON device system; and
- Successful deployment and correct positioning of the first intended device; and
- Freedom from emergency surgery or reintervention related to the device or access procedure.

The first two factors are modifications of the MVARC (mitral valve academic research consortium) consensus endpoint[19], specific for LAMPOON procedure.

10.2.2 Co-Primary endpoint

Based on feedback from the FDA, the co-primary endpoint is **Technical Success OPTIMAL** (measured at exit from the catheterization laboratory). This differs from "Technical Success ACCEPTABLE" only in the magnitude of the peak LVOT gradient.

All of the following must be present:

- Successful LAMPOON traversal and laceration; and
- Peak LVOT gradient < 30 mm Hg; and
- Absence of procedural mortality; and
- Successful access, delivery, and retrieval of the LAMPOON device system; and

- Successful deployment and correct positioning of the first intended device; and
- Freedom from emergency surgery or reintervention related to the device or access procedure.

10.2.3 Exploratory Endpoints

- LVOT obstruction measured as a pressure gradient on catheterization and echocardiography
- Incidence of LVOT obstruction > 20 mm Hg before discharge and at 30 days, including as an alternative LVOT gradient threshold to the primary endpoint
- Predicted neo-LVOT area based on THV frame had LAMPOON not been performed
- MVARC 30-day Device Success
- MVARC 30-day Procedure Success
- MVARC 1-year Patient Success
- Mortality, all-cause, cardiovascular vs non-cardiovascular, peri- vs non-periprocedural, LAMPOON and TMVR relatedness)
- Neurological events as reported by the site clinicians only
- Pre-discharge stroke, alone, and in combination with the primary endpoint
- Myocardial infarction
- Access and vascular complications
- MVARC bleeding complications
- AKIN acute kidney injury
- Arrhythmia and conduction disturbances
- Freedom from infection related to the TMVR at each time point
- Freedom from hemolytic anemia related to TMVR/LAMPOON
- Device related technical failure: Device Failure, Paravalvular Leak, Pericardial effusion, Conversion to open surgery, Device mal-positioning or migration or detachment, Device fracture, Unintended damage to native mitral valve apparatus
- Aortic valve regurgitation change
- Device thrombosis
- Outcomes of subjects greater than 65 years (i.e. eligible for Medicare based on age), to determine generalizability to the Medicare population[1]

10.2.4 Rationale for primary endpoint

The main clinical objective of LAMPOON is to allow TMVR without causing death from acute severe LVOT obstruction, which often is greater than 100 mm Hg. This is in contrast to MVR or TMVR in patients who are not believed to be at risk of life threatening LVOT obstruction.

[1] Guidance for the Public, Industry, and CMS Staff Coverage with Evidence Development Document Issued on November 20, 2014, https://www.cms.gov/medicare-coverage-database/details/medicare-coverage-document-details.aspx?MCDId=27

There are few data to guide clinical estimations of acceptable thresholds for iatrogenic LVOT obstruction. As for other elements of this protocol, we sought and found guidance in hypertrophic cardiomyopathy, which is a better-characterized but related phenotype of non-valvular LVOT obstruction.

Based on these data we estimate that residual iatrogenic LVOT obstruction less than 50mm is tolerable, because by consensus[21, 22] it appears not sufficiently severe to warrant surgical intervention in HCM. Moreover, a systematic review by Maron [23] distinguished obstructive from non-obstructive HCM at a threshold of ≥50 mm Hg. In addition, there is evidence that peak-instantaneous echocardiographic assessment of LVOT gradient appears to correspond to an equivalent catheter peak-to-peak measurement of LVOT gradient, in contrast to valvular aortic stenosis where the echocardiographic measurement corresponds to a lower catheter peak-to-peak LVOT gradient[24].

The primary endpoint is designed around the MVARC guidelines[19], to allow comparison with other mitral valve implantation trials, although tailored for the unique features of LAMPOON TMVR. We believe these data and guidelines justify a residual LVOT threshold of up to 50 mm Hg as a component of the study **primary** endpoint.

However, we concur with the FDA reviewer that the gradient in 0 is not optimal, especially in a patient with cardiomyopathy treated for pure mitral valve regurgitation. Therefore, we introduced a co-primary endpoint in 10.2.2 with a lower allowed peak LVOT gradient.

10.2.5 Independent Clinical Events Adjudication

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

- Deaths
- Primary endpoints
- Valve embolization events
- Site-reported strokes

The CEAC will classify relatedness of the above events to the LAMPOON procedure.

10.3 Stopping Rules and 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. 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. Unanticipated Adverse Device Effects (UADEs) will be submitted to the DSMB following the same timelines as the IRB (See section 9.2.4).

In the case of death or serious UADE, if the sponsor and the principal investigator determine that the event presents an unreasonable risk to the participating subjects, 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.

Each institutional IRB will review all Serious Adverse Events, 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.

Stopping rules were changed in Amendment A to be more statistically robust, to accommodate two strata of patients, and to focus on 30-day survival. There are two clearly different strata of subjects to be enrolled in this study. For TMVR in the setting of prior annuloplasty (aka "valve-in-ring" or "valve-in-band"), the risk of valve migration and of severe paravalvular leak, attendant mortality, are much lower. For TMVR in the setting of mitral annular calcification (aka "valve-in-MAC"), patients are older and have more comorbidity, and the procedures are much more technically complex. Accordingly, valve-in-MAC TMVR has higher mortality. The reported 30-day mortality of valve-in-MAC in the global registry of 64 patients was 30%[14].

We propose two different stopping rules, one for valve-in-ring and valve-in-band, and another for valve-in-MAC. While rules are provided for up to 30 subjects in each stratum, the total treated within both strata combined will not exceed 30.

10.3.1 Stopping Rules for valve-in-ring and for valve-in-band stratum

The study will be monitored to ensure that the mortality with 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 [25]. The stopping boundary is reached if the posterior probability that the 30-day mortality rate exceeds 10% is at least 90%. 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 study data, which 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 would lead to a recommendation to stop the study due to the excess 30-day mortality.

Number of subjects in the stratum	Stop if the number of deaths within 30 days reaches
2-4	2
5-10	3
11-17	4
18-24	5
25-30	6

We investigated the performance of the above stopping rule by a simulation study. In each simulation run, we generated a study with 30 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	5%	10%	15%	20%	25%	30%	35%	40%
Proportion of Stopped Studies	2.9%	16.9%	42.1%	68.7%	86.0%	94.9%	98.6%	99.7%
Average number of subjects	29.4	27	22.8	17.9	13.8	10.6	8.2	6.6
Average number of 30-day mortality	1.5	2.7	3.4	3.6	3.4	3.2	2.9	2.7

These simulation results suggest that our stopping rule has a low probability 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 Bayesian stopping rule for 30-day mortality has satisfactory statistical properties.

10.3.2 Stopping Rules for valve-in-MAC stratum

The study will be monitored to ensure that the mortality with 30-days after the procedure does not substantially exceed an anticipated rate. We anticipate the rate of 30-day mortality is 30% or less and determine the stopping rule by a Bayesian approach [25]. The stopping boundary is reached if the posterior probability that the 30-day mortality rate exceeds 30% is at least 90%. 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 = 1.8, b =4.2. 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 would lead to a recommendation to stop the study due to the excess 30-day mortality.

Number of subjects in the "valve-in-MAC" stratum	Stop if the number of deaths within 30 days reaches
3	3
4-6	4
7-8	5
9-11	6
12-14	7
15-16	8
17-19	9
20-22	10
23-25	11
26-27	12
28-30	13

We investigated the performance of the above stopping rule by a simulation study. In each simulation run, we generated a study with 30 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	20%	25%	30%	35%	40%	45%	50%	55%
Proportion of Stopped Studies (%)	3.9	10.2	21.8	38.9	58.5	76.6	89.1	95.9
Average number of subjects	29.2	28.1	26.1	23.3	20	16.4	13.2	10.5
Average number of 30-day mortality	5.8	7	7.8	8.2	8	7.4	6.6	5.8

These simulation results suggest that our stopping rule has a low probability stopping a study when the true 30-day mortality rate is 30% or less, and the probability of stopping a study is high when the true 30-day mortality rate exceeds 30%. There, we believe that our Bayesian stopping rule for 30-day mortality has satisfactory statistical properties.

10.4 Off study criteria

- Completion of the 5-year follow-up
- The subject voluntarily withdraws
- Significant subject non-compliance with follow-up visits
- Death

11.0 ADVERSE EVENT REPORTING

11.1 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:

- LAMPOON procedure
- Edwards *Sapien 3* transcatheter heart valve or accessories
- Asahi-Intecc *Astato XS 20* guidewire

An event will be considered NOT related to the LAMPOON procedure when it is the result of:

- A pre-existing medical condition
- Clearly attributable to TMVR but not LAMPOON part of procedure (example: commissural paravalvular leak)

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 previous human experience:

- LAMPOON device failure including failure to traverse, to lacerate, or to position catheters or guidewires
- Valve malposition, reposition, dislocation, migration, or embolization or deployment in unintended location
- Interatrial shunt

- LVOT gradient
- Aortic valve injury
- Paravalvular leak
- Atrial-ventricular conduction defects to include bundle branch block and complete heart block requiring placement of a temporary or permanent pacemaker
- Cardiac arrhythmia including ventricular tachycardia and atrial fibrillation
- Transient myocardial dysfunction attributed to rapid ventricular pacing required for mitral valve implantation, including brady-asystole or pulseless electrical activity, or requiring cardiopulmonary resuscitation
- Angina and myocardial ischemia
- Coronary artery obstruction or injury that may require intervention
- Myocardial infarction
- Congestive heart failure or BNP elevation
- Cardiogenic shock that may require intervention
- Infective endocarditis
- Left ventricular or left atrial perforation
- Pericardial effusion or tamponade
- Hypertension
- Hypotension requiring vasopressor support or mechanical circulatory support
- Stroke or TIA or seizure
- Hemolysis which requires transfusions and which requires confirmatory dramatic schizocytes and haptoglobin decline
- Low platelets or thrombocytopenia or increased or reduced leukocytes
- Mechanical injury to the myocardium, access vasculature, cardiac valves that may require intervention or that may elevate Troponin
- Bleeding causing anemia and blood transfusions
- Mitral valve thrombosis
- Embolization of air, calcific valve material, atheroma, or thrombus to coronaries, brain, limbs, or viscera causing myocardial infarction, stroke, or limb ischemia
- Retroperitoneal bleed or hematoma or access site injury
- Contrast-induced nephropathy requiring temporary or permanent hemodialysis or medical treatment
- Volume overload, pleural effusion, or dyspnea from procedure-related volume perturbations
- Respiratory failure requiring oxygen or mechanical support or mechanical ventilation
- Infection including access site or urinary or pulmonary or including sepsis
- Pain including back pain and access site and generalized
- Cardiac arrest
- Death

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
- Places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Protocol Deviation: A protocol deviation is any change, divergence, or departure from the study design or procedures of an IRB-approved research protocol.

11.2 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:

11.2.1 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.

11.2.2 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.

11.2.3 Adverse Event Reporting

Adverse event recording will start on Day (0) of the LAMPOON TMVR procedure and will continue through the 12-month Follow Up. 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 investigator to report adverse events and adverse device effects to their respective IRBs or 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.

11.2.4 Adverse event reporting timeframes:

Serious Adverse Events (SAEs)

- All serious adverse events will be reported to the Sponsor immediately but not later than 3 working days from the event. The respective institutional IRB should be notified according to their requirements.
- The serious adverse event will be evaluated by the sponsor. If determined to be an unanticipated adverse device effect that increases the risk to the participating subjects, the sponsor will terminate the investigation within 5 days after making the determination, and not later than 15 working days after the sponsor was first notified of the event. [21 CFR 812.46]

Unanticipated Adverse Device Effects (UADE)

- Must be reported to the Sponsor and the institutional IRB immediately but no later than 10 working days after the investigator learns of the event. [21 CFR 812.150]
- Unanticipated Adverse Device Effects should be reported via telephone as well as on the adverse event section of the case report form.
- If the event is determined by the Sponsor to be a UADE, the Sponsor will report the event to all investigators to enable reporting to their respective IRB/regulatory bodies. The Sponsor will provide this notification to participating sites and to the FDA within 10 working days after they first receive notice of the effect. [21 CFR 812.150]

- All Unanticipated Adverse Device Effects will be reported by the Sponsor to the NIH IRB per NIH Policy 801 “Reporting Research Events”.

Deaths

- The investigator will notify the Sponsor immediately but within 3 working days of notification of a subject’s death, whether the death is device related or clinical condition. Institutional IRB’s will be notified according to the specific institutional regulatory requirements for reporting a death.
- The Sponsor will notify the NIH IRB of a subject’s death, if applicable, per NIH Policy 801 “Reporting Research Events”.
- A subject’s death will be recorded on the Case Report Form.

12.0 HUMAN SUBJECT PROTECTION

12.1 Rationale for Subject Selection

12.1.1 Study population:

Subjects are selected for being adults who are determined otherwise likely to benefit from transcatheter mitral valve replacement yet are expected to suffer TMVR-related left ventricular outflow tract (LVOT) obstruction. 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.

Subjects who are unable to provide consent may be enrolled, if allowed by participating IRBs.

12.2 Risks and Discomforts

There are no approved commercial devices indicated for TMVR.

A formal risk analysis is provided in APPENDIX A.

Risks of TMVR will be considered separately from the risks of preparatory LAMPOON before TMVR. Known risks of TMVR include

- Death
- Left ventricular outflow tract obstruction
- Toxic reaction to anesthesia, medications, contrast media, or device materials
- Bleeding, hypotension, shock, anemia and complications of their treatment
- Vascular complications including requiring mechanical repair
- Conduction system injury which may require pacemaker therapy
- Embolization of air, calcific valve material, atheroma, or thrombus to coronaries, brain, limbs, or viscera causing myocardial infarction, stroke, etc
- Paravalvular leak
- Malposition or embolization of the TMVR device
- Transcatheter heart valve dysfunction, including mechanical, degenerative, or thrombotic
- Myocardial perforation and pericardial tamponade
- Complications of transcatheter or surgical transapical access including hemorrhage, pericardial tamponade, hemothorax
- Cardiac valvular or subvalvular injury causing myocardial dysfunction
- Congestive heart failure, cardiomyopathy, cardiogenic shock, respiratory failure

- Renal injury or failure
- TMVR failure requiring emergency cardiac surgery or emergency mechanical circulatory assistance
- Radiation injury including intractable skin injury
- Endocarditis or endarteritis or sepsis
- Hemolysis

Anticipated risks of preparatory LAMPOON before TMVR include:

- Death
- Avulsion or other injury of the aortomitral curtain, which is expected to lead to death
- Failure of the LAMPOON procedure, leading to LVOT obstruction, the life-threatening complication the LAMPOON procedure is intended to obviate
- Early or late thrombosis or thromboembolism causing stroke or acute visceral or limb ischemia
- Hemorrhage requiring blood transfusion
- Hemorrhagic shock requiring vasopressor support
- Injury to the aortic valve causing aortic valve regurgitation
- Aortic injury such as aortic dissection or pseudoaneurysm
- Hemolytic anemia or thrombocytopenia as a consequence of blood flow across the struts of the THV
- Infective endocarditis related to the TMVR of the lacerated mitral valve leaflet
- Nephrotoxic injury due to iodinated radiocontrast used in follow-up CT assessment, including causing temporary or permanent hemodialysis
- Embolization of the THV is a theoretical risk of LAMPOON although we do not expect LAMPOON to contribute to this life-threatening complication.

The sponsor and investigators recognize these risks are high and reflect the underlying comorbidities yet consider procedural hemorrhage overall to be an acceptable compromise to enable treatment of the underlying mitral valve failure in patients otherwise ineligible.

12.2.1 Risks Related to Radiation

In this research protocol, subjects will be exposed to radiation from 2 CT scans. 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 3-4 REM from the CT scans, and 72mSv[26] from approximately 60-100 minutes of fluoroscopy during performance of LAMPOON and TMVR. This is equivalent to 740 chest X-rays.

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.

12.2.2 Data collection from patients who have undergone LAMPOON at participating sites before this protocol begins enrollment

As of the time of submission of this protocol for review, 9 patients are known to have undergone standalone antegrade TMVR with LAMPOON. We wish to aggregate all available follow-up data on these patients to the extent possible, including patients who have died during the follow-up period. This number of patients analyzed retrospectively will not count against (“reduce”) the number of prospectively enrolled patients.

Subjects must have undergone LAMPOON and TMVR before enrollment begins in this protocol, which is expected April 2017. Retrospective findings will be analyzed separately from the subjects in the main (prospective) investigational IDE arm.

12.2.3 Personal Identifiable Information

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

13.0 TEST ARTICLES and INDICATIONS FOR USE

The study uses two main test articles, a transcatheter heart valve and a guidewire.

13.1 Edwards SAPIEN 3 transcatheter heart valve, PMA P140031

This protocol tests a method (LAMPOON). It also uses marketed devices off-label. The indications for use of these devices are shown below.

> The **Edwards SAPIEN 3 transcatheter heart valve**, model 9600TFX, and accessories are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a Heart Team, including a cardiac surgeon, to be at intermediate or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 3% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator).

We do not plan to market these devices. We plan to employ these devices in a valve position different from the intended use, in the mitral valve position whether in the presence of a surgical annuloplasty ring or band, or in the presence of native mitral annular calcification. For this off-label use, the Sapien 3 THV is delivered using its intended delivery system, but it is loaded with the orientation reversed for antegrade implantation via a transfemoral transseptal catheter route.

The LAMPOON method is described in the study procedures.

13.2 Asahi-Intecc Astato XS 20, 510(k) K103057

The Astato 0.014" guidewire is used for transcatheter electrosurgery in two steps in this procedure. First it is used for leaflet traversal during electrification. This procedure is similar to the use of the Astato XS20 and an amputated Asahi Confienza Pro 12 in the transcaval IDE investigation recently published [27].

Second, the midshaft is focally denuded and electrified for the leaflet traversal step. This is described in the pre-clinical [15] and early clinical [17] manuscript.

Neither of these procedures are addressed in the indications for use:

> **Asahi-Intec Astato XS 20:** This product is intended to facilitate the placement and exchange of diagnostic and therapeutic devices during intravascular procedures. This device is intended for peripheral vascular use only.

14.0 INVESTIGATOR ADMINISTRATIVE REQUIREMENTS

14.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) E6 (Guideline for Good Clinical Practice), the ethical principles that have their origin in the Declaration of Helsinki, 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 Investigator will be thoroughly familiar with the LAMPOON-TMVR 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.

14.2 IRB Submissions

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. 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 Investigator.

14.3 Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the subject or his/her legal representative 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 be enrolled, if allowed by participating IRBs. Consent for these subjects must be obtained from a legally authorized representative. The process for obtaining this consent must conform to local human subject's protection policies and to state laws.

14.4 Subject Confidentiality

In order to maintain subject privacy, all CRFs, accountability records, study reports, and communications will identify the subject by initials and the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority (ies) access to the subject's original medical records for verification of data gathered on the CRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

14.5 Protocol Compliance

The Investigator will conduct the study in compliance with the protocol provided by the Sponsor and given approval/favorable opinion by the IRB/IEC and other appropriate institutional regulatory bodies. Modifications to the protocol should not be made without agreement of both the Investigator and the Sponsor. Changes to the protocol will require written IRB/IEC and other appropriate institutional regulatory body approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to subjects. The IRB/IEC may provide, if applicable regulatory authority (ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that

have the approval /favorable opinion of the IRB/IEC and other appropriate institutional regulatory bodies. The Sponsor will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the Sponsor, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the CRF and source documentation.

14.6 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 Investigator, who must provide support at all times for these activities.

14.7 Case Report Form Completion

CRFs will be completed for each study subject. It is the 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.

The Principal Investigator or designated representative, should complete the CRF screens as soon as possible after information is collected, preferably on the same day that a study subject is seen for an examination, treatment, or any other study procedure but no more than 5 days post procedure. An explanation should be given for all missing data.

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

14.8 Record Retention

The 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, that may occur when performing the study.

14.9 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 Investigators participating in the study and representatives from the Sponsor, as appropriate, will be formed to oversee the publication and presentation of the study results, which will reflect the experience of all participating clin-

ical sites. No publication or disclosure of study results will be permitted except under the terms and conditions of a separate written agreement between Sponsor and the investigator and/or the investigator's institution.

15.0 SPONSOR REGULATORY REQUIREMENTS

15.1 Role of Sponsor

As the study sponsor of this clinical study, Dr. Robert 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.

15.2 General Duties

The Sponsor'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.

15.3 Monitoring

The study will be monitored by the Sponsor designee, an independent contract research organization. Monitoring will be done by personal visits and will include on-site review of the informed consent documents and case report forms for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained. The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications (letter, e-mail, telephone, and fax).

15.4 Site Selection and Training

The sponsor or its designee (national co-principal investigator) will ensure appropriate training in the technique of caval-aortic access prior to enrollment at any participating institution.

15.4.1 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 10 antegrade transseptal transcatheter mitral valve replacement procedures, to assure competence in TMVR procedures
- Physician prior experience performing or proctoring 10 transcaval TAVR procedures to assure competence in transcatheter electrosurgery
- Site prior participation in IDE protocols evaluating a treatment of structural heart disease
- Site ability to obtain CT examinations that are satisfactory for consideration of LAMPOON TMVR.
- Site investigators willing and able to comply with the requirements of this protocol.

15.4.2 Site training:

Site training will consist of

- Principal investigator and/or sponsor didactic training about the technique, preclinical, and clinical experience to date.
- Proctored conduct of LAMPOON TMVR procedures in patients at the local site, at the sole discretion of the Sponsor and/or Principal Investigator.
- Completion of training, and suitability for independent LAMPOON TMVR enrollment, will be certified by the Principal Investigator and with the concurrence of the Sponsor.

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APPENDIX A: Risk Analysis

This is a patient-centered risk analysis[28] in accordance with 21 CFR 812.25(c). It considers probable and not possible risk. This risk analysis applies to candidates for TMVR with LAMPOON, who have a fatal disease with few or no therapeutic options.

Category	Failure	Impact	Severity	Likelihood / frequency	Score	Available evidence to consider risk	Mitigation
LAMPOON devices	Failure to traverse or lacerate	Small to large hole in AML exacerbate mitral regurgitation; Loss of therapeutic option	4	2	8	Preclinical and early clinical experience	Abandon procedure with loss of therapeutic option; implant nitinol occluder
	Char forms on denuded shaft of guidewire	Loss of traversal or laceration during electrosurgical steps	2	3	6	Preclinical and early clinical experience	Minimize electrification time; Consider non-ionic insulating (dextrose 5%) flush during electrification
	Cavitation bubble forms during electrification	Silent gas embolization	2	3	6	Preclinical and early clinical experience with ICE and TEE; EP ablation literature	Heparinization, minimum ablation energy. Cavitation is common to all left-sided (EP) RF ablation procedures
	Thrombus from electrification of guidewire	Thromboembolism including cerebral	4	1	4	Preclinical and early clinical experience; EP ablation literature; Transcaval experience	Heparin to ACT>300; Minimize electrification; Escalation of power from lower to higher energy settings
LAMPOON technique	Failure to lacerate completely	MR exacerbation; Procedure failure	5	2	10	Preclinical and early clinical experience	Careful technique
	Avulsion of aortomitral curtain	Death	5	2	10	Theoretical	Careful technique
	Insulation failure: Piggyback	Increased laceration force required	3	3	9	Preclinical and early clinical experience	Careful technique

KEY LEVEL	**1**	**2**	**3**	**4**	**5**
Probability	Rare	Uncommon	Common	Normal	
Severity	Easy to correct, no anticipated harm to patient	Difficult to correct, no anticipated harm to patient	Potentially harmful to patient	Likely harmful, even with immediate correction	Life threatening
Risk Score	1-4	5-9	10-20	>20	
Risk Interpretation	Negligible	Tolerable	Tolerable but undesirable	Intolerable	

Category	Failure	Impact	Severity	Likelihood / frequency	Score	Available evidence to consider risk	Mitigation
	Kink / denudation failure	Increased laceration force required	3	3	9	Preclinical and early clinical experience	Careful technique
	Wrong orifice traversal	LAMPOON failure	4	2	8	Preclinical and early clinical experience	Technique assurance major orifice: BWEC & TEE
	Longitudinal inadequate crossing	Inadequate LAMPOON	3	2	6	Theoretical	TEE positioning close to AML base, ,but no QA postprocedure available except necropsy
	Failure to traverse	LAMPOON failure	2	2	4	Theoretical	Clinical technique: assure proper electrosurgery technique, proper insulating catheter
	Failure to lacerate at all	LAMPOON failure	2	2	4	Theoretical	Careful technique
	Bystander tissue injury such as aortic valve	Aortic regurgitation, thromboembolism	4	1	4	Theoretical	Minimize exposed lacerating guidewire between two guiding catheters
	Avulsion TAVR	Life-threatening repeat TAVR	4	1	4	Theoretical	Careful technique; Exclude recent TAVR from protocol
	Wire or device entanglement with TMVR	Failure, hemo instability, recrossing	2	1	2	Theoretical	Careful technique to assure no entanglement
	Guidewire lacerates JL catheters	Bystander tissues are not protected from guidewire injury	1	1	1	Early clinical experience	Careful technique
	Hemodynamic instability from successful LAMPOON	Hypotension, shock	3	3	9	Preclinical and early clinical experience	Pre-position THV at operator discretion
TMVR	Geographic miss causing skirt leak	LV failure, acute & subacute	5	2	10	Clinical literature	Careful THV positioning;

KEY LEVEL	**1**	**2**	**3**	**4**	**5**
Probability	Rare	Uncommon	Common	Normal	
Severity	Easy to correct, no anticipated harm to patient	Difficult to correct, no anticipated harm to patient	Potentially harmful to patient	Likely harmful, even with immediate correction	Life threatening
Risk Score	1-4	5-9	10-20	>20	
Risk Interpretation	Negligible	Tolerable	Tolerable but undesirable	Intolerable	

Category	Failure	Impact	Severity	Likelihood / frequency	Score	Available evidence to consider risk	Mitigation
	Paravalvular Leak	LV failure, acute & subacute	2	3	6	Clinical literature	Careful THV sizing; careful THV positioning with regard to THV skirt and target tissue; Off-label implantation of nitinol occluder devices to close PVL
	THV dysfunction from stent deformation	THV dysfunction chronic	3	2	6	Clinical literature	None
	LVOTO	LV failure, acute & subacute	5	1	5	Clinical literature, clinical experience	LAMPOON procedure; Bailout transcoronary alcohol septal ablation
	Embolization	Rescue ectopic implantation, LV failure, death	2	2	4	Clinical literature, clinical experience	Careful THV technique including "flare" of LV aspect
	Redundant native mitral leaflet causing THV dysfunction	THV dysfunction, acute	4	1	4	Clinical literature, clinical experience	LAMPOON procedure; Major orifice traversal
	THV Thrombosis	THV dysfunction, stroke	4	1	4	Clinical literature, clinical experience	Post-procedure anticoagulation as tolerated
Follow-up	ATN from contrast CT	Temporary or permanent hemodialysis	3	2	6	Clinical literature, clinical experience	Request low-energy and low-contrast time-resolved CT to minimize contrast. Follow operator discretion about timing of contrast exposure

KEY LEVEL	**1**	**2**	**3**	**4**	**5**
Probability	Rare	Uncommon	Common	Normal	
Severity	Easy to correct, no anticipated harm to patient	Difficult to correct, no anticipated harm to patient	Potentially harmful to patient	Likely harmful, even with immediate correction	Life threatening
Risk Score	1-4	5-9	10-20	>20	
Risk Interpretation	Negligible	Tolerable	Tolerable but undesirable	Intolerable	

Appendix B: Kansas City Cardiomyopathy Questionnaire

KEY LEVEL	1	2	3	4	5
Probability	Rare	Uncommon	Common	Normal	
Severity	Easy to correct, no anticipated harm to patient	Difficult to correct, no anticipated harm to patient	Potentially harmful to patient	Likely harmful, even with immediate correction	Life threatening
Risk Score	1-4	5-9	10-20	>20	
Risk Interpretation	Negligible	Tolerable	Tolerable but undesirable	Intolerable	