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Title: *NHLBI SESAME (SEptal Scoring Along Midline Endocardium) Early Feasibility Study*

Investigational Device(s):	AstatoXS-20 and AstatoXS-40 guidewires ConfianzaPro-12 guidewire
IDE Number:	G220158
Sponsor:	Office of Clinical Director, National Heart Lung and Blood Institute, National Institutes of Health, USA
Sponsor Representative & NHLBI Principal Investigator	Robert J. Lederman, MD Cardiovascular Branch, Division of Intramural Research, National Heart Lung and Blood Institute, National Institutes of Health, Building 10, Rm 2c713 MSC 1538, 9000 Rockville Pike Bethesda, MD 20892-1538 Phone: +1-301-402-6769 E-mail: lederman@nih.gov
Data Coordinating Center:	National Heart Lung and Blood Institute Division of Intramural Research
Data and Safety Monitoring Board (DSMB)	National Heart Lung and Blood Institute

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2 STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

3 PROTOCOL SUMMARY

3.1 Synopsis

Title	NHLBI SESAME (SEptal Scoring Along Midline Endocardium) Early Feasibility Study
Background / Précis	Cardiac interventricular septal reduction therapies — to relieve left ventricular outflow tract obstruction from transcatheter valve replacement or hypertrophic cardiomyopathy — have inherent limitations including dependence on coronary anatomy, high pacemaker implantation rate, and surgical morbidity. We developed a novel transcatheter ventricular myotomy called SEptal Scoring Along the Midline Endocardium (SESAME) that relies on intramyocardial guidewire navigation and transcatheter electrosurgery. SESAME has been performed on a small number of patients using off label devices. This study systematically characterizes the safety and early feasibility of SESAME at 2 enrolling site. SESAME is performed as septal reduction therapy in a heterogeneous group of subjects, including symptomatic hypertrophic cardiomyopathy and resting or provoked left ventricular outflow obstruction (LVOTO); and severe symptomatic mitral and/or aortic valve disease at high risk of standard heart surgical therapy and requiring later transcatheter heart valve implantation combined with manifest or potential LVOTO. A key goal of this study is to attempt to capture generalizable knowledge from as many patients as possible, and to add a limited number of research procedures to characterize the safety and provisional effectiveness of SESAME. Absent realistic non-clinical models of HCM or LVH combined with aortomitral disease, we believe little more information can be gleaned without clinical investigation. This protocol was revised to add a second enrolling medical center, and to focus inclusion criteria on research participants with hypertrophic cardiomyopathy (HCM). This protocol was further revised after the first subject died as a result of excessively-deep SESAME laceration. The required septal thickness for eligibility was increased from ≥12mm to ≥16mm.
Risk classification	Significant risk device protocol requiring Investigational Device Exemption (IDE)
Device classification	Class II

Test articles	Asahi-Intecc Astato XS 20, 510(k) K103057 & Astato XS 40, 510(k) K153443, Asahi-Intecc Confianza Pro 12, 510(k) K171933
Design overview	Prospective, 2-enrolling site, single arm, open-label, early feasibility study of the SESAME procedure
Study phase	Early feasibility study
Sponsor / Representative	NHLBI Office of the Clinical Director (NHLBI/OCD) / Robert J. Lederman, MD, NHLBI/DIR/CB/LCI
Study Manager	Annette M. Stine, RN
Objective	The objective of this protocol is to test the safety and effectiveness of the SESAME septal debulking in patients with left ventricular outflow tract obstruction.
Hypotheses	We hypothesize that the interventricular septum can be engaged, traversed, and lacerated with SESAME to increase the predicted neo-LVOT. We also hypothesize that intracameral gradients can be relieved by SESAME.
Number of subjects	15 subjects enrolled at up to 2 investigational site in the US. Up to 30 subjects may be screened for participation.
Sample Size Justification	The sample size is arbitrary.

Inclusion Criteria	• Adults age ≥ 21 years
	• Requires debulking of left ventricular septum for hypertrophic cardiomyopathy
	• Septal diastolic thickness of obstructive "hump" on CT:
	  o Total ≥16 mm, and
	  o Predicted residual septal thickness ≥ 8 mm, and
	  o Predicted laceration depth ≥ 6 mm
	• Severely symptomatic, any of
	  o NYHA Class III or greater
	  o Canadian Angina Class CCS III or greater
	• Explicitly chooses investigational SESAME over conventional treatment approaches including (1) cardiac myosin inhibitor therapy, if eligible; (2) transcoronary alcohol septal ablation, if eligible; or (3) surgical left ventricular myotomy and/or myectomy, if eligible
	• Concurrence of the multidisciplinary institutional heart team that the candidate is at high risk for surgical myectomy
	• Concurrence of the study Central Clinical Eligibility Committee
	• Willing to return for all scheduled follow-up activities, and eligible or able to undergo required protocol and testing

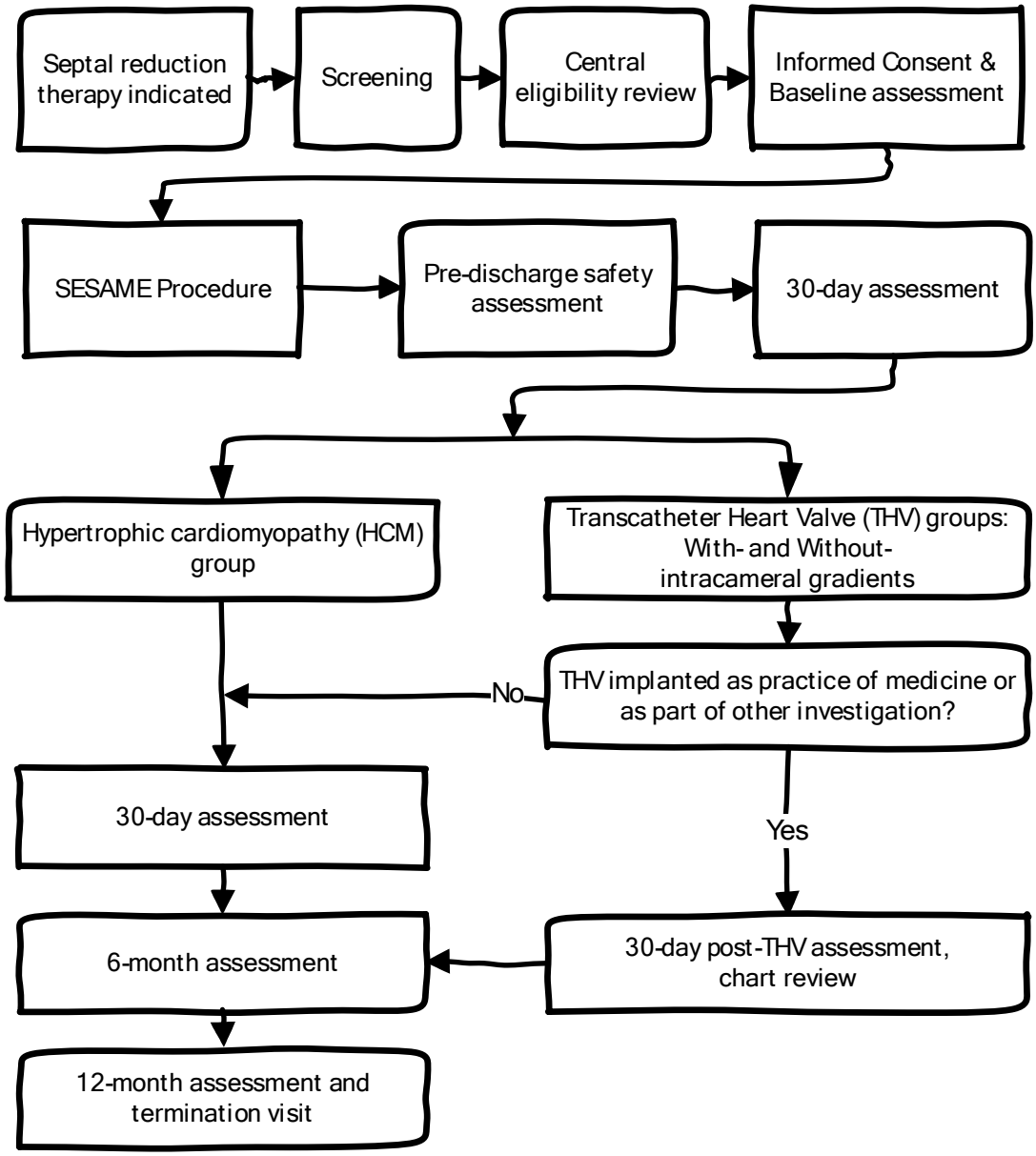
Exclusion Criteria	• Does not consent to participate, or unable to consent to participate • Requires antegrade SESAME access (because of mechanical aortic valve) • Prior completed transcoronary alcohol septal ablation, or prior surgical myectomy • Pregnant • Hemodynamic instability or emergency procedure • eGFR < 30 mL/min/1.73m^2 • Survival despite successful procedure expected < 12months

Primary Feasibility Endpoint	The primary feasibility endpoint is **Technical success** (measured at exit from the catheterization laboratory). All of the following must be present:
	• Alive
	• Procedure success including
	  o Successful myocardial entry, navigation, and snaring of guidewire traversal system; and
	  o Successful laceration of septal myocardium

Primary Safety Endpoint	The primary safety endpoint at 30 days, is freedom from all of the following: • All-cause mortality • All stroke (disabling and non-disabling) • Major cardiac structural complication requiring intervention (such as iatrogenic ventricular septal defect, iatrogenic aortic valve regurgitation, iatrogenic mitral regurgitation, or pericardial tamponade) related to SESAME
Secondary endpoint	The secondary endpoint is complete heart block requiring permanent pacemaker implantation, assessed at discharge.
Exploratory endpoints	• Gradient reduction among subjects with hypertrophic cardiomyopathy, residual gradient ≤ 30mmHg at procedure conclusion and after 30 days • 30d VARC-3 complications of SESAME including access, bleeding, vascular, stroke, myocardial infarction • Symptom and functional status assessed at baseline, 30d, and 12 mo assessed by KCCQ-23 OS and CS, NYHA and CCS classifications, and 6 minute walking test • Change in laceration dimensions and, when applicable, neo-LVOT and skirt neo-LVOT assessed by CT between baseline and 30 days • Undergoes attempted septal reduction therapy ablation after SESAME during the study period • Freedom from new permanent ventricular pacemaker implantation • New electrocardiographic conduction defects before discharge • Freedom from ventricular septal defect • Freedom from pericardial effusion • Freedom from stroke assessed at discharge

Study Overview	NHLBI Data Coordinating Center Central IRB Selected site operators have experience with transcatheter electrosurgery, especially LAMPOON, BASILICA, or SESAME Subjects are identified by site investigators CT, CMR, Echo, and procedure fluoroscopy are analyzed by core laboratory Subject eligibility is proposed by institutional multidisciplinary heart team, and is confirmed by study Central Clinical Eligibility committee Subjects are enrolled prospectively Primary analysis based on 30 day outcomes. Other datapoints undergo 100% source-data verification Subjects go “off-study” after 12 months visit
Study Duration	30 months for enrollment + follow-up
Sites	Data Coordinating Center: NHLBI, including core laboratories. Enrolling site(s): 1. Emory University Hospital, Atlanta, GA 2. St Francis Hospital, Roslyn, NY All enrolling sites will perform same research activities.
Enrollment	Subjects are not enrolled until after they (1) are invited to participate by the study Central Clinical Eligibility Committee; (2) thereafter consent to participate
Duration of Participation for Subjects	12 months

3.2 Schema


Septal reduction therapy indicated
Screening
Central eligibility review
Informed Consent & Baseline assessment
SESAME Procedure
Pre-discharge safety assessment
30-day assessment
Hypertrophic cardiomyopathy (HCM) group
Transcatheter Heart Valve (THV) groups: With- and Without- intracameral gradients
THV implanted as practice of medicine or as part of other investigation?
No
Yes
30-day assessment
30-day post-THV assessment, chart review
6-month assessment
12-month assessment and termination visit

3.3 Schedule of Activities (SOA)

	Screening (± 6 mo)	Baseline (± 6 wk)	Day 0 (procedure)	Pre-discharge	30 d (-7+14d) FU	TMVR data, if applicable (post-TMVR d30)	6 mo (± 4 wk)	12 mo (± 4 wk) FU
Research informed consent:		X						
Local multidisciplinary heart team eligibility determination	X							
Central Clinical Eligibility Committee concurrence	X							
Clinical in-person assessment including vital signs, NYHA & CCS classification		X		X	X		X	X
Stroke assessment: mRS and NIHSS		X		X	X			
6 minute walk test		X			X		X	X
Kansas City Cardiomyopathy Questionnaire (KCCQ-23)		X			X		X	X
Blood test for pregnancy (hCG) **for CT or MR** if premenopausal woman		X						X
Blood tests: CBC, Platelet, Chemistry Panel,		X		X	X			
Blood test: BNP/Pro-BNP		X			X			X
Blood test: Troponin I 24-48 hours post-procedure		X		X				
Blood test and buccal mucosal swab: optional commercial genetic testing panel for HCM and phenocopies		§						
Cardiac CT gated dynamic, with contrast	Screening or baseline*, **			§	X			X
Cardiac MR including function, volume, relaxometry, (Gadolinium contrast if not contraindicated)		§		X				§
SESAME index procedure including hemodynamic catheterization			X					
Optional follow-up hemodynamic cath					§			
Procedural echocardiography (transthoracic, transesophageal, and/or intracardiac)			X					
Transthoracic echocardiogram, including exercise	Screening or baseline*, **			X	X		X	X
ECG		X		X	X		X	X
Exercise VO2 exam		X			X			
Pacemaker interrogation (when applicable)		X		X	X			
Adverse event assessment			X	X	X	X	X	X

Unscheduled clinically-driven cardiac imaging exams are analyzed by the core laboratories.

* Standard of care tests will be used to determine eligibility if obtained within 6 months.
**Screening CT, CMR, and echocardiography may be used for baseline exams if obtained for standard medical care, otherwise research exams will be obtained. “Out-of-window” baseline imaging exams may be employed if deemed acceptable by study eligibility committee.
§ Optional exams.
Optional CT scan before discharge as clinically-indicated and as determined by the treating physicians. If obtained, it will be analyzed for research.

3.3.1 Blood tests

All of the blood tests specified here are mandatory for routine medical care before, during, and after transcatheter SESAME 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 only if they change from baseline > 10% AND out-of-range.

Test	Detail	Inpatient value to record	Timepoints to collect
Blood count: white blood cell count	Nonspecific marker of inflammation and infection.	Highest	Baseline through 30d
Chemistry: Creatinine	Marker of renal excretion. eGFR	Highest	Baseline through 30d
Chemistry: Estimated glomerular filtration rate (eGFR)	Calculated from age, sex, race, and creatinine	Lowest	Baseline through 30d

The following blood tests will be acquired and **will not be reported as adverse events**, because they are expected to be abnormal in every patient/subject.

Chemistry: Cardiac troponin	Marker of cardiomyocyte injury, institution-specific subtype (Troponin-I or Troponin-T).	Highest	Baseline & 24-48 hrs postprocedure.
Chemistry: NT-Pro-Brain natriuretic peptide (NT-Pro-BNP) or Brain natriuretic peptide (BNP)	Marker of volume overload. Sites must use identical BNP/NT-Pro-BNP assay for each subject throughout the first 12 months of the study	Lowest	Baseline, 30d, 12 mo
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: platelet	Nonspecific marker of coagulation and of inflammation.	Lowest	Baseline through 30d
Genetic test: HCM phenocopies	Inherited cause of primary cardiac hypertrophy if identifiable	All	Baseline

Commercial genetic testing for HCM phenocopies is optional pending CMS or insurance coverage of the genetic test, typically under CMS CTP program coverage (see section 8.7.1 "Costs").

4 INTRODUCTION

4.1 Public précis (for clinicaltrials.gov)

This is an early study of a new catheter-based minimally invasive procedure called SESAME to slice thick heart muscle as described below.

Excessively-thick heart muscle can cause serious heart disease, especially heart failure with preserved ejection fraction, which causes shortness of breath and heart failure symptoms such

as edema (swelling) and pulmonary congestion (lung water). Specific circumstances of excessively-thick heart muscle can block outflow of blood from the main heart pumping chamber (left ventricle).

We have developed a new catheter technique called SESAME (SEptal Scoring Along Midline Endocardium) to slice the excessively-thick heart muscle causing such problems. SESAME can be used in patients who have symptoms related to excessively-thick heart muscle in a part of the heart that restricts blood ejection from the heart; the problem is called “left ventricular outflow tract obstruction (LVOTO).”

One group of patients who might benefit from SESAME suffer from a common inherited heart muscle disease called “hypertrophic cardiomyopathy (HCM).” Patients with HCM and symptoms from LVOTO can be treated with medications, open heart surgery, or catheter-based destruction of heart muscle in “alcohol septal ablation.” If these treatments fail or are not suitable, then SESAME may be an option, because it resembles surgery treatment without open heart surgery.

This is an early feasibility study of SESAME in some of the first patients in the world to undergo the procedure, to understand how well it works and whether it is safe.

4.2 Study Rationale

Cardiac interventricular septal reduction therapies — to relieve left ventricular outflow tract obstruction from transcatheter valve replacement or hypertrophic cardiomyopathy — have inherent limitations including dependence on coronary anatomy, high pacemaker implantation rate, and surgical morbidity. We developed a novel transcatheter ventricular myotomy called SEptal Scoring Along the Midline Endocardium (SESAME) that relies on intramyocardial guidewire navigation and transcatheter electrosurgery. SESAME has been performed on a small number of patients using off label devices.

This study systematically characterizes the safety and early feasibility of SESAME at 2 enrolling site. SESAME is performed as septal reduction therapy in a heterogeneous group of subjects, including symptomatic hypertrophic cardiomyopathy and resting or provoked left ventricular outflow obstruction (LVOTO); and severe symptomatic mitral and/or aortic valve disease at high risk of standard heart surgical therapy and requiring later transcatheter heart valve implantation combined with manifest or potential LVOTO.

A key goal of this study is to attempt to capture generalizable knowledge from as many patients as possible, and to add a limited number of research procedures to characterize the safety and provisional effectiveness of SESAME. Absent realistic non-clinical models of HCM or LVH combined with aortomitral disease, we believe little more information can be gleaned without clinical investigation.

This protocol was revised to add a second enrolling medical center, and to focus inclusion criteria on research participants with hypertrophic cardiomyopathy (HCM). This protocol was further revised after the first subject died as a result of excessively-deep SESAME laceration. The required septal thickness for eligibility was increased from ≥12mm to ≥16mm.

5 BACKGROUND

5.1 Left ventricular outflow tract (LVOT) obstruction

LVOT obstruction is present in 75% of patients with hypertrophic cardiomyopathy (HCM)[1]. Obstruction is due to hypertrophy of the interventricular septum and symptoms are exacerbated by abnormalities in the mitral valve apparatus (long anterior leaflet, anterior dislocation of the papillary muscle) causing a Bernoulli effect and systolic anterior motion (SAM) of the anterior mitral leaflet. Symptoms may improve with negative-inotropic pharmacologic therapy (beta-adrenergic blockers and new myosin inhibitors). Surgical septal myectomy and percutaneous trans-coronary alcohol septal ablation (TCASA) are invasive septal reduction treatment options that relieve LVOT obstruction in symptomatic patients with HCM despite guideline directed medical therapy[2].

There are limitations to these septal reduction and leaflet modification therapies, including surgical morbidity, anatomic feasibility, technical complexity, conduction system injury and inadequate LVOT enlargement. Maron and colleagues graphically depicted the incidence of LVOT obstruction after conventional therapy (*Figure 1*).

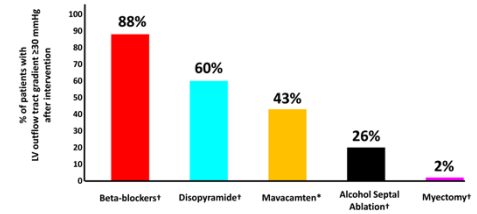


Figure 1. Incidence of residual LVOT obstruction after treatment. From Maron, Circulation, 2021;143:1181.

Although no longer directly relevant to this study, LVOT obstruction also complicates transcatheter mitral valve replacement (TMVR)[3], and is a leading cause of ineligibility for TMVR[4]. Pre-emptive trans-coronary alcohol septal ablation (TCASA) and laceration of the anterior mitral leaflet to prevent outflow obstruction (LAMPOON) are two widely-employed techniques to prevent LVOT obstruction from TMVR[5-8]. Even despite LAMPOON, TMVR in patients with small cardiac chambers may still result in functionally significant, if non-lethal, narrow LVOT. Septal debulking combined with LAMPOON may further reduce residual LVOT

obstruction at rest or during exercise. Surprisingly, a significant poorly-defined proportion of patients undergoing planned septal reduction therapy in anticipation of TMVR derive symptomatic benefit sufficient to delay or defer the planned TMVR[8, 9]. The mechanism of this benefit is not understood, and may reflect alterations in diastolic compliance of the hypertrophied ventricles from septal reduction, or even placebo effect. Deferral of TMVR may be desirable in the treatment of mitral valve stenosis associated with mitral annular calcification (MAC), wherein residual TMVR-transmitral gradient limits the functional benefit of therapy. In combination these clinical considerations warrant collection of additional data.

5.2 Preclinical SESAME to relieve LVOT obstruction

An early surgical technique to treat LVOT obstruction in hypertrophic cardiomyopathy was a simple ventricular myotomy without myectomy[10]. An incision is made across the hypertrophied bar of septal muscle in line with the left-right coronary cusp commissure. The cut muscle splays apart, reducing septal encroachment into the LVOT without removal of muscle tissue, relieving LVOT obstruction. A longitudinal series of 36 patients demonstrated symptomatic benefit maintained at 4-year mean follow-up[11]. In 21 patients with hemodynamic assessment available, the LVOT pressure gradient was abolished in 71% and reduced to below 20mmHg in 24% with this surgical technique[11]. Surgical myotomy and myectomy have evolved into standard therapy[12-14] incorporated into treatment guidelines for appropriately-selected symptomatic patients[2].

Combining techniques developed in our laboratory for transcatheter electrosurgery [15] and intramyocardial guidewire navigation[16], we developed a new transcatheter procedure for septal reduction therapy, mimicking surgical ventricular myotomy, called SEptal Scoring Along the Midline Endocardium (SESAME)[17, 18].

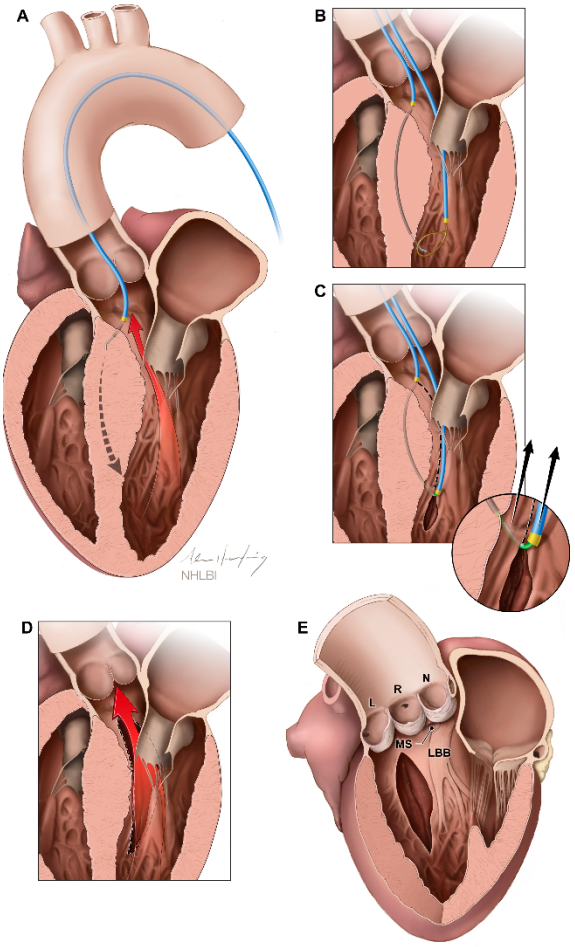


Figure 2. SESAME Schematic. A. A guiding catheter directs a coronary guidewire and microcatheter into the base of the hypertrophied interventricular septum. The broken gray arrow depicts the intended guidewire trajectory. The red arrow depicts blood flow through a narrowed LVOT. B. The guidewire completes the intramyocardial trajectory, with microcatheter support, and re-enters the left ventricle cavity into a a snare. C. A modified “flying V” lacerating surface is created and traction applied to the guidewires and catheters during electrification to create the SESAME laceration. D. Following transcatheter SESAME, the muscle splays creating extra space in the LVOT, with increased area for blood flow, depicted by the red arrow. E. The left ventricle and aorta are displayed opened at the left-noncoronary cusp commissure, depicting the SESAME laceration in

We developed SESAME in naïve swine and in a porcine model of mild (minimal) left ventricular hypertrophy[17]. SESAME myotomy was achieved in all animals, including septal entry, intramyocardial navigation, septal exit, and laceration along the intended trajectory. The myocardial laceration was splayed immediately (median 11.2mm) and at follow-up (median 14.8mm). One animal developed a conduction abnormality (left axis deviation on ECG, representing injury of a branch of the left bundle) but no higher conduction block was seen in any animal. Two naïve pigs with thin baseline septa, developed ventricular septal defects due to excessively deep lacerations, that were an expected complication in this exploratory preclinical technique development protocol. Coronary angiography and CMR perfusion imaging revealed no abnormalities. Cardiac function by chamber volumes, aortic flow and strain analysis was preserved. No acute myocardial oedema was evident on CMR T1 mapping. The preclinical experience demonstrated feasibility of SESAME and highlighted the importance of careful trajectory planning, and avoidance of excessively thin septa, to prevent iatrogenic ventricular septal defect which also complicates standard septal reduction therapy.

5.3 Potential applications of SESAME, and phenotypic classifications of candidates

Transcatheter myotomy can splay the interventricular septum and either relieve manifest intraventricular pressure gradients, or it can create space to allow valve implantation that might otherwise obstruct left ventricular outflow. Accordingly there are several potential clinical applications.

SESAME can relieve basal or mid-chamber outflow obstruction complicating primary hypertrophic cardiomyopathy, an inherited phenotype common to numerous genotypes. In practice, hypertrophic cardiomyopathy is diagnosed on clinical and not genetic criteria. Hypertrophic cardiomyopathy is often associated with functional mitral valve regurgitation, related to Bernoulli-force-induced systolic anterior motion of the mitral valve towards the septum. Hypertrophic cardiomyopathy is also often associated with primary mitral valve regurgitation related to architectural chordal or papillary abnormalities.

Severe secondary left ventricular hypertrophy, presumably related to systemic hypertension and other forms of excessive afterload, is common and often accompanies degenerative aortic and mitral valve disease. It is possibly that some patients exhibiting these features may have underlying primary hypertrophic cardiomyopathy, but we classify them as “secondary” left ventricular hypertrophy. These patients may have not heretofore undergone systematic genetic screening for HCM phenocopies.

Infrequently, septal left ventricular hypertrophy that accompanies aortic valve stenosis is so severe that sudden unloading of the left ventricular by aortic valve replacement causes acute life-threatening dynamic left ventricular outflow tract obstruction, sometimes described as “suicide left ventricle.” Such patients benefit from prophylactic or emergency bailout septal reduction therapy[19-22].

Severe left ventricular hypertrophy is associated with mitral annular calcification, a degenerative phenomenon associated with mitral valve failure, both stenotic, regurgitant, or mixed. The pathophysiology of mitral annular calcification appears to be related, perhaps

causally, to tissue stress imparted by the underlying ventricular hypertrophy[23-27]. Affected patients are typically older, women, and have moderate or severe pulmonary artery hypertension; collectively these indicate high risk of surgical morbidity and mortality. Moreover, at least half of patients with symptomatic mitral valve disease related to mitral annular calcification, have insufficiently large left ventricular cavities to accommodate transcatheter mitral valves[28]. And of these, approximately half also have manifest (resting or provoked) intraventricular pressure gradients. Treatment of primarily-regurgitant mitral valve failure may better relieve symptoms than treatment of primarily-stenotic mitral valve failure attending mitral annular calcification, in part because of residual prosthetic transmitral gradients.

Still others with left ventricular hypertrophy and mitral annular calcification develop serious or life-threatening left ventricular outflow tract obstruction immediately following mitral valve implantation, either predictably or as a result of a technical complication, and require urgent or emergency septal reduction therapy.

Ventricle	**Valve**	**Intracameral gradient present**	**At-risk for intracameral gradient**
Primary LVH (HCM)	Mitral leaflets intact despite functional (*e.g.* SAM) MR	Present (HCM)	—
Secondary LVH	Aortic stenosis	LVOTO present, risking "suicide left ventricle" (Gradient)	—
	Prosthetic mitral valve	After TMVR or SMVR (Gradient)	—
	MAC with MR	Present at baseline (Gradient)	Small neo-LVOT (No Gradient)
	MAC with MS or mixed MS/MR	Present at baseline (Gradient)	Small neo-LVOT (No Gradient)
	Native mitral failure without MAC, or after mitral ring annuloplasty	—	Small neo-LVOT (No Gradient)

Table 1. Proposed phenotype scheme

The many permutations of left ventricular hypertrophy, mitral annular calcification and forms of mitral valve failure, and intracameral geometry or obstruction, make clinical evaluation of

septal reduction therapy complex. We propose a working following phenotypic classification scheme for SESAME transcatheter myotomy candidates, below and in Table 1:

1: Hypertrophic cardiomyopathy with intracameral gradient (LVOTO), described as "HCM" and depicted in green.

2: Secondary left ventricular hypertrophy (LVH) with aortic or mitral valve disease and resting or provocable intracameral gradient, described as "Gradient group" and depicted in orange.

3: Secondary left ventricular hypertrophy (LVH) with aortic or mitral valve disease AND **no** intracameral gradient, but at risk for LVOT obstruction as a predicted complication of mitral valve replacement because of small neo-LVOT, described as "No gradient group" and depicted in light blue.

This three-category phenotypic classification may be crude and imprecise, especially because of our failure to distinguish primary from secondary LVH. Nevertheless we find it useful to try to dissect the value of SESAME on diverse clinical scenarios.

5.4 Clinical SESAME using off-label devices

Greenbaum and colleagues at Emory University recently reported the first case of SESAME using off-label devices[18], with one-year of clinical and CT-follow-up, in an elderly patient with concomitant obstructive HCM and symptomatic mitral stenosis associated with mitral annular calcification. Her neo-LVOT was prohibitively small. Her LVOT area increased, and her resting and provoked LVOT gradients fell immediately after SESAME and were nearly absent one month later. She then underwent TMVR without LVOT obstruction. Analogous to surgical ventriculo-myotomy, she exhibited no evolution of SESAME myotomy splay dimensions or septal thinning over one year of follow-up.

During the period January 1 2021 to November 23 2022, the team at Emory University undertook 37 attempted SESAME procedures as the practice of medicine. In addition, we are aware of at least 7 additional attempts at two other medical centers that are not further described here. The Emory data below derive from retrospective chart abstraction and did not undergo source-data verification. We apply our three-category phenotypic classification described earlier, despite potential imprecision.

Of the 37 patients, 86% were women, and median age was 75 (72, 81) years. Twenty-eight (78%) underwent SESAME with the intent to perform TMVR afterwards. The remainder had HCM or required TAVR. Half of those intending TMVR had baseline LVOT gradients (≥30mm Hg at rest of ≥50mm provoked). All but one had high or prohibitive operative risk; median STS predicted risk of mortality from mitral surgery was 9% (5, 14); 26 had severe mitral annular calcification; and 32 had severe pulmonary artery hypertension.

Six of 37 would have been excluded from this proposed protocol: two because of cardiogenic shock at baseline, one who underwent SESAME as emergency bailout during Tendyne TMVR

implantation for shock, one with HCM and systemic-level pulmonary artery hypertension at baseline, and two with end-stage renal disease on hemodialysis.

Nine underwent concomitant procedures during the same procedure as SESAME, including 7 TAVR, 1 TEER, and 1 Tendyne TMVR (creating the requirement for rescue SESAME).

The SESAME procedure was technically successful in all (defined as in this protocol as surviving the cath lab procedure with successful myocardial traversal and SESAME laceration).

Four (11%) had serious complications. One patient had a free wall perforation successfully managed conservatively. It was attributed to a "steam pop" caused by excessively prolonged radiofrequency energy application in an otherwise intended laceration trajectory. Three patients had new ventricular septal defects (VSD), including the one with the free wall perforation. All were small and did not require treatment. Two underwent one-time pericardial drainage, including the patient with the free-wall perforation; the etiology of the other is unknown but likely related to trans-septal intracardiac echocardiography probe. One underwent uneventful defibrillation for iatrogenic ventricular fibrillation induced by septal guidewire navigation. None had iatrogenic aortic or mitral valve injury. All survived to discharge.

Intracameral gradients were measured in all 37 before and after SESAME:

Phenotype	HCM		Gradient Group		NoGradient Group	
	baseline, N = 5	post, N = 5	baseline, N = 17	post, N = 17	baseline, N = 15	post, N = 13
proc.lvot.peak.peak (mmHg)	62 (50, 82)	26 (18, 31)	43 (32, 81)	22 (12, 46)	10 (3, 18)	4 (3, 12)
proc.lvot.peak.peak.pvc (mmHg)	136 (106, 172)	104 (84, 122)	105 (66, 154)	53 (19, 92)	18 (6, 34)	10 (7, 32)

Data are median (1st quartile, 3rd quartile).

Thirty four of 37 (91%) survived to discharge. Of the three inpatient deaths, two had cardiogenic shock at baseline; a third with severe MAC/MS/MR, aortic stenosis, failed prior alcohol septal ablation, and dementia suffered pulmonary edema during convalescence and transitioned to hospice at family request.

One patient had a stroke recognized in retrospect after discharge. One underwent permanent pacemaker implantation (and recovered normal atrioventricular conduction afterwards). Six had VARC3 major bleeding, two had VARC3 major vascular complications.

Cumulative post-discharge adverse events are reported here. During follow-up a median of 44 (38, 117) days, there were 7 cumulative deaths (19%), 2 cumulative strokes (6%, one ischemic

and one hemorrhagic), and 1 permanent pacemaker. Twelve (32%) were readmitted to a hospital (8 non-cardiac, 4 non-cardiac).

On preliminary evaluation of baseline- and follow-up CT, among all patients, and ascribing baseline values to missing values, SESAME effectively enlarged LVOT as assessed by neo-LVOT and skirt-neo-LVOT:

Phenotype	HCM Group		Gradient Group		NoGradient Group	
	baseline, N = 5	post, N = 5	baseline, N = 17	post, N = 17	baseline, N = 15	post, N = 13
ct.neo.lvot (mm^2)	—	—	4 (0, 27)	107 (65, 320)	35 (7, 107)	171 (105, 208)
ct.skirt.neo.lvot (mm^2)	—	—	197 (154, 254)	236 (195, 311)	207 (174, 251)	248 (210, 300)

Data are median (1^{st} quartile, 3^{rd} quartile).

We assessed the evolution of the thinnest portion of the lacerated septum in 29 patients available for at least two CT examinations after discharge. There were no new ventricular septal defects or perforations after discharge. The table below summarizes the findings:

Characteristic	HCM, N = 3	Gradient Group, N = 13	NoGradient Group, N = 13
min.discharge.sysstole	8.9 (7.9, 10.9)	4.8 (2.2, 6.2)	6.6 (5.1, 9.2)
min.latest.sysstole	11.7 (10.2, 11.9)	6.5 (2.5, 9.0)	6.6 (3.6, 9.3)
delta.systole	1.90 (0.55, 2.35)	0.30 (0.00, 2.20)	0.00 (-1.77, 1.22)
min.discharge.diastole	7.4 (7.1, 8.7)	3.9 (3.2, 6.3)	6.0 (4.4, 7.4)
min.latest.diastole	6.0 (5.7, 8.6)	6.1 (1.9, 7.0)	5.6 (4.0, 7.5)
delta.diastole	-0.80 (-1.45, 0.20)	0.00 (-0.40, 2.30)	0.00 (-1.10, 0.73)
days.after.discharge	30 (30, 34)	42 (33, 242)	42 (35, 49)

Data are median (1^{st} quartile, 3^{rd} quartile).

During follow-up, of 28 subjects who underwent SESAME with an intent to undergo TMVR:

- 6 underwent TMVR
- 10 reported sufficient symptomatic improvement that TMVR was deferred (of these 9/10 had baseline significant MS or MS/MR)
- 1 did not have sufficient enlargement of the neoLVOT allowing TMVR, which was therefore deferred
- 3 deferred TMVR because of frailty (n=2) or ultimately proved ineligible for large-annulus investigational TMVR (n=1)
- 2 died without TMVR
- 6 await disposition regarding TMVR at the time of this preliminary report

The off-label Emory experience, including 76 total patients, was recently reported[29] and extended the observations described above.

5.4.1 Summary of off-label clinical experience

In summary, during initial human application of SESAME for diverse indications, technical success was high (100%), and death (8%) and non-fatal serious complications (11%) were common. There appeared to be no SESAME-related complications after hospital discharge, analogous to the experience after surgical myotomy/myectomy. A large proportion of patients who underwent SESAME intending to enable TMVR either await disposition or were able to defer TMVR. These observations warrant further systematic investigation.

The off-label clinical experience informed selection criteria for the proposed protocol, which excludes patients with baseline hemodynamic instability.

5.5 Risk/Benefit Assessment

A formal risk assessment is included in Section 19.

5.5.1 Known Potential Risks (Anticipated Adverse Device Effects)

Complications of SESAME

- Ventricular septal defect from excessively deep cut
- Free wall ventricular perforation from excessively deep cut
- Pericardial effusion or tamponade, possibly requiring catheter-based or surgical drainage or repair
- Insufficiently deep cut causing procedural failure, and possibly requiring an alternative approach such as alcohol septal ablation, radiofrequency ablation, surgical ablation, or perhaps a second attempt at SESAME.
- Cardiac arrhythmia including atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation including cardiac arrest
- Conduction system defect which may require a temporary or permanent pacemaker
- Mitral valve injury, possibly requiring transcatheter or surgical repair
- Injury to the aortic valve causing aortic regurgitation, possibly causing hypotension or cardiogenic shock
- Coronary-cameral fistula, coronary artery spasm, or other coronary artery injury requiring treatment
- Thrombus formation in the laceration pocket
- Embolization of air, thrombus/clot, heart tissue, or atheroma, to coronary, cerebral, visceral, pulmonary or systemic circulation possibly causing symptomatic ischemia/infarction
- Heart enlargement (“remodeling”) over time, including causing heart failure
- Stroke or transient ischemic attack or paralysis
- Permanent disability
- Death

Complications of diagnostic and interventional catheterization

- Complications of percutaneous venous and/or arterial access including bleeding, retroperitoneal hematoma, local hematoma, perforation, fistula, pseudoaneurysm, compartment syndrome, peripheral nerve injury, chronic pain, infection, among other things
- Hypotension or shock or cardiopulmonary arrest including requiring cardiopulmonary resuscitation, chest compressions, cardioversion/defibrillation, vasoactive medications, and/or mechanical circulatory support and/or extracorporeal membrane oxygenation
- Myocardial ischemia or infarction (acute coronary syndrome or heart attack)
- Cardiac perforation from the catheterization tools, including the guiding catheters, electrified and non-electrified guidewires, snares, and intracardiac echocardiography catheters
- Mechanical failure of catheter tools including breakage and unintended retention of catheter or guidewire fragments
- Thromboembolism including venous thrombosis
- Other blood vessel perforation or injury, including requiring catheter or surgical treatment
- Acute kidney injury related to SESAME procedure or CT requiring temporary or permanent hemodialysis or other medical treatment
- Congestive heart failure, elevated natriuretic peptides, or cardiogenic shock that may require intervention
- Volume overload, pleural effusion, pulmonary edema, dyspnea, edema, pericardial effusion, or other congestion from procedure-related volume perturbations or other heart failure
- Respiratory failure requiring oxygen therapy, mechanical support or mechanical ventilation
- Infection including device infection, endocarditis, infection of a blood vessel
- Infection or sepsis including access sites, lung, urinary tract, or other system
- Abnormal blood tests including serum chemistry tests (creatinine, troponin), electrolyte imbalance, and including hematology tests (hemoglobin, hematocrit, platelets, white blood cells)
- Hemorrhage requiring transfusion or intervention
- Pain including chest pain, angina, back pain, access site pain, neuropathy, and generalized pain
- Pericardial effusion or tamponade requiring percutaneous or surgical treatment
- Pneumothorax, hydrothorax, and hemothorax
- Syncope, pre-syncope, seizure, delirium, or other loss of consciousness
- Other venous thrombosis or thromboembolism including deep vein thrombosis, and pulmonary thromboembolism
- Radiation injury including intractable skin injury
- High blood pressure

Allergic or inflammatory reactions to

- anesthesia,
- contrast media

5.5.2 Risks related to Radiation

In this research protocol, subjects will be exposed to fluoroscopy to guide SESAME. It is estimated (conservatively) that the amount of research radiation that a subject will be exposed to during participation in this research protocol will be approximately 3.6 rem from approximately 30 minutes of fluoroscopy during performance of SESAME, and 0.79 rem (each of two CT exams), and 5 minutes of fluoroscopy during follow-up catheterization. The total amount of radiation exposure from these procedures is equal to approximately 6.0 rem. This is equivalent to 20 years' worth of background terrestrial radiation exposure estimated at 0.3 rem per year.

We believe the total fluoroscopy exposure to be justifiable in this setting, given the seriousness of their cardiovascular disease. We estimate the benefit to the research subjects for these procedures to outweigh the risks.

5.5.3 Risks of Other Study Tests and Procedures

Electrocardiogram:

Skin irritations can occur where the adhesives attach.

Echocardiogram:

Some people feel discomfort during the echo with pressure from the echo probe. Some people feel tired from optional exercise.

Blood collection and Intravenous catheter:

Minor complications including bleeding, pain, and hematoma formation at the site of blood draws, vasovagal reactions or infections may rarely occur.

Six-minute walk test:

Fatigue, chest pain, rapid heart rate, and shortness of breath may occur.

Exercise VO2 test:

A mask placed over the face while you walk on a treadmill or peddle a bicycle. Some people feel claustrophobic from the mask. Some people feel tired from the exercise.

CT Scan:

Oral and/or intravenous contrast agents will be used and are usually well tolerated. However, some subjects will experience allergic reactions to intravenous contrast. Some patients who receive contrast agents may experience a temporary reduction in kidney function lasting up to

2 weeks following infusion. In rare instances, permanent renal damage can result from the use of the IV contrasting agent.

MRI

Magnetic fields in MRI scanners can cause dangerous interactions in patients with metallic foreign bodies: projectile effect, twisting, burning, artifacts, and device malfunction (interference with a pacemaker). Therefore, all patients need to thoroughly be screened individually for foreign bodies before undergoing an MRI scan.

The noise from the scanner may damage hearing, hearing protection must be used.

Risks from Gadolinium Based Contrast Agents (GBCA)

Gadolinium is a relatively very safe contrast; however, it rarely might cause allergic reactions in patients. Patients with impaired kidney function need to be evaluated carefully before injection of gadolinium for MRI procedure.

5.5.4 Risks to privacy: Personal Identifiable Information

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

Abstracted data will be coded (personally identifiable information removed but linking codes retained) and for transmission to participating investigators, clinical events adjudication committee, statistician.

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

5.5.5 Known Potential Benefits

5.5.5.1 Direct benefits

SESAME is intended to treat three related clinical problems described in Table 1 and listed below:

1: Hypertrophic cardiomyopathy with intracameral gradient (LVOTO), described as “HCM” and depicted in green.

2: Secondary left ventricular hypertrophy (LVH) with aortic or mitral valve disease and resting or provocable intracameral gradient, described as “Gradient group” and depicted in orange.

3: Secondary left ventricular hypertrophy (LVH) with aortic or mitral valve disease AND no intracameral gradient, but at risk for LVOT obstruction as a predicted complication of mitral valve replacement because of small neo-LVOT, described as “No gradient group” and depicted in light blue.

As such, SESAME may avert complications of standard treatments or techniques to prevent left ventricular outflow obstruction:

- SESAME is expected to reduce the frequency of failure known to complicate transcoronary alcohol septal ablation, which relies on anatomic coincidence of septal perforator coronary arteries and the obstructing ventricular septal tissue. SESAME may also avert other known complications of transcoronary alcohol septal ablation, including complete heart block requiring permanent pacemaker implantation, and including potentially-catastrophic non-target coronary injury from alcohol spillage.
- SESAME is expected to avert the known morbidity and complications of surgical ventricular myectomy related to cardiac surgery and cardiopulmonary bypass.

5.5.5.2 Indirect benefits

There is an indirect benefit of this protocol to society, through generalizability of findings to future patients.

5.5.6 Alternatives to research participation

Recently updated AHA/ACC guidelines on the management of hypertrophic cardiomyopathy confer a “Class I” indication, to patients with persistent LVOTO symptoms despite standard pharmacologic therapy, for septal reduction therapy or myosin inhibitors[30].

Surgical myotomy and/or myectomy is an alternative to SESAME.

Transcoronary alcohol septal ablation is an alternative to SESAME. Especially among patients requiring TMVR, transcoronary septal ablation is associated with a high incidence of complete heart block requiring permanent pacing therapy with attendant myocardial dyssynchrony, and with a high incidence of inadequate septal reduction related to coronary-artery-septal geographic mismatch[8]. Candidates for this study may already have undergone attempts at transcoronary alcohol septal ablation.

SESAME can be performed as “practice of medicine” outside of this research protocol.

Another alternative is pharmacologic management, which applies mostly to left ventricular outflow obstruction caused by hypertrophic cardiomyopathy. Pharmacologic options include monotherapy or combined therapy with agents including Class Ia sodium-blockers such as disopyramide, beta-adrenergic blockers, non-dihydropyridine calcium-channel blockers such as verapamil, and myosin inhibitors such as mavacamten.

Another alternative is conservative management, which typically combines pharmacologic management with deferral of surgical or transcatheter heart valve therapy and possibly of other therapies.

5.5.7 Investigator assessment of Potential Risks and Benefits

This is an early feasibility evaluation. The risks described above have been characterized and accumulated for this completely new strategy through the early clinical application of SESAME

technique in the care of patients at Emory to date. These risks appear necessary to endure in order to undergo SESAME for septal reduction therapy.

These risks appear appropriate to achieve medically-necessary septal reduction therapy using investigational SESAME given the selection criteria. Because of the medical necessity of septal reduction therapy, combined with the risk profile of participants meeting the selection criteria, and the potential clinical benefit, we believe the risks of undergoing investigational therapy are outweighed by the potential clinical benefits.

6 OBJECTIVES AND ENDPOINTS

6.1 Objective

The objective of this protocol is to test the safety and effectiveness of the SESAME septal debulking in patients with left ventricular outflow tract obstruction.

6.2 Hypotheses

We hypothesize that the interventricular septum can be engaged, traversed, and lacerated with SESAME to increase the predicted neo-LVOT. We also hypothesize that intracameral gradients can be relieved by SESAME.

6.3 Primary Feasibility Endpoint

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

- Alive
- Procedure success including
    - Successful myocardial entry, navigation, and snaring of guidewire traversal system; and
    - Successful laceration of septal myocardium

6.4 Primary Safety Endpoint

The primary safety endpoint at 30 days, is freedom from all of the following:

- All-cause mortality
- All stroke (disabling and non-disabling)
- Major cardiac structural complication requiring intervention (such as iatrogenic ventricular septal defect, iatrogenic aortic valve regurgitation, iatrogenic mitral regurgitation, or pericardial tamponade) related to SESAME

6.5 Secondary endpoint

The secondary endpoint is complete heart block requiring permanent pacemaker implantation, assessed at discharge.

6.6 Exploratory Endpoints

- Gradient reduction among subjects with hypertrophic cardiomyopathy, residual gradient ≤ 30mmHg at procedure conclusion and after 30 days
- 30d VARC-3 complications of SESAME including access, bleeding, vascular, stroke, myocardial infarction
- Symptom and functional status assessed at baseline, 30d, and 12 mo assessed by KCCQ-23 OS and CS, NYHA and CCS classifications, and 6 minute walking test
- Change in laceration dimensions and, when applicable, neo-LVOT and skirt neo-LVOT assessed by CT between baseline and 30 days
- Undergoes attempted septal reduction therapy ablation after SESAME during the study period
- Freedom from new permanent ventricular pacemaker implantation
- New electrocardiographic conduction defects before discharge
- Freedom from ventricular septal defect
- Freedom from pericardial effusion
- Freedom from stroke assessed at discharge

6.7 Rationale for Endpoints

Preliminary experience with clinical SESAME performed in the practice of medicine suggest that SESAME-related clinical events and myocardial septal remodeling appear largely complete within the first 30 days. We therefore propose to assess primary endpoints in the first 30 days.

The primary feasibility and safety endpoints capture the main intent of the SESAME procedure, which is to achieve anatomic lengthwise LVOT laceration (primary feasibility endpoint), without major complications (primary feasibility, safety, and exploratory endpoints), and with corresponding functional and anatomic benefit (exploratory endpoints).

The primary safety endpoint is assessed at 30d rather than at discharge to capture theoretical risk of stroke complicating intentional myocardial tissue injury.

Exploratory functional and anatomic outcomes are characterized at 30 days. MVARC endpoints are defined by Stone and colleagues[31].

7 STUDY DESIGN

7.1 Constant values

Number of subjects	15
Number of candidates screened, up to	30
Number of enrolling sites	2
Follow-up duration per subject	12 months
Expected study duration	30 months for enrollment + follow-up
Threshold of intracameral gradient considered significant	(30mmHg peak while resting; 50mmHg peak when provoked)

7.2 Overall Design

This is a prospective, open-label, single-arm, 2-enrolling site, independently-adjudicated early feasibility investigation of the SESAME (SEptal Scoring Along Midline Endocardium) procedure in subjects with manifest or potential left ventricular outflow tract obstruction.

Subjects are assessed before discharge and after 30 days, before follow-on procedures may be performed. Timing and rationale for endpoints are discussed in section 6.7 on page 28. Additional assessments are made at additional timepoints during the 12 months of study follow-up.

Enrolling site volunteer participation without direct financial support. NHLBI Division of Intramural Research is the data coordinating center that will not enroll subjects. Subjects undergo the study intervention and all screening and follow-up tests and procedures only at enrolling site(s).

7.3 Scientific Rationale for Study Design

The study is open-label and single-arm because it is an early feasibility study. It is premature to compare against other treatments.

7.4 Regulatory Rationale for Initiating the Study

SESAME was first developed and characterized in large-mammal non-clinical experiments. Thereafter SESAME was applied to a small number of patients as a practice of medicine. We have been unable to collect data adequately to characterize the risks, limitations, and benefits of SESAME without a significant-risk medical device study utilizing commercial devices off-label. Therefore we seek FDA license and ethics oversight.

8 STUDY POPULATION

8.1 Inclusion Criteria

In order to be eligible to participate in the study, candidates must meet all of the following criteria:

- Adults age ≥ 21 years
- Requires debulking of left ventricular septum for hypertrophic cardiomyopathy
- Septal diastolic thickness of obstructive “hump” on CT:
    - Total ≥16 mm, and
    - Predicted residual septal thickness ≥ 8 mm, and
    - Predicted laceration depth ≥ 6 mm
- Severely symptomatic, any of
    - NYHA Class III or greater
    - Canadian Angina Class CCS III or greater

- Explicitly chooses investigational SESAME over conventional treatment approaches including (1) cardiac myosin inhibitor therapy, if eligible; (2) transcoronary alcohol septal ablation, if eligible; or (3) surgical left ventricular myotomy and/or myectomy, if eligible
- Concurrence of the multidisciplinary institutional heart team that the candidate is at high risk for surgical myectomy
- Concurrence of the study Central Clinical Eligibility Committee

8.2 Willing to return for all scheduled follow-up activities, and eligible or able to undergo required protocol and testingExclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Does not consent to participate, or unable to consent to participate
- Requires antegrade SESAME access (because of mechanical aortic valve)
- Prior completed transcoronary alcohol septal ablation, or prior surgical myectomy
- Pregnant
- Hemodynamic instability or emergency procedure
- eGFR < 30 mL/min/1.73m^2
- Survival despite successful procedure expected < 12months

8.3 Rationale for selection criteria

The selection criteria identify candidates elaborated in section 5.3 on page 17.

The selection criteria allow enrollment of the intended population with little anticipated selection bias. 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.

Candidates who are eligible, if high risk, for standard transcoronary alcohol septal ablation or standard surgical myotomy/myectomy must be willing instead to undergo investigational SESAME.

Septal thickness used for selection criteria are measured at the thickest septal “hump” believed to cause LVOT obstruction. Candidates with thin interventricular septa are at increased risk of iatrogenic ventricular septal defect from SESAME. Specific septal thickness thresholds are estimated according to best available clinical judgement and preclinical data. Planned minimum residual septal thickness ≥ 8mm is intended to provide a safety margin against excessively deep laceration. Similarly, candidates with prior transcoronary alcohol septal ablation or prior surgical myectomy may have excessive septal fibrosis interfering with successful SESAME navigation or splay in this early investigation.

Candidates must have severe (Class III or Class 3) symptoms as specified to justify undergoing an early-stage investigational procedure.

Candidates with hemodynamic instability, such as requiring vasopressor medications, ongoing mechanical ventilation, or mechanical circulatory support are excluded.

Candidates with eGFR < 30 mL/min/1.73m^2 are excluded because follow-up research contrast imaging risks contrast-induced renal injury (after CT) or nephrogenic systemic sclerosis (after CMR).

Cognitively-impaired candidates are excluded based on our experience with inability to comply with quality-of-life questionnaire instruments, and frequent unwillingness to return for follow-up in protocols such as this one.

Pregnant candidates are excluded because of the risk of radiation injury to the fetus during the research procedure.

Children are excluded because this is an early feasibility study and additional safety information is warranted before SESAME is applied to children. There is no maximum eligibility age because there is no scientific basis for age-based exclusion *per se*.

We believe there is no justification to select candidates based on left ventricular ejection fraction (LVEF) in the proposed SESAME IDE protocol, which selects subjects with primary or secondary LVH and/or small ventricles. These have largely-preserved left ventricular systolic function as assessed by LVEF.

8.4 Inclusion of Vulnerable Participants

8.4.1 Inclusion of Pregnant Women

Pregnant women will be excluded from the enrollment into this study.

Pregnancy after SESAME will not lead to study discontinuation. The inclusion of pregnant women into this protocol is necessary for completion of the study objectives. In addition, continuing participation in the study holds out the prospect of direct benefit to the pregnant woman during the post-procedure follow up as it ensures subject's safety. All follow-up visits will continue through the 12 month period. Pregnant subject can undergo all follow-up procedures through the 12 month except for CT scans to avoid medical radiation exposure to the fetus.

8.4.2 Inclusion of adult subjects who lack capacity to consent to research participation

Cognitively-impaired candidates unable to provide consent will be excluded from the enrollment into this study. In the event subjects become cognitively-impaired after the index SESAME procedure, they may remain enrolled in the study for the follow up assessments as it is necessary for completion of the study objectives. In addition, continuing participation in the study holds out the prospect of direct benefit to the subject during the post-procedure follow up as it ensures subject's safety. All post-procedure data, while collected for research, are required for clinical care, and the only residual risk is to privacy and confidentiality. If subjects will remain in the study, a Legally Authorized Representative (LAR) will be identified and informed consent obtained from the LAR, as described in Section 14.10.3.

8.5 Lifestyle Considerations

Not applicable

8.6 Screen Failures

Study eligibility is based entirely on clinical records and medically indicated imaging studies.

Subjects consent to participate in the study before undergoing any study-specific activity.

Subjects are classified as screen failures if they undergo study-specific catheterization but NOT an attempt at SESAME.

Baseline data acquired for screen failures are retained to facilitate reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

In the case of aborted SESAME without evident sequelae, subjects may go off-study as soon as they are clinically stable, but will undergo at least 30 day follow-up. Such subjects need not undergo additional follow-up for exploratory efficacy or natural history assessment, and will be recorded as screen failures.

By contrast, in case of failed SESAME, subjects must complete scheduled follow-up.

Subjects are eligible for repeat screening and enrollment, in which case they are assigned new subject specific identifying numbers (SSPIN).

8.7 Strategies for Recruitment and Retention

Subjects will be recruited from the Structural Heart Disease clinical programs of the participating medical center(s).

We expect to accrue two subjects per month. There is no subject enrollment at NIH Clinical Center.

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.

8.7.1 Costs

Subjects are responsible for the costs of medical care associated with participating in this protocol.

NHLBI is the Sponsor, which automatically qualifies sites for CMS reimbursement for costs of research-related medical care, according to the CMS Clinical Trial Program (CTP), for CMS beneficiaries. The CTP policy is described on

https://www.cms.gov/Medicare/Coverage/ClinicalTrialPolicies/index.html.

The result is that 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.”

8.7.2 Compensation

Candidates and subjects receive no compensation for screening or for participating in this study.

9 TEST ARTICLES AND INDICATIONS FOR USE

The test articles are commercially available. They are used off-label in this research protocol. The manufacturer is not participating in this protocol.

9.1 Asahi-Intecc Astato XS 20, 510(k) K103057, and Astato XS 40, 510(k) K153443

9.1.1 Labeled Indications For Use

Asahi-Intec Astato XS 20 and XS 40: 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.

The two devices differ only in tip load rating (20g vs 40g), and share a common instructions for use (IFU) document.

9.1.2 Intended Use in the Protocol

The intended use is traversal and laceration of left ventricular myocardium to accomplish transcatheter interventricular septal myotomy.

The intended use is not addressed in the labeled indications for use (above).

The Astato 0.014” guidewires are used for transcatheter electrosurgery in this procedure. The midshaft is focally denuded and electrified for the leaflet traversal step. Our group has employed this off-label guidewire configuration to lacerate native and bioprosthetic heart valve leaflets in patients[5, 6, 15, 32-44]. These LAMPOON- and BASILICA-related procedures have become *de facto* standards of care.

9.2 Asahi-Intecc Confianza Pro 12, 510(k) K171933

9.2.1 Labeled Indications For Use

Asahi-Intecc Confianza Pro 12. ASAHI PTCA Guide Wires are intended to facilitate the placement of balloon dilation catheters during percutaneous transluminal coronary angioplasty (PTCA) and percutaneous transluminal angioplasty (PTA). The ASAHI PTCA Guide Wires are not to be used in the neurovasculature.

9.2.2 Intended Use in the Protocol

The intended use is traversal and laceration of left ventricular myocardium to accomplish transcatheter interventricular septal myotomy. The intended use is not addressed in the labeled indications for use (above).

In SESAME, the ConfianzaPro12 0.014” guidewire is used mechanically to pierce and engage the basal septal myocardium. It is modified at the bedside by scissor-amputation of the distal ~10mm to enhance tip stiffness. This had been standard technique of electrosurgical transcaval access to the abdominal aorta in patients[45-49]. Transcaval access has become a standard medical practice.

This bedside-modified guidewire configuration has been employed in swine [17] and a small number of SESAME procedures in patients. [See Clinical SESAME in section 5.4 on page 19, and reference[18]]. The same guidewire configuration, electrified, had been used widely to accomplish transcaval access to the abdominal aorta[46, 48-50].

10 STUDY INTERVENTION

10.1 Study Intervention Description

Candidates will be identified by the participating structural heart disease program(s).

Candidates will undergo clinical evaluation, echocardiography, coronary arteriography, contrast-enhanced gated cardiac CT, and (when possible) cardiovascular magnetic resonance. Eligibility will be reviewed and proposed by the local multidisciplinary heart teams. The multidisciplinary institutional heart team consists of structural interventional cardiologists, structural imaging cardiologists, and cardiac surgeon(s). Additional disciplines may also participate.

Candidates will then undergo central eligibility review by the sponsor and designated investigators (Central Clinical Eligibility Committee). If deemed eligible, candidates will be offered participation in the study.

Once enrolled, subjects will undergo baseline assessment and blood tests not already available from prior medical care (see Schedule or Activities in section 3.3).

If CMS or insurance coverage is available, they will undergo optional commercial genetic testing for HCM "phenocopies" to determine etiology of primary LV hypertrophy.

10.1.1 SESAME procedure

Subjects will be admitted to the hospital and undergo SESAME.

The SESAME procedure is planned from contrast-enhanced CT to plan a suitable traversal and laceration trajectory, projection angles, and radiographic fiducial landmarks. Trajectory plans identify basal septal entry points, aligned with the LVOT, and aim to “shave the hump” of

excess septal tissue evident on CT. The trajectory plan results in an intended LV- and RV-septal depth and length which can be corroborated by intraprocedural echocardiography.

The SESAME procedure is performed under general anesthesia or under moderate sedation at the discretion of the institutional heart team. The SESAME procedure has multiple steps:

- Echocardiography to guide septal catheter and guidewire position, and to assess procedural myocardial anatomy and performance , including transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and when necessary intracardiac echocardiography (ICE) via a deflectable transvenous guiding sheath in the right atrium, right ventricle, or positioned trans-septally or retrograde transaortic.

- Antithrombin anticoagulation at the discretion of the operators, which is typical for structural interventional catheterization procedures.

- Transfemoral arterial retrograde introduction of a deflectable introducer sheath into the ascending aorta to position a preshaped guiding catheter across the aortic valve to engage the basal interventricular septum. An additional retrograde transfemoral catheter is positioned across the aortic valve into the left ventricle as a anatomic marker and to exchange for a snare-catheter system.

- Baseline hemodynamics and echocardiographic gradients and valvular function are recorded, typically along with left ventriculography. This includes conductance catheters and venous preload-altering balloon catheters when possible, to examine end-diastolic and end-systolic pressure-volume relationships.

- A guidewire test article (amputated stiff 0.014” *ConfianzaPro*-12 guidewire or *AstatoXS-20/40*) is advanced to enter the basal septum and deliver a 0.014” microcatheter. The guidewire may then be removed to exchange for a 0.014” *AstatoXS-20/40* guidewire (test article). Multiple guidewires and microcatheters may be employed.

- The *AstatoXS-20/40* guidewire is navigated through the ventricular septal myocardium and the microcatheter advanced in tandem until a suitable endocavitary left ventricular reentry is accomplished. Fluoroscopy, echocardiography, intracardiac electrocardiography, and contrast left ventriculography are used to guide navigation and confirm guidewire position.

- Myocardial entry or traversal may be assisted by electrosurgery 5-50W as needed.

- Navigation guidewires may be connected to hemodynamic monitoring or recording systems to display unipolar electrogram morphology, and may also be connected to a marketed electroanatomic mapping system.

- The guidewire is ensnared, and a modified “Flying-V” lacerating surface introduced[15], which has been typical for electrosurgical laceration of cardiac leaflets. Operators take care to form the “Flying-V” using the blunt edge, not the sharp edge, of a scalpel. The guidewire limbs are insulated with coaxial microcatheters and/or catheters and/or balloon catheters.

- The guidewire position is examined and confirmed.
- The modified “Flying-V” is energized while the field is flooded with 5% dextrose or 0.9% saline infusion through the guiding catheters to minimize thromboembolism[15], and laceration is performed. Care is exerted to assure the aortic valve leaflets are not exposed to energized laceration wires. Flush is a least 2mL/s through each catheter. Guidewire is energized for maximum of 2s, separated by pause of at least 5s to allow tissue to cool, for multiple energy applications until laceration is complete.
- Concomitant TAVR, if indicated, is allowed during the same interventional catheterization encounter as SESAME, at the discretion of the operators
- Cerebral embolic protection devices are employed at the discretion of the operator.
- Completion hemodynamics and echocardiographic gradients and valvular function are recorded. This includes conductance catheters and venous preload-altering balloon catheters when possible, to examine end-diastolic and end-systolic pressure-volume relationships.
- Finally, percutaneous arterial and venous vascular hemostasis is obtained.

10.1.2 Post-Procedure

- The subject convalesces in the appropriate inpatient recovery unit.
- Anticoagulation and antiplatelet therapy is prescribed after discharge at the physicians’ discretion, and is recorded.
- For subjects who have permanent pacemakers, devices are interrogated at baseline, before discharge, and at 30 days follow-up to determine fraction of paced ventricular beats.
- Follow-up blood tests, ECG, transthoracic echocardiography, optional CT, exercise exams, CMR are recorded as described in the Schedule of Activities (3.3). Clinically-indicated blood test results are recorded for research. These are repeated at multiple timepoints.
- Additional scheduled visits include assessments of adverse events, symptom and functional status, and imaging examinations as listed in section 3.3 on page 12.

10.1.3 Termination visits

- For subjects who die during the study, autopsy evaluation is requested to examine the heart at NIH.
- Subjects’ participation in the study concludes at the 12 months follow-up and off-study visit.

10.1.4 Study duration

Subjects participate through the 12 months follow-up and off-study visit.

We aim to complete the study in 30 months for enrollment + follow-up.

10.1.5 Number of enrolling sites

Up to 2 site(s) will enroll and treat subjects in this study.

10.2 Preparation/Handling/Storage/Accountability

Commercial devices will be acquired, maintained, and stored in standard clinical inventory. Lot numbers will be recorded in the medical record.

Bedside modification of the test articles will be performed as described above.

10.3 Measures to Minimize Bias: Randomization and Blinding

Not applicable to this open-label study.

10.4 Study Intervention Compliance

Protocol compliance will be assured by source document (medical record) to case-report-form data verification by independent data monitors.

10.5 Concomitant Therapy

There are no restrictions on concomitant therapy.

11 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

11.1 Discontinuation of Study Intervention

SESAME employs single-use disposable devices with no components implanted.

In general, once a subject consents and undergoes the SESAME catheterization procedure, the procedure is either not initiated, it is aborted because of technical failure, or it is completed.

11.2 Aborted or abandoned SESAME

In the case of aborted SESAME without evident sequelae, subjects may go off-study as soon as they are clinically stable, but will undergo at least 30 day follow-up. Such subjects need not undergo additional follow-up for exploratory efficacy or natural history assessment, and will be recorded as screen failures.

By contrast, in case of failed SESAME, subjects must complete scheduled follow-up.

11.3 Subject Discontinuation/Withdrawal from the Study

Reasonable efforts will be made to undertake protocol-specified safety follow-up procedures to capture adverse events and adverse device effects, both serious and not, as well as unanticipated problems, through the 30-day follow-up visit.

Subjects are free to withdraw from participation in the study at any time upon request. If a subject repeatedly and consistently declines to return for follow-up evaluation, the investigators may be forced to withdraw the subject from the study prematurely.

However, since the study intervention (SESAME procedure) will already have been performed, withdrawal means these subjects would be withdrawing from follow-up of endpoints and adverse events. For the sake of safety, subjects will be advised not to withdraw.

Pregnancy after SESAME will not lead to study discontinuation, although research-related radiation (CT) will be avoided to avoid medical radiation exposure to the fetus.

11.4 Loss to Follow-up

A subject will be considered lost to follow-up if he or she fails to return for 3 consecutive scheduled visits and despite attempts at contact by the study site staff.

The following actions must be taken if a subject fails to return to the enrollment site for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls to the subject, contact to the referring physician, and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

12 STUDY ASSESSMENTS AND PROCEDURES

12.1 Screening Procedures

Screening prior to consent is based entirely on clinically-indicated medical encounters, blood tests, laboratory and clinical examinations (cardiac catheterization, echocardiography, CT, CMR, blood tests), review of medical records, and communication with candidates (in-person, via telephone, via telepresence, in writing, or via email).

The screening data are reviewed by the local multidisciplinary heart team, and then are reviewed by the Central Clinical Eligibility Committee before screening is complete. Candidates are only invited to participate if eligible.

Enrolling sites will comply with Health Insurance Portability and Accountability Act (HIPAA) if applicable.

12.1.1 Clinical activities performed to screen for eligibility prior to obtaining research informed consent

Minimal risk activities that may be performed before the subject has signed a research consent include the following:

- Email, written, in person or telephone communications with candidates.
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing medical imaging examinations

These data may be analyzed for the research study after the subjects consents to participate.

12.2 Efficacy Assessments

Efficacy assessments are performed by qualified laboratories and staff at enrolling sites. Standard clinical examinations (such as vital signs and symptom classification), clinical blood testing, and clinical cardiac imaging procedures (such as echocardiography, cardiac CT, CMR) are performed by clinical laboratories at the enrolling sites.

Unscheduled clinically-driven imaging exams (echocardiography, CT, CMR) are analyzed for efficacy and safety in this study.

CT assessments: septal geometry, septal split geometry, cardiac chamber dimensions and function. The schedule of first post-SESAME CT can be altered at the discretion of the attending physician, which can be performed before discharge rather than at 30 days. CT exams are analyzed by a NHLBI core laboratory. Complications, such as VSD, trigger non-structured analysis and reporting not reflected in the case report form..

Fluoroscopy assessments include procedure step clock times extracted from DICOM headers, and qualitative assessment of procedure steps such as intramyocardial navigation, distances, and ventriculography measurements. Fluoroscopy assessments include accompanying invasive hemodynamic measurements. These are analyzed by a NHLBI core laboratory.

Echocardiography assessments include

- Procedural assessments: intracameral gradients, and septal split geometry. These are analyzed by a NHLBI core laboratory.
- Function assessments: Chamber size and function, global strain, at baseline and follow-up
- Complications, such as VSD, trigger non-structured analysis and reporting not reflected in the case report form.

Cardiac magnetic resonance (CMR) assessments include chamber size, function, relaxometry, extracellular volume (ECV), late gadolinium enhancement, regional strain, at a single inpatient timepoint, felt to combine baseline (morphological, relaxometry) and local iatrogenic (oedema) characteristics of the heart immediately following-SESAME. A copy of the FDA medication guide will be provided to subjects as part of research-related gadolinium-contrast-enhanced CMR.

Electrocardiography assessment includes conduction and rhythm assessment, at baseline and follow-up. Local site automated measurements are recorded, and ECG records are stored for central re-analysis as needed.

Standard research assessments (questionnaires such as KCCQ-23) are performed by qualified staff at enrollment sites according to a study Manual of Operations and according to an instruction-oriented Case Report Form.

12.3 Safety and Other Assessments

Standard safety assessments (adverse event assessments) are performed by qualified staff at enrollment sites according to the Protocol Schedule of Activities and a study Manual of Operations and according to an instruction-oriented Case Report Form.

Safety assessments follow a structured adverse event case report form and are corroborated by independent data monitors and, for primary endpoints, by an independent clinical events adjudication committee.

12.4 Assessment of neurovascular events (stroke and TIA)

Formally-trained and certified research coordinators will perform baseline and follow-up assessments of modified Rankin Score and NIH Stroke Score.

Training and certification will be obtained from an educational service such as BlueCloud.

12.5 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

12.5.1 Definition of Adverse Event

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 (21 CFR 312.32 (a)).

This includes:

- 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 SESAME cardiac catheterization procedure and recovery from the procedure and do not directly result from use of the investigational devices.

12.5.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Event (SAE): A serious adverse event that results in any of the following and NOT directly related to the device (21 CFR 812.3(s)). 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.

12.5.3 Definition of Adverse Device Effect (ADE)

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.

This includes procedural events directly related to the SESAME procedure and recovery from the procedure in addition to use of the investigational devices used for SESAME.

12.5.4 Definition of Serious Adverse Device Effect (SADE), Anticipated Adverse Device Effect (AADE), and Unanticipated Adverse Device Effect (UADE)

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.

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. Please refer to the list of anticipated adverse device effects (AADE) in section 5.5.1 on page 22.

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.

12.5.5 Classification Adverse Events

12.5.5.1 Severity of Event

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.

12.5.5.2 Relationship (Attribution) to Study Intervention

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.

12.5.5.3 Expectedness

Please see the list of anticipated adverse device effects (AADE) in section 5.5.1 on page 22.

The Principal Investigator and the Site Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

12.5.6 Intervals and Frequency for Event Assessment and Follow-Up

Adverse event assessment, recording, and reporting will start on Day (0), upon attempt at a SESAME procedure and will continue through the 12 months follow up.

New events or conditions present at baseline that increase in severity will be recorded and evaluated and reported on the adverse event 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 using study specific case report forms, and then entry into the NIH electronic data base, CTDB (or equivalent). Adverse event case report forms and all source documentation supporting the adverse event will be transmitted to the Sponsor for review prior to entering the event into CTDB. Unanticipated adverse device effects (UADE) and Unanticipated problems (UP) must be submitted to the Sponsor for review and approval prior to submitting to the Central IRB. Sponsor will review, and if appropriate, provide suggestions to the site Primary Investigator. The enrolling site will then enter event into CTDB, and submit the report to the IRB using the electronic IRB system. Sponsor will then submit final report to the NHLBI Office of the Clinical Director (OCD).

Monitoring visits will be conducted by the Sponsor to review source documentation, and accuracy and completion of the adverse event case report forms.

12.5.7 Adverse Event Reporting

Reporting obligations and deadlines are summarized in Appendix A: Tables of Reporting Obligations.

12.5.8 Enrolling site reporting to local institutional and ethics bodies

It is the responsibility of the Site Investigator to report adverse events and adverse device effects to their institutional ethics and regulatory bodies according to their local reporting requirements.

12.5.9 Events of Special Interest

Not applicable

12.5.10 Reporting of Pregnancy

Pregnancy occurring during follow-up after the initial SESAME procedure, should be reported to the enrolling site primary investigator and research coordinator. Pregnancy after SESAME will not lead to study withdrawal, although there will be no subsequent research-related radiation

(CT) to avoid research radiation exposure to the fetus. All follow-up visits will continue through the 12 month period.

12.6 Unanticipated Problems

12.6.1 Definition of Unanticipated Problems (UP)

Any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; and
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others (which many include research staff, family members or other individuals not directly participating in the research) at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or expected.

12.6.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the Sponsor and Institutional Review Board (IRB).

12.7 Protocol Deviations and Non-Compliance

It is the responsibility of the investigator to use continuous vigilance to identify and report deviations and/or non-compliance to the Institutional Review Board The investigator is responsible for knowing and adhering to the reviewing IRB requirements.

Reporting obligations and deadlines are summarized in Appendix A: Tables of Reporting Obligations. All protocol deviations must be reported by the Sponsor to the NHLBI Clinical Director as specified.

12.7.1 NIH Definition of Protocol Deviation

A protocol deviation is any changed, divergence, or departure from the 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.

13 STATISTICAL CONSIDERATIONS

13.1 Statistical Hypothesis

There are no statistical hypotheses for this single-arm device evaluation study.

13.2 Sample Size Determination

The sample size is not statistically derived.

Up to 30 subjects will be consented until 15 subjects undergo attempted SESAME in this protocol.

13.3 Populations for Analyses

The analysis will be per-protocol, and as-treated, of subjects who undergo an attempt at SESAME.

13.3.1 Evaluable for toxicity

Complications are reflected in the primary safety endpoint, in secondary endpoints, and exploratory endpoints described in section 6.3 beginning on page 27.

13.3.2 Evaluable for objective response

Efficacy is evaluated in the primary efficacy endpoint, in secondary endpoints, and exploratory endpoints beginning in section 6.3 beginning on page 27

13.4 Statistical Analyses

Exploratory data analysis will assess for missing values and will generate data clarification requests as required.

The primary analyses will be descriptive including demographic values and primary, secondary, and exploratory endpoints. Descriptive statistics will include appropriate measures of central tendency and variance, and tests of normality as appropriate. Post-hoc analyses will be performed as unusual observations and novel questions arise, including those requiring additional data abstraction from the source documents or images.

Statistical analysis will be performed or confirmed by the NHLBI DIR study statistical investigator.

13.5 Stopping Rule Guidance for Data and Safety Monitoring Board (DSMB)

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[51]. 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 = 0.3, b =2.7. 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	Consider stopping if the number of deaths within 30 days reaches
2 - 5	2
6 - 11	3
12 - 15	4

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%
Proportion of Stopped Studies	4%	20%	46%	71%	87%	96%
Average number of subjects	29.2	26.2	21.6	16.9	12.8	9.7
Average number of 30-day mortality	1.5	2.6	3.3	3.4	3.2	2.9

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.

14 STUDY GOVERNANCE AND OTHER OPERATIONAL CONSIDERATIONS

14.1 Sponsor Representative

As the study Sponsor representative 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.

The Sponsor Representative is the point of contact for enrolling sites to report all events of regulatory significance.

14.1.1 General Sponsor Duties

The Sponsor's general duties consist of submitting the appropriate regulatory applications, selecting investigators and enrolling sites, obtaining their signed agreement, providing them with the information necessary to conduct the study, assuring proper clinical protocol conduct, ensuring proper clinical site monitoring, and ensuring study subject informed consent is obtained.

14.1.2 Data Coordinating Center

NHLBI will serve as data coordinating center (DCC) for the study. The DCC will provide study protocol, questionnaires, data collection forms, and data analysis; will collaborate in manuscript preparation; and will provide overall study training, coordination and quality assurance, including coordination of the activities of the Data and Safety Monitoring Board (DSMB) and the Study Central Clinical Eligibility Committee.

14.2 Site Selection and Training

14.2.1 Site selection:

Site selection is based on

- Physician expression of interest and availability of suitable study candidates at the site.
- Site prior participation in IDE protocols evaluating a treatment of structural heart disease, with investigators willing and able to comply with the requirements of this protocol.
- Preference is given to sites with high volume structural heart intervention programs, operators with high technical proficiency, and successful prior collaboration with NHLBI Division of Intramural Research.
- Further preference is given to sites that have achieved high volume and proficiency with SESAME-related procedures such as LAMPOON.
- Sites must demonstrate ability to obtain CT examinations that are technically satisfactory for consideration of SESAME.
- Sites should have biplane fluoroscopy available to conduct SESAME procedures until alternative image guidance modalities are available

Site(s) must have telepresence transmission capability for remote biplane viewing and teleproctoring (such as *Medinbox*, Toulouse), at no cost to the sponsor

14.2.2 Site training:

The Sponsor Representative will ensure appropriate training in the technique of SESAME prior to enrollment at any participating institution.

Site training will consist of

- NHLBI Investigator and/or Sponsor didactic training about the technique, preclinical, and clinical experience to date.

- When logistically feasible, site investigator observation of SESAME procedures at a luminary site such as Emory University.
- Proctored conduct of SESAME procedures in subjects at the study site, at the discretion of the Sponsor representative, in-person or via telepresence.

Completion of training, and suitability for independent SESAME enrollment, will be certified by the NHLBI Principal Investigator and Sponsor Representative.

14.3 Study Central Clinical Eligibility Committee

Clinical data for all research candidates are confirmed by the study Central Clinical Eligibility Committee in telepresence or in-person meetings before enrollment.

The Study Central Clinical Eligibility Committee consists of the NHLBI Principal Investigator and associate investigators, the site Principal Investigators, a non-interventional cardiologist, 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 NHLBI 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 Central Clinical Eligibility Committee will be recorded.

14.4 Core Laboratories

CT, Fluoroscopy, and CMR, and Echocardiography Core Laboratories will analyze baseline, procedure, and follow-up exams. Their activity is summarized in section 12.2.

14.5 Clinical Events Adjudication Committee (CEAC)

An independent CEAC will review monitored data to assure accuracy. The CEAC will be an independent contractor, and the charter will be agreed between the NHLBI Principal Investigator and the CEAC after the contract is awarded, which will be after final IRB approval.

The CEAC will review all of the following events that occur in the 30-day follow-up interval

- Primary (Efficacy) and (Safety) Endpoints

The CEAC will classify relatedness of the above events to the SESAME system devices. CEAC adjudication prevails over Principal Investigator classifications.

14.6 Data and Safety Monitoring Board (DSMB)

The standing Data and Safety 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. For oversight of this protocol, DSMB will employ full-time or ad hoc members with expertise in **transcatheter structural heart disease intervention.** Members of the DSMB are independent from the study conduct and free of conflicts of interest.

The NHLBI DSMB charter is on file with NHLBI and is approved by the NHLBI Director and/or NHLBI Clinical Director.

The NHLBI DSMB will review the protocol progress report at pre-specified intervals, or more frequently upon request of PI, IRB, and/or NHLBI Clinical Director. These progress reports are prepared by the NHLBI Principal Investigator and study staff. The DSMB may recommend early termination of the study for considerations of safety and efficacy. Unanticipated Adverse Device Effects (UADEs) will be reported to the DSMB following the same timelines as the IRB (See section 12.5.7 on page 43.

In the case of death or serious UADE, if the Sponsor and the NHLBI Principal Investigator or DSMB 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 sites will be notified of this action.

A “stopping rule” is described in section 13.5 on page 45 as non-binding guidance for the Investigators and the DSMB to assure subject safety. This is based on anticipated 30-day mortality. This is intended to assist and not automate decision-making.

14.7 Publications Committee

The study publications committee consists of the NHLBI Principal Investigator and the local site Principal Investigators.

Investigators may not independently publish, present, or disclose study results, in whole or in part, without permission of the Publications Committee.

14.8 Publication and Data Sharing Policy

14.8.1 Human Data Sharing Plan

Results of the study will be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. The results of the study will be released within 12 months of study completion.

Investigators may not independently publish or disclose study results without permission of the Publications Committee (See section 14.7).

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. All dataset(s) that can be shared will be deposited in NIH Biomedical Translational Research Information System (BTRIS).

Data from this study may be requested by other researchers indefinitely, beginning one year after the completion of the study by contacting the NHLBI Principal Investigator.

14.8.2 Posting of anonymized image data on public data repository

Anonymized (personally identifiable information and linking codes removed) data and images may 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, 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).

14.8.3 Data transfer to collaborators

De-identified images (with linking codes retained) will be transferred to collaborating investigators at academic and industry sites, for the purposes of research, education, and quality assurance. These collaborators include

Recipient	Organization	Location	Linkable
D. Korel Yildirim	NHLBI Division of Intramural Research	Bethesda, MD	Linked
Nasser Rafiee	Transmural Systems	Andover, MA	Linked
Rebecca Hahn	Columbia University	New York, Y	Linked

14.9 Intellectual Property

The Sponsor has full rights over any invention, discovery, or innovation, patentable or not, that may occur when performing the study.

14.10 Informed Consent Process

14.10.1 Consent/Assent Procedures and Documentation

Subjects who are UNABLE to provide consent may NOT be enrolled. The use of a legally authorized representative (surrogate), or telephone consent is not permitted.

The method of obtaining and documenting the informed consent and the contents of the consent complies with ICH- GCP and all applicable regulatory requirement(s). Informed consent will be obtained by the enrolling site Principal Investigator and enrolling site personnel who are listed on the Delegation of Authority Log. The most recent IRB-approved consent will be used.

The candidate will be asked to consider participating (consent) during a clinical encounter to discuss structural heart disease treatment.

The investigational nature and objectives of the trial, the procedures and treatments involved, and the risks and discomforts and potential benefits will be carefully explained in person to the candidate. The consenting process will be a verbal review of the IRB-approved consent in a language understandable to the subject, free of any exculpatory language to avoid any possibility of coercion. Candidates will be given ample opportunity to read the study consent in private and to discuss with family, personal physicians, or others as desired; to ask questions; and to allow sufficient time to determine whether or not to participate in the research study.

The informed consent document will be signed and dated in the presence of the authorized study staff, who will also sign and date as appropriate. The subject will then receive a hard copy of the informed consent document.

The research consenting process will be documented in the subjects medical record with the signed and dated IRB research consent. Electronic consent will not be employed in this research study.

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.

14.10.2 Informed consent for non-English speaking subjects

Enrolling sites will follow IRB processes for short form consent of non-English speaking research participants. This includes use of pre-approved short form consent templates. If no short form consent is pre-approved in the candidate's native language, or if a different short form consent is used, the certified translation 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

14.10.3 Consent of Subjects who lose decision-making ability during the study

Adults with decisional impairment are not eligible to enroll in the study.

In the event subjects lose the ability to consent after the index SESAME procedure, they will remain in the study, because the main risk of investigation is confined to the index procedure. All additional data, while collected for research, are required for clinical care, and the only residual risk is to privacy and confidentiality.

Decision-making is assessed during scheduled follow-up events. When subjects lose decision-making ability, affirmation of consent is sought directly from the Legally Authorized Representative (LAR) at the enrolling site. Local State laws apply.

If the study team is unable to identify a Legally Authorized Representative, the team will seek guidance from the local institutional ethics service.

Having failed to obtain affirmation of consent, the subject is withdrawn from the study.

14.11 Unscheduled Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to affected regulatory bodies including enrolling site Investigators, central IRB, Sponsor (NHLBI Office of Clinical Director), NHLBI Principal Investigator, Device Manufacturer, and FDA.

If the study is prematurely terminated or suspended, the NHLBI Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension.

Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, IRB and, as applicable, the Food and Drug Administration (FDA).

14.12 Confidentiality and Privacy

In order to maintain subject privacy, accountability records, study reports, and communications will identify the subject by initials and the assigned subject number.

However, medical records will be transmitted and stored as source documents and will retain patient names and/or medical record numbers, to allow physician-investigators to recommend medical therapies as appropriate, to avoid risk of mis-identification.

In addition, electronic (DICOM-format) medical images transmitted for the purpose of this study **will retain patient identifiers**.

The study monitor, other authorized representatives of the Sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical

records (office, clinic, or hospital) and pharmacy records for the participants in this study. The enrolling study site will permit access to such records.

The study participant's contact information will be securely stored at each enrolling site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or Sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NHLBI. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by enrolling sites and by NHLBI research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NHLBI.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14.13 Future use of Stored Specimens and Data

Data may be stored indefinitely. Imaging data in PACS may be stored indefinitely.

Subjects are asked consent to future use of their clinical and imaging data indefinitely. Following analyses of data for primary research purposes as described in the protocol, images suitable for future research will be stored. Any future research use of identifiable data not defined in the research protocol will occur only after IRB review and approval.

Upon withdrawal of consent, we undertake diligently to destroy imaging data that might be used for future research.

Autopsy specimens will be handled according to local institutional medical standards and will be disposed accordingly. We do not intend to store these specimens for future use.

See also Section 14.12, Confidentiality and Privacy and Section 14.16, Data Handling and Record Keeping, for further information on future use of study records.

14.14 Clinical Monitoring

As per ICH-GCP 5.18 and FDA 21 CFR 312.50 clinical protocols are required to be adequately monitored by the study sponsor. Clinical site monitoring is conducted to ensure that the rights

and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

14.14.1 Independent Data Monitor:

Independent data monitors will visit sites in-person or using remote telepresence with the following visit objectives:

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

The monitors also will inspect the enrolling 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.

The Sponsor and sites will be provided copies of monitoring reports within 30 days of visit.

Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.

14.14.1.1 Schedule of Monitoring Activities

Monitoring visits will be conducted after the first subject is treated and returns 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 enrolling site must be resolved within 7 days of site notification.

14.14.1.2 Extent of monitoring activities

The monitors will provide 100% source-data verification of case report forms including adverse event reports.

Routine independent audits will not be conducted.

14.14.2 NHLBI Principal Investigator Monitoring:

Accrual and safety will be monitored by the NHLBI Principal Investigator, seeking unusual or unexpected events, morbidity, or mortality.

14.14.3 Institutional Review Board (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.

14.14.4 Data and Safety Monitoring Board (DSMB) Monitoring

DSMB activities are described in section 14.6 on page 48

14.15 Quality Assurance and Quality Control

Quality assurance measures include

- Diligent investigator procedure training in SESAME technique and device operation
- Sponsor and investigator participation (when available) and review of SESAME procedures
- Site initiation visit by NHLBI Principal Investigator, NHLBI Study Manager, and independent data monitors

Quality control measures include

- Site Principal Investigator review of completed case report forms
- Study Manager review of case report forms with data clarification request reconciliation
- Data entry into an auditable electronic case report database
- Independent data monitor source-data verification with data clarification request reconciliation
- NHLBI Principal Investigator review of case report form data
- Independent core lab review of imaging endpoints
- Study Statistician review of case report form data. Errors will be corrected by investigators and data manager
- Independent Clinical Events Adjudication committee adjudication of primary endpoints

14.16 Data Handling and Record Keeping

Clinical data (including adverse events (AEs), concomitant medications, and adverse reactions data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant data capture system provided by the study Sponsor. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

14.16.1 Case Report Form Completion

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The site investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source document worksheets should be prepared in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Case Report Forms (CRFs) will be completed for each study subject. It is the site Principal Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's Case Report Forms. Source documentation supporting the Case Report Forms 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 site Principal Investigator or designated representative, should complete the Case Report Forms 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.

14.16.2 Direct Access to Source Data

Site investigators will follow Sponsor monitoring and auditing procedures to assure compliance with GCP guidelines.

The site 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.

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

14.16.3 Data transmission and storage

Medical records source documents will be copied and transmitted electronically to the study Sponsor representative.

These documents will include the entire electronic health record for the inpatient SESAME encounter. They also will include the physician notes for all baseline and follow-up visits, and site interpretations of all relevant medical imaging examinations.

Source documents also include the following medical imaging data in DICOM format. These are collected as obtained both for clinical and/or research purposes. They include cardiac catheterization fluoroscopy images, echocardiography, cardiac CT, and CMR. These all will retain patient identifiers. Examinations performed for clinical evaluation prior to signing informed consent may be used as the baseline images.

As indicated in section 14.12 (confidentiality):

> **medical records will be transmitted and stored as source documents and will retain patient names and/or medical record numbers, to allow physician-investigators to recommend medical therapies as appropriate, to avoid risk of mis-identification.**

Imaging data will be transmitted electronically to NHLBI for central laboratory analysis. Imaging data will be transmitted via secure file transfer mechanisms abiding FIPS 140-2, HIPAA and local institutional standards (such as https://nih.box.com). Imaging data are stored in a secure Picture Archive Computer System (PACS) or vendor-neutral archive, according to local institutional standards.

14.17 Study Records Retention

The site 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 site 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.

14.18 Collaborative Agreements

Not applicable.

14.19 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NHLBI has established policies and procedures for all study group members to disclose all conflicts of

interest and will establish a mechanism for the management of all reported dualities of interest.

15 ABBREVIATIONS

ADE	Adverse device effect
AE	Adverse Event
AR	Aortic valve regurgitation
AS	Aortic valve stenosis
BASILICA	Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction
CI	Confidence Interval
CMR	Cardiovascular magnetic resonance
CRF	Case Report Form
CT	Computed tomography
CTDB	Clinical Trials electronic Data Base for case report form capture
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECV	Extracellular volume, typically measured at CMR
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICE	Intracardiac echocardiography
IDE	Investigational Device Exemption
IRB	Institutional Review Board
LAMPOON	Intentional Laceration of the Anterior Mitral leaflet to Prevent left ventricular Outflow tract ObstructioN
LVOT(O)	Left ventricular outflow tract (obstruction)
MACE	Major adverse clinical events
MVARC	Mitral Valve Academic Research Consortium endpoint definitions
mRS	Modified Rankin Scale of stroke disability
NHLBI	National Heart Lung and Blood Institute
OHSRP	NIH Office of Human Subjects Research Protections
PI	Principal Investigator
SADE	Serious adverse device effect
SAE	Serious adverse event
SESAME	SEptal Scoring Along Midline Endocardium
TAVR	Transcatheter aortic valve implantation
TMVR	Transcatheter mitral valve implantation
TEE	Transesophageal echocardiography
TEER	Transcatheter edge-to-edge repair (of the mitral valve)

THV	Transcatheter heart valve
TTE	Transthoracic echocardiography
UADE	Unanticipated adverse device effect
UP	Unanticipated problem
VARC	Valve academic research consortium (criteria)

16 REVISIONS

2023-02-17	Initial NIH IRB Review Submission after CDRH issues IDE license
2023-03-13	Response to NIH IRB Pre-Review
2023-09-12	Response to NHLBI DSMB stipulations, including changes to the selection criteria and consent. Response to additional NIH IRB Pre-Review and housekeeping revisions
2023-12-19	Response to stipulations from NIH IRB Attendant changes to: Schema diagram
2024-01-22	Response to stipulations from NIH IRB
2024-12-04	Add a second site in response to poor enrollment at a single site; Remove TMVR as an allowable inclusion criterion to focus enrollment on a single disease entity, hypertrophic cardiomyopathy (HCM); delete the TMVR-related informed consent document; Some optional endpoints changed to non-optional
2024-12-30	Change selection criteria to increase required septal thickness
2025-01-06	Change Risk Analysis Outcomes Classification Change procedure detail in attempt to reduce risk of steam pop
2025-02-14	Changes stipulated by NHLBI DSMB

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18 Appendix A: Tables of Reporting Obligations

Reporting obligations of NHLBI Principal Investigator

Reports from NHLBI PI 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	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; FDA
Death of a research subject at least possibly related to research	Within 24 hours	IRB; CD
Death unlikely or unrelated to research	At continuing review Report within 7 calendar days (CD)	IRB; FDA CD
Unanticipated Problems (UP) involving subject risk	Within 7 calendar days	IRB; CD
Major Protocol Deviations (PD)	Within 7 days Annual progress report	IRB; CD FDA
Minor Protocol Deviations (PD)	Annual progress report; Within 14 days(CD)	FDA; IRB; CD;
Serious or Continuing Non-compliance	Within 7 days	IRB; CD
Use of a device without obtaining informed consent	Within 5 working days	FDA
Withdrawal of IRB approval	Within 5 working days	FDA; 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	IRB; CD
Recall and Device disposition	Within 30 working days	All PIs; IRB; FDA
Sponsor suspend or terminate protocol	Within 7 calendar days	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 = NHLBI Principal Investigator / Sponsor Representative

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

Reporting obligations of Enrolling Site Principal Investigator to the Sponsor*

Site PI Obligation: **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, IRB
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 unlikely or unrelated to research	Immediately but within 3 working days	Sponsor
Death of a research subject at least possibly related to research	Within 24 hours	Sponsor, IRB
Unanticipated Problems (UP) involving subject risk	Within 3 working days, Within 7 days	Sponsor, IRB
Major Protocol Deviations (PD)	Within 3 working days Within 7 days	Sponsor IRB
Minor Protocol Deviations (PD)	Within 7 working days	Sponsor
Non-compliance, Serious	Within 3 working days Within 7 days	Sponsor IRB
Non-compliance, Continuing	Within 3 days working days	Sponsor

19 Appendix B. Risk Analysis

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	Undesirable	Intolerable	

Category	Failure	Impact	Severity	Likelihood / frequency	Score	Available evidence to consider risk	Mitigation

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	Undesirable	Intolerable	

Category	Failure	Impact	Severity	Likelihood / frequency	Score	Available evidence to consider risk	Mitigation
Electro-surgery	Ventricular fibrillation	Life-threatening but reversible	3	2	6	VF from electrosurgical and/or mechanical stimulation of septum during laceration	Data: Observed in ~5% of clinical SESAME, responding promptly to defibrillation Strategy: Monitor rhythm, apply defibrillation pads before SESAME procedures.

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	
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Category	Failure	Impact	Severity	Likelihood / frequency	Score	Available evidence to consider risk	Mitigation
	Iatrogenic aortic regurgitation	From errant electrosurgery	4	1	4	Aortic injury has been observed in tip-to-base LAMPOON by inexperienced operator	Prevent: ensheath laceration surface below aortic valve. Slow traction during electrosurgical laceration. Discontinue application of energy before withdrawing retrograde laceration catheters across aortic valve

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	Undesirable	Intolerable	

Category	Failure	Impact	Severity	Likelihood / frequency	Score	Available evidence to consider risk	Mitigation
SESAME	Ventricular Septal Defect from excessively deep cut	Acute VSD with left-to-right shunt causing hemodynamic compromise	5	2	10	This is a known complication of surgical myectomy and of trans-coronary alcohol septal ablation	Prevention: Image-guidance (echocardiography, EDEN intracardiac electrograms), limit duration of RF application Therapy: Conservative, transcatheter VSD device implantation, or conversion to cardiac surgery, as indicated

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	Undesirable	Intolerable	

Category	Failure	Impact	Severity	Likelihood / frequency	Score	Available evidence to consider risk	Mitigation
	Free wall ventricular perforation from excessively deep and non-target cut or from catheter manipulations including during SESAME-induced tachycardia	Pericardial effusion and tamponade	5	2	10	This is a catastrophic complication that would be difficult to remedy.	Imaging guidance Treatment: bailout pericardial drainage, transcatheter or surgical repair. Withdraw ICE probe from LV before electrosurgery.
	"Steam pop"	Intramyocardial tissue disruption contributing to VSD or free-wall perforation	5	1	5	Serious complication of cardiac electrosurgery	Limit duration of intramyocardial radiofrequency ablation without traction to allow communication with blood pool
	Insufficiently deep laceration	Clinical failure of procedure	2	2	4	Analogous to insufficiently deep surgical myectomy or to coronary-target mismatch after alcohol septal ablation	Would require an alternative therapy such as radiofrequency or alcohol or surgical ablation, or a repeat attempt at SESAME

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	Undesirable	Intolerable	

Category	Failure	Impact	Severity	Likelihood / frequency	Score	Available evidence to consider risk	Mitigation
	Mitral chordal laceration	Mitral valve regurgitation	4	1	1	Mitral valve regurgitation	Strategy: Snare in apical position below chordal apparatus. Use imaging to assure freedom from chordal entrapment. Use traction to assure freedom from chordal entrapment. Treatment: TEER, surgery, or conservative as indicated.
	Thromboembolism	Electrosurgery may cause intravascular coagulation and char	3	1	3	Thromboembolism including stroke	Prevent: Anticoagulation; limit electrosurgery duration and energy; Use dextrose flush to displace blood from the LV catheter; Ensheath both free ends of the laceration guidewire; Consider analogy to LV endocardial radiofrequency ablation for EP
	High-degree atrioventricular conduction defect	Requires temporary or permanent pacemaker therapy	3	2	6	Catheter or surgical ventriculotomy is performed near the Bundle of His and Left Bundle; the latter often induces left anterior fascicle block or more advanced conduction defects	Observe for electrocardiographic conduction abnormalities and offer cardiac pacing therapy as indicated

KEY LEVEL	1	2	3	4	5
Probability	Rare	Uncommon	Common	Normal	
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Risk Interpretation	Negligible	Tolerable	Undesirable	Intolerable	

Category	Failure	Impact	Severity	Likelihood / frequency	Score	Available evidence to consider risk	Mitigation
	Coronary cameral procedure	This is an expected complication of surgical or transcatheter myotomy across septal perforator coronary artery branches	1	4	4	Septal perforator coronary cameral fistula into the left ventricular cavity has been observed and is expected to have little or no clinical consequence	Observation
Catheter mechanical	Laceration guidewire fracture and separation	May require device replacement	1	1	1	One case of “flying V” guidewire fracture was observed in the LAMPOON IDE trial 2017, attributed to over-aggressive denuding/kinking, not observed in clinical LAMPOON or BASILICA thereafter	Operator training on proper bedside preparation of “flying-V”
Per-cutaneous procedures	ATN from procedural contrast and from follow-up contrast CT	Temporary or permanent hemodialysis	3	2	6	Temporary or permanent hemodialysis	Minimize contrast exposure. 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	
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Risk Score	1-4	5-9	10-20	>20	
Risk Interpretation	Negligible	Tolerable	Undesirable	Intolerable	