Protocol with Statistical Analysis Plan Cover Page:

Official Title:	NHLBI Transmural Electrosurgery LeafLet Traversal And Laceration Evaluation (TELLTALE) BASILICA-TAVR Trial
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NIH Institutional Review Board (IRB) #: 000673H

Version Date: 2024-10-31, Amendment C

Title: *NHLBI Transmural Electrosurgery LeafLet Traversal And Laceration Evaluation (TELLTALE) BASILICA-TAVR Trial*

Investigational Device:	TELLTALE Electrosurgical Guidewire System
IDE Number:	G220207
Sponsor:	Office of Clinical Director, National Heart Lung and Blood Institute, National Institutes of Health, USA
Sponsor Representative & NIH 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
Manufacturer:	Transmural Systems, 4 Dundee Park Dr, Andover, MA, 01810, USA
Manufacturer Representative:	Nasser Rafiee
Data and Safety Monitoring Board (DSMB)	National Heart Lung and Blood Institute

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1 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.

2 PROTOCOL SUMMARY

2.1 Synopsis

Title	NHLBI Transmural Electrosurgery LeafLet Traversal and Laceration Evaluation (TELLTALE) BASILICA-TAVR Trial
Background / Précis	Transcatheter aortic valve implantation (TAVR) may cause life threatening coronary artery obstruction, whether implanted in native aortic stenosis or bioprosthetic aortic valve failure. We have developed and validated the techniques of BASILICA (Bioprosthetic Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction during transcatheter aortic valve replacement), using bedside modification of off-the-shelf guidewires. These bedside modifications require additional assembly steps and special expertise, and thereby risks procedure failure and complications. Transmural Systems and NHLBI have developed a purpose-built electrosurgical guidewire system (TELLTALE) to simplify the BASILICA-TAVR procedure. The purpose of this protocol is to test the efficacy and safety of this purpose-built guidewire in the setting of BASILICA-TAVR.
Risk classification	Significant risk device protocol requiring Investigational Device Exemption (IDE)
Device classification	Class II
Intended Use	The TELLTALE Guidewire System is intended for transcatheter electrosurgical traversal and laceration of native and bioprosthetic tissue.
Indications for use	The TELLTALE guidewire is indicated for transcatheter electrosurgical traversal and/or laceration of native and bioprosthetic tissue for the applicable procedures listed below. Applicable traversal and laceration procedures including BASILICA (Bioprosthetic Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction during transcatheter aortic valve replacement). The TELLTALE Guidewire System is available only by physician prescription.
Design overview	Prospective, multicenter, single arm, open-label, evaluation of the NHLBI Transmural TELLTALE Guidewire System
Study phase	Not applicable

Sponsor / Representative	NHLBI Office of the Clinical Director (NHLBI/OCD) / Robert J. Lederman, MD, NHLBI/DIR/CB/LCI
Study Manager	Annette M. Stine, RN
Hypothesis	We hypothesize that the TELLTALE guidewire system traverses and lacerates intended native and bioprosthetic aortic valve leaflets that threaten coronary artery obstruction during TAVR. We further hypothesize that BASILICA using the TELLTALE guidewire system prevents TAVR-related acute coronary obstruction in patients at risk, and with acceptable safety.
Number of subjects	90 subjects enrolled at up to 15 investigational sites in the US. Up to 180 subjects may be screened for participation.
Sample Size Justification	The sample size is not statistically derived. Up to 180 candidates will be screened until 90 subjects undergo attempted TELLTALE BASILICA-TAVR in this protocol. There is a quota of 30 subjects who must have native TELLTALE BASILICA-TAVR of the 90 total enrolled subjects.

Inclusion Criteria	• Adults age ≥ 21 years
	• High or prohibitive risk of surgical aortic valve replacement according to the local multidisciplinary heart team
	• Undergoing TAVR for bioprosthetic aortic valve failure or native aortic stenosis (“on-label” TAVR)
	• Local multidisciplinary heart team determines subject to be at high risk of TAVR-induced coronary artery obstruction
	• Deemed likely to suffer coronary artery obstruction from TAVR based on NHLBI Core lab analysis of CT, any of
	  • Risk is narrow Sinus of Valsalva: (a) Leaflet height is greater than coronary artery height, and (b) Virtual transcatheter valve-to-coronary (VTC) distance < 4mm
	  • Risk is Sinus sequestration: (a) Threatening leaflet height is greater than sinotubular junction, and (b) Virtual transcatheter valve-to-sinotubular-junction distance (VTS) < 2mm at the affected Sinus
	• Concurrence of the Study Eligibility Committee
	• Able to understand the protocol, consents in writing to participate, and willing to comply with all study procedures for the duration of the study

Exclusion Criteria	• Requires doppio (two-leaflet) BASILICA • Flail target leaflet at baseline • Excessive target aortic leaflet calcification (no basal calcium-free window or potentially obstructive calcific masses) on baseline CT • Planned provisional (pre-position coronary artery) stents despite BASILICA • Requires non-femoral access • Requires concomitant procedures during TAVR (such as percutaneous coronary intervention for baseline obstructive coronary artery disease) • Chronic kidney disease KDIGO stage 4 or 5 (eGFR < 29 ml/min/1.73m2) or renal replacement therapy • Not expected to survive for 12 months • Pregnant at the time of intended treatment (day 0)
Selection quota	A subset of subjects will have native aortic valve failure (initially n=15). Sequential enrollment will accommodate this quota. A "study expansion" IDE amendment increased this quota from 15 to a maximum 30.
Primary Efficacy Endpoint	The primary efficacy endpoint is **Device (technical) success**, assessed upon exit from the cardiac catheterization laboratory, including all of the following: • Successful electrosurgical leaflet traversal using the TELLTALE Guidewire, when attempted; and • Successful electrosurgical leaflet laceration using the TELLTALE Guidewire; and • Successful retrieval of the TELLTALE Guidewire System
Primary Safety Endpoint	The primary safety endpoint is **Inpatient safety**, which is a composite of all of following assessed upon discharge from the index hospital admission: • (Freedom from) all-cause mortality • (Freedom from) stroke, both disabling and non-disabling • (Freedom from) acute coronary artery obstruction • (Freedom from) emergency cardiac surgery or reintervention related to the TELLTALE BASILICA procedure or device • (Freedom from) BASILICA-related complications including coronary artery perforation, coronary artery dissection, aortic dissection, cardiac free wall perforation, or systemic embolization of a native or bioprosthetic leaflet

Secondary endpoints	The secondary endpoint is **<u>30-day safety</u>**, as assessed by freedom from MACE (according to VARC-3 [30]) at 30 days, including freedom from all of the following: • All-cause mortality • All stroke (disabling and non-disabling) • Bleeding VARC-3 Type 2 or greater (requiring two or more units of transfused blood or hemoglobin drop >3g/dL) • Major vascular, access-related, or cardiac structural complication (according to VARC-3, which includes coronary obstruction) • Acute kidney injury stage 3 or 4 • Moderate or severe aortic regurgitation • New permanent pacemaker due to procedure-related conduction abnormalities • Surgery or intervention related to the TELLTALE device
Exploratory endpoints	• Primary and secondary endpoints among subjects with native versus bioprosthetic disease • Stroke: disabling and non-disabling • Coronary stenting: snorkel (heterotopic) and orthotopic (through TAVR stent cells), to prevent or treat leaflet-induced coronary obstruction before (preemptive) and after (bailout or cautionary) TAVR. • Facilitated BASILICA procedure success, as defined in section 0. • Composite safety (secondary endpoint) assessed at 90 days • Ability selectively to engage threatened coronary ostia after BASILICA-TAVR • Acute hemodynamic deterioration in the interval between BASILICA and TAVR • Outcomes of subjects who participate in live case demonstrations compared with those who do not

Study Overview	NHLBI Data Coordinating Center Central IRB Selected site operators have experience with off-label BASILICA Subjects are identified by site investigators Baseline CT and procedure fluoroscopy are analyzed by core laboratory Subject eligibility is confirmed by institutional multidisciplinary heart team, and is confirmed by study eligibility committee Subjects are enrolled prospectively Stroke assessment by trained and certified staff Analyses based on day 0 and day 30 outcomes Subjects go “off-study” after [90 days] visit
Study Duration	12 months for enrollment + follow-up
Duration of Participation for Subjects	90 days
Enrollment	Candidates may use screening consent based on local institutional preference. Candidates do not sign research informed consent until after they are reviewed and invited by the Central Clinical Eligibility Committee.

2.2 Schema

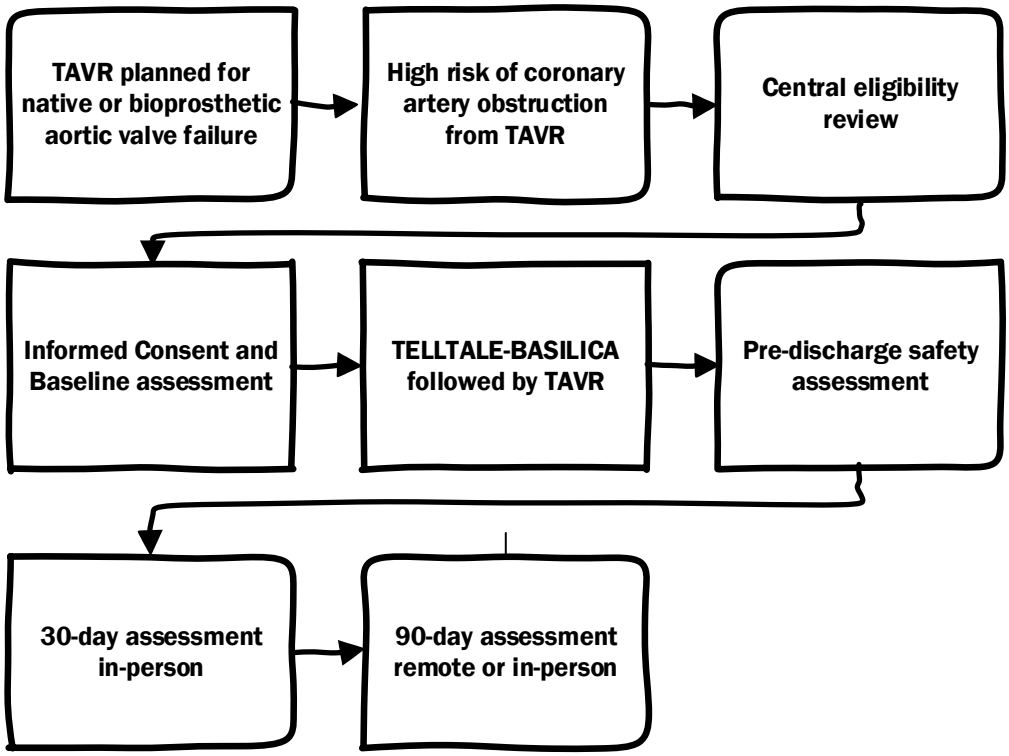

Figure 1. Protocol Schema

2.3 Schedule of Activities (SOA)

	Screening (± 6 mo)	Baseline (± 6 wk)	Day 0 (procedure)	Inpatient	30 d (±3wk)	90-day (± 3 wk)
Baseline informed consent		X				
Multidisciplinary heart team eligibility determination	X					
Clinical study eligibility committee concurrence (*)	X					
Clinical in-person assessment including vital signs		X		X	X	
Clinical remote or in-person assessment						X
NYHA Classification		X			X	
Kansas City Cardiomyopathy Questionnaire (KCCQ-23) (*)		X			X	
NIH Stroke Scale (Severity) Assessment (*)		X		X	X	
Modified Rankin Stroke Disability Score (*)		X		X	X	
Frailty tests: Katz ADL, 5MW, Albumin		X				
Blood test for pregnancy (hCG) if premenopausal woman		X				
Blood tests: CBC, Platelet, Chemistry Panel		X		X	X	
Blood test: Troponin I		X	Post-procedure		#	
ECG		X	X	X	X	
Cardiac CT contrast-enhanced ECG-gated (up to 6 months before procedure recommended ¤)	Screening or baseline	Screening or baseline				
Coronary arteriography§	Screening or baseline	Screening or baseline	X			
BASILICA using TELLTALE (*) followed by TAVR			X			
Echocardiogram, surface or transesophageal	Screening or baseline	Screening or baseline	X	X	X	
Adverse event assessment (*)			X	X	X	X

(*) denotes research activity. (#) denotes obtain if abnormal at discharge

(§)coronary arteriograms are obtained only as clinically indicated and, only if obtained, will be analyzed at NIH for research

(¤) CT scans beyond the 6-month recommended window if the treating physician would proceed with BASILICA TAVR without an updated CT scan if outside the TELLTALE protocol

2.4 Blood tests

All of the blood tests specified here are mandatory for routine medical care before, during, and after the TAVR 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 meet the criteria for a serious adverse event (SAE), serious adverse device effect (SADE), unanticipated adverse device effect (UUADE) or an unanticipated problem (UP) as described below:

Test	**Detail**	**Inpatient value to record**	**Timepoints to collect**	**Criteria for reporting as serious AE or serious ADE**
Blood count: hemoglobin	Marker of anemia and hemodilution.	Lowest	Baseline through 30d	Decrease in conjunction with a VARC-3 major or minor - Access site complication - Cardiac structural complication - Bleeding complication that requires prolonged hospitalization, unplanned surgical or interventional treatment or a blood or platelet transfusion
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	
Blood count: white blood cell count	Nonspecific marker of inflammation and infection.	Highest	Baseline through 30d	Elevation in conjunction with suspected clinical infection or inflammation and requiring treatment
Chemistry: Creatinine	Marker of renal excretion. eGFR	Highest	Baseline through 30d	Classified as VARC-3 acute kidney injury (AKI) grade 3 or higher and requires treatment
Chemistry: Estimated glomerular filtration rate (eGFR)	Calculated from age, sex, race, and creatinine	Lowest	Baseline through 30d	
Chemistry: Cardiac troponin	Marker of cardiomyocyte injury, institution-specific subtype (Troponin-I or Troponin-T).	Highest	Baseline & postprocedure. 30-day if abnormal at discharge	Elevated in association with symptoms and signs of acute myocardial infarction including ECG and/or imaging

2.5 Clinical versus research activities

All activities except Consent, TELLTALE BASILICA-TAVR, KCCQ-23, NIH Stroke Scale Assessment, Modified Rankin Score, and Adverse event assessment are performed for standard clinical care.

3 INTRODUCTION

3.1 Public précis

Transcatheter aortic valve replacement (TAVR) is a lifesaving treatment option for many patients with symptomatic severe aortic stenosis or failure of a surgically-implanted bioprosthetic valve. Rarely, TAVR can block blood flow to the coronary arteries, which supply blood to the heart, by displacing the leaflets of the prior valve outwards. TAVR-associated coronary artery obstruction is associated with up to 50% death rate.

BASILICA (Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction) is a procedure developed to prevent coronary artery obstruction by cutting the threatening leaflet immediately before TAVR. The NHLBI TELLTALE study investigates the use of a dedicated electrosurgical guidewire system to perform BASILICA and tests the safety and effectiveness of using this device in patients at risk of coronary artery obstruction from TAVR.

3.2 Background and Clinical Justification

Study Rationale

Coronary artery obstruction is a rare complication of transcatheter aortic valve replacement (TAVR) but is associated with an inpatient mortality of up to 50%[1]. Coronary artery obstruction occurs when the diseased native or bioprosthetic valve leaflets obstruct blood flow at the coronary ostia or sinotubular junction and can be predicted on pre-procedure CT[1, 2]. BASILICA prevents coronary artery obstruction by lacerating the culprit leaflet immediately before TAVR[3].

BASILICA (Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction) is currently performed using off-the-shelf commercial equipment ("off label"). This adds complexity and potentially unpredictability to the procedure. The TELLTALE Guidewire System by Transmural Systems is a dedicated guidewire for transcatheter electrosurgical traversal and laceration of valve leaflets. The NHLBI TELLTALE Study investigates the use of this novel guidewire in performing BASILICA safely and effectively to prevent coronary obstruction in at-risk patients undergoing TAVR.

The BASILICA procedure has been shown to be feasible, safe and effective at preventing coronary obstruction in at risk patients undergoing TAVR in an IDE study[3] and large multicenter registry[4]. However, the procedure uses off-the-shelf equipment off-label. This adds complexity (Figure 2) and potential for complications. In our unpublished experience, the complexity includes the temptation to avoid dextrose flooding during laceration (see below), with its attendant risk for leaflet mechanical avulsion. Furthermore, the self-assembled co-axial systems currently used may divert physicians to apply the much less attractive, though simpler, bail-out procedure of snorkel stenting, with its attendant complications of stent under-expansion, thrombosis, delayed coronary obstruction, loss of future coronary access and long term dual antiplatelet therapy. The TELLTALE Guidewire System is purpose-designed for electrosurgical traversal and laceration of leaflets. This study tests whether the TELLTALE

Guidewire System can be used to successfully perform BASILICA to safely and effectively prevent coronary artery obstruction from TAVR in at risk patients.

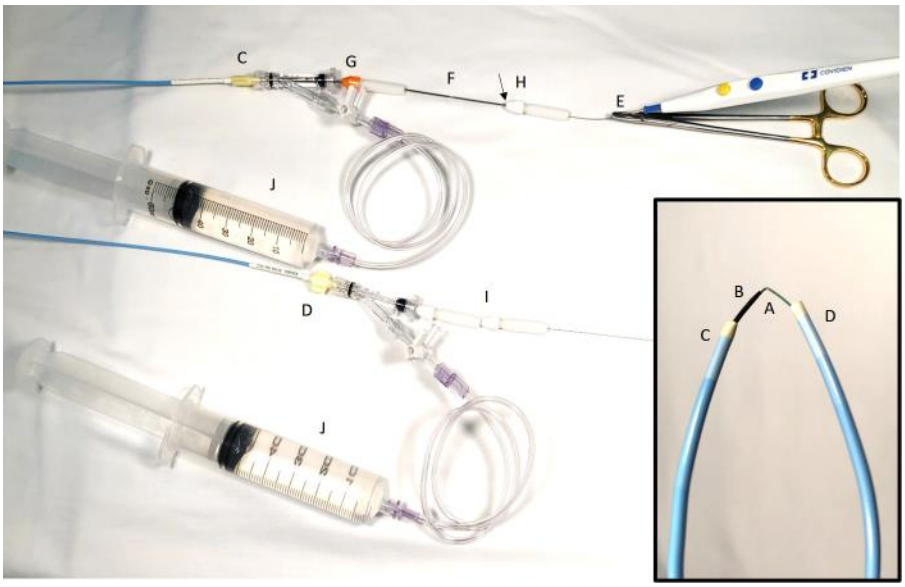

Figure 2.Complicated set-up for BASILICA using bedside-modified devices, from [5].

Transcatheter electrosurgery

Transcatheter electrosurgery is a technique to vaporize tissue using radiofrequency alternating current directed through guidewires and catheters and concentrated in the tissue to cause rapid heating. Cells vaporize when intracellular temperatures reach 100 degrees C. This technique has been used for “traversal”, for example in recanalizing occlusive lesions and crossing cardiovascular chambers, and for “laceration”, for example in cutting aortic and mitral leaflets to prevent blood flow obstruction from transcatheter valve replacement.

Electrosurgery relies on tissue conducting alternating current between two electrodes. High frequency alternating currents (~500KHz, or ‘radiofrequency’) do not stimulate nerve and muscle tissue and thus avoid pain, muscle contraction, and myocardial fibrillation [6].

We previously performed current density simulations using the AC/DC module on Comsol Multiphysics (Comsol Inc. MA,USA) simulation software to find the optimal configuration for guidewire insulation for traversal and laceration (Figure 3)[7]. The biological structures were represented as simplified geometries. A 100W power source was used with 100V and 1A voltage and current outputs at 700kHz to simulate commercially available electrosurgery units. The conductivity and the relative permittivity values for blood, leaflet, myocardium, dextrose and PTFE were derived from published literature[8-10].

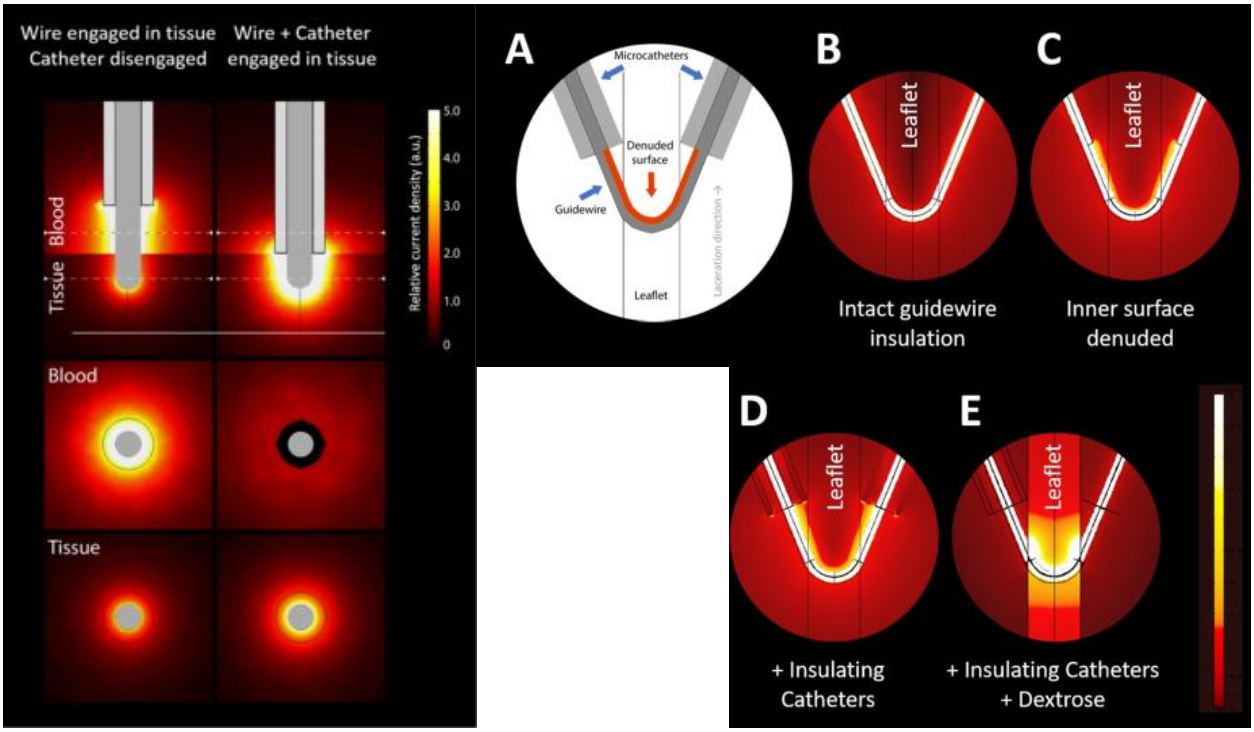

Figure 3. Simulated traversal (top) and laceration systems (A-E) depicting the value of focused current and displacement of conductive fluid. From [7].

These simulations were replicated on the benchtop (Figure 4). These experiments highlight the importance of inner curvature charge concentration via selective denudation, and of robust insulation with both microcatheters and non-ionic fluid, to concentrate charge for tissue laceration[7].

Failure to recapitulate these benchtop-derived observations during standard clinical BASILICA risks failure and complications.

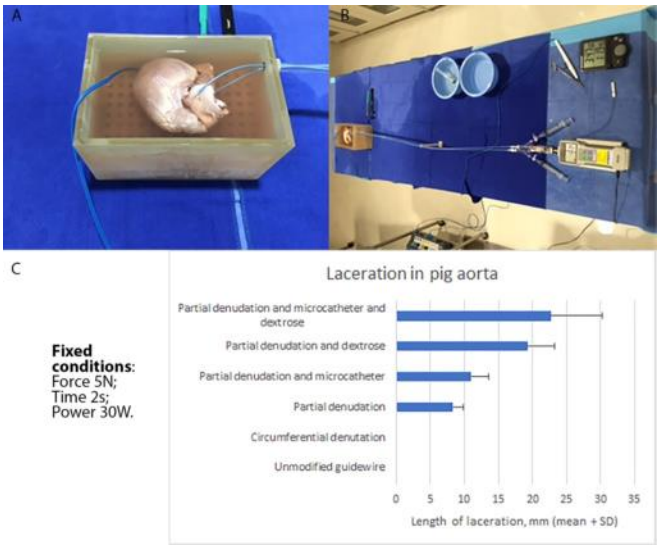

Figure 4. Benchtop validation of the electrosurgical laceration, from [7]

Clinical applications for transcatheter electrosurgery

The table below summarizes some of the clinical applications for transcatheter electrosurgery [7].

Application	References	Study type	Total patients	Procedure success	Complications
Pulmonary valve atresia traversal in newborns	Veldtman 2004 [11]	Case series	136	87% successful in establishing antegrade flow	Procedural death (7%); Arrhythmia, RVOT perforation (16%)
Central chronic total venous occlusion traversal (subclavian vein, SVC)	Baerlocher 2006; Iafrati 2012; Foerst 2017 [12-14]	Case reports	6	100%	None reported
Coronary chronic total occlusion	Baim 2004 [15]	Prospective multicenter registry	116	54%	Perforation and tamponade (2.6%)
Transseptal puncture	Hsu 2013 [16]	Randomized control trial	36 RF; 36 conventional	100% RF; 72% conventional (with cross-over to RF and subsequent success)	Pericardial effusion (2.8%)
Interventricular septum puncture (for LV lead placement)	Gamble 2018 [17]	Prospective single center single arm clinical trial	20	100% success in ventricular traversal	Disabling stroke (5%)
Transcaval for large bore access for TAVR	Greenbaum 2017[18] Lederman 2019[19] Costa 2019[20]	Prospective multicenter single arm clinical trial Retrospective registry	150	99%	Life-threatening or disabling bleeding (4-12%) Note late complications
LAMPOON to lacerate the anterior mitral valve leaflet prior to TMVR	Khan 2019 [21]	Prospective multicenter single arm clinical trial	30	100%	More than mild paravalvular leak (23%); LVOT obstruction from valve skirt (10%).
BASILICA to lacerate aortic leaflets prior to TAVR	Khan 2019 [3]	Prospective multicenter single arm clinical trial	30	93%	Disabling stroke (3%)
ELASTIC to enable TMVR after mitral edge-to-edge repair	Lisko 2020 [22]	Retrospective case series	5	100%	Moderate paravalvular leak (40%)

BASILICA using bedside modification of commercial devices ("off-label")

The BASILICA procedure was developed in pigs and subsequently performed in a compassionate basis in seven patients[23]. All patients had successful TAVR, with no coronary obstruction, stroke, hemodynamic compromise or any major complications. All patients survived to 30 days.

The prospective FDA IDE NHLBI BASILICA study enrolled 30 patients at high risk of coronary artery obstruction from TAVR who underwent BASILICA with an Astato guidewire with benchtop modification[3]. All patients were at high risk of coronary obstruction as determined by the NHLBI CT core laboratory. Seven (23%) were double-leaflet BASILICA. Primary success of successful BASILICA and TAVR without coronary obstruction or reintervention was met in 28 (93%) subjects. BASILICA traversal and laceration was successful in 28 (93%) subjects. There was 100% freedom from coronary obstruction and reintervention. Primary safety of freedom from MACE was met in 21 (70%), driven by six (20%) major vascular complications related to TAVR but not BASILICA. There was one death at 30 days. There was one (3%) disabling stroke and two (7%) non-disabling strokes. Transient hemodynamic compromise was rare (7%) and resolved promptly with TAVR. At one year, there were no late complications associated with BASILICA[24]. Specifically, after 30 days there was no stroke, myocardial infarction, coronary intervention, transcatheter aortic valve failure or increase in valve gradients. The coronaries remained clinically patent and there were no BASILICA related deaths.

The international multicenter BASILICA Registry reported results on 214 patients undergoing BASILICA and TAVR in patients at high risk of coronary artery obstruction[4]. 22% were *doppio* (double-leaflet) BASILICA. Procedural success, a composite of successful traversal and laceration, survival and freedom from coronary obstruction or re-intervention was seen in 87%. The 30-day mortality was 2.8% and stroke rate 2.8% (0.5% disabling stroke).

The EURO-BASILICA multicenter registry reported 76 patients at 10 centers undergoing BASILICA and TAVR in patients at high risk of coronary artery obstruction, using commercial off-the-shelf devices [25]. Nine (12%) were *doppio* (double-leaflet) BASILICA. Technical success was 98%, freedom from coronary obstruction was 91%, stroke was 3%. Ten patients required coronary intervention, typically because of avulsed or prolapsed leaflets amenable to orthotopic stenting.

An interim analysis of this open-label study for amendment B (September 2023) was triggered by consent of 15 subjects with native aortic valve failure. At this timepoint 27 subjects were treated by TELLTALE BASILICA TAVR, including 14 with native aortic valve failure. Using non-adjudicated data, the primary success rate is 100%, the incidence of coronary obstruction is 0%, and the incidence of stroke/TIA is 0%. Based on these data we propose amending the protocol in Amendment B to expand the study cohort having native aortic valve failure, from 15 to 30 subjects.

These studies provide reassuring data in support of the BASILICA procedure to prevent coronary artery obstruction in this patient cohort with few good options.

Available literature about risks of coronary obstruction

Reported and expected outcomes of patients undergoing TAVR despite risk of coronary obstruction

Setting	n with CTs evaluated	At-risk population	Cor obstruction in at-risk population	30-day Death	Stroke	Reference
ViV	20 obstructed, 90 control	VTC<4mm	89%	53% (in obstructed population)	0%	VIVID registry [2]
Native AS	28 obstructed, 345 control	coronary height<12mm and SOV width <30mm	87%	41% (in obstructed population)	9%	Multicenter Registry [1]
Native AS	60 obstructed, 60 control	Leaflet height ≥ coronary height AND VTC<4mm	90%	27% (in-hospital death, obstructed)	Not collected	CRT 2020 late breaking trial presentation, not published
VIV and Native	30 attempted BASILICA	Leaflet height ≥ coronary height AND VTC<4mm; Leaflet height ≥ STJ AND VTSTJ<2mm	0%	3%	10%	[3]
VIV and Native	214 attempted BASILICA	Leaflet height ≥ coronary height AND VTC<4mm; Leaflet height ≥ STJ AND VTSTJ<2mm	5%	3%	3%	[4]
VIV and Native	15 attempted BASILICA	Leaflet height ≥ coronary height AND VTC<4mm; Leaflet height ≥ STJ AND VTSTJ<2mm	7%	0%	0%	[26]
VIV and Native	21 attempted BASILICA	Leaflet height ≥ coronary height AND VTC<4mm; Leaflet height ≥ STJ AND VTSTJ<2mm	5%	0%	0%	[27]

Compared with pivotal trials in which all candidates at risk of coronary obstruction are EXCLUDED

Setting	**Population**	**n**	**Cor obstruction**	**30-day Death**	**Stroke**	
Native AS	Excluded "Bulky calcified aortic valve leaflets in close proximity to coronary ostia"	348	0%	3.4%	3.8%	PARTNER 1
Native AS	Excluded "Bulky calcified aortic valve leaflets in close proximity to coronary ostia"	1011	0.4%	3.9%	5.5%	PARTNER 2
Native AS	Excluded "Bulky calcified aortic valve leaflets in close proximity to coronary ostia"	496	0.2%	0.4%	0.6%	PARTNER 3
Native AS	Excluded "Sinus of Valsalva anatomy that would prevent adequate coronary perfusion."	390	0.6%	3.3%	4.9%	CoreValve
Native AS	Excluded "Sinus of Valsalva anatomy that would prevent adequate coronary perfusion."	879	?	2.2%	4.5%	SURTAVI
Native AS	Excluded "Sinus of Valsalva anatomy that would prevent adequate coronary perfusion."	734	0.9%	0.5%	3.4%	Evolut Low Risk
	Weighted average of subjects selected to be at low risk of coronary obstruction	3858	0.5%	2.3%	4.0%	

Bioprosthetic versus native mortality and stroke after BASILICA

Publication	Setting	Coronary Obstruction	Death	All Stroke
Registry [4]	Bioprosthetic (n=155)	7 (4.5%)	3%	3%
	Native (n=58)	3 (5.2%)	2%	2%
Adjudicated NHLBI [3]	Bioprosthetic (n=17)	0	1 (6%)	2 (12%)
	Native (n=13)	0	0 (0%)	1 (10%)

Based on the above:

	Coronary Obstruction	30-day Death	Stroke
Expected without BASILICA	90%	40%	5%
Expected after TELLTALE BASILICA	5%	3%	5%

Complications of BASILICA using bedside modification of commercial devices ("off-label")

Bleeding

Some blood loss is typical during BASILICA using off-label equipment through the multiple co-axial systems. These are mainly related to access-site bleeding and to procedural blood wastage.

Inability to traverse

This is the commonest reason for procedure failure, and often due to incorrect equipment setup, inability to get orthogonal to the target leaflet using geometrically-unsuitable commercially available catheters, inadequate electrical charge concentration because of difficulty deploying optimal insulation around the traversal guidewire, and extensive leaflet calcification including at the leaflet nadir.

We expect this complication to be mitigated by using a purpose-built device.

Incorrect (non-target) traversal

Misdirected guidewires may traverse into the left atrium or interventricular septum or anterior mitral valve leaflet. These are often easily recognized on TEE or by inability to snare the guidewire in the LVOT. The guidewire is withdrawn and re-directed, typically without adverse effect.

We expect this complication to be reduced by using dedicated-shape guiding catheters.

Mechanical laceration and leaflet avulsion

If there is insufficient charge concentration on the leaflet during laceration, for example when dextrose flush is not used or inner surface denudation is not effectively performed, then the leaflet may avulse through excessive mechanical force. This can cause serious hemodynamic compromise and risk leaflet prolapse into the coronary arteries. This can be avoided with effective insulation and avoiding excessive mechanical force.

We expect this complication to be mitigated by using a purpose-built device.

Mitral apparatus damage

If the guidewire is snared below the level of the LVOT, there is risk of mitral chord entanglement and subsequent laceration leading to severe mitral regurgitation. This complication can be avoided by only snaring the guidewire in the LVOT.

Conventional Treatment Options and Alternatives

Current options for prevention of TAVR-related coronary obstruction include conservative management (essentially palliative care in patients with symptomatic severe aortic stenosis or bioprosthetic valve failure), surgical aortic valve replacement, snorkel stenting, or BASILICA using off-the-shelf equipment off-label.

While surgical aortic valve replacement is an excellent option for some patients, many are at high risk of mortality or morbidity from surgery, often including patients undergoing redo procedures for failing bioprosthetic valves. Many patients demur when offered surgery and insist on a transcatheter alternative.

Snorkel stenting is not a preventative measure but is a bail-out procedure with risks of stent compression, stent under-expansion, thrombosis, loss of coronary access and long term dual antiplatelet therapy.

BASILICA directly addresses the pathophysiology of coronary obstruction but there are no dedicated devices at present to democratize this procedure.

3.3 Risk/Benefit Assessment

Known Potential Risks (Anticipated Adverse Device Effects)

TELLTALE/BASILICA-specific complications

- Embolization of air, valve debris, atheroma, or thrombus/clot to coronary, cerebral, visceral, or systemic circulation possibly causing symptomatic ischemia/infarction
- Myocardial ischemia or infarction (acute coronary syndrome or heart attack)
- Aortic regurgitation after laceration before TAVR, possibly causing hypotension or cardiogenic shock
- Avulsion or other injury of the native or prosthetic aortic valve leaflet, including leaflet prolapse into the coronary arteries, and including embolism of the leaflet into the coronary, cerebral, visceral, or other systemic arteries
- Inadvertent injury of the mitral valve apparatus requiring transcatheter or surgical repair
- Traversal into the left atrium or other non-target chamber
- Electrical coupling of TELLTALE guidewire and (a) bioprosthetic valve frame, (b) guiding catheters, (c) guidewires and snares causing heating, thromboembolism, tachyarrhythmia, and electrosurgery failure
- Native coronary artery injury from mechanical or electrosurgery injury requiring percutaneous catheter or surgical treatment
- Other arterial perforation or injury or dissection, including requiring surgical treatment
- Failure to engage the intended native or bioprosthetic aortic valve leaflet with TELLTALE system to initiate traversal at the intended location
- Mechanical failure of the TELLTALE Guidewire System including fracture and embolization of the guidewire or of the delivery catheters
- Stroke or transient ischemic attack or paralysis
- Permanent disability
- Death

General complications of TAVR and BASILICA-TAVR catheter procedure including TELLTALE system

- BASILICA failure: Failure to prevent coronary obstruction and acute myocardial ischemia requiring transcatheter therapy including percutaneous coronary stenting in a heterotopic ("snorkel") or orthotopic (through TAVR struts) position, or requiring emergency cardiac surgery repair
- BASILICA failure: coronary obstruction caused by the malorientation of struts of TAVR device, or by fabric skirt of TAVR device, despite successful leaflet laceration
- 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
- 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
- Acute kidney injury related to BASILICA 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
- Transcatheter heart valve failure including hypo-attenuated leaflet thickening (HALT), reduced leaflet motion, valvular regurgitation, valvular stenosis, prosthetic valve endocarditis, paravalvular leak, structural deterioration, or non-structural valve dysfunction, and/or murmur
- 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
- Hemolysis related to blood flow around the lacerated aortic leaflets
- 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
- Cardiac arrhythmia including atrial fibrillation, atrial flutter, ventricular tachycardia, ventricular fibrillation including cardiac arrest requiring cardioversion/defibrillation or cardiopulmonary resuscitation

- Conduction system defect which may require a temporary or permanent pacemaker, for example high-degree atrioventricular block or His-Purkinje block
- 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 reaction to

- anesthesia,
- contrast media,
- materials in the TELLTALE Guidewire System

The Sponsor and investigators recognize these risks are high and reflect the underlying comorbidities, yet consider procedural risks overall to be an acceptable compromise to enable TAVR in patients otherwise ineligible.

Risks related to Radiation

In this research protocol, subjects will be exposed to incremental radiation fluoroscopy to add the BASILICA procedure using the TELLTALE system to conventional TAVR. 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 30mSv from approximately 30 minutes of fluoroscopy during performance of BASILICA-TAVR using TELLTALE. This is equivalent to 750 chest X-rays.

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

Risks to privacy: Personal Identifiable Information

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

Abstracted data will be coded (personally identifiable information removed but linking codes retained) and for transmission to participating subcontracting investigators, clinical events adjudication committee, statistician, and to Transmural Systems which is the collaborating manufacturer of the TELLTALE system.

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

Known Potential Benefits

Subjects are expected to benefit from investigational BASILICA using the TELLTALE purpose-built leaflet traversal and laceration system. TELLTALE BASILICA-TAVR is expected to be non-inferior to bedside-modified and off-label use of devices for electrosurgical traversal and

laceration for BASILICA to prevent acute and subacute coronary obstruction from TAVR. BASILICA is believed to enable TAVR not otherwise possible without "snorkel stenting," which many physicians believe to be unsafe.

Subjects may also benefit indirectly from increased medical attention from participating in an early feasibility study.

Future patients, and therefore society, may benefit should the TELLTALE system prove safe and effective.

Alternatives to research participation

Candidates for TAVR with BASILICA have no good treatment alternatives. They are not eligible for surgical aortic valve replacement because of high or prohibitive risk of perioperative death or serious morbidity. They are not candidates for conventional TAVR, which risks life-threatening coronary obstruction. TAVR using pre-positioned coronary stents ("snorkel-stents") risks early and late catastrophic stent failure and coronary obstruction, which has high mortality[28, 29].

Candidates for TAVR with BASILICA who do not consent to participate in this study are eligible for "standard" BASILICA using off-label medical devices, including bedside modification of commercial devices. This approach, developed by the investigators of this trial, has become the "best practice." Such off-label BASILICA is likely inferior to the research intervention using the TELLTALE guidewire system because of risk of thromboembolism from inferior electrical performance of bedside-modified devices, risks of device fracture or other failure from inferior mechanical performance of bedside-modified devices, risks of mal-preparation during bedside modification including asymmetric denudation, risks of mal-positioning of the lacerating surface in bedside-modified devices, among others. The study devices, which are purpose-built to address these risks, are considered intrinsically superior to bedside-modified devices used off-label.

Assessment of Potential Risks and Benefits

These subjects have few or no good therapeutic alternatives to BASILICA-TAVR and have the potential to benefit from this procedure.

Risk of investigational BASILICA-TAVR using the TELLTALE system is mitigated by including highly capable and experienced operators and highly experienced medical centers. The TELLTALE system device will be used only by interventional cardiologists who have specific expertise in BASILICA and TAVR.

Overall, the potential benefits of participation appear to exceed the risks to the subjects.

4 OBJECTIVES AND ENDPOINTS

4.1 Objective

The objective of this protocol is to test the safety and effectiveness of the TELLTALE guidewire system in accomplishing BASILICA leaflet traversal and laceration to prevent coronary artery obstruction in patients whose native or bioprosthetic TAVR threatens coronary artery obstruction because of narrow sinus of Valsalva and/or sinotubular junction.

An additional objective is added in Amendment B, to offer study expansion to the investigational BASILICA-TAVR using the TELLTALE system for patients with native aortic valve failure at risk of coronary obstruction and who otherwise meet the selection criteria.

4.2 Hypotheses

We hypothesize that the TELLTALE guidewire system traverses and lacerates intended native and bioprosthetic aortic valve leaflets that threaten coronary artery obstruction during TAVR.

We further hypothesize that BASILICA using the TELLTALE guidewire system prevents TAVR-related acute coronary obstruction in patients at risk, and with acceptable safety.

4.3 Endpoint Design Considerations

The intent of this protocol is to demonstrate safety and efficacy of BASILICA-TAVR using the TELLTALE guidewire system to mitigate the risk of TAVR-induced coronary obstruction in at-risk patients. The primary endpoint is selected based on the clinical characteristics and implications of BASILICA success and failure, which are described below.

Definitions of BASILICA Success

BASILICA technical success" in lacerating a leaflet requires successful traversal and successful leaflet laceration only.

"BASILICA procedure success" in preventing coronary obstruction requires successful leaflet traversal and laceration and further requires post-TAVR leaflet splay to preserve coronary artery blood flow. Some causes of BASILICA procedure failure despite BASILICA technical success include

(1) THV malrotation causing coronary obstruction by the THV struts;

(2) BASILICA slice malorientation with regard to the ostium of the threatened coronary ostium combined with very small valve-to-coronary distance (VTC); and

(3) protrusion of aortic leaflet material into the coronary artery after BASILICA and TAVR, either because of bulky leaflet calcification or because of mechanical avulsion rather than electrosurgical BASILICA laceration.

"Facilitated BASILICA procedure success" includes immediate orthotopic coronary stenting to mitigate aortic leaflet protrusion and protect flow to the threatened coronary artery without "snorkel" stenting between the THV and the sinotubular junction. Orthotopic stenting is not possible without BASILICA leaflet laceration. Facilitated BASILICA procedure success is considered clinically acceptable. Sometimes orthotopic-stent-facilitated BASILICA can mitigate THV- or slice- malorientation and preserve coronary flow. While clinically a success, "facilitated BASILICA procedure success" is nevertheless classified as failure in this protocol.

Immediate consequences of BASILICA Failure

Unsuccessful traversal precludes BASILICA. Typically there are no sequelae to failed traversal *per se*. The subject continues to risk coronary obstruction as a consequence of TAVR.

Given successful traversal, the outcomes after attempted laceration are:

(1) Successful electrosurgical laceration of the native or bioprosthetic leaflet that threatens coronary obstruction after TAVR. Typically there is no immediate hemodynamic compromise after electrosurgical leaflet laceration because appropriately split leaflets continue to coapt and the result is a mild increment in acute aortic regurgitation. After this BASILICA technical success, the results of TAVR will determine BASILICA procedure success as described previously; OR
(2) Unsuccessful electrosurgical laceration but successful mechanical laceration or avulsion. This is clinically manifest by a significant increment in aortic regurgitation and hemodynamic compromise requiring expedited TAVR. Acute coronary occlusion is typically averted, but orthotopic coronary artery stenting is sometimes required because the avulsed leaflet may prolapse into the target coronary artery ostium. With appropriate operator training, there are typically few sequelae other than orthotopic stenting of a non-atherosclerotic ostial coronary artery. We believe orthotopic stenting is safer than heterotopic ("snorkel") stenting in which a stent extends far proximal to the coronary ostium and risks mechanical crush by the transcatheter heart valve against the sinotubular junction. Despite these undesirable characteristics, mechanical avulsion can be classified as BASILICA technical success according to our definition; OR
(3) Aborted or abandoned laceration. Typically there are no sequelae.

BASILICA is considered failed after unsuccessful traversal or after aborted/abandoned laceration. BASILICA may be successful (clinically) after orthotopic stenting, but in this protocol such procedures are classified as unsuccessful investigational BASILICA.

Alternatives to BASILICA, and remaining options after failed BASILICA

Remaining options for the patient after failed BASILICA includes:

(1) Aborting the TAVR procedure with further consideration for surgical aortic valve replacement despite predicted high or prohibitive risk of death or severe morbidity; OR
(2) Proceed with TAVR using snorkel stenting (that the study investigators consider inadequate); OR
(3) Conservative management or hospice; OR
(4) A repeat attempt at BASILICA during the same, or during a different catheterization procedure.

Implications for trial design

Patients requiring TAVR who are at risk of TAVR-induced coronary obstruction and who are at high or prohibitive risk of surgical aortic valve obstruction have few satisfactory clinical options. Increasing these options beyond zero is desirable.

As described above, BASILICA technical failure typically has no sequelae, and returns patients to their baseline state of high spontaneous risk of adverse outcomes.

Based on our investigational and registry experience with BASILICA using bedside-modified commercial devices off-label, there is no evidence of post-discharge complications of BASILICA[3, 4, 24].

Subjects in this trial have an approximately 90% likelihood of acute coronary obstruction after TAVR without BASILICA, and if obstructed, an approximately 40% 30-day mortality. The primary endpoint for this trial captures both technical and clinical safety events, and therefore is appropriate to characterize the safety and efficacy of BASILICA-TAVR using the TELLTALE guidewire system.

4.4 Primary Efficacy Endpoint

The primary efficacy endpoint is **Device (technical) success**, assessed upon exit from the cardiac catheterization laboratory, including all of the following:

- Successful electrosurgical leaflet traversal using the TELLTALE Guidewire, when attempted; and
- Successful electrosurgical leaflet laceration using the TELLTALE Guidewire; and
- Successful retrieval of the TELLTALE Guidewire System

Successful traversal is defined as guidewire traversal from the aortic root across the intended aortic leaflet into the left ventricular outflow tract confirmed by either by angiography or by leaflet traction upon guidewire ensnarement.

Successful laceration is defined as intact liberation of the TELLTALE guidewire loop across a leaflet, with restoration of guidewire mobility allowing removal from the body. It may be confirmed by transesophageal echocardiography.

Successful retrieval of the TELLTALE guidewire is defined as successful removal from the body of an intact TELLTALE guidewire after successful laceration.

Rationale for primary efficacy endpoint

The primary efficacy endpoint tests the efficacy of the TELLTALE guidewire, which according to the Instructions for Use (IFU) is "…indicated for transcatheter electrosurgical traversal and laceration of native and bioprosthetic tissue."

This endpoint tests only the efficacy of the TELLTALE guidewire, not of the BASILICA procedure nor of the TAVR procedure. Safety endpoints are tested in a separate primary safety endpoint.

4.5 Primary Safety Endpoint

The primary safety endpoint is **Inpatient safety**, which is a composite of all of following assessed upon discharge from the index hospital admission:

- (Freedom from) all-cause mortality
- (Freedom from) stroke, both disabling and non-disabling
- (Freedom from) acute coronary artery obstruction
- (Freedom from) emergency cardiac surgery or reintervention related to the TELLTALE BASILICA procedure or device
- (Freedom from) BASILICA-related complications including coronary artery perforation, coronary artery dissection, aortic dissection, cardiac free wall perforation, or systemic embolization of a native or bioprosthetic leaflet

Rationale for primary safety endpoint

The primary safety endpoint tests whether a subject tolerates attempted BASILICA using the TELLTALE guidewire. The endpoint is assessed at discharge to allow subjects to recover from general anesthesia, when required, to assess for stroke. Recovery of debris inside cerebral embolic protection devices, if employed, does not constitute systemic embolization, which is a common event after TAVR.

4.6 Secondary Endpoint: 30-day Safety

The secondary endpoint is **30-day safety**, as assessed by freedom from MACE (according to VARC-3 [30]) at 30 days, including freedom from all of the following:

- All-cause mortality
- All stroke (disabling and non-disabling)
- Bleeding VARC-3 Type 2 or greater (requiring two or more units of transfused blood or hemoglobin drop >3g/dL)
- Major vascular, access-related, or cardiac structural complication (according to VARC-3, which includes coronary obstruction)
- Acute kidney injury stage 3 or 4
- Moderate or severe aortic regurgitation
- New permanent pacemaker due to procedure-related conduction abnormalities
- Surgery or intervention related to the TELLTALE device

Rationale for secondary endpoints

The secondary endpoint is derived from a community safety standard that has recently been updated, VARC-3[30]. It is assessed at thirty-days according to VARC-3.

4.7 Exploratory Endpoints

- Primary and secondary endpoints among subjects with native versus bioprosthetic disease
- Stroke: disabling and non-disabling
- Coronary stenting: snorkel (heterotopic) and orthotopic (through TAVR stent cells), to prevent or treat leaflet-induced coronary obstruction before (preemptive) and after (bailout or cautionary) TAVR.
- Facilitated BASILICA procedure success, as defined in section 0.
- Composite safety (secondary endpoint) assessed at 90 days
- Ability selectively to engage threatened coronary ostia after BASILICA-TAVR
- Acute hemodynamic deterioration in the interval between BASILICA and TAVR
- Outcomes of subjects who participate in live case demonstrations compared with those who do not

Rationale for Exploratory Endpoints

Coronary stenting related to leaflet obstruction is undesirable and may reflect failed or aborted BASILICA, typically in the heterotopic (“snorkel”) position. Orthotopic coronary stenting is

typically required to treat leaflet prolapse related to mechanical avulsion manifest typically as severe acute aortic regurgitation with hemodynamic compromise.

TAVR can render coronary arteries inaccessible for later emergency PCI. We will capture the ability to selectively engage coronary arteries after BASILICA-TAVR.

5 STUDY DESIGN

5.1 Constant values

Number of subjects	90
Number of subjects with native aortic valve failure, initially	15
Number of additional subjects with native aortic valve failure invited to participate as part of study expansion	15
Maximum number of subjects with native aortic valve failure	30
Number of candidates screened, up to	180
Number of enrollment sites	15
Follow-up duration per subject	90 days
Expected study duration	12 months for enrollment + follow-up

5.2 Overall Design

This is a prospective, open-label, single-arm, multi-center, independently-adjudicated investigation of BASILICA (Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Coronary Artery obstruction) using the Transmural TELLTALE guidewire system immediately before TAVR (transcatheter aortic valve replacement) in subjects at high risk of coronary artery obstruction, as defined in the selection criteria.

NHLBI Division of Intramural Research is the data coordinating center. Subjects undergo the study intervention only at enrolling centers.

5.3 Scientific Justification for Initiating this Study

The purpose of the study is prospectively to evaluate the safety and efficacy of BASILICA-TAVR performed with the TELLTALE guidewire system.

Because coronary artery obstruction is a predictable and life-threatening complication, because pre-emptive “snorkel” stenting is considered an inappropriate and undesirable strategy, because subjects are not good candidates for alternative surgical aortic valve replacement treatment, and because the study devices are considered intrinsically superior to bedside-modified commercial devices used for standard BASILICA, there is no control arm in this investigation.

The study is intended to support commercialization of the TELLTALE Guidewire System. We believe the study objectives cannot be met *in vitro*, using cadaver or surgical specimens *ex vivo*, nor using naïve or diseased animal models *in vivo*. Moreover, this study offers the prospect of direct benefit to subjects. Therefore clinical evaluation is reasonable.

5.4 Scientific Justification for Duration of Study Follow-up

The complications of BASILICA are evident upon procedure conclusion. Out of caution, adverse events are assessed upon hospital discharge and again after 30 days.

In the prospective BASILICA IDE trial, using "off-label" bedside modification of commercially available catheter tools, there were no new adverse events that could be attributed specifically to BASILICA after 30 days. Specifically, there were no new thrombotic events (no stroke, no MI, no coronary obstruction, no transcatheter aortic valve failure, no increase in valve gradients), the coronaries remained clinically patent, no heart failure admissions, and no BASILICA related deaths.

Moreover, we do not believe there is a plausible scientific rationale to suspect adverse events after discharge. In native and valve-in-valve TAVR, the prior valve tissue is disrupted and distorted by TAVR implantation. BASILICA does not significantly alter this disruption.

It is not clear whether BASILICA increases the risk of stroke compared historically against TAVR without BASILICA. Neurological events were identified in our early prospective BASILICA IDE trial (n=30) [3, 24] but not evident in the non-adjudicated BASILICA registry (n=213) [4]. We do not believe BASILICA-related strokes occur after hospital discharge. Moreover, the "Protected TAVR" trial [NCT04149535] of TAVR stroke prevention using the Sentinel Cerebral Protection System (Boston Scientific), has a primary endpoint of "All stroke (hemorrhagic, ischemic, or undetermined status; disabling or nondisabling) through 72 hours post TAVR procedure or discharge."

Based on feedback from FDA CDRH, we plan a final follow-up encounter, remote or in-person, at 90 days.

5.5 Justification for single-arm study design

We do not believe there is an appropriate comparator group for BASILICA TAVR using the TELLTALE guidewire.

First, redo surgical aortic valve replacement appears to have higher risk of death, major bleeding, or prolonged hospital stay than valve-in-valve TAVR in general, among both intermediate and higher risk patients (Summarized in a recent meta-analysis [31]). Therefore surgical therapy is not an appropriate comparator, especially among high- or prohibitive-risk subjects.

Second, we do not believe "snorkel stenting" is appropriate therapy or prophylaxis for patients at risk for acute TAVR-associated coronary obstruction. Snorkel stenting is "off-label," the devices lack sufficient radial strength to separate the TAVR from the wall of the aortic root or sinotubular junction, coronary stents in this heterotopic position risk deformation and thrombosis, expose the patient to prolonged or indefinite antiplatelet and antithrombotic pharmacotherapy with attendant bleeding risk, and interfere with safe future re-access to the coronary arteries for PCI. We do not endorse snorkel stenting for any patient when BASILICA or surgery is an option.

Third, we believe many candidates are offered no definitive therapy for aortic valve stenosis or bioprosthetic valve failure when they are at high risk of coronary obstruction. We attribute this un-documented phenomenon to operator inexperience and the recent guidance provided to transcatheter heart valve manufacturers that BASILICA proctorship may be construed as inappropriate marketing. Part of our motivation to develop the TELLTALE guidewire system is to empower industry-supported proctors and operators to offer BASILICA when needed by their patients.

Absent standard of care for patients at risk of TAVR-induced coronary obstruction and at high or prohibitive risk of surgical aortic valve replacement, we are unable to identify a suitable comparator group. Among our clinical investigation group, several physicians believe randomization to surgery or snorkel-stenting to be unethical.

6 STUDY POPULATION

6.1 Inclusion Criteria

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

- Adults age ≥ 21 years
- High or prohibitive risk of surgical aortic valve replacement according to the local multidisciplinary heart team
- Undergoing TAVR for bioprosthetic aortic valve failure or native aortic stenosis (“on-label” TAVR)
- Local multidisciplinary heart team determines subject to be at high risk of TAVR-induced coronary artery obstruction
- Deemed likely to suffer coronary artery obstruction from TAVR based on NHLBI Core lab analysis of CT, any of
    - Risk is narrow Sinus of Valsalva: (a) Leaflet height is greater than coronary artery height, and (b) Virtual transcatheter valve-to-coronary (VTC) distance < 4mm
    - Risk is Sinus sequestration: (a) Threatening leaflet height is greater than sinotubular junction, and (b) Virtual transcatheter valve-to-sinotubular-junction distance (VTS) < 2mm at the affected Sinus
- Concurrence of the Study Eligibility Committee
- Able to understand the protocol, consents in writing to participate, and willing to comply with all study procedures for the duration of the study

6.2 Exclusion Criteria

- Requires doppio (two-leaflet) BASILICA
- Flail target leaflet at baseline
- Excessive target aortic leaflet calcification (no basal calcium-free window or potentially obstructive calcific masses) on baseline CT
- Planned provisional (pre-position coronary artery) stents despite BASILICA
- Requires non-femoral access
- Requires concomitant procedures during TAVR (such as percutaneous coronary intervention for baseline obstructive coronary artery disease)
- Chronic kidney disease KDIGO stage 4 or 5 (eGFR < 29 ml/min/1.73m^2) or renal replacement therapy
- Not expected to survive for 12 months
- Pregnant at the time of intended treatment (day 0)

6.3 Enrollment Quota

A subset of subjects will have native aortic valve failure (initially n=15). Sequential enrollment will accommodate this quota. A "study expansion" IDE amendment increased this quota from 15 to a maximum 30.

6.4 Rationale for selection criteria

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

Children are excluded because children in general are not eligible for transcatheter aortic valve replacement. There is no maximum eligibility age because there is no scientific basis for age-based exclusion *per se*.

The CT criteria for anatomic eligibility based on valve-to-coronary distance and valve-to-sinus distance are based on prior reports [2] and experience [3].

Excessive target leaflet calcification can exclude candidates from BASILICA based on two criteria:

(1) Confluent leaflet calcification on CT at the intended basal traversal target reduces the likelihood of successful electrosurgical leaflet traversal. Conversely, any size calcium-free window at the leaflet traversal target will allow successful electrosurgical traversal.
(2) Calcific masses, defined as aortic native or bioprosthetic leaflet masses that, if displaced centrifugally by TAVR, are predicted by CT ("displacement/rotation along the hinge point") to obstruct coronary artery ostia by "mass effect." Such pathology is not amenable to BASILICA [5].

Subjects are eligible if they are at high or prohibitive risk of surgical aortic valve replacement based on two randomized clinical trials, with two different transcatheter heart valves, that showed non-inferiority of TAVR versus surgical aortic valve replacement[32, 33].

Flail baseline leaflet is excluded because of risk of leaflet prolapse after successful traversal and laceration [35]. Excessive leaflet calcification is excluded because it prohibits traversal, or when

it risks coronary obstruction through a mechanism (such as mass) not amenable to prevention by BASILICA.

Concomitant procedures might induce complications that confound assessment of TELLTALE-related complications, and are therefore excluded. Non-femoral access is associated with a higher risk of complications and such candidates are therefore excluded.

Pregnant candidates are excluded because they are generally excluded from elective transcatheter aortic valve replacement. Contraception is not required of subjects because research-related radiation is confined to the chest and only occurs on study day 0.

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 after TAVR in protocols such as this one.

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.

Doppio BASILICA is excluded because discordant first and second leaflet results would impact assessment of the primary efficacy endpoint. [34][34][4][25]

6.5 Inclusion of Vulnerable Subjects

Inclusion of Pregnant Women, fetuses or neonates

Not applicable.

6.6 Lifestyle Considerations

Not applicable

6.7 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 BASILICA using the TELLTALE guidewire system.

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 case of attempted but unsuccessful TELLTALE BASILICA-TAVR leaflet traversal or laceration, subjects are followed for 30 days to assure freedom from screening- or procedure-related adverse events.

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

6.8 Strategies for Recruitment and Retention

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

We expect to accrue at least one subject per month per site from among enrollment centers. There is no subject enrollment at NIH Clinical Center.

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

Once recruited, subject retention rate is expected to be high because follow-up activities are not onerous and are timed to correspond with routine follow-up medical care.

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.”

The TELLTALE system test articles are provided without cost by the manufacturer, Transmural Systems.

Compensation

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

7 STUDY INTERVENTION

7.1 Test articles and Indications for Use

Device Description

Based on the clinical learnings from the NIH-sponsored BASILICA IDE with off-label/off-shelf devices, Transmural Systems collaborated with Dr. Lederman at the NIH and principal site investigators of the IDE (Drs. Jaffar Khan, Toby Rogers, Adam Greenbaum and Vasilis Babaliaros) to design the TELLTALE Electrosurgical Guidewire System, providing more reliable devices for the procedure.

The TELLTALE Electrosurgical Guidewire System is comprised of the TELLTALE Guidewire and accessories to aid with the preparation, placement and use of the guidewire. The System includes:

- TELLTALE Guidewire
- TELLTALE Accessories
    - Spring-loaded connector cable
    - Guide catheters (for left coronary cusp and for right coronary cusp)
    - Insulation Envelope
    - Insulation Tube
    - Denuder/Kinker
    - Guidewire grippers

Indications for Use

The TELLTALE Electrosurgical Guidewire System is indicated for transcatheter electrosurgical traversal and laceration of native and bioprosthetic tissue in patients at risk of coronary obstruction during TAVR.

System Components

TELLTALE Guidewire

The TELLTALE Guidewire has an outer diameter of 0.014" and a working length of 310cm (Figure 5). It is composed of a 304V stainless steel guidewire covered with an outer insulative layer. The distal tip and proximal end of the guidewire are uninsulated. The TELLTALE Guidewire mid-shaft is provided to the user fully insulated to protect the operator from RF energy when the uninsulated guidewire tip is used for electrosurgical leaflet traversal inside the patient (Figure 5).

The proximal end of the TELLTALE Guidewire, which has no patient contact, is uninsulated and gold-plated to allow for connection to an electrosurgery generator to facilitate the delivery of monopolar RF energy to the cutting surfaces of the device.

There are two cutting surfaces of the TELLTALE Guidewire.

1) the distal tip for leaflet traversal
2) a mid-shaft cutting location for leaflet laceration (approximately 160cm from the distal tip).

The mid-shaft of the TELLTALE guidewire is identified by a 10mm gold marker band which is radiopaque. The mid-shaft cutting surface is created by the user by removing the insulative coating (denuded) after the distal tip is used to traverse through tissue. Therefore, the mid-shaft cutting surface does not contact the patient during electrosurgery using the distal tip. When used for the BASILICA procedure, the distal tip does not contact the patient during electrosurgery when RF energy is turned on for use at the mid-shaft cutting location.

The TELLTALE Guidewire design and procedure outlined in the Instructions for Use (IFU) will ensure that the non-insulated portions of the wire are only in contact with the patient in an intentional way during the procedure.

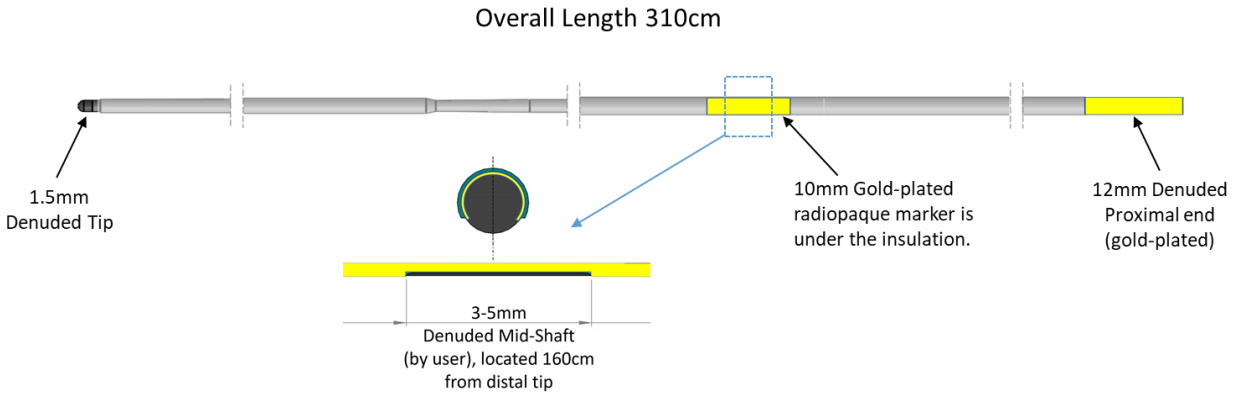

Figure 5. Image of TELLTALE Guidewire with cross section of the denuded area (prior to kinking). The insulative outer layer of the guidewire is clear but is represented in figure 4 with the gray color.

TELLTALE System Accessories:

- Spring Loaded Connector (Figure 6): A detachable spring-loaded connector cable that plugs into the RF generator and allows for a secure insulative connection between the TELLTALE Guidewire and the generator. The detachable connector allows for exchange of catheters over the TELLTALE Guidewire as needed during the procedure.
- Transmural *Pachyderm* Guide catheters (Figure 7): The guide catheters are specifically shaped to aid in leaflet traversal by allowing physicians to select the traversal location and providing backup support for TELLTALE Guidewire leaflet traversal.
- Insulation Envelope (Figure 8): The insulation envelope is only used during the traversal procedure. It is provided as an added layer of insulation to protect the user and patient from un-intended RF energy.
- Insulation Tube: The insulation tube is a plastic tube provided for use during laceration of the leaflet only. It is provided as an insulated cover for the denuded distal tip of the guidewire to protect the user and patient from un-intended RF energy.

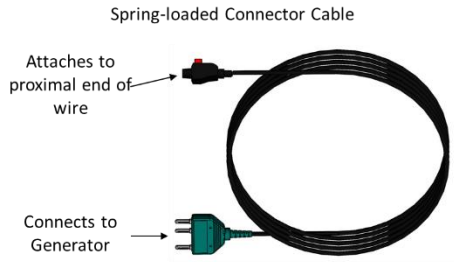

Figure 6. Image of Spring-loaded connector cable for connection to RF Generator

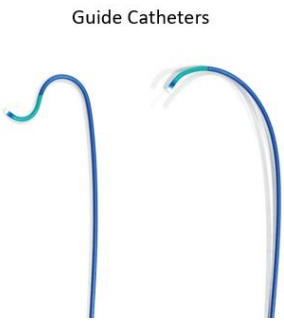

Figure 7. Image of Transmural Pachyderm Guide Catheters for the left and right coronary cusps, respectively

Figure 8. Image of Insulation Envelope

- Denuder/Kinker (Figure 9): The Denuder/kinker is provided to (1) create a reproducible denuded, or uninsulated, area at the mid-shaft location of the TELLTALE Guidewire for laceration and (2) kink the TELLTALE Guidewire at the lacerating surface to produce the required angle for the BASILICA procedure.

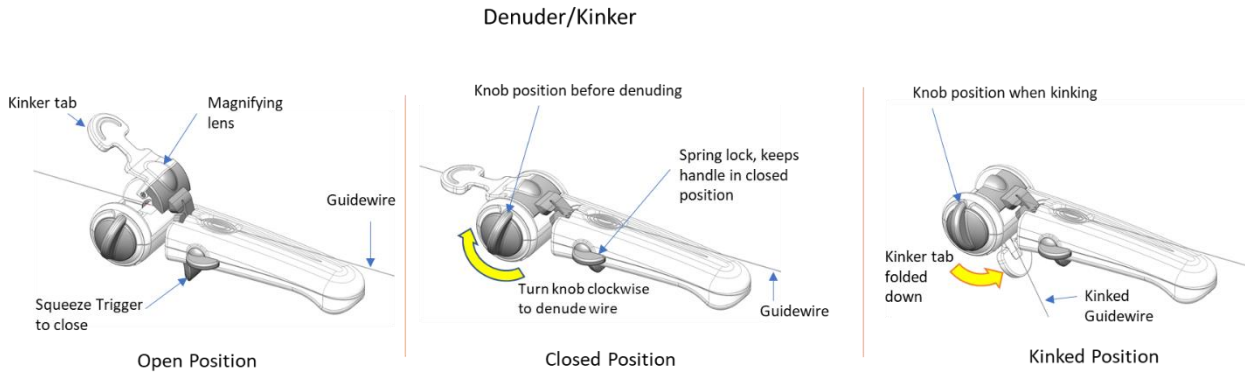

Figure 9. Image of Denuder and kinker. (Left) Open position, (Middle) Closed position, (Right) Denuded and Kinked guidewire

- Guidewire gripper (Figure 10): The guidewire gripper is attached to a standard Y-adaptor and clamps onto the TELLTALE Guidewire to assist with guidewire traction during the procedure.

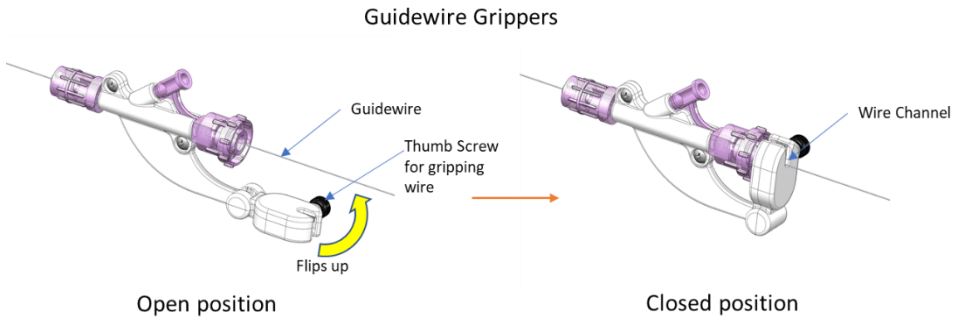

Figure 10. Image of Guidewire Grippers (Left) Open position, (Right) Closed position

The generator connector cable, gripper insulation envelope, insulation tube, and denuder/kinker are non-patient contact parts and are constructed of standard medical materials.

7.2 BASILICA-TAVR using the TELLTALE System

Study Intervention Description

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

Once enrolled, subjects will undergo baseline assessment and blood tests.

Subjects will be admitted to the hospital and undergo TAVR with BASILICA using the Transmural TELLTALE guidewire system. They will undergo primary endpoint assessment before discharge.

The TELLTALE BASILICA-TAVR procedure is planned from a contrast-enhanced CT of the heart to select a suitable transcatheter heart valve size, predict suitability of the sub- and supra-annular

landing zone, and predict post-TAVR coronary obstruction related leaflet encroachment on the sinotubular junction and coronary artery ostia. Knowledge of the aortic valve operative history is integrated into this assessment. These data are used to select a BASILICA traversal point, radiographic landmarks, and fluoroscopic projection angles.

The procedure is performed under general anesthesia or under moderate sedation at the discretion of the institutional heart team. The TELLTALE BASILICA procedure has five steps: (1) engagement of the target leaflet with a guiding catheter and optional commercial deflectable guiding sheath; (2) electrosurgical leaflet traversal with the TELLTALE guidewire, (3) preparation and positioning of the TELLTALE guidewire electrosurgical leaflet laceration surface; (4) electrosurgical leaflet laceration with the TELLTALE guidewire, immediately followed by (5) TAVR. These are all guided by fluoroscopy, with adjunctive echocardiography as needed.

Research study participation is defined as beginning the moment BASILICA traversal is attempted. This is in case TAVR is found not to be indicated at the time of the index invasive procedure, or in case BASILICA guidewire traversal is not otherwise attempted.

First catheter access is obtained typically via two arterial introducer sheaths (one for hemodynamics and angiography, one for TAVR, both also used for BASILICA) and at least one venous introducer sheath for temporary transvenous pacing. Large hydraulic-hub introducer sheaths may allow multiple guiding catheters to be introduced via a smaller number of arterial access sites. Anticoagulation with heparin or equivalent achieves an activated clotting time > 300s.

Hemodynamic and echocardiography measurements are recorded at baseline including gradients across the aortic valve, severity of valvular obstruction and severity of valvular regurgitation.

Two retrograde catheters are positioned, using a guidewire anchor as needed, in the LVOT and aorta respectively. Care is taken to avoid entrapment of mitral valvular structures. A snare catheter is positioned in the LVOT. A TELLTALE system guiding catheter, with- or without- a tandem coaxial catheter or microcatheter, directs the TELLTALE electrosurgery guidewire, against the base of the coronary cusp targeted for laceration, using fluoroscopic and/or echocardiographic guidance. Alternative guiding catheters are employed as described in the TELLTALE Instructions for Use.

Leaflet traversal is accomplished by transcatheter electrosurgery by connecting the TELLTALE.014” guidewire to an electrosurgery generator during a short burst of “pure, cutting” radiofrequency energy at approximately 10-30W as required. The guidewire is repositioned as needed until it crosses the aortic leaflet and is snare-retrieved and externalized. Nonionic flush (dextrose 5%) can be administered as needed via the guiding catheters to reduce guidewire char and thromboembolism.

Operators are encouraged to perform contrast angiography through the traversal guiding catheter to demonstrate position of TELLTALE guidewire traversal.

Next the TELLTALE guidewire is appropriately kinked and denuded to prepare the leaflet laceration surface, which is positioned across the intended valve leaflet.

A left ventricular pigtail catheter, with or without guidewire, may be positioned before or after the laceration step, at operator discretion.

Transcatheter cerebral embolic protection devices are employed at operator discretion.

Next TELLTALE BASILICA is accomplished by electrosurgical laceration during nonionic flush and traction on the TELLTALE guidewire. Electrosurgery is applied in short bursts until laceration is successful and complete, as evidenced by free withdrawal of the guidewire.

Hemodynamics are recorded quickly after laceration before TAVR. Predilatation, including intentional disruption of the bioprosthetic valve frame, is performed at operator discretion, before or after TAVR. Then TAVR is performed using established techniques typically during rapid ventricular pacing. The device size and inflation volumes are selected and applied at the discretion of the operator. Post-dilatation is performed at operator discretion to achieve an optimum TAVR result.

Coronary artery patency, and access through TAVR device struts, is established using selective coronary angiography.

Completion hemodynamics and echocardiography are recorded. Finally, percutaneous arterial and venous vascular hemostasis is obtained and the subject convalesces in the appropriate inpatient recovery unit.

Before discharge, follow-up transthoracic echocardiography is recorded. Clinically-indicated blood test results are recorded for research. These are repeated at 30 days.

Anticoagulation and antiplatelet therapy is prescribed after discharge at the physicians' discretion, and is recorded.

All subjects are to be enrolled in the TVT-Registry post-marketing TAVR registry.

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

Subjects may undergo a post-TAVR medically-indicated contrast-enhanced CT at their physicians' discretion, in which case NHLBI requests to receive and analyze the images.

Subjects' participation in the study concludes at the 90 days follow-up and termination visit.

Study duration

Subjects participate through the 90 days follow-up and termination visit.

We aim to complete the study in 12 months for enrollment + follow-up.

Number of enrollment sites

Up to 15 sites will enroll and treat subjects in this study.

7.3 Preparation/Handling/Storage/Accountability

Acquisition and Accountability

The investigational TELLTALE systems will be shipped to sites and stored in a secured location with a written receipt and accountability log. Alternatively the systems may be transported and handled by manufacturer representatives, and comparably recorded in the accountability log.

Formulation, Appearance, Packaging, and Labeling

This is described in the manufacturer instructions for use.

Product Storage and Stability

This is described in the manufacturer instructions for use.

Preparation

The TELLTALE system is prepared according to the accompanying manufacturer instructions for use.

7.4 Measures to Minimize Bias: Randomization and Blinding

Not applicable for an open-label study.

7.5 Study Intervention Compliance

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

7.6 Concomitant Therapy

There are no restrictions on concomitant therapy.

8 DISCONTINUING OR WITHDRAWING STUDY INTERVENTION OR SUBJECT

8.1 Discontinuation of Study Intervention

The TELLTALE guidewire system is a single-use device with no components implanted. It is used during a single BASILICA-TAVR procedure involving a permanent implant that is not intended to be removed.

8.2 Aborted or abandoned TELLTALE BASILICA-TAVR

In the case of aborted TELLTALE BASILICA-TAVR without successful leaflet laceration, subjects may go off-study as soon as they are clinically stable, but at least 30 day follow-up. Such subjects need not undergo additional follow-up for exploratory efficacy or natural history assessment.

8.3 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 (TELLTALE BASILICA-TAVR 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 TELLTALE BASILICA-TAVR will not lead to study discontinuation because there is no research-related radiation or other research procedures that threaten the fetus or the pregnancy.

8.4 Loss to Follow-up

A subject will be considered lost to follow-up if he or she fails to return for 2 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 center 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."

9 STUDY ASSESSMENTS AND PROCEDURES

9.1 Screening Procedures

Screening prior to consent is based entirely on clinically-indicated medical encounters, blood tests, laboratory and clinical examinations (cardiac catheterization, echocardiography, CT, MRI, 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.

Some sites will use a screening consent to abide local institutional requirements before transmitting medical records to screen for eligibility.

Screening centers will comply with Health Insurance Portability and Accountability Act (HIPAA) if applicable.

9.2 Efficacy Assessments

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

CT assessments (on baseline exam, not efficacy): valve-to-coronary (VTC) and valve-to-sinus (VTS) distance. These are analyzed by a NHLBI core laboratory.

Fluoroscopy assessments (post-TAVR coronary arteriography) includes coronary patency and ability to engage the coronary artery ostium with a catheter. These are analyzed by a NHLBI core laboratory.

Echocardiography assessments include transvalvular gradient, paravalvular leak, mitral valve injury . These echocardiographic assessments are standard and do not require core lab analysis. These are not analyzed by a NHLBI core laboratory. Instead, parameters are extracted for official reports from local echocardiography laboratories. As a result, certain fields may be missing for individual or focused examinations, such as volumes, continuity-equation valve areas, etc. These will be recorded as missing and not as protocol deviations.

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

9.3 Safety and Other Assessments

Standard safety assessments (adverse event assessments) are performed by qualified staff at enrollment centers 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.

Assessment of neurovascular events (stroke and TIA)

For candidates without prior stroke or transient ischemic attack (TIA), formally-trained and certified research coordinators will perform baseline assessments of modified Rankin Score and

NIH Stroke Score. If there is no clinically evident TIA or stroke, the predischarge assessments of modified Rankin Score and NIH Stroke Score will be performed by certified research coordinators. Otherwise they will be performed by consulting neurology specialists.

For candidates with prior stroke or TIA , consulting neurology specialists will perform baseline and pre-discharge assessments including modified Rankin Score and NIH Stroke Score.

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

9.4 Adverse Events and Serious Adverse Events

In this protocol, TAVR is clinically indicated. BASILICA using the TELLTALE Guidewire System is performed for the purpose of research.

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 BASILICA-TAVR cardiac catheterization procedure and recovery from the procedure and do not directly result from use of the investigational device.

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.

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 TELLTALE BASILICA procedure and recovery from the procedure in addition to use of the investigational TELLTALE devices.

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 0 on page 21.

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.

Classification Adverse Events

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.

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.

Expectedness

Please see the list of anticipated adverse device effects (AADE) in section 0 on page 21.

The NHLBI Principal Investigator and the Participating Site Principal 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.

Intervals and Frequency for Event Assessment and Follow-Up

Adverse event assessment, recording, and reporting will start on Day (0), upon attempt at a TELLTALE BASILICA-TAVR procedure and will continue through the 90 days 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.

All adverse events (AE) and adverse device effects (ADE) will be recorded and reported to the Sponsor using study specific case report forms, and then entry into the NIH electronic data base, CTDB (or equivalent), **through the 30 days follow-up**. All serious adverse device effects (SADE), serious adverse events (SAE), unanticipated device effects (UADE), and unanticipated problems (UP) will be recorded **through the 90 days follow up**. 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.

Adverse Event Reporting

Unanticipated adverse device effects (UADE) and Unanticipated problems (UP) must be submitted to the Sponsor for review and approval prior to submitting to the Reviewing IRB (Advarra). Sponsor will review, and if appropriate, provide suggestions to the site Principal Investigator. The enrolling site will then enter event into CTDB, and submit the report to Advarra in accordance with Advarra's policies. Sponsor will then submit final report to the NHLBI Office of the Clinical Director (OCD).

It is the responsibility of the site investigator to report adverse events and adverse device effects to their respective HRPP/IRB offices or other regulatory bodies according to their local institutional reporting requirements.

Reporting obligations and deadlines are summarized in Appendix B.

Site reporting to local institutional bodies

In addition to reporting to Advarra and the Sponsor, the Site Principal Investigator is responsible for further reporting of events to their own institution per local reporting requirements.

The NIH PI will report events to the NIH Office of Human Subjects Research Protections (OHSRP) in accordance with NIH HRPP Policy 801: Reporting Research Events found here: https://policymanual.nih.gov/3014-801

Device Safety Reporting

The Sponsor is responsible for device safety reporting to FDA.

Investigators are required to submit a report of a UADE to the Sponsor. The Sponsor must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, Advarra, and participating investigators within 10 working days after the Sponsor first receives notice of the effect. Events of Special Interest

Not applicable

Reporting of Pregnancy

Not applicable

9.5 Unanticipated Problems

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.

Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the Sponsor and Advarra. Reporting obligations and deadlines are summarized in Appendix B.

9.6 Protocol Deviations and Non-Compliance

It is the responsibility of the investigator to use continuous vigilance to identify deviations and/or non-compliance. The investigator is responsible for knowing and adhering to Advarra requirements.

Reporting obligations and deadlines are summarized in Appendix B.

Definition of Protocol Deviation and Non-compliance

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.

Non-Compliance is a failure of an investigator to follow the applicable laws, regulations, or institutional policies governing the protection of human subjects in research, or the requirements or determinations of the Institutional Review Board (IRB), whether the failure is intentional or not.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypothesis

The objective of this protocol is to test the safety and effectiveness of the TELLTALE guidewire system in accomplishing BASILICA leaflet traversal and laceration to prevent coronary artery obstruction in the study population. The primary efficacy endpoint and the primary safety endpoint are defined in sections 4.4 and 4.5. We will use the data from this study to estimate the event rates for the primary efficacy and safety endpoints. Due to limited sample size, the study is not powered to evaluate any statistical hypotheses based on these endpoints.

10.2 Sample Size Determination

The sample size is not statistically derived.

Up to 180 candidates will be consented until 90 subjects undergo attempted TELLTALE BASILICA-TAVR in this protocol.

There is a revised quota of 30 subjects who must have native TELLTALE BASILICA-TAVR of the 90 total enrolled subjects. This is based on initial quota of 15 subjects and subsequent study expansion by 15 additional subjects with native aortic valve failure. All subjects, including the expanded native cohort, will undergo analysis for primary, secondary, and exploratory endpoints.

Rationale for Sample Size

TAVR-induced coronary obstruction is rare but devastating [1, 2]. Therefore the potential patient population is small.

The key clinically meaningful outcome is successful TAVR without coronary obstruction. We believe we are able to accomplish this using bedside-modified guidewires for BASILICA-TAVR.

It is not clear whether BASILICA increases the risk of stroke compared historically against TAVR without BASILICA. Neurological events were identified in our early prospective BASILICA IDE trial (n=30) [3, 24] but not evident in the non-adjudicated BASILICA registry (n=213) [4].

FDA CDRH reviewers transmitted the following recommendation:

> We recommend increasing the size of the bioprosthetic valve subgroup to 60 subjects. This is based on a literature review of mortality and stroke rates in ViV TAVR studies that reported an average stroke rate (the lower of the two event rates) of approximately 1.4%. We suggest that the sample size be large enough to have potential to detect whether the stroke rate with TELLTALE BASILICA increases 2-fold or greater compared to clinically reported rates. For an event with anticipated incidence rate of 2*1.4% = 2.8%, a sample size of 60 will provide > 80% probability that at least one stroke event will be observed. While we acknowledge that the study will not be hypothesis-based nor powered to detect differences in stroke/mortality, we believe these are important endpoints to consider when assessing safety and effectiveness of the BASILICA procedure with TELLTALE device, and will be incorporated into our final assessment of the totality of data. The suggested sample size of 60 provides reasonable confidence that the sample size is large enough to detect a rare event.
>
> The bioprosthetic and native valve subgroups do not necessarily need to be balanced in size. We continue to believe that if they are not balanced, that enrollment should be weighted in favor of the bioprosthetic group, since this group appears more likely to have adverse events. As noted above, we suggest that the bioprosthetic group sample size be increased to 60. You may consider maintaining an n=15 native valve sample size, for a total sample size of n=75.

The investigators accept this recommended sample size.

In amendment B, the sample size is increased from 15 to 30 among subjects with native aortic valve failure, for a total sample size of 90.

10.3 Cohorts for Analyses

The analysis will be per-protocol, of subjects who undergo an attempt at TELLTALE BASILICA-TAVR.

Evaluable for toxicity

Complications are reflected in the primary safety endpoint, in secondary endpoints, and exploratory endpoints described in section 4 beginning on page 24.

Evaluable for objective response

Efficacy is evaluated in the primary efficacy endpoint, in secondary endpoints, and exploratory endpoints described in section 4 beginning on page 24.

10.4 Statistical Analyses

Exploratory data analysis will assess for missing values and will generate data clarification requests as required. We expect few missing data. If there are missing data to evaluate the primary efficacy endpoint or primary safety endpoint for a study subject, the endpoint with missing information will be considered a failure for the applicable subject. The primary analysis will be based on the intention-to-treat (ITT) population that includes all study subjects. We will also perform an as-treated analysis in a sensitivity analysis.

For the primary efficacy endpoint, primary safety endpoint and secondary endpoint, we will estimate the event rate by the sample proportion of subject who meet the given endpoint with 95% confidence interval. Descriptive statistics will be used to summarize the baseline demographic characteristics, subject and procedure characteristics, and the exploratory endpoints. For continuous variables, the mean (standard deviation) or median (interquartile range) will be presented. For categorical variables, the frequency and the percentage in each category will be presented. Exploratory 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.

In an exploratory analysis, results including the primary efficacy endpoint for device technical success and 30-day VARC3 safety will be compared with those outcomes from a previously completed study, the NHLBI BASILICA IDE protocol (NCT03381989) of bedside-modified traversal and laceration guidewires. Fisher's exact tests will be used to compare these outcomes between two studies.

The key study results (primary and secondary endpoints) will be analyzed by subgroups including indication (bioprosthetic versus native), site, census region, age (dichotomized by the sample median), non-white status, and sex. For each of the above baseline characteristics, the subgroup differences in the study outcome will be evaluated by the two-sided Fisher's exact test at a significance level of 0.05. For the subgroup analysis of study sites, the sites with smallest number of patients will be combined to have at least 5 subjects in the pseudo-site group.

Statistical analysis will be performed or confirmed by the NHLBI study statistician.

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

The mortality observed in the prospective NHLBI BASILICA IDE study (n=30) was 3.3%, and the 12-month mortality was 10% [24]. The 30-day mortality observed in the retrospective multicenter international BASILICA registry (n=214) was 2.8%, and 12-month mortality was 21.5% [4].

In Amendment A, the stopping rules are adjusted to become more conservative, as stipulated by the DSMB before enrollment began. 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 5% or less and determine the stopping rule by a Bayesian approach [36]. The stopping boundary is reached if the posterior probability that the 30-day mortality rate exceeds 5% 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 =0.75, b =14.25. 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. The custom calculator is posted at https://rconnect.nhlbi.nih.gov/CTStopRule/.

Number of subjects in the stratum	Consider stopping if the number of deaths within 30 days reaches
2 - 5	2
6 - 18	3
19 - 31	4
32 - 46	5
47 - 61	6
62 - 75	7

We investigated the performance of the above stopping rule by a simulation study. In each simulation run, we generated a study with 75 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	0.025	0.05	0.075	0.1	0.15	0.2
Proportion of Stopped Studies	0.022	0.169	0.454	0.72	0.963	0.997
Average number of subjects	73.8	67.6	56	43.3	24.7	15.6
Average number of 30-day mortality	1.9	3.4	4.2	4.3	3.7	3.1

These simulation results suggest that our stopping rule has a low probability stopping a study when the true 30-day mortality rate is 5% or less, and the probability of stopping a study is high

when the true 30-day mortality rate exceeds 5%. There, we believe that our Bayesian stopping rule for 30-day mortality has satisfactory statistical properties.

11 STUDY GOVERNANCE AND OTHER OPERATIONAL CONSIDERATIONS

11.1 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 study sites to report all events of regulatory significance.

General Sponsor Duties

The Sponsor's general duties consist of submitting the appropriate regulatory applications, selecting investigators and 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, ensuring proper monitoring of the investigation, ensuring study subject informed consent is obtained, and informing IRB and FDA promptly of any significant new information about the investigation.

11.2 Site Selection and Training

Site selection:

Site selection will be 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 the BASILICA procedure.
- Sites must demonstrate ability to obtain CT examinations that are technically satisfactory for consideration of BASILICA.

Site training:

The Sponsor Representative will ensure appropriate training in the technique of TELLTALE BASILICA-TAVR 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.
- Manufacturer training about operation of TELLTALE system study devices

- Proctored conduct of TELLTALE BASILICA procedures in patients at the study site, at the sole discretion of the Sponsor and/or NHLBI Principal Investigator.
- Completion of training, and suitability for independent TELLTALE BASILICA-TAVR enrollment, will be certified by the NHLBI Principal Investigator and Sponsor Representative.
- Other TELLTALE investigators and manufacturer representatives provide ongoing proctorship and observe procedures, in-person or remotely via video telepresence.

11.3 Study Central Clinical Eligibility Committee

Clinical data for all research candidates are confirmed by the study Central Clinical Eligibility Committee before enrollment.

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

11.4 Core Laboratories

The NHLBI CT and Fluoroscopy Core Laboratories will analyze baseline CT and procedure fluoroscopy.

There is no echocardiography core laboratory for this study.

11.5 Independent Data Monitor

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).

Monitoring for this study will be performed by the independent data monitor.

Remote or on-site monitoring will be performed during the site initiation visit and periodically throughout study enrollment. There will be 100% source-data verification.

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.

Independent audits will not be conducted by Study Sponsor.

11.6 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 30 days follow-up interval

- Deaths
- Primary (Efficacy) and (Safety) Endpoints
- Secondary (30-day safety) Endpoints

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

11.7 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 conflict 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 six month 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 0 on page 46).

In the case of death or serious UADE, if the Sponsor and the NIH 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 clinical sites will be notified of this action.

A “stopping rule” is described in section 10.5 on page 50 as non-binding guidance for the Investigators and the Data and Safety Monitoring Board to assure subject safety. This is based on anticipated 30-day mortality. This is intended to assist and not automate decision-making.

11.8 Publications Committee

The study publications committee consists of the NIH 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.

11.9 Publication and Data Sharing Policy

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 11.8).

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.

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

Data transfer to collaborators

De-identified (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).

De-identified images will also be transferred to collaborating investigators at academic and industry sites. They are provided for the purpose of medical education and research.

Coded **but linked** data are provided to collaborators who require additional information, and with IRB approval of this protocol. This approach is used for the sake of quality control and/or quality assurance of the test article. These collaborators are:

Recipient	Organization	Location	Linkable
Nasser Rafiee	Transmural Systems	Andover, MA	Linked
Stephanie Sellers, PhD	University of British Columbia	Vancouver, BC, CANADA	Linked

11.10 Intellectual Property

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

11.11 Informed Consent Process

Consent/Assent Procedures and Documentation

Subjects who are UNABLE to provide consent may NOT be enrolled. The use of a legally authorized representative (surrogate), is not permitted. Telephone or electronic consent are allowed for the optional screening consent; in-person consent is required for participation in the TELLTALE BASILICA TAVR protocol.

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). Research informed consent will be obtained by the local site Principal Investigator and local 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 transcatheter aortic valve replacement (TAVR). The research procedure is a procedure adjunct to TAVR.

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 given sufficient time to determine whether or not to participate in the research study.

The research 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-approved research consent. Electronic tools may be employed for the optional screening consent.

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.

Informed consent for non-English speaking subjects

Enrolling sites will follow Advarra processes for short form consent of non-English speaking research participants. Advarra provides pre-approved short form consent templates in multiple languages. All other institutionally/organizationally-approved short form consents and translations in use at a research location or institution do not need to be submitted for Advarra review. If using a local short form consent, however, the investigator/site will need to also provide the subjects with the Advarra Short Form IRB Oversight Addendum, to ensure notification to the subject of Advarra as the IRB of record.

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 TELLTALE BASILICA-TAVR, they will remain in the study, because the risk of investigation is confined to the index procedure. All additional data collected 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. Individual sites will follow applicable laws, regulation and institutional policy.

If the study team is unable to identify a Legally Authorized Representative, the team will seek guidance from their local institution.

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

11.12 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 Principal Investigators, Advarra, Sponsor (NHLBI Office of Clinical Director), NIH Principal Investigator, Device Manufacturer, and FDA.

If the study is prematurely terminated or suspended, the NIH Principal Investigator (PI) will promptly inform study participants, the 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).

11.13 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**.

Representatives from Transmural Systems may be present during the TELLTALE BASILICA-TAVR procedure. This is disclosed in the informed consent.

The study monitor, other authorized representatives of the Sponsor, representatives of the 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 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 the time period dictated by Advarra, Institutional policies, or Sponsor requirements, whichever is the longest.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the NIH. 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 clinical 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.

As identifiable private information will be collected and stored for/by the NIH, the prospective subject will receive a privacy notice and be informed of the NIH Certificate of Confidentiality policy in the consent form.

11.14 Future use of Stored Specimens and Data

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

Subjects consent to future use of their clinical and imaging data indefinitely, even upon withdrawal of consent. 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.

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 11.13, Confidentiality and Privacy and Section 11.17, Data Handling and Record Keeping, for further information on future use of study records.

11.15 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).

Independent Data Monitor:

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

- to verify the existence of signed research 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 clinical site regulatory files to ensure that regulatory requirements (Office for Human Research Protections, OHRP), FDA and applicable guidelines (ICH-GCP) are being followed. During the monitoring visits, the site Principal Investigator (and/or designee) and other study personnel will be available to discuss the study progress and

monitoring visit. The site Principal Investigator (and/or designee) will make study documents (e.g., consent forms and pertinent electronic and/or paper medical records readily available for inspection by the IRB, the FDA, the site monitors, and the NIH staff for confirmation of the study findings.

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 study site must be resolved within 7 days of site notification.

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.

NIH Principal Investigator Monitoring:

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

Institutional Review Board (IRB) of Record:

Accrual and safety data will be monitored and reviewed annually by the Reviewing IRB (Advarra) 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). Advarra 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.

Data and Safety Monitoring Board (DSMB) Monitoring

DSMB activities are described in section 11.7 on page 53.

11.16 Quality Assurance and Quality Control

Quality assurance measures include

- Diligent investigator procedure training in TELLTALE BASILICA-TAVR technique and device operation
- Sponsor and investigator participation (when available) and review of TELLTALE BASILICA-TAVR procedures
- Site initiation visit by NIH Principal Investigator, NIH 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
- NIH 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

11.17 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.

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. Sample Case Report Forms are provided in (APPENDIX A: Sample Case Report Forms).

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.

Direct Access to Source Data

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

The site Principal 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 and other appropriate institutional regulatory bodies, and/or the Sponsor may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the site Principal Investigator, who must provide support at all times for these activities.

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 TELLTALE BASILICA-TAVR 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, cardiac MRI, and chest radiographs. 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 11.13 (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 the NIH 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 or Nuance Powershare). Imaging data are stored in a secure Picture Archive Computer System (PACS) or vendor-neutral archive, according to local institutional standards.

11.18 Study Records Retention

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

11.19 Collaborative Agreements

This protocol will be conducted under a Clinical Trials Cooperative Research and Development Agreement between NHLBI and Transmural Systems, (date pending).

11.20 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.

12 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
CRF	Case Report Form
CT	Computed tomography
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
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
HRPP	(NIH) Human Research Protection Program
IDE	Investigational Device Exemption
IRB	Institutional Review Board
MACE	Major adverse clinical events
mRS	Modified Rankin Scale of stroke disability
NHLBI	National Heart Lung and Blood Institute
NIH	National Institutes of Health
OHSRP	NIH Office of Human Subjects Research Protections
PI	Principal Investigator
SADE	Serious adverse device effect
SAE	Serious adverse event
TAVR	Transcatheter aortic valve implantation

TEE	Transesophageal echocardiography
TELLTALE	Transmural Electrosurgery LeafLet Traversal And Laceration Evaluation device
THV	Transcatheter heart valve
TTE	Transthoracic echocardiography
UADE	Unanticipated adverse device effect
UP	Unanticipated problem
VARC	Valve academic research consortium (criteria)
VTC	Virtual transcatheter Valve-To-Coronary distance
VTS	Virtual transcatheter Valve-To-Sinotubular-junction distance

13 APPENDIX A: Sample Case Report Forms

14 Appendix B: Reporting Obligations

14.1 Reporting obligations of NIH Principal Investigator

Reports from NIH 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 calendar 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 calendar 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 calendar 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 calendar 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 calendar 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 = NIH Principal Investigator / Sponsor Representative

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

14.2 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 7 calendar days	Sponsor
Serious Anticipated Adverse Device Effect (SADE)	Within 3 working days	Sponsor
Anticipated Adverse Device effect (ADE)	Within 7 working days	Sponsor
Serious Adverse Events (SAE-not directly related to the device)	Within 5 working days	Sponsor
Adverse Events (AE)	Within 7 working days	Sponsor
Death 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
Unanticipated Problems (UP) involving subject risk	Within 3 working days	Sponsor
Major Protocol Deviations (PD)	Within 3 working days	Sponsor
Minor Protocol Deviations (PD)	Within 7 working days	Sponsor
Non-compliance, Serious	Within 3 working days	Sponsor
Non-compliance, Continuing	Within 3 days working days	Sponsor

* In addition to reporting to the Sponsor, the Site Principal Investigator is responsible for further reporting of events to their own institution per local reporting requirements and to Advarra (see Advarra IRB Handbook).

15 VERSIONS

Version	Revision
2022-11-30	First FDA approved version
2023-05-25	• Increase number of sites from 10 to 15 • More-conservative stopping rules, as stipulated by DSMB • More-focused reporting of abnormal blood tests as adverse events • Clarification that only one post-TAVR troponin measurement is required, to resolve inconsistency between section 2.4 text and Schedule of Activities • Reference to upcoming IFU revisions for possible alternative guiding catheters • Telephone/electronic consent allowed, for screening only • Housekeeping, list additional exploratory endpoints • Additional recipient of anonymized research data • Additional/optional imaging exams (coronary arteriography and CT) if obtained in the course of standard medical care are transmitted to NHLBI for analysis. • Lengthened allowable window for baseline CT scan

	• Updated background on global reported clinical experience • Clarify CEAC endpoint review covers only 30d data, when primary and secondary endpoints assessments are due
2023-10-01	• Study expansion to 15 additional subjects with native aortic valve failure, after initial enrollment quota of 15 is met, in coordination with CDRH. • Clarify ongoing proctorship may be offered in-person or via telepresence, and other housekeeping changes.
2024-10-31	• Increase number of candidates allowed to be screened, to 180 (should have been requested with Amendment B)

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