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NHLBI DIR Protocol Title:

Early feasibility evaluation of Transmural Systems Transcaval Closure Device (TCD) for transcaval access ports during transcatheter aortic valve replacement (TAVR)

Short title

Transcaval closure device (TCD) for transcaval TAVR

Version History

2017-05-20	Draft
2017-06-13	After NHLBI Branch Review
2017-11-15	IDE application
2017-12-14	FDA interactive IDE review
2017-12-22	NHLBI IRB Stipulations
2018-01-17	Amendment A-consent amendment only
2018-02-12	Amendment B, clarification of time-and-events schedule

Investigational Device Exemption

G170286 December 15, 2017

Sponsor-Investigator:

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

Key Roles

Role	Individual	Affiliation
Principal Investigator (NIH)	Robert J. Lederman, MD	NHLBI Division of Intramural Research
National Co-Principal Investigators	Toby Rogers, PhD, BM BCh Adam B. Greenbaum, MD Vasilis C. Babaliaros, MD	Medstar Washington Hospital Center Henry Ford Hospital Emory University Hospital
Study Manager	Annette M. Stine, RN	NHLBI Division of Intramural Research
CT core lab	Marcus Chen, MD	NHLBI Division of Intramural Research
Monitoring service	TBD	Harris Contractors or equivalent
Independent Clinical Events Adjudication Committee	TBD	TBD
Data Safety Monitoring Board	Jamieson M. Bourque, MD, MHS	NHLBI via University of Virginia
IDE Study Sponsor	Robert J. Lederman, MD, on behalf of NHLBI	NHLBI Division of Intramural Research
Data Coordinating Center	Robert J. Lederman, MD	NHLBI Division of Intramural Research
Study Statistician	Xin Tian, PhD	NHLBI Office of Biostatistics Research
Site 1 PI	Adam B. Greenbaum, MD	Henry Ford Hospital, Detroit, MI
Site 2 PI	Vasilis C. Babaliaros, MD	Emory University Hospital, Atlanta, GA
Site 3 PI	Toby Rogers, PhD, BM BCh	Medstar Washington Hospital Center
Site 4 PI	TBD	

Study Site:	Site Principal Investigator:
National Heart, Lung and Blood Institute, NIH **FWA #00005897** **(Data Coordinating Center)***	Robert J. Lederman, MD, Senior Investigator National Heart Lung and Blood Institute, National Institutes of Health Building 10, Room 2c713, MSC 1538 Bethesda, MD 20892-1538 Voice: 301-402-6769 Email: lederman@nih.gov Statistician: Xin Tian, PhD NHLBI Office of Biostatistics Research NHLBI associate investigators Jaffar M. Khan, BM BCh
Henry Ford Hospital FWA#: 00005846	Adam B. Greenbaum, MD Director, Cardiac Catheterization Laboratory Henry Ford Hospital, Cardiac Cath Lab K-2 2799 West Grand Blvd, Detroit, MI. 48202 Phone: 313-916-3875 Email: agreenb1@hfhs.org Robert J. Lederman, MD (will participate in interventional procedures)
Emory University FWA #: 00005792	Vasilis C. Babaliaros, MD Emory University 1364 Clifton Rd. NE, Suite F606 Atlanta, GA 30322 Phone: 678-557-4514 Fax: 404-712-0884 Email: vbabali@emory.edu
Medstar Washington Hospital Center FWA#: 00000504	Toby Rogers, PhD, BM BCh Medstar Washington Hospital Center 110 Irving Street, NW Suite 4B-1 Washington, DC 20010
Site #4	To be determined

* No subject enrollment

Estimated Duration of Study:

18 months

Estimated Completion Date of Study:

June 31, 2019

Subjects of study and sites:

Subjects	Sex	Age range	Sites
30 consented but not treated 15 treated	Men & Women	≥21 years	Up to 4

DISCLOSURES

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

ABG serves as a proctor for Edwards Lifesciences and Abbott Vascular.

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

ABBREVIATIONS

CEAC	Clinical events adjudication committee
CRF	Case Report Form
CT	Computed tomography
DSMB	Data Safety Monitoring Board
EFS	Early feasibility study
eGFR	Estimated glomerular filtration rate
IVC	Inferior vena cava
LDH	Lactate dehydrogenase
MACE	Major adverse cardiovascular events
TAVR	Transcatheter aortic valve implantation
TCD	Transcaval closure device
THV	Transcatheter heart valve
VARC-2	Valve academic research consortium (criteria), second edition

PRÉCIS

Transcaval access to the abdominal aorta from the neighboring inferior vena cava (IVC) enables transcatheter aortic valve replacement (TAVR) in patients not eligible for femoral artery access. Currently the procedure is performed using devices, off-label, designed and marketed to close holes inside the heart and great vessels, manufactured by Abbott St Jude (Amplatzer Duct Occluder and Amplatzer Muscular VSD Occluder). Because these Amplatzer occluders are not designed to close transcaval access sites, they may not completely prevent bleeding.

This is an early feasibility study (EFS) evaluation of a purpose-built closure device for transcaval access. The device, the Transcaval closure device (TCD) will be evaluated for safety and performance to close transcaval access sites in patients ineligible for femoral artery access for TAVR.

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1.0 OBJECTIVE

The objective of this study is to evaluate the safety and early feasibility of closure of transcaval aortic access sites using the TCD after transcatheter aortic valve replacement (TAVR).

2.0 BACKGROUND

Transcatheter aortic valve implantation (TAVR) avoids the morbidity and mortality of surgical aortic valve replacement in high and intermediate risk patients [1-5]. Transthoracic (transapical and transaortic) access is inferior to femoral-artery access[5]. Discomfort and morbidity are more pronounced from transthoracic access for TAVR, probably because of invasiveness and pulmonary insults. Operator ergonomics are more favorable for transfemoral than for non-transfemoral access, and these human factors may impact procedure outcomes. An alternative transfemoral access approach to TAVR might be desirable in these patients to reduce the hazards and discomfort of transthoracic access and because of the superior operator ergonomics.

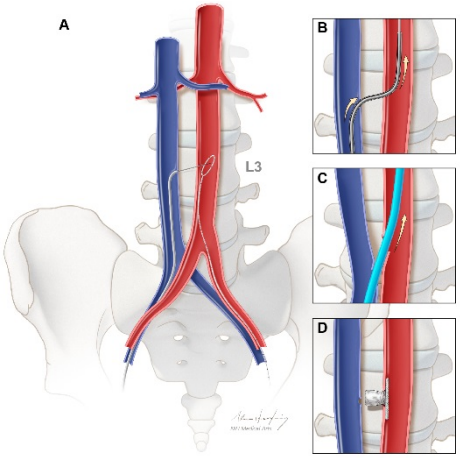


Figure 1. Illustration of transcaval access and closure.

3.0 CLINICAL AND SCIENTIFIC JUSTIFICATION

We developed a technique of transfemoral venous access for retrograde TAVR by entering the abdominal aorta through the adjoining inferior vena cava, called transcaval access [6] (Figure 1). The procedure relies on the observation that interstitial pressure always exceeds venous pressure. Animals tolerate the resulting acute aorto-caval fistula even without repair, because the retroperitoneal space appears to pressurize and cause aortic blood to return immediately through the corresponding hole in the vena cava (Figure 2). Patients tolerate transcaval access after nitinol cardiac occluders are implanted to close the aortic entry site. Transcaval access and closure was uniformly successful in the first 19 patients, all of whom had no good TAVR access options[7]. Thereafter, we performed a multi-center trial of transcaval TAVR in 100 patients (STS predicted risk of mortality 9.6±6.3%) ineligible for transfemoral and high or prohibitive risk for transthoracic access. Transcaval access was successful in 99/100. Device success (access and closure with a nitinol cardiac occluder without death or emergency surgical rescue) was 98/99. Inpatient survival was 96% and 30-day survival was 92%. Transcaval-related life-threatening bleeding was 7%. Transcaval access enabled TAVR in patients who were not good candidates for transthoracic access. Bleeding and vascular complications were common but acceptable in this high-risk cohort.

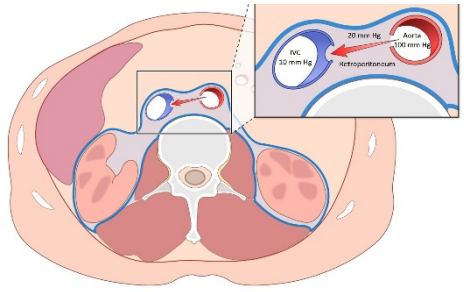


Figure 2. Interstitial pressure exceeds venous pressure and drives decompression of aortic bleeding.

Currently transcaval access sites are closed using Amplatzer Duct Occluders and Amplatzer Muscular VSD Occluders (Abbott St Jude Medical), off-label. These polyester-seeded self-expanding nitinol devices are designed to close intravascular communications between the aorta and pulmonary artery or between the

left and right ventricles, and are by-design tolerant of post-procedure blood flow. As a result, the Amplatzer devices are not immediately hemostatic. While the majority of patients experience and tolerate residual aorto-caval fistula through Amplatzer occluder devices, a minority do not tolerate the acute left-to-right cardiovascular shunt because of severe cardiomyopathy and require adjunctive covered stent implantation. In addition, Amplatzer devices are also designed to elongate during delivery when tension is applied, which risks intra-procedure pull-through and mal-deployment. As a result, closure with Amplatzer devices requires special operator skill for deployment [8].

The Transmural Systems Transcaval Closure Device (TCD) is purpose-built for this application. It was designed in collaboration by NHLBI investigators and Transmural Systems, Incorporated. The preclinical development was funded by a SBIR contract from NHLBI to Transmural Systems. The TCD is designed to facilitate rapid hemostasis and fistula occlusion by virtue of polyester covering. The TCD is also designed to resist pull-through because of an incorporated spring that flattens the aortic disc. As a result of these design features, the TCD is expected to exhibit hemostasis, fistula occlusion, and ease-of-use compared with the *Amplatzer* devices that had been used off-label to close transcaval access sites.

3.1 Preclinical testing

Extensive preclinical testing has been performed on the TCD System. The TCD has been evaluated through a series of bench tests to verify that the design met specification both as-manufactured as well as after exposure to representative shipping and environmental conditioning. All studies were completed, and results passed prospective endpoint criteria.

In addition to extensive bench testing, an in vivo GLP study assessed key safety and performance characteristics of the TCD. Nine (9) swine were implanted with the TCD and followed for 30- and 90-day endpoints to evaluate device placement, ability to achieve hemostasis, and chronic device integrity. The results of the study demonstrate that the TCD can be advanced, repositioned, retrieved, and deployed without safety or performance events. Immediate hemostasis was achieved in all implanted devices, and no acute or chronic aorto-caval fistulae were observed.

In addition, the chronic histopathology found acceptable fibrosis and inflammation, which was reduced compared with non-GLP histopathologic evaluation of the Amplatzer Duct Occluder that has been used in hundreds of patients to date. End organ analysis including, kidney, liver, spleen, heart, and coronary bands in the legs showed no thromboemboli. In addition, the Implant and delivery system passed all ISO-10993 requirements.

The results of the preclinical bench and in-vivo testing justify the use of the TCD in human subjects.

4.0 TREATMENT OPTIONS

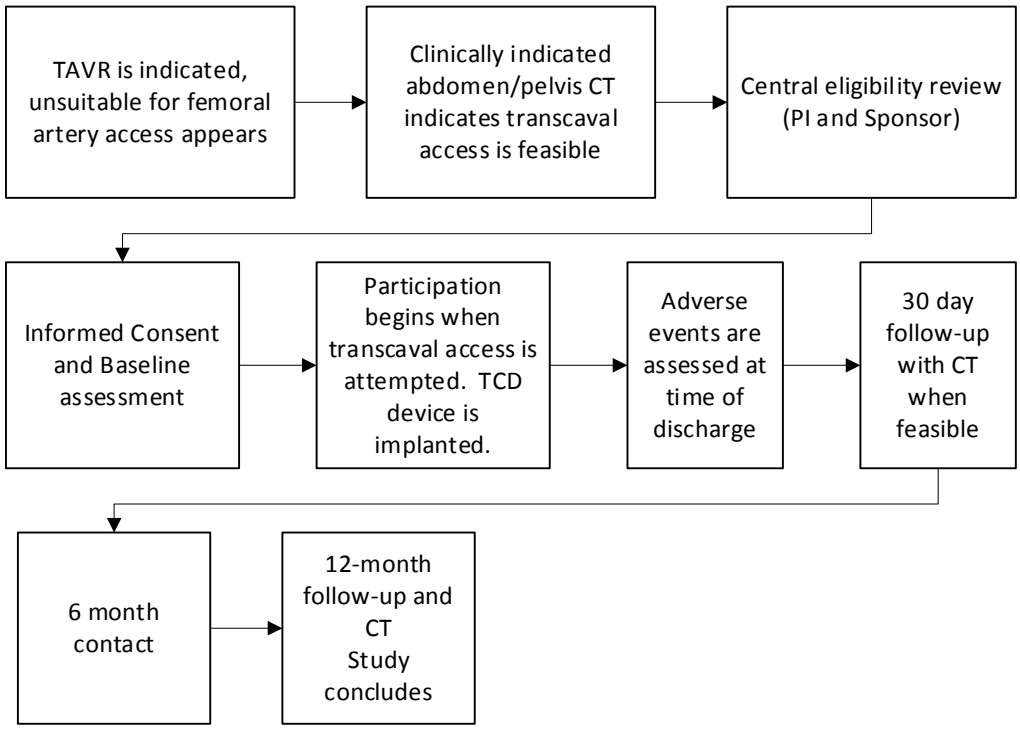
Several “alternative access” approaches are available for patients ineligible for transfemoral artery access for TAVR. Trans-apical and trans-aortic access, both of which are “trans-thoracic” approaches, require open chest surgery and confer the pulmonary and other risks of operative morbidity and mortality. In the only independently adjudicated study of the Sapien 3 THV[5], life-threatening bleeding occurred in 22.6% of intermediate-risk patients after transthoracic TAVR and 6.7% after transfemoral TAVR, compared with 12% after transcaval TAVR closed with Amplatzer devices in a separate NHLBI IDE study. It is noteworthy that the operative risk score of subjects in the PARTNER-II study were higher (mean STS predicted risk of mortality score 9.6%) than in the NHLBI IDE study (mean STS score 5.8%)

There are several extra-thoracic alternative access approaches, including trans-carotid, mediastinal, and trans-subclavian approaches. These also generally require operative exposure and confer operative morbidity and vascular complications.

Medical therapy, or balloon aortic valvuloplasty, of severe aortic valve disease is considered an unsatisfactory strategy with high mortality.

5.0 STUDY DESIGN

5.1 Schematic of study design



5.2 Overview of study design

This is an early feasibility study of the TCD. It is a prospective, open-label, single-arm, multi-center, investigator-initiated, and independently-adjudicated investigation of the TCD in patients undergoing TAVR who are not eligible for standard transfemoral artery access.

Candidates will be identified by the participating structural heart disease programs. Standard TAVR planning includes contrast-enhanced abdomen and pelvis CT, typically during the same contrast exposure as the cardiac CT. Eligibility will be reviewed and proposed by the local multidisciplinary heart teams. Anatomic eligibility will be confirmed by the core CT analysis laboratory using the clinically indicated CT. Candidates will then undergo central eligibility review by the Study Eligibility Committee. If deemed eligible, candidates will be offered participation in the study.

Once enrolled, subjects will undergo protocol baseline assessment. If eligible, subjects will be admitted to the hospital and undergo transcaval TAVR under this protocol. The transcaval access site will be closed with the TCD. They will undergo follow-up testing including CT scan at 30 days and 12 months.

5.3 Transcaval TAVR Procedure

The transcaval TAVR procedure is planned from a CT of the abdomen and pelvis, preferably with thin-slice <1.5mm reconstructions, and preferably with contrast enhancement[9]. The goal is to select a crossing target free of significant calcium or interposed structures, far from visceral branches that might be compromised by the closure device or by bailout covered stent implantation.

The procedure is performed under general anesthesia or under moderate sedation at the discretion of the institutional heart team. Prophylactic antimicrobials are administered according to institutional routine.

Participation in the investigational protocol (for follow-up and surveillance) begins only when transcaval access is attempted. We select this timepoint lest physicians successfully undertake transfemoral artery access in patients who have consented but who have "borderline" femoral artery access vessels. If there is any intent or attempt to perform transcaval access, the candidate is treated as enrolled.

The technique of transcaval access is described in detail elsewhere[8]. Percutaneous right femoral vein access is obtained for the transcaval sheath, and percutaneous femoral artery access is obtained for thoracic and abdominal aortography, for the required intravascular snare, for adjunctive balloon aortic tamponade if necessary, and for bailout covered stent implantation if necessary. Separate vascular access is obtained according to operator routine for temporary transvenous pacing. Heparin is the recommended TAVR anticoagulant because it is amenable to pharmacologic reversal with protamine before closing the transcaval access port.

Typically baseline abdominal aortography is performed to register the fluoroscopy with the baseline CT plan. Coaxial crossing catheters (such as a renal length guiding catheter, 0.035" braided microcatheter, Piggyback 0.014-to-0.035" polymer jacket exchange catheter, and 0.014" Astato-XS-20 guidewire) are positioned at the crossing target in the IVC and aimed at an aortic snare catheter. The guidewire is electrified briefly at 30-50W, by connecting to a standard monopolar electrosurgery generator, during advancement from the IVC into the aorta. The ensnared guidewire is then used in turn to advance the exchange catheter, microcatheter, and rigid guidewire all to allow advancement of the THV introducer sheath from the femoral vein into the abdominal aorta. The sheath is secured with suture.

Next the transfemoral TAVR procedure is performed according to operator preference and institutional routine.

At the conclusion of the TAVR procedure, heparin anticoagulation is reversed with protamine. Hemodynamics are recorded. The TCD delivery system is positioned over a 0.014" guidewire though the THV introducer sheath into the abdominal aorta, and the appropriate orientation confirmed. The THV introducer sheath is withdrawn fully from the aorta into the lower IVC. The TCD aortic disc is exposed and the appropriate orientation again confirmed. The TCD aortic disc is retracted against the endoluminal wall of the aorta, and position confirmed by angiography. The TCD body is then withdrawn outside the aorta to occupy the iatrogenic aortocaval tract. The hemostatic (against extravasation) and occlusive (against fistula) performance of the TCD is assessed by serial angiography and instantaneous hemodynamics. If necessary, the TCD is recaptured into the delivery system and repositioned. After satisfactory positioning, the TCD may be released, and the 0.014" guidewire removed.

If necessary, balloon aortic tamponade is performed according to standard transcaval technique and operator preference, using a balloon size selected from baseline CT. Use of the balloon aortic tamponade technique is recorded, but is not considered a device or procedure failure.

Covered stent implantation is performed at the discretion of the operator for unsatisfactory performance of the TCD, at the discretion of the operator, and the indications are recorded.

Completion angiography is performed using digital subtraction angiography and the immediate hemostatic performance (against extravasation) and occlusive performance (against fistula) are assessed. Percutaneous vascular site hemostasis is obtained according to usual techniques.

Should the TCD fail, treatment contingencies include balloon aortic tamponade, covered stent implantation, and closure using an Amplatzer closure device.

Before discharge, changes in hemoglobin and blood transfusions are recorded carefully to determine VARC-2 bleeding scores. Other pre-discharge blood tests are obtained to measure hemolysis and infection. Post-procedure antiplatelet and anticoagulation regimens are selected according to physician preference.

Unscheduled abdomen/pelvic CT are analyzed if they are available.

Contrast-enhanced abdominal/pelvic CT is obtained in follow-up after 30 days, when permitted by renal function, as determined by the local physician.

A follow-up encounter (telephone or in-person) is performed at 6 months to assess interval adverse events.

A final study-mandated in-person visit is performed at 12 months, with contrast-enhanced abdomen/pelvic CT, when permitted by renal function, as determined by the local physician.

5.4 Time and Events Schedule

	Screening (-30 to 0D)	Baseline	Day 0	Inpatient	30 d (±14d) FU	6 mo (± 3 wk)	12 mo (± 4 wk) FU
Baseline informed consent		X					
Multidisciplinary heart team eligibility determination		X					
Baseline clinical assessment		X					
Blood tests		X		X	X		X
Vital signs and in-person visit		X			X		X
Abdomen/pelvis CT (contrast-enhanced) analyzed by core lab	X				X		X
Study eligibility committee concordance	X						
Transcaval TAVR with implantation of transcaval closure device (TCD)			X				
Vital status and adverse event assessment				X	X	X	X

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

For subjects who die, necropsy evaluation is requested to examine the abdominal aorta and cava *en bloc* at NIH.

5.5 Blood tests

Blood test	Rationale	Schedule
Lactate dehydrogenase (LDH) Haptoglobin	A combination of low or undetectable plasma haptoglobin (≤25 mg/dL) and elevated LDH (above institutional normal limit) will screen for **hemolysis** after the procedure [10]. A positive combination of these tests will prompt confirmatory evaluation by peripheral red blood cell smear and reticulocyte test.	Baseline Pre-discharge 30-day 12-month
Complete blood count including - Hemoglobin - Platelet count - White blood cell count and differential	Test for hemoglobin Test for low platelets Screen for infection related inflammation	Baseline Pre-discharge 30-day 12-month
Creatinine and estimated glomerular filtration rate (eGFR)	Test of renal excretory function	Baseline Pre-discharge 30-day 12-month

6.0 ELIGIBILITY ASSESSMENT

6.1 Inclusion Criteria

- Consents to participate in this study and all related clinical follow-up procedures
- Adults age ≥ 21 years
- Undergoing transcatheter aortic valve replacement (TAVR) based on the clinical assessment of the multidisciplinary heart team
- Ineligible for femoral artery access for the selected transcatheter heart valve (THV) according to the THV manufacturer instructions for use.
  [Note Corevalve Evolut R: ≥5mm; Evolut PRO 23, 26, 29 mm valves and Evolut R 34 mm: ≥ 5.5 mm; Edwards Sapien 3, 23-26mm: 5.5 mm; Edwards Sapien 3, 29mm: 6.0mm;
  Anatomic ineligibility also considers patient-specific pattern of iliofemoral calcium and tortuosity.]
- Eligible for transcaval access based on Core Lab analysis of the baseline abdomen/pelvis CT indicating a calcium-free target window on the abdominal aorta; a target ≥ 15mm from the lowest main renal artery or aorto-iliac bifurcation; no important interposed structures; a projected intravascular centerline distance from the lower femoral head to the target at least 5cm less than the intended THV introducer sheath; patent celiac or superior mesenteric artery;

- Aorta diameter ≥ 11mm at the target crossing site
- Concordance of the study eligibility committee

6.2 Exclusion criteria

- High risk features on baseline CT including porcelain aorta (confluent calcification); pedunculated aortic atheroma; or leftward aortic angle ≥ 20^{o} with regard to vertical;
- Renal dysfunction limiting follow-up contrast-enhanced CT (estimated glomerular filtration rate, eGFR < 30 mL/min/1.73m^2 if not already on renal replacement therapy)
- Pregnancy or intent to become pregnant prior to completion of all protocol follow-up procedures

6.3 Rationale for selection criteria

The selection criteria allow enrollment of the intended population with little anticipated selection bias. The main selection criteria are ineligibility for standard transfemoral artery access, and anatomic eligibility for transcaval access as published[9]. Patients are excluded if there are high risk features such as high risk of atheroembolism. Preclinical data are limited supporting application of the TCD in aortas smaller than 11mm, and therefore such subjects are excluded.

Contrast-enhanced CT during follow-up risks acute and chronic renal failure in patients with baseline renal dysfunction if they are not already on renal replacement therapy. Therefore candidates are excluded if they are not on renal replacement therapy and have eGFR < 30 mL/min/1.73m^2.

No patient will be excluded from participation based on sex, gender, race or ethnicity. There is no biological rationale or evidence for sex-specific risk for complications of transcaval TAVR or TCD closure.

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, despite the small sample size. Specifically, the results are expected to be generalizable to Medicare and Medicaid beneficiaries because of age and disease-related disability.

A study eligibility committee led by the NHLBI sponsor is convened to assure each subject meets selection criteria before treatment (see section 13.4), and that at least one member has no actual or perceived financial conflict of interest.

7.0 STRATEGIES FOR RECRUITMENT

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

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

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

8.0 SAMPLE COLLECTION, STORAGE AND TRACKING PLAN

Imaging data (from angiography and CT) constitute the only specimens to be collected. CT examinations performed for clinical evaluation prior to signing informed consent may be used as the baseline scan, and will be analyzed using patient identifiers to assure no misidentification.

CT and Angiography data will be analyzed at the NHLBI Imaging Core Laboratory. These data will be transmitted on electronic media such as a DVD via carrier or using secure file transfer mechanisms abiding HIPAA and local institutional standards (such as https://secureemail.nih.gov).

Imaging data are stored at a central facility (NHLBI) using secure HIPAA compliant methods and are stored in a secure Picture Archive Computer System (PACS), known as NHLBIPACS.

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

8.1 Data transfer to collaborators

De-identified and de-linked data and images will be transferred to collaborators at Transmural Systems LLC, the manufacturers of the test article. The de-identification assures individual subjects cannot be identified.

Transcatheter valve registry is a nationwide CMS-mandated registry of patients undergoing TAVR. All sites are encouraged to enroll subjects into the TVT registry. TVT registry numbers will be collected and used for collaboration with the TVT registry and TAVR device manufacturers such as Edwards Lifesciences. These TVT registry numbers are linking codes that do not identify subjects. De-identified and de-linked data may be transferred to collaborators at Edwards Lifesciences.

9.0 BIOSTATISTICAL AND ANALYTICAL CONSIDERATIONS

9.1 Sample Size

The sample size is not statistically derived.

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

Up to 30 subjects will be consented until 15 subjects undergo attempted transcaval closure using the test article.

9.2 Study Analysis and Endpoints

We will adhere to a subset of consensus guidelines for the analysis and reporting of transcatheter aortic valve implantation procedures (VARC-2) [11], focusing on vascular access, and modified where necessary to adapt to transcaval access [12]. This excludes TAVR-only complications. Bleeding will be classified according to MVARC-2, which adds specificity to VARC-2 bleeding classification.

Clinical events are classified by the local site Principal Investigator and confirmed by the NHLBI Principal Investigator. Key clinical events are independently adjudicated (see section 9.2.6). The results of the study will be released within 12 months of study completion.

The study will be analyzed using descriptive statistics. Afterwards, we will survey for parameters associated with an increased risk of major adverse events.

Analyses will be performed using principles both of (1) intention-to-treat, defined as attempting or initiating transcaval crossing procedures (introducing a transcaval crossing guide catheter into the body to attempt traversal), and (2) as-treated, defined as completing transcaval closure attempts. We expect these to be the same.

There are no prespecified acceptance criteria for failure rate.

9.2.1 Primary endpoint

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

- Alive
- Successful delivery of the TCD, and retrieval of the TCD delivery system
- Deployment and correct positioning of a single intended TCD. Repositioning and recapture of the device, if needed, is not classified as failure.
- No additional unplanned or emergency surgery or re-intervention related to the TCD or delivery system
- Adjunctive balloon aortic tamponade is permissible and consistent with technical success

9.2.2 Secondary endpoint: Closure success

This secondary endpoint is a composite of the primary endpoint and hemostasis of the transcaval aortic access site. This endpoint is measured at exit from the catheterization laboratory. All of the following must be present:

- Alive
- Successful delivery of the TCD, and retrieval of the TCD delivery system
- Deployment and correct positioning of a single intended TCD. Repositioning and recapture of the device, if needed, is not classified as failure.
- No additional unplanned or emergency surgery or re-intervention related to the TCD or delivery system. Adjunctive balloon aortic tamponade is permissible and consistent with technical success
- Complete occlusion of the aortocaval fistula on the completion aortogram.

9.2.3 Secondary endpoint: Device Success

A key performance endpoint is **Device success**. This endpoint is measured at 30 days and 12-months. All of the following must be present

- Alive
- Original intended TCD in place
- No additional surgical or interventional procedures related to access or the device after exit from the cath lab
- Intended performance of the TCD, including all of

- Structural Performance: No migration, embolization, detachment, fracture, hemolysis, or endarteritis related to the TCD
- Hemodynamic performance: No abdominal aortic obstruction caused by the TCD implant
- Absence of para-device complications (large retroperitoneal hematoma, pseudoaneurysm, distal thromboembolism, or pulmonary thromboembolism)

9.2.4 Secondary endpoint: Procedural Success

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

- Device success
- No device-related Serious Adverse Events, defined as VARC-2 life-threatening bleeding, major vascular or cardiac complications related to the TCD requiring unplanned reintervention or surgery (such as covered stent implantation at the transcaval access site).

9.2.5 Additional Secondary Endpoints

Additional secondary endpoints include

- Procedure success classifying covered stent implantation as a normal provisional part of the procedure.
- Covered stent implantation at the TCD implantation site
- Acute aorto-caval fistula score at procedure completion [12]: 0=occlusion, 1=patent fistula, 2=cruciform fistula pattern, 3=extravasation.
- Modified VARC-2 vascular complications [12] at 30 days
- VARC-2 bleeding complications [12] at 30 days
- Major adverse cardiovascular events (MACE), defined as VARC-2 Early Safety composite: No mortality, stroke, life-threatening bleeding, AKI stage 2+, major vascular complication, valve-related complication
- Closure success at 30 days and 12 months.
- Mortality, all-cause, cardiovascular vs non-cardiovascular, peri- vs non-periprocedural, related to TCD or not)
- Aorto-caval fistula patency at each timepoint, assessed combining completion angiography and arterial-phase follow-up CT.
- AKIN acute kidney injury
- Freedom from infection related to the TCD at each time point
- Thrombocytopenia < 50,000 attributable to residual aorto-caval fistula or the TCD
- Hemolysis attributable to residual aorto-caval fistula or the TCD
- CT analysis: Device position; Device integrity; Aortocaval fistula patency; Aortocaval tract pseudoaneurysm; Aortic pseudoaneurysm; Retroperitoneal hematoma grade (stranding {=absent and not

evidence of overt bleeding;} small; moderate; larger); Intracaval mass or thrombus; Aortic dissection and inferred relatedness to TCD (adjacent to access port) or procedure (remote to access port)

- Outcomes of subjects greater than 65 years (i.e. eligible for Medicare based on age), to determine generalizability to the Medicare population.[1]

9.2.6 Independent Clinical Events Adjudication

An independent Clinical Events Adjudication Committee will review all of the following that occur in the first year. The CEAC adjudication will be performed after 30-day and after 12-month data are collected. The CEAC will rely on independently-monitored data collected in the electronic case report forms, with additional source document review upon request. The adjudicated endpoints will include:

- Deaths
- Primary endpoint (technical success) and key secondary endpoints (device success, procedure success)
- Modified VARC-2 vascular complications
- VARC-2 bleeding complications
- Major adverse cardiovascular events (MACE), defined as VARC-2 Early Safety composite: No mortality, stroke, life-threatening bleeding, AKI stage 2+, major vascular complication, valve-related complication

The CEAC will classify relatedness of the above events to the TCD device.

9.3 Core Laboratory

The NHLBI CT core laboratory will analyze follow-up CT scans in comparison with baseline. Analysis will include

- TCD position
- TCD integrity
- Aortocaval fistula patency
- Aortocaval tract pseudoaneurysm
- Aortic pseudoaneurysm
- Retroperitoneal hematoma grade (stranding {=absent and not evidence of overt bleeding}; small; moderate; large)
- Intracaval mass or thrombus
- Aortic dissection and inferred relatedness to TCD (adjacent to access port) or procedure (remote to access port)

9.4 Data Safety Monitoring

A Data Safety and Monitoring Board (DSMB) appointed by the NHLBI Division of Intramural Research will monitor the safety of subjects in the study as described in the investigational plan. All members of the

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

DSMB are unaffiliated to the study. The NHLBI DSMB will review the protocol progress report at six month intervals. The DSMB may recommend early termination of the study for considerations of safety and efficacy. Unanticipated Adverse Device Effects (UADEs) will be submitted to the DSMB following the same timelines as the IRB (See section 10.2.4).

In the case of death or serious UADE, if the sponsor and the principal investigator determine that the event presents an unreasonable risk to the participating subjects, the clinical trial will be terminated within 5 working days after making that determination and not later than 15 working days after the sponsor first receives notice of the effect. [21 CFR 812.46]. All clinical sites will be notified of this action.

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

9.4.1 Stopping Rules

The study will be monitored to ensure that the mortality within 30-days after the procedure does not substantially exceed an anticipated rate. We anticipate the rate of 30-day mortality is 10% or less and determine the stopping rule by a Bayesian approach [13]. The stopping boundary is reached if the posterior probability that the 30-day mortality rate exceeds 10% is at least 90%. We take our prior distribution to be a beta distribution so that our prior clinical opinion is worth 20% of the weight we will place on the new data. This gives the prior parameters a = 0.3, b =2.7. Hence when we make decisions about stopping the study, the data from the study will dominate over the prior opinion.

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

Number of subjects	Stop if the number of deaths within 30 days reaches
2-5	2
6-11	3
12-15	4

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

True 30-day mortality rate	2.5%	5%	10%	15%	20%	25%	30%	35%
Proportion of Stopped Studies (%)	0.7	3.1	13.8	30.4	48.6	65.5	78.6	88
Average number of subjects (n)	14.9	14.7	13.8	12.5	11	9.5	8.1	6.9
Average number of 30-day mortality (n)	0.4	0.7	1.4	1.9	2.2	2.4	2.4	2.4

These simulation results suggest that our stopping rule has a low probability of stopping a study when the true 30-day mortality rate is 10% or less, and the probability of stopping a study is high when the true 30-day mortality rate exceeds 10%. There, we believe that our stopping rule for 30-day mortality has satisfactory statistical properties.

9.5 Off study criteria

- Completion of the 12-month follow-up
- The subject voluntarily withdraws
- Significant subject non-compliance with follow-up visits, despite repeated investigator effort to assure compliance, including baseline counseling and consent, telephone encouragement, and registered letter reminders if necessary. Such non-compliance will be documented and monitored independently.
- Death

10.0 ADVERSE EVENT REPORTING

10.1 Definitions

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

This will include:

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

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

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

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

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

- Delivery and implantation of the TCD
- Retrieval of the TCD delivery system
- Adjunctive balloon aortic tamponade if performed

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

- A pre-existing medical condition
- Clearly attributable to TAVR or to transcaval aortic access before undertaking transcaval site closure (example: paravalvular leak or transcaval guidewire crossing)

Anticipated Adverse Device Effects (ADEs): An ADE is an adverse event with a reasonable possibility that the device or procedure caused or contributed to the event. The following ADEs are considered anticipated based on previous human experience:

- Transcaval closure device (TCD) failure, including failure to deliver, failure to deploy, failure to position or align correctly, failure to achieve hemostasis, and catastrophic mechanical failure requiring transcatheter or surgical retrieval, device fracture, device embolization
- Death
- Persistent aorto-caval fistula
- Intolerable acute left-to-right cardiovascular shunt across the aorto-caval access port causing myocardial dysfunction
- Bleeding causing decreased hemoglobin and anemia and possible blood transfusion. Hemoglobin is also known to decline after conventional transfemoral TAVR.
- Shock requiring intravenous fluid resuscitation, vasoactive medications, or mechanical circulatory support.
- Hypotension or hypertension requiring pharmacologic intervention. These are also commonly also observed after conventional transfemoral TAVR.
- Retroperitoneal or perivascular hematoma
- Aortic injury such as aortic dissection or pseudoaneurysm or perforation
- Vascular access site complications including femoral artery and vein hematoma, pseudoaneurysm, and arteriovenous fistula. These are also commonly also observed after conventional transfemoral TAVR.
- Thrombocytopenia (<50,000/mm^2) as a consequence of residual aorto-caval fistula. Platelet counts are known to decline after standard transfemoral TAVR.
- Hemolysis (decreased hemoglobin and decreased haptoglobin, increased LDH, positive schizocytes on blood smear) attributable to residual aorto-caval fistula or the TCD.
- Venous thrombosis or thromboembolism, including pulmonary thromboembolism, related to the femoral or caval access site or device
- Atheroembolism or thromboembolism related to catheter and device manipulations in the descending aorta
- Infection/inflammation of the caval-aortic access site related to the TCD , or endocarditis or endarteritis or sepsis
- Elevated white blood count, inflammation, infection, and/or fever post procedure involving the TCD or other body system infections such as urinary or pulmonary.
- Acute kidney injury (reduced urinary output, elevated creatinine, decreased eGFR), whether transient or permanent, that may be caused by iodinated radiocontrast and/or by acute hypovolemia from the TCD, from the conventional TAVR procedure, and/or from the follow-up CT scan.

- Volume overload, congestive heart failure, pleural effusion, or dyspnea from procedure-related volume perturbations causing respiratory failure or prolonged mechanical ventilation
- Respiratory failure requiring oxygen or mechanical support or mechanical ventilation
- Pain including back pain and access site and generalized
- Cardiac arrhythmia, including atrial fibrillation, supraventricular tachycardia, ventricular tachycardia, ventricular fibrillation, advanced atrioventricular conduction block. These are known to accompany conventional transfemoral TAVR.
- Allergic or toxic reactions to medicine, anesthesia, contrast dye, or materials in the catheters.
- Hypersensitivity or anaphylactoid reaction to the delivery system or TCD or its components

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

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

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

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

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

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

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

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

Non-Compliance: Non-compliance is defined as failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects. Non-compliance may be further characterized as:

1. Serious non-compliance: Non-compliance that:
    a. Increases risks, or causes harm, to participants.
    b. Decreases potential benefits to participants.
    c. Compromises the integrity of the NIH HRPP.
    d. Invalidates the study data.
2. Continuing non-compliance: Non-compliance that is recurring.
3. Minor (non-serious) non-compliance: Non-compliance that is neither serious nor continuing.

10.2 Adverse event management:

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

10.2.1 Grading of adverse events and adverse device effects

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

10.2.2 Attribution of adverse events to the research protocol

The relatedness of adverse events will be classified as:

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

10.2.3 Adverse Event Reporting

Adverse event recording will start on Day (0) of the Transcaval TAVR procedure and will continue through the 12 month Follow Up. New events or conditions present at baseline that increase in severity will be recorded and evaluated and reported on the case report form. Once the subject has completed the 30 day follow up, only serious adverse events (SAE), serious adverse device effects (SADE), unanticipated device effects (UADE) and unanticipated problems (UP) will be reported to the Sponsor. It is the responsibility of the site investigator to report adverse events and adverse device effects to their respective IRBs or other regulatory bodies according to their reporting requirements. Monitoring visits will be conducted by the Sponsor to review source documentation, and accuracy and completion of the adverse event case report forms.

10.2.4 Adverse event reporting timeframes:

Serious Adverse Events (SAEs)

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

Unanticipated Adverse Device Effects (UADE)

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

Deaths

- The investigator will notify the Sponsor immediately but within 3 working days of notification of a subject's death, whether the death is device related or clinical condition. Institutional IRB's will be notified according to the specific institutional regulatory requirements for reporting a death.
- The Sponsor will notify the NHLBI IRB of a subject's death within 7 days.
- A subject's death will be recorded on the Case Report Form.

10.3 Scheduled reporting to FDA

Given that this is a first-in-human study, FDA requests reporting of 30 day outcomes via IDE progress report after every 5 subjects for the first 15.

These reports may contain data that have not yet undergone independent data monitoring. These reports will not have undergone independent adjudication, which is performed after completion of the study.

11.0 HUMAN SUBJECTS PROTECTION

11.1 Rationale for Subject Selection

11.1.1 Study population:

Subjects are selected for being adults undergoing transcatheter aortic valve replacement (TAVR) who are not eligible for conventional transfemoral artery access, and who are anatomically suitable for transcaval access based on analysis of a baseline CT.

No patient will be excluded from participation based on gender, race or ethnicity.

11.2 Risks and Discomforts

There are no approved commercial devices indicated to close transcaval access ports.

A formal risk analysis is provided in APPENDIX A.

The risks of transcaval access for transcatheter aortic valve replacement are elaborated on the section describing Adverse Device Effects (ADE) on page 19.

The most common access-agnostic complications of conventional TAVR are listed here myocardial perforation and pericardial tamponade, aortic annular disruption, acute coronary artery occlusion and myocardial ischemia or infarction, paravalvular aortic regurgitation, stroke, pacemaker-induced myocardial dysfunction, conduction abnormalities requiring temporary or permanent pacemaker therapy, cardiac arrhythmias, cardiogenic shock, respiratory failure, renal injury or failure, THV failure requiring emergency cardiac surgery or emergency mechanical circulatory assistance, radiation injury including intractable skin injury, hypertension or hypotension.

11.2.1 Risks Related to Radiation

In this research protocol, subjects will be exposed to radiation from 2 follow-up CT scans and from fluoroscopy related to deployment of the TCD. It is estimated that the amount of research radiation that a subject will be exposed to during participation in this research protocol will be approximately 3-4 REM from the CT scans and 0.03 Gy from approximately 3-5 minutes of fluoroscopy during deployment of the TCD. We believe this amount to be reasonable in this setting, given the seriousness of their cardiovascular disease and risks of non-transfemoral artery access for TAVR. We estimate the benefit to the research subjects for these procedures to outweigh the risks. Each participating site will obtain approval by an Institutional Radiation Safety Office to confirm with local requirements.

11.2.2 Personal Identifiable Information

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

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

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

12.0 TEST ARTICLES and INDICATIONS FOR USE

The Transmural Systems Transcaval Closure Device (TCD) is a percutaneous, catheter-based system designed to close an opening in the abdominal aorta created by a large-caliber vascular introducer sheath and is fully retrievable using its delivery system. The TCD consists of two main elements: (1) a delivery system and (2) the closure implant.

The transcaval closure implant is designed to close an opening in the abdominal aorta created when using a large-caliber vascular introducer sheath advanced from the nearby inferior vena cava (IVC) during a transcaval catheter-based procedure. The closure device body is constructed from a nitinol wire which creates a mesh frame consisting of a Intravascular Disk (Distal Disk), Neck region and an EXTRAVASCULAR Disk (Proximal Disk). The nitinol wire provides visibility during the implant procedure using fluoroscopy. When implanted, the Intravascular Disk is placed within the lumen of the aorta and the Extravascular Disk is placed on the exterior (adventitia) of the aorta. An inner spring coil, attached at each end of the nitinol mesh frame, provides a mechanical compressive force that brings the center of the intravascular and extravascular disks together across the adventitia and aortic lumen when deployed. A cranial paddle made from Nitinol wire is attached to the inner surface of the intravascular disk and covered with the knitted polyester fabric. The cranial paddle acts as an extension of the intravascular disk and is designed to reduce the likelihood of a pull-through.

High density, woven polyester fabric is incorporated inside of both the Intravascular and Extravascular Disks, which creates a sealing hemostatic patch on either side of the opening in the aortic vessel. A knitted polyester fabric is shaped and secured to the outside of the closure device, covering the neck and a woven polyester fabric is secured to the insides of the Intravascular and Extravascular Disks. These polyester fabrics are designed to aid with hemostasis by sealing around the opening in the aorta as the neck area expands during deployment.

The transcaval delivery system consists of three separate components, used as a system, to load, deliver and release the closure device: The Outer Delivery Catheter, a Delivery shaft and an inner Extension Rod. The components of the delivery system are designed to provide the flexibility necessary to be advanced through the vasculature but the stability required to position and deploy the TCD.

12.1 Indications for use

Transcaval Closure Device (TCD) is intended for the closure of percutaneous aortic vascular access for patients who have undergone diagnostic or interventional transcaval catheterization procedures using introducer sheaths up to 26Fr as long as the expanded outer diameter (OD) does not exceed 8.9mm .

This study will evaluate subjects undergoing transcaval TAVR procedures.

13.0 INVESTIGATOR ADMINISTRATIVE REQUIREMENTS

13.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) E6 (Guideline for Good Clinical Practice), the ethical principles that have their origin in Title 21 of the Code of

Federal Regulations, Parts 50 (Protection of Human Subjects), and 56 (Institutional Review Boards), and other appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the transcaval technique as described in the protocol and the Investigational plan. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Regulatory files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

13.2 IRB Submissions

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

13.3 Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the subject or his/her legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

Subjects who are unable to provide consent may be enrolled, if allowed by participating IRBs. Consent for these subjects must be obtained from a legally authorized representative. The process for obtaining this consent must conform to local human subjects protection policies and to state laws.

13.4 Study Eligibility Committee

Clinical data for all research candidates are confirmed by the study eligibility committee before enrollment.

The study eligibility committee consists of the NHLBI investigators, the local site principal investigators, and the NHLBI Core Lab. A quorum of the committee requires a local site investigator where the candidate is not to be enrolled, as well as at least two NHLBI investigators and the NHLBI Core Lab. This also assures that at least one member of the Study Eligibility Committee is not an inventor of the TCD and does not have an actual or perceived financial conflict of interest.

The considerations and determination of the Study Eligibility Committee will be recorded.

13.5 Protocol Compliance

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

The Sponsor will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

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

13.6 Investigational Device Accountability

Access to investigational devices shall be controlled and the investigational devices shall be used only in the clinical investigation and according to the investigational plan. The Sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal. The Principal Investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include

- The date of receipt,
- Identification of each investigational device (serial number or unique code),
- The expiry date, if applicable,
- The date or dates of use,
- Subject identification,
- Date on which the investigational device was returned/explanted from subject, if applicable, and
- The date of return of unused, expired or malfunctioning investigational devices, if applicable.

The investigational devices will include the following labeling “CAUTION: Investigational Device. Limited by United States law to investigational use.”

13.7 Data monitoring plan

13.7.1 Direct Access to Source Data

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

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

13.7.2 Subject Confidentiality

In order to maintain subject privacy, all CRFs, accountability records, study reports, and communications will identify the subject by initials and the assigned subject number. The Investigator will grant research data 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.

13.7.3 Case Report Form Completion

CRFs will be completed for each study subject. It is the Principal Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the subject's CRF. Source documentation supporting the CRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status.

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

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

Data recordation will not necessarily be 21CFR11 compliant (which describes data management quality practices for electronic data recordation when collecting research data for regulatory filings towards commercialization). If not, data recordation will use paper documents.

Datasets will be locked for analysis after appropriate monitoring against source documentation, and locked scanned or electronic copies sequestered that correspond to the primary publication and the report(s) of findings to FDA.

13.7.4 Record Retention

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years following marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

The Sponsor and Transmural Systems, LLC, have full rights over any invention, discovery, or innovation, patentable or not, that may occur in performing the study.

13.8 Publication and Presentation of Study Findings and Use of Information

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

14.0 SPONSOR REGULATORY REQUIREMENTS

14.1 Role of Sponsor

As the study sponsor of this clinical study, Dr. Robert Lederman has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the appropriate regulatory bodies.

14.2 General Duties

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

14.3 Research Monitoring Plan

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

Data from all treated subjects will be monitored (100% subject monitoring).

14.4 Site Selection and Training

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

14.4.1 Site selection:

Site selection will be based on

- Physician expression of interest and need to apply this treatment approach to patients at the site.
- Physician prior experience with at least 10 successful transcaval access and closure procedures, to assure operator competence
- Site prior participation in IDE protocols evaluating a treatment of structural heart disease
    - Site ability to obtain CT examinations that are satisfactory for consideration of transcaval access.
    - Site investigators willing and able to comply with the requirements of this protocol.

14.4.2 Site training:

Site training will consist of

- Principal investigator and/or sponsor didactic training about the technique, preclinical, and clinical experience to date.
- Proper use of the TCD System and protocol requirements.
- Site Initiation Visits (SIV) will be conducted by the designated monitoring contractor and will be attended by research coordinators, research assistants and other staff participating in this research study. The SIV will typically be conducted prior to enrollment of the first subject.

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15.0 Appendix A: Risk Analysis

Event	Narrative	Probability	Severity	Risk (Probability x Severity)	Available Evidence to Consider Risk	Conclusion and risk mitigation strategy
Death	Death is an expected complication of complex and high risk structural heart interventional procedures, especially in those with no good conventional options.	1	5	5	All testing performed to date in both animal and bench studies has demonstrated that the device is robust and will perform as expected. The TCD was specifically designed to overcome challenges associated with off-label use of commercially-available devices.	The risk, while appreciable, is graded as tolerable in light of the potential benefit. Risk will further be mitigated with informed consent.
Hemorrhage requiring blood transfusion	Hemorrhage is expected after transcaval access and closure. Bleeding attributed to transcaval access is expected to be retroperitoneal (see below).	1	4	4	Animal testing with the TCD demonstrated immediate hemostasis. The TCD was specifically designed to overcome challenges associated with off-label use of commercially-available devices.	This risk is graded as negligible, and justified in light of the potential benefit. Risk will be further mitigated by monitoring of subjects for signs and symptoms of blood loss to allow for early treatment. In addition, the clinical protocol will instruct physicians to deploy a covered stent if required to control bleeding.
Hemorrhagic shock requiring intervention	Persistent bleeding, presumed retroperitoneal, may require additional management including crystalloid, vasopressor, blood transfusion, and mechanical intervention.	1	5	5	Animal testing with the TCD demonstrated immediate hemostasis. The TCD was specifically designed to overcome challenges associated with off-label use of commercially-available devices.	The risk, while tolerable, is considered justified in light of the potential benefit. Risk will be further mitigated by monitoring of subjects for signs and symptoms of blood loss to allow for early treatment. In addition, the clinical protocol will instruct physicians to deploy a covered stent if required to control bleeding.
Persistent aorto-caval fistula requiring intervention	Residual aorto-caval fistula is expected to be universal	1	3	3	Animal testing with the TCD demonstrated immediate hemostasis. The TCD was specifically designed to overcome challenges associated with off-label use of commercially-available devices. Based on clinical features, this aorto-caval shunt is hemodynamically insignificant, especially compared with intentional arteriovenous shunts such as those implanted to facilitate hemodialysis.	This risk is graded as negligible, and justified in light of the potential benefit. Risk will be further mitigated by having the protocol include CT examinations at each follow up through 1 year to monitor the presence of A/V Fistula.

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

Event	Narrative	Probability	Severity	Risk (Probability x Severity)	Available Evidence to Consider Risk	Conclusion and risk mitigation strategy
Retroperitoneal hemorrhage	Retroperitoneal bleeding is expected in all patients undergoing transcaval access for TAVR. The expected mechanism is that aortic hemorrhage pressurizes the retroperitoneal space causing decompression of the hemorrhage into the hole in the inferior vena cava.	1	3	3	Animal testing with the TCD demonstrated immediate hemostasis. The TCD was specifically designed to overcome challenges associated with off-label use of commercially-available devices.	The risk is rated as negligible. It is considered justified in light of the potential benefit. Risk will further be mitigated with informed consent.
Aortic or other vascular injury such as aortic dissection, pseudoaneurysm or perforation	Heavily diseased aortas may be injured during caval-aortic crossing or during closure device deployment	2	4	8	The TCD Implant and delivery system are designed to overcome challenges associated with off-label use of commercially-available devices. Iatrogenic aortic pseudoaneurysm is part of the spectrum of retroperitoneal hemorrhage, and represents a volume of blood in continuity with the aorta that is partly or completely surrounded by fresh or organized thrombus. We expect the pseudoaneurysm and hematoma, both in physical proximity to the implanted TCD, to resolve in follow-up as part of healing.	The risk is rated as tolerable. It is considered justified in light of the potential benefit. Risk will be further mitigated by monitoring of subjects for signs and symptoms of blood loss to allow for early treatment. The clinical protocol will instruct physicians to use either balloon aortic tamponade or a covered stent in the case of aortic injury. The protocol will include CT examinations at each follow up through 1 year to monitor vascular injury.
Thrombocytopenia or hemolytic anemia as a consequence of aorto-caval fistula	Mechanical injury to blood cells may result from residual aorto-caval shunt after device closure of the caval-aortic access site	1	3	3	Animal testing with the TCD demonstrated immediate hemostasis. The TCD was specifically designed to overcome challenges associated with off-label use of commercially-available devices.	The risk is rated as negligible. It is considered justified in light of the potential benefit. Risk will be further mitigated by monitoring of subjects for signs and symptoms of blood loss to allow for early treatment. The clinical protocol will instruct physicians to use either balloon aortic tamponade or a covered stent in the case of aortic injury. The protocol will include CT examinations at each follow up through 1 year to monitor vascular injury.

KEY LEVEL	1	2	3	4	5
Probability	Rare	Uncommon	Common	Normal	
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Event	Narrative	Probability	Severity	Risk (Probability x Severity)	Available Evidence to Consider Risk	Conclusion and risk mitigation strategy
Late erosion or migration or unexpected perivascular pathology	There is a theoretical risk of unexpected late complications of caval-aortic access and closure, including device erosion, failure, migration, or late vascular or perivascular remodeling or other pathology.	1	4	4	The adaptive geometry of the Intravascular disk and neck along with compression element and outer PET fabric is designed to conform to aortic pathology and irregular mural rents to achieve hemostasis under a range of anatomies. In addition, outer PET fabric is designed to allow for tissue ingrowth for long-term hemostasis.	This risk is graded as negligible and justified in light of the potential benefit. Risk will be further mitigated by the protocol including CT examinations at each follow up through 1 year to monitor the presence of erosion
Nephrotoxic injury due to additional iodinated radiocontrast during transcaval TAVR and associated follow-up	Iodinated radiocontrast is necessary for X-ray procedures including TAVR. Aortography is performed as part of transcaval access and closure and requires iodinated contrast. This may be offset in part or in whole by iodinated contrast not administered as part of management of large-bore arterial access for conventional TAVR	1	3	3		The risk is rated as negligible. It is considered justified in light of the potential benefit. Risk will further be mitigated with informed consent.
Infection, early or late	Prosthetic implants risk early or late infection	2	4	8	Sterilization and packaging validation results confirm that the product, as packaged, will maintain a sterility assurance level (SAL) of 10^{-6} and that the sterile barrier is maintained through transit. Antimicrobial prophylaxis is a routine component of TAVR performed during the same session as the transcaval access and closure.	This risk is graded as tolerable. It is considered justified in light of the potential benefit. Risk will be further mitigated by the IFU including a precaution for physicians to evaluate the packaging at the time of use and to not use product where the sterile barrier may be compromised. In addition, prophylactic antibiotics will be prescribed per standard TAVR follow up.

KEY LEVEL	1	2	3	4	5
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Risk Score	1-4	5-9	10-20	>20	
Risk Interpreta-	Negligible	Tolerable	Tolerable but undesirable	Intolerable	

Event	Narrative	Probability	Severity	Risk (Probability x Severity)	Available Evidence to Consider Risk	Conclusion and risk mitigation strategy
Aortic lumen reduction/ occlusion	During or after placement of the TCD implant, the aortic lumen could be reduced or occluded due to improper placement of the implant.	1	5	5	The TCD implant is designed to be repositionable and re-deployable to allow the physician to optimally place the device. Animal testing has been performed which demonstrates that the TCD can be repositioned and re-deployed with no safety concerns.	The risk is rated as tolerable. It is considered justified in light of the potential benefit. Risk will be further mitigated by the instructions for use and user training providing users information on how to recognize improper device orientation under imaging and how to correct the orientation. The clinical protocol will instruct physicians to use either balloon aortic tamponade or a covered stent to aid with re-opening of the lumen.
Thromboembolism / Thrombosis	During or after placement of the TCD implant, thrombosis of the implant could occur due to improper placement of the implant.	1	4	4	The TCD implant is designed to be repositionable and re-deployable to allow the physician to optimally place the device. Animal testing has been performed which demonstrates that the TCD can be repositioned and re-deployed with no safety concerns. Animal testing has been performed and no thromboembolism/thrombosis observed grossly or via histopathology.	This risk is graded as negligible, and justified in light of the potential benefit. Risk will be further mitigated by the instructions for use and user training providing users information on how to recognize improper device orientation under imaging and how to correct the orientation.
Venous thrombosis or thromboembolism	Thrombosis may occur related to the femoral vein access site, related to the TCD implant, or causing thromboembolism from either nidus.	2	4	5	Large-bore femoral vein access is a common step in structural heart interventional procedures such as *Mitraclip* and transcatheter mitral valve implantation. Catheter related femoral thrombosis is treated only if clinically symptomatic and manifest. TCD thrombogenicity is evaluated pre-clinically. TCD is expected to encroach on IVC less than comparator Amplatzer devices implanted in the transcaval position.	The risk is rated as tolerable. It is considered justified in light of the potential benefit. Risk will be further mitigated through CT evaluation of the TCD implant site during follow-up, and by clinical surveillance for adverse events.

KEY LEVEL	1	2	3	4	5
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Event	Narrative	Probability	Severity	Risk (Probability x Severity)	Available Evidence to Consider Risk	Conclusion and risk mitigation strategy
Adverse biological reaction	The materials of the TCD implant or delivery system have the potential to illicit a biological response due to non-compatibility.	1	4	4	The materials for the delivery system and the implant were selected based upon known previous biocompatibility with blood and tissue. A suite of biocompatibility testing has been performed which demonstrates the delivery system and the implant are non-toxic and not expected to illicit an adverse biological response.	This risk is graded as negligible, and justified in light of the potential benefit. Risk will be further mitigated by monitoring of subjects for signs and symptoms of allergic reactions. Labeling will include a contraindication for patients allergic to nickel.
Thermal injury	The TCD is a permanent implant constructed of metal and therefore may be susceptible to heating in a MRI environment	1	3	3	1.5T and 3.0T testing in a standard MRI demonstrates that the TCD Implant is MR Conditional.	This risk is graded as negligible, and justified in light of the potential benefit. Risk will be further mitigated by the IFU and patient implant card providing the information to support appropriate MRI use.

KEY LEVEL	1	2	3	4	5
Probability	Rare	Uncommon	Common	Normal	
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