EmStop, Inc.

CAPTURE-1: Controlled Arterial Protection to Ultimately Remove Embolic Material

Clinical Study Protocol

Protocol Number: EMS-CL-5000

Revision: B (10Oct2023)

ClinicalTrials.gov NCT Number: NCT06103591

EmStop, Inc.
1080 Green Gables Road
Brainerd, MN 56401 USA
Phone: 320-420-1992

Sponsor Signatures

Signature: DocuSigned by Scott Thome — Scott Thome | I approve this document 10/5/2023 | 5:16:58 PM PDT — 9A52421D23B14FBA82CEEBF245D12E34

Date: 10/5/2023

Sponsor
Scott Thome, Chief Executive Officer, EmStop, Inc.

Signature: DocuSigned by Emily Vollbrecht — Emily Vollbrecht | I approve this document 10/10/2023 | 11:57:13 AM PDT — 90B4839166F245FAA6A7D470A7F0CE1B

Date: 10/10/2023

Study Director (CRO)
Emily Vollbrecht, Assoc. Study Director, BRIGHT Research Partners

Signature: DocuSigned by Brandon Scott Brown — Brandon Scott Brown | I approve this document 10/10/2023 | 11:53:46 AM PDT — B9331EF4F03B4104A7B59288D638B192

Date: 10/10/2023

Statistician (CRO)
Scott Brown, PhD, Chief Scientific Strategist, BRIGHT Research Partners

EmStop, Inc.	**CLINICAL STUDY PROTOCOL SYNOPSIS** **EmStop Study Number: EMS-CL-5000**
Study Title	CAPTURE-1: Controlled Arterial Protection to Ultimately Remove Embolic Material
Identifying Regulatory Numbers	FDA IDE number – G220288
Study Objective	The objective of this study is to demonstrate safety and investigate performance of the EmStop Embolic Protection System when used as indicated.
Device Description	The EmStop Embolic Protection System (EmStop System) is a catheter-based filter system that captures and removes debris dislodged during transcatheter aortic valve replacement (TAVR) procedures. The EmStop System is composed of a preloaded introducer sheath, delivery catheter, and filter sheath.
Proposed Device Indications for Use	The EmStop Embolic Protection System is indicated for use as an embolic protection device to capture and remove thrombus/debris while performing transcatheter aortic valve replacement procedures. The diameters of the aorta at the site of filter placement should be between 25 – 40 mm.
Study Design	The investigation is a prospective, multi-center, single arm feasibility study. Subjects will undergo treatment with a currently marketed TAVR device and the EmStop Embolic Protection System and will then be followed to 30 days post-procedure. This is a treatment-only feasibility investigation intended to capture and characterize outcomes, especially safety outcomes, with the EmStop System.
Number of Sites & Subjects	The study will be conducted in up to 2 investigational sites in the U.S. This study will enroll up to 15 subjects.
Study Population	The population for this study is subjects with severe native aortic valve stenosis who meet clinically approved indications for TAVR. The investigation population aligns with the EmStop System proposed indications. The study will be conducted in adult subjects and does not include any other age, gender, or racial and ethnic origin restrictions.
Primary Safety and Performance Endpoints	The primary safety endpoint for the study is the occurrence of MACCE at 30 days, defined as a composite of the following VARC-2 defined components: • All-cause mortality • All stroke (disabling and non-disabling) • Acute kidney injury (AKI) Stage 2 or 3 (including renal replacement therapy) within 72 hours The primary performance endpoint for the study is device procedural success, defined as successful insertion, deployment, positioning, and removal of the EmStop System in the absence of device interference.

EmStop, Inc.	**CLINICAL STUDY PROTOCOL SYNOPSIS** **EmStop Study Number: EMS-CL-5000**
Secondary Endpoints	The following secondary endpoints will be evaluated: • Gross and histologic evaluation of captured embolic debris, including particle presence, count, size, and composition (assessed by an independent pathology core laboratory) • Average number of captured particles ≥140 µm in diameter (assessed by an independent pathology core laboratory) • Total acute infarct burden, as measured by diffusion-weighted imaging (DWI) within 14 days pre-procedure and at 18-36 hours post-procedure (assessed by an independent reader). This outcome will be evaluated and tabulated to include total lesion count, average (mean) lesion volume and median lesion volume. • Occurrence of Transient Ischemic Attack (TIA)
Study Eligibility Criteria	Patients must meet all the following inclusion criteria: <u>Clinical inclusion criteria</u> 1. Between 21 and 90 years of age at the time of consent 2. Meets FDA approved indications for transcatheter aortic valve replacement (TAVR) procedure on a native aortic valve using a commercially available Abbott or Medtronic transcatheter heart valve 3. Willing and able to provide written informed consent and written HIPAA authorization prior to initiation of study procedures 4. Willing and able to comply with the protocol-specified procedures and assessments <u>Angiographic Inclusion Criteria (assessed via computed tomography)</u> 5. Subject anatomy is compatible with correct device deployment and positioning with: • Ability to achieve access with a 21 French equivalent femoral access sheath • Ascending aorta length ≥8 cm • Ascending aorta/aortic arch diameter is <u>≥</u> 25 or ≤40 mm • Ascending aorta or aortic arch exhibits ≤ Grade 1 atheromatous disease and limited wall calcification Patients must not meet any of the following exclusion criteria: 1. Requires urgent or emergent TAVR procedure 2. Contraindicated to MRI

EmStop, Inc.	CLINICAL STUDY PROTOCOL SYNOPSIS EmStop Study Number: EMS-CL-5000
	3. Previously implanted aortic or mitral valve bioprosthesis 4. Hepatic failure (Child-Pugh class C) 5. Hypercoagulable state that cannot be corrected by additional periprocedural heparin 6. Planned to undergo any other cardiac surgical or interventional procedure (e.g., concurrent coronary revascularization) during the TAVR procedure or within 30 days prior to the TAVR procedure. NOTE: Diagnostic cardiac catheterization is permitted up until baseline MRI is obtained. Once baseline MRI is obtained, no additional intra-aortic or intracardiac procedure may occur. 7. Acute myocardial infarction within 30 days of the planned index procedure 8. Renal failure, defined as estimated glomerular filtration rate (eGFR) <30 mL/min 9. Documented history of stroke or TIA within the prior 6 months, or any prior stroke with a permanent major disability or deficit (NIHSS >1 at baseline) 10. Left ventricular ejection fraction ≤30% within 3 months prior to procedure 11. History of intolerance, allergic reaction, or contraindication to any of the study medications, including heparin, aspirin, clopidogrel, or a sensitivity to contrast media or anesthesia that cannot be adequately pre-treated 12. Known allergy or sensitivity to nickel-titanium 13. Active endocarditis or ongoing systemic infection, defined as fever (>38°C) and/or white blood cell (WBC) >15,000 IU 14. Undergoing therapeutic thrombolysis 15. History of bleeding diathesis or a coagulopathy 16. Known or suspected to be pregnant, or is lactating; female subjects of child-bearing potential must have a negative serum or urine pregnancy test within 48 hours prior to the index study procedure. 17. Currently participating in another drug or device clinical study

EmStop, Inc.	CLINICAL STUDY PROTOCOL SYNOPSIS EmStop Study Number: EMS-CL-5000
	18. Any other clinical reason, as deemed by the investigators of the study, by which the patient would not be an appropriate candidate for the study 19. Vulnerable subject populations (e.g., incarcerated or cognitively challenged adults)
Study Duration	Enrollment is expected to take approximately 3 months. Each study subject will actively participate in the study through 30-day follow-up. The overall study duration, from screening the first patient to the final follow-up visit, data analysis, and final report, is expected to be approximately 6-9 months.
Study Sponsor	EmStop, Inc. Detailed contact information is maintained in a separate Sponsor Contact List managed by the CRO
Contract Research Organization (CRO)	BRIGHT Research Partners 730 2nd Avenue South, Suite 500 Minneapolis, MN 55402 Telephone: 612-345-4544 (general office line) www.brightresearchpartners.com
Pathology Core Lab	CVPath Institute 19 Firstfield Road Gaithersburg, MD 20878 Telephone: 301-208-3570

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

1.0 ABBREVIATIONS

The following is a list of abbreviations used in the body of this document. Abbreviations solely used in tables (e.g., table headers) are described in the table footer and are not included below.

ADE	Adverse device effect
AE	Adverse event
AS	Aortic valve stenosis
CFR	Code of federal regulations (U.S.)
CRF	Case report form
(e)CRF	(electronic) case report form
CRO	Contract Research Organization
DWI	Diffusion-weighted imaging
EDC	Electronic data capture database
FDA	Food and Drug Administration (U.S.)
GCP	Good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed consent form
ICH	International Conference on Harmonization
IFU	Instructions for use
IRB	Institutional review board
ISO	International Organization for Standardization
MoCA	Montreal cognitive assessment
mRS	Modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
PI	Principal investigator
SAE	Serious adverse event
SAP	Statistical analysis plan
SAVR	Surgical aortic valve replacement
TAVR	Transcatheter aortic valve replacement
UADE	Unanticipated (serious) adverse device effect

2.0 CLINICAL BACKGROUND

Aortic valve stenosis (AS) is a common condition in which the aortic heart valve thickens and calcifies, preventing it from opening fully. This dysfunction limits blood flow from the heart to the rest of the body and leads to significant left ventricular hypertrophy. Untreated AS leads to heart failure, syncope, stroke, sudden cardiac arrest, and premature death. Treatment requires mechanical replacement of the diseased valve as there is no medical therapy.

Treatment of severe AS has traditionally been performed by cardiac surgeons with surgical aortic valve replacement (SAVR). This open-heart surgery requires complete cardiac arrest and cardiopulmonary bypass. Because of the magnitude of the procedure, higher risk patients with aortic stenosis are frequently not candidates for SAVR.

Transcatheter aortic valve replacement (TAVR), a minimally invasive procedure that uses catheter-based systems to percutaneously deliver self-expanding and balloon-expanding heart valves, was approved by the FDA in 2011. While this minimally invasive approach has revolutionized treatment methods for high-risk surgical patients who have aortic valve stenosis, there are risks associated with the use of large-bore catheters in the cardiovascular system. Even with recent technological advances, periprocedural stroke remains a devastating complication that significantly impacts mortality (Shimamura). This risk has been of increased concern since 2016, when TAVR was expanded to include intermediate risk patients. The average age of patients undergoing the TAVR procedure was found in a meta-analysis of 31 studies to be 81.5 years with a standard deviation of 7.0 years (Chakos), while the average age of patients undergoing the TAVR procedure in the large PARTNER trial was 84.0 years with a standard deviation of 7.2 years (Kapadia).

During the TAVR procedure, cerebral emboli have been shown to originate from atheromatous plaques within the aorta and from the degenerate stenotic aortic valve itself. An analysis on 3,687 subjects from the CoreValve (Medtronic) U.S. Extreme Risk and High Risk Pivotal Trials and Continued Access Registry reported a stroke rate of 4.1% in the first 10 days post-TAVR (Kleiman). The PARTNER trial, which evaluated the Sapien device (Edwards Lifesciences) in 2,621 subjects, reported cerebrovascular events in 3.8% at 30 days (Kapadia). This data illustrates the clinical need for embolic protection, which may have a significant role to play in the continued safety and adoption of TAVR as a treatment, especially for the intermediate risk patient population for which TAVR is currently being offered.

Several embolic protection devices are in different stages of investigation in the U.S. PROTECTED TAVR is a landmark randomized control clinical trial currently underway comparing non-embolic protected TAVR to embolic protected TAVR using the Sentinel device (Boston Scientific, Inc.), which is the only embolic protection device currently cleared by FDA.

The embolic protection products that are currently approved or under investigation are stand-alone from the TAVR systems that require separate procedures with separate anatomical access points, thus increasing the complexity and risk. The investigational device is intended to provide a transformative development in the safety and ease of use of embolic protection

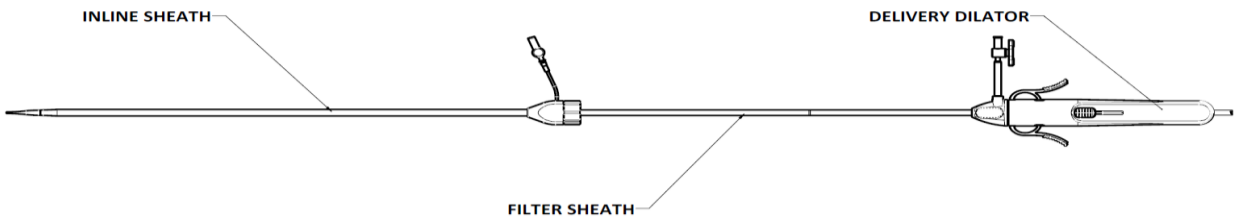
products by providing full cerebral protection using a technology platform that is integrated into the normal workflow of the TAVR procedure.

3.0 TREATMENT DESCRIPTION

3.1 Device Description

The EmStop Embolic Protection System (EmStop System) is a catheter-based filter system that captures and removes debris dislodged during transcatheter aortic valve replacement (TAVR) procedures. The EmStop System is composed of a preloaded introducer sheath, delivery catheter, and filter sheath (**Figure 1**), as described below. Refer to **Table 1** for system specifications.

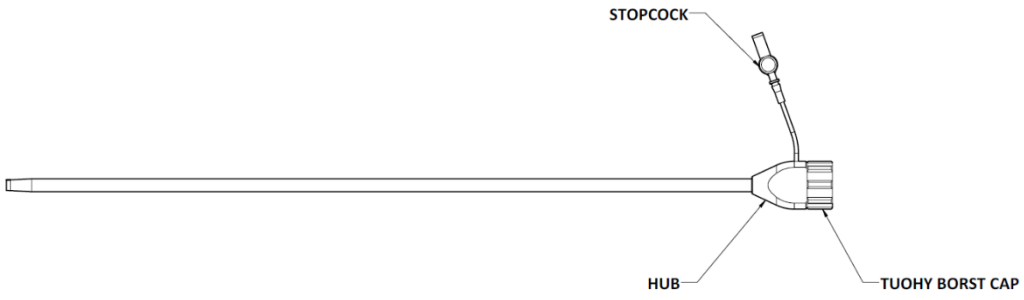
- Figure 1: EmStop Embolic Protection System



3.1.1 Introducer sheath

The introducer sheath is a single lumen, braid-reinforced catheter used to gain access to the vasculature and to facilitate placement and removal of the filter sheath and delivery catheter (**Figure 2**). The proximal end of the introducer sheath comprises a hub with Tuohy Borst cap and a one-way stopcock for flushing.

Figure 2: Introducer Sheath

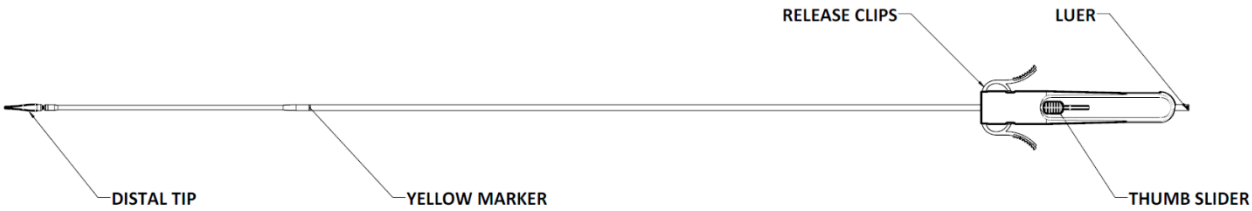


3.1.2 Delivery catheter

A single lumen, braid-reinforced catheter that facilitates delivery of the filter sheath into the aortic arch and controls deployment of the filter via internal actuation wires and a thumb slider

interface on the proximal handle (**Figure 3**). The distal end of the delivery catheter handle contains release clips for connection with the filter sheath. The delivery catheter has a radiopaque distal tip and a nonradiopaque (yellow) marking on the shaft to identify the shaft outside diameter (OD) transition; the force required to remove the device changes at this transition. A Luer connector on the proximal end of the handle is used for flushing.

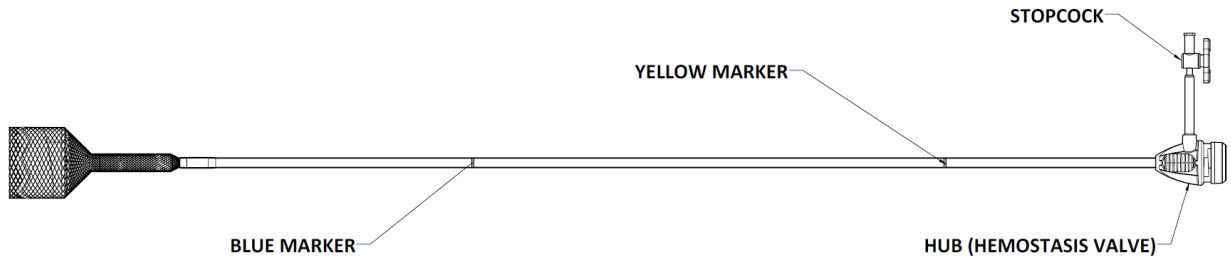
Figure 3: Delivery Catheter



3.1.3 Filter sheath

The filter sheath is a single lumen, braid reinforced catheter with a distal filter (**Figure 4**). This sheath provides a central lumen that allows for passage of TAVR devices. The proximal hub contains a hemostasis valve to allow for connection with the delivery catheter and passage of the TAVR system. The one-way stopcock allows for filter sheath flushing. The filter sheath shaft has a blue depth marker to indicate when the filter has been “sheathed” and a yellow depth marker to indicate an approximate 1” zone (at the transition between the filter and the shaft) where higher resistance is expected during sheath removal.

Figure 4: Filter Sheath



The distal end of the filter sheath has an attached filter, which is retained in a low-profile delivery state by the actuation wires. During deployment of the filter sheath, the actuation wires are operated via the thumb slider on the delivery catheter handle. The filter is composed of an exterior self-expanding nitinol braid and an interior attached nylon mesh (**Figure 5**).

Figure 5: EmStop Filter

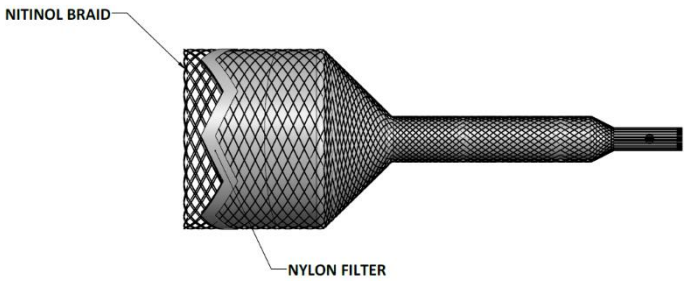


Table 1: EmStop Embolic Protection System Specifications

Aorta size compatibility	25 - 40 mm
TAVR delivery system compatibility	• Abbott FlexNav Delivery System (14F equivalent, 6.00 mm capsule outer diameter) • Medtronic CoreValve EnVeo PRO Delivery System (14F equivalent, 6.00 mm capsule outer diameter) • Medtronic CoreValve Evolut PRO+ Delivery System (14F equivalent, 6.00 mm capsule outer diameter)
Working length (delivery catheter & filter sheath)	90.17 cm (35.5 in)
Guidewire compatibility	0.035”, 260 cm, high support
Introducer sheath size	21F
Introducer sheath working length	43.5 cm
Delivery catheter	18F OD, 0.035” ID
Filter sheath ID	18.5F
Filter pore size	140 µm

The device is provided to users in its delivery state, as shown in **Figure 1** above. A packaging mandrel is placed in the distal tip and the system is packaged on a backer card, sealed within a single sterile barrier Tyvek pouch, and placed into a shelf box. The EmStop Embolic Protection System is sterilized by ethylene oxide (EtO).

3.1.4 Device Manufacturer

The EmStop System is manufactured for the study sponsor by Resolution Medical (Fridley, MN, USA).

3.1.5 Device Labeling / Instructions for Use

The device instructions for use will be included with the investigational product.

3.2 Principle of Operation / Mechanism of Action

The EmStop System provides embolic protection during TAVR procedures while preserving virtually the same sequence and number of steps as unprotected TAVR. The EmStop System contains a central lumen for TAVR device insertion, which eliminates the need for a concomitant vascular entrance point.

After femoral access is obtained and the guidewire is advanced to the targeted location, the EmStop System is loaded onto the guidewire and advanced to the targeted location. Next, the filter sheath is advanced under fluoro guidance, and the filter is deployed in the target location within the ascending aorta (i.e., between the innominate takeoff and the aortic valve; the specific location may vary from patient to patient). The TAVR device is inserted through the EmStop System, and the procedure is conducted per the TAVR device IFU. After the TAVR procedure, the EmStop device is withdrawn, and the emboli captured in the filter is removed from the patient.

The EmStop expanded filter provides filtration, collection, and removal of emboli liberated into the proximal aorta during the TAVR procedure. The filter is deployed in the ascending aorta proximal to any branch artery, thus protecting the brain and vital organs from embolic damage. Embolic material may be aspirated through the filter sheath during the TAVR procedure. Upon completion of the TAVR procedure, the filter and the captured embolic material are withdrawn into the sheath and removed from the patient.

3.3 Proposed Indications for Use

The EmStop Embolic Protection System is indicated for use as an embolic protection device to capture and remove thrombus/debris while performing transcatheter aortic valve replacement procedures. The diameters of the aorta at the site of filter placement should be between 25 – 40mm.

4.0 OBJECTIVE

The objective of this study is to demonstrate safety and investigate performance of the EmStop Embolic Protection System when used as indicated.

5.0 ENDPOINTS

5.1 Primary Safety Endpoint

The primary safety endpoint for the study is the occurrence of MACCE at 30 days, defined as a composite of the following VARC-2 defined components:

- All-cause mortality
- All stroke (disabling and non-disabling)
- Acute kidney injury (AKI) Stage 2 or 3 (including renal replacement therapy) within 72 hours

5.2 Primary Performance Endpoint

The primary performance endpoint for the study is device procedural success, defined as successful insertion, deployment, positioning, and removal of the EmStop System in the absence of device interference.

5.3 Secondary Endpoints

The following secondary endpoints will be evaluated:

- Gross and histologic evaluation of captured embolic debris, including particle presence, count, size, and composition (assessed by an independent pathology core laboratory)
- Average number of captured particles ≥140 μm in diameter (assessed by an independent pathology core laboratory)
- Total acute infarct burden, as measured by diffusion-weighted imaging (DWI), also referred to as DW-MRI, within 14 days pre-procedure and at 18-36 hours post-procedure (assessed by an independent reader). This outcome will be evaluated and tabulated to include total lesion count, average (mean) lesion volume and median lesion volume.
- Occurrence of Transient Ischemic Attack (TIA)

5.4 Ancillary Measures

Additional ancillary data to be collected and evaluated include:

- Physician usability evaluation of:
    - Device usage
    - Device deployment
    - Device retrieval
    - Filter sheath advancement
    - Delivery catheter removal
    - Filter sheath removal
- Filter retraction
- Use of bail out procedures

5.5 Rationale for Study Endpoints

Study endpoints have been selected to align with the objectives of the trial (safety and performance). In particular, the primary safety endpoint, occurrence of MACCE at 30 days, is the same as used in prior regulated investigations of similar devices, while the primary performance endpoint is defined in a manner to permit evaluation of deployment, usage and retrieval of the EmStop System. Secondary endpoints were then selected to provide additional information on both safety and performance, as listed above.

6.0 STUDY DESIGN

6.1 Overall Design

The investigation is a prospective, multi-center, single arm feasibility study. Subjects will undergo treatment with a currently marketed TAVR device and the EmStop Embolic Protection System and will then be followed to 30 days post-procedure.

This is a treatment-only feasibility investigation intended to capture and characterize outcomes, especially safety outcomes, with the EmStop System. Results from this study will inform the design of larger future studies.

6.2 Number of Sites & Subjects

The study will be conducted in up to 2 investigational sites in the U.S. This study will enroll up to 15 subjects. Each site will enroll a minimum of 5 subjects and a maximum of 10 subjects.

6.3 Study Population

The population for this study is subjects with severe native aortic valve stenosis who meet clinically approved indications for TAVR. The investigation population aligns with the EmStop System proposed indications.

The study will be conducted in adult subjects and does not include any other age, gender, or racial and ethnic origin restrictions. Women who have known pregnancy or who are nursing are excluded because of the risks of radiation exposure that occurs during the TAVR procedure and the medications (e.g., blood thinners) that may be needed.

6.4 Study Duration

Enrollment is expected to take approximately 3 months. Each study subject will actively participate in the study through 30-day follow-up. The overall study duration, from screening the first patient to the final follow-up visit, data analysis, and final report, is expected to be approximately 6-9 months.

6.5 Subject Eligibility Criteria

6.5.1 General Inclusion Criteria

Subjects must meet all the following inclusion criteria:

Clinical inclusion criteria

1. Between 21 and 90 years of age at the time of consent
2. Meets FDA approved indications for transcatheter aortic valve replacement (TAVR) procedure on a native aortic valve using a commercially available Abbott or Medtronic transcatheter heart valve

3. Willing and able to provide written informed consent and written HIPAA authorization prior to initiation of study procedures
4. Willing and able to comply with the protocol-specified procedures and assessments

6.5.2 Angiographic Inclusion Criteria (assessed via computed tomography)

5. Subject anatomy is compatible with correct device deployment and positioning with:
    - Ability to achieve access with a 21 French equivalent femoral access sheath
    - Ascending aorta length ≥8 cm
    - Ascending aorta/aortic arch diameter is ≥ 25 or ≤40 mm
    - Ascending aorta or aortic arch exhibits ≤ Grade 1 atheromatous disease and limited wall calcification

6.5.3 General Exclusion Criteria

Subjects must not meet any of the following exclusion criteria:

1. Requires urgent or emergent TAVR procedure
2. Contraindicated to MRI
3. Previously implanted aortic or mitral valve bioprosthesis
4. Hepatic failure (Child-Pugh class C)
5. Hypercoagulable state that cannot be corrected by additional periprocedural heparin
6. Planned to undergo any other cardiac surgical or interventional procedure (e.g., concurrent coronary revascularization) during the TAVR procedure or within 30 days prior to the TAVR procedure. NOTE: Diagnostic cardiac catheterization is permitted up until baseline MRI is obtained. Once baseline MRI is obtained, no additional intra-aortic or intracardiac procedure may occur.
7. Acute myocardial infarction within 30 days of the planned index procedure
8. Renal failure, defined as estimated glomerular filtration rate (eGFR) <30 mL/min
9. Documented history of stroke or TIA within the prior 6 months, or any prior stroke with a permanent major disability or deficit (NIHSS >1 at baseline)
10. Left ventricular ejection fraction ≤30% within 3 months prior to procedure
11. History of intolerance, allergic reaction, or contraindication to any of the study medications, including heparin, aspirin, clopidogrel, or a sensitivity to contrast media or anesthesia that cannot be adequately pre-treated
12. Known allergy or sensitivity to nickel-titanium
13. Active endocarditis or ongoing systemic infection, defined as fever (>38°C) and/or white blood cell (WBC) >15,000 IU

14. Undergoing therapeutic thrombolysis
15. History of bleeding diathesis or a coagulopathy
16. Known or suspected to be pregnant, or is lactating; female subjects of child-bearing potential must have a negative serum or urine pregnancy test within 48 hours prior to the index study procedure.
17. Currently participating in another drug or device clinical study
18. Any other clinical reason, as deemed by the investigators of the study, by which the patient would not be an appropriate candidate for the study
19. Vulnerable subject populations (e.g., incarcerated or cognitively challenged adults)

7.0 STUDY METHODOLOGY

Study assessments and data collection points are visually represented in **Figure 6** and **Table 2** and are described below. To avoid missing data in the study, subjects should be followed for all regularly scheduled visits for safety and effectiveness assessments. Any reason for withdrawal from the study should be documented as described later in the protocol. See **Section 13.0** for definitions of endpoint-related terms used in this section.

Study procedures should be followed carefully as they have been designed to address any known or foreseeable factors that may compromise the outcome of the clinical study or the interpretation of results (e.g., subject baseline characteristics, concomitant medication, the use of other medical devices, and subject-related factors such as age, gender, or lifestyle) and methods for addressing these factors (e.g., subject selection, statistical analysis).

Figure 6: Study Flow Diagram

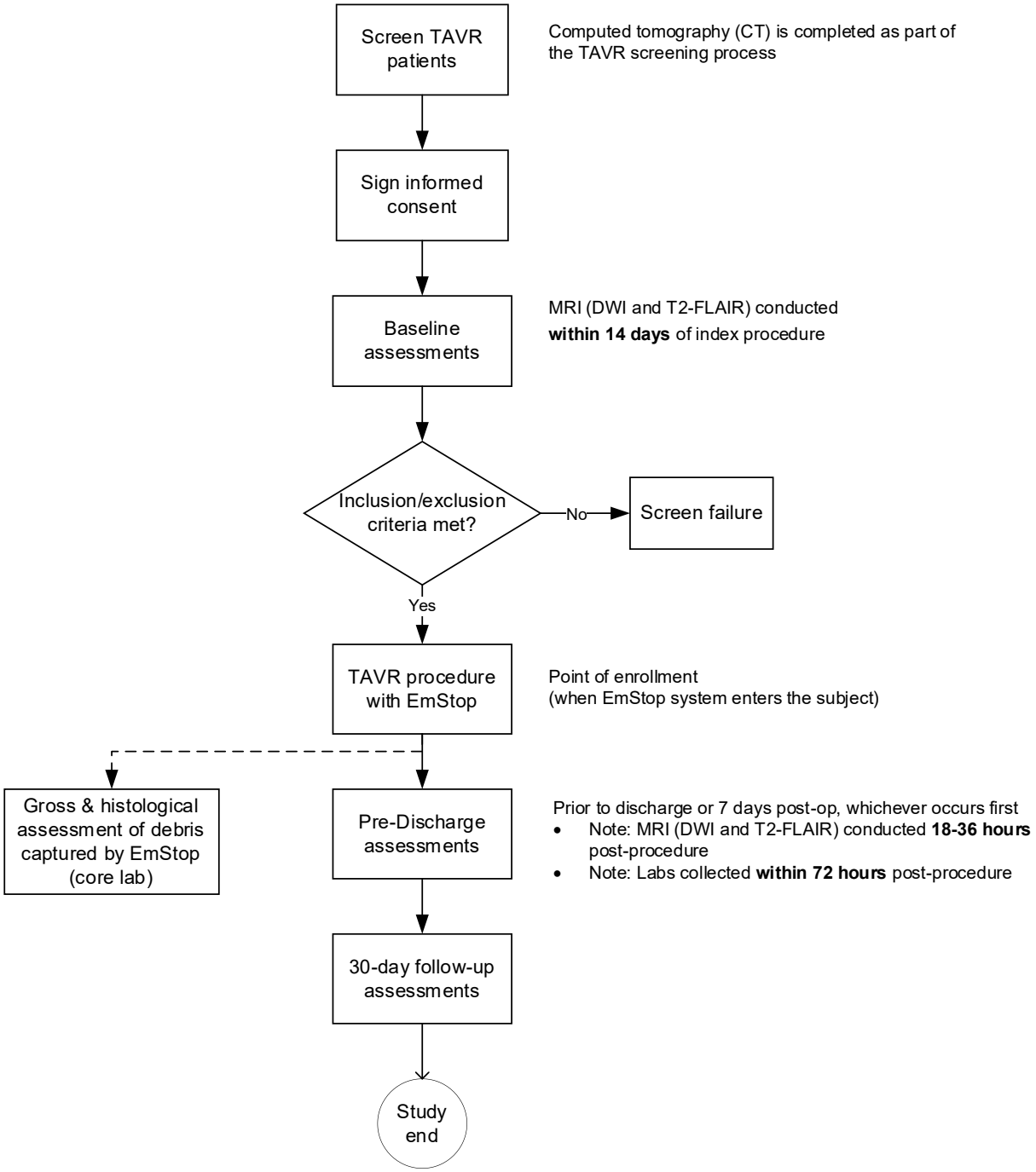


Table 2: Schedule of Study Activities

	Screening / Baseline (within 14 days of procedure, unless specified)	**Treatment Procedure**	**Follow-Up**	
			Pre-Discharge[1]	**30 Days** (+/- 7 days)
Visit type ►	Clinic	Clinic	Clinic	Clinic
Subject informed consent	X			
Demographics & medical history	X			
Ejection fraction[2]	X			
Inclusion/exclusion criteria	X			
Pregnancy test (serum/urine)[3]	X			
National Institute of Health Stroke Scale (NIHSS)	X		X	
Montreal cognitive assessment	X			X
Modified Rankin Scale	X			X
Computed Tomography (CT)	X[4]			
MRI (assessed by independent reader)	X[5]		X[6]	
Medication assessment (anticoagulants and antiplatelet agents only)	X	X	X	X
Labs (GFR, troponin, CBC)	X		X[7]	X[8]
Device performance assessment		X		
Gross & histological assessment of debris captured by the EmStop (assessed by core lab)		X		
Adverse event assessment		X	X	X

[1]Assessments occur prior to discharge or 7 days post-op, whichever occurs first.

[2]Will be obtained as standard of care within 3 months of procedure. If not in medical history, must be obtained prior to TAVR procedure per exclusion criteria.

[3]If female with child-bearing potential.

[4]CT is performed during TAVR screening; the images will be reviewed to confirm that angiographic eligibility criteria are met.

[5]MRI (DWI and T2-FLAIR) is conducted within 14 days pre-procedure and will be assessed by an independent reader.

[6]MRI (DWI and T2-FLAIR) is conducted 18-36 hours post-procedure and will be assessed by an independent reader.

[7]Pre-discharge labs will be collected within 72 hours post-procedure. CBC to include RBC, hemoglobin, hematocrit, WBC, and platelets.

[8]Only lab collected at 30 days is GFR.

7.1 Screening Visit

The study team will screen patients for the study. Screening is defined as the process of reviewing a patient's medical records against the study eligibility criteria to determine if the patient is eligible to enroll in the study. It is expected that the medical records will contain adequate information to determine if a patient meets most of these criteria; this includes the computed tomography (CT) completed as part of the standard of care TAVR screening process. The investigator will visually assess the CT imaging to ensure angiographic inclusion criteria are met.

If the investigator (or designee) determines the patient meets all clinical inclusion and exclusion criteria (except criteria verified by blood or urine testing after consent), they can be consented for study participation, after which all remaining non-angiographic eligibility criteria will be verified prior to the procedure.

Sites will be required to maintain a screen failure log that contains rationale for subjects who became screen failures after consent.

7.2 Informed Consent Process

Prior to enrolling subjects in this study, the site will be required to have an Institutional Review Board (IRB) approved informed consent form (ICF). To ensure compliance with informed consent requirements, the sponsor or contract research organization (CRO) must review any modifications made to the sponsor's template ICF prior to IRB submission.

Written informed consent will be obtained from the patient (or the patient's legal representative, if applicable) prior to participation as a subject in the study. The investigator (or authorized designee) will explain the nature of the planned treatment and objectives of the study to the patient, along with any costs to the subject, payments for participation, and types of insurance provided (if applicable). The investigator will allow adequate time for the patient to read and review the consent form and to ask questions. When the investigator has reasonable assurance that the patient (or legal representative) has an acceptable level of comprehension and the patient (or legal representative) voluntary agrees to participate, the patient (or legal representative) and the investigator (or authorized designee) will sign and date the ICF.

The site will retain the original signed ICF in the subject's study records and will provide a copy of the signed ICF to the subject. The site will document the consent process (e.g., that the subject was consented, the date on which the consent was obtained, and that a copy of the signed ICF was given to the subject) in the subject's medical records.

Subjects will be informed of any new information that may make him/her change their mind about staying in the study. Subjects may be asked to sign a new ICF if this occurs.

7.2.1 Vulnerable Population

To preserve the ethical integrity of this study, the sponsor does not intend to enroll vulnerable subject populations (e.g., incarcerated persons or adults with severe cognitive challenges) in

this study since such populations may be coerced or compelled to participate in a clinical study without a full understanding or against their will these subjects should be excluded (in consideration of ISO 14155:2020 sections 5.7 and A.6.3).

7.3 Point of Enrollment & Numbering of Study Subjects

A patient will be considered enrolled as a study subject once an investigational EmStop System has entered the subject. The lowest available subject number will be assigned, progressing sequentially for each enrolled subject thereafter. The CRO will be notified of subject enrollment via the electronic data capture (EDC) database.

7.4 Baseline Visit

The following standard of care evaluations and study assessments will be performed at baseline and documented on the relevant electronic case report forms (eCRFs):

- Demographics & medical history
- Pregnancy test (urine/serum), if female with childbearing potential
- Ejection fraction
- Medication assessment (anticoagulants and antiplatelet agents only)
- Labs (GFR, troponin, CBC)
- MRI, including DWI and T2-FLAIR, conducted according to study MRI procedures; images sent to independent reader per site instructions
    - MRI is conducted **within 14 days pre-procedure**
- National Institute of Health Stroke Scale (NIHSS)
- Montreal cognitive assessment (MoCA)
- Modified Rankin Scale (mRS)

After the baseline evaluations, the general inclusion and exclusion criteria should be reviewed to ensure that the subject continues to be eligible for the study.

7.5 Treatment Visit

The EmStop System will be prepared and flushed per the device Instructions for Use (IFU). A guidewire will be advanced to the ascending aorta, and the EmStop System will be loaded onto the proximal end of the guidewire for delivery and deployment within the ascending aorta. A commercially available Abbott or Medtronic transcatheter heart valve delivery catheter will be inserted through the EmStop System filter sheath, and the TAVR procedure will proceed according to standard of care. After the TAVR delivery catheter is removed, the EmStop filter will be collapsed into the in-line sheath and the EmStop System will be removed.

The assessments described below will be performed and results will be recorded on the relevant eCRFs.

- Adverse event assessment
- Device performance assessment
- Medication assessment (anticoagulants and antiplatelet agents only)
- Debris captured by the EmStop System filter will be sent for gross and histological assessment following the Pathology Core Lab Guidelines

7.6 Pre-Discharge

Unless specified otherwise below, the following assessments will be performed before discharge or 7 days post-op, whichever occurs first, and documented on the relevant eCRFs:

- Adverse event assessment
- Medication assessment (anticoagulants and antiplatelet agents only)
- MRI, including DWI and T2-FLAIR, conducted according to study MRI procedures; images sent to independent reader per site instructions
    - MRI is conducted **18-36 hours post-procedure**
- Labs (GFR, troponin, CBC)
    - Pre-discharge labs will be collected **within 72 hours post-procedure**
- National Institute of Health Stroke Scale (NIHSS)

7.7 30-Day [± 7 days] Follow-up Visit

The assessments described below will be performed, and results will be recorded on the relevant eCRFs.

- Adverse event assessment
- Medication assessment (anticoagulants and antiplatelet agents only)
- Labs (GFR)
- Montreal cognitive assessment (MoCA)
- Modified Rankin Scale (mRS)

At the conclusion of this follow-up visit, subjects will exit from this study via completion of the Study Completion eCRF. Subjects will continue to be followed by their physician per usual care.

7.8 Unscheduled Visits

Assessments completed during an unscheduled visit will be recorded on the applicable eCRFs.

7.9 Early Withdrawal/Premature Discontinuation of Subjects

Subjects may be withdrawn early from the study for several reasons including:

- Subject death
- Subject lost to follow-up

- Subject request for withdrawal (withdrawal of consent)
- Adverse event
- Investigator decision

If a subject is withdrawn from the study early, a Study Completion CRF must be completed to describe the reason for early withdrawal. The investigator should make all attempts to conduct an “Early Withdrawal” visit at the time of the withdrawal from the study. If a subject has withdrawn consent for the study or is lost to follow-up, the completion of this visit is not imperative. In situations where study withdrawal is due to an adverse event, subjects will be followed until resolution of the adverse event or determination that the subject’s condition is stable.

If a subject chooses to withdraw from the study and also withdraws consent for disclosure of further information, no further study assessments should be performed, and no additional data collected. The sponsor may retain and continue to use any data collected prior to the withdrawal of consent.

7.10 Handling Subjects Lost to Follow-Up

Every attempt must be made to have all subjects complete the follow-up visit schedule. A subject will be considered lost-to-follow-up when all efforts to obtain compliance are unsuccessful. At a minimum, the effort to obtain follow-up information must include three attempts to make contact via telephone, and if contact via phone is not successful, a certified letter from the principal investigator (PI) or authorized delegate must be sent to the subject’s last known address. Both telephone and letter contact efforts to obtain follow up must be documented in the subject’s medical records and on the Study Completion eCRF.

7.11 Handling of Samples Obtained from Subjects

No subject samples will be retained by the sponsor.

8.0 STATISTICAL METHODS

8.1 Analysis Data Sets

The primary analysis will consist of all available data on all subjects enrolled, referred to in ICH E9 (“Statistical Principles for Clinical Trials”) as the full analysis set. As the study is a treatment-only, single arm design, summaries of results will principally be presented for the entire study population.

8.2 General Statistical Principles

Continuous data will be summarized using the following descriptive statistics: mean, standard deviation, median, and range or interquartile range. Categorical variables will be summarized using frequency counts and percentages. For events that can occur more than once in a single

subject, such as adverse events (AEs), the percentage will be based on the number of subjects experiencing the event; both subject and event counts will be reported.

All statistical analyses will be performed using SAS (version 9.4 or higher, SAS Institute Inc. Cary, NC), R (version 3.2 or higher, R Foundation for Statistical Computing, Vienna, Austria) or other widely accepted statistical or graphical software.

8.3 Analysis of Primary Safety Endpoint

The primary safety endpoint will be summarized descriptively per the general statistical principles described above. The intent of this analysis is to capture, characterize, and report safety outcomes associated with the use of the EmStop System.

8.4 Analysis of Primary Performance Endpoint

The primary performance endpoint will be summarized descriptively per the general statistical principles described above. The intent of this analysis is to capture, characterize and report performance outcomes associated with the use of the EmStop System.

8.5 Analysis of Secondary Endpoints

Secondary endpoints will be summarized descriptively per the general statistical principles described above.

8.6 Safety Analysis

Summary tables and listings will be provided for all reported adverse events, which will additionally be reported by seriousness and relatedness. Such summaries will comprise the number and percentage of subjects with an adverse event and the total number of such events. The proportion of subjects with events will be considered primary for analysis of adverse events.

8.7 Subgroup Analysis: Learning Curve

As it is plausible that a learning curve will be observed in the use of this novel technology, to assess the effect of operator experience on outcomes, subgroup analyses of the primary endpoints distinguishing the first from all subsequent subjects per attending physician will be performed.

8.8 Sample Size

The sample size of 15 was selected to provide clinical and statistical information, including assessment of point estimates, frequencies, and variability in key outcomes, to inform design elements of a subsequent pivotal study.

As the objective of this investigation is to characterize outcomes under treatment, sample size is not driven by formal evaluations of power against predefined success criteria. Where performed, hypothesis testing will have one-sided tests with p-values less than 0.025 deemed significant and two-sided tests with p-values less than 0.05 deemed significant.

8.9 Statistical Analysis Plan

Refer to the Statistical Analysis Plan (SAP) for details on statistical design, method and analytical procedures including testing of poolability across clinical sites and handling of missing data.

9.0 MEASURES TO AVOID & MINIMIZE BIAS

The study has several measures that have been implemented to avoid and minimize bias, including the following: use of an independent CRO for study operations management, monitoring, and data management; identification of an independent medical monitor; and use of an independent pathology core laboratory and independent MRI reader for systematic review of the debris captured by the EmStop System and study MRIs, removing any potential for investigator bias.

9.1 Medical Monitor

A Medical Monitor with clinical expertise in TAVR procedures will oversee and evaluate safety events to provide formal safety monitoring and independent, objective expert counsel for this feasibility study. The Medical Monitor will follow pre-specified guidelines to adjudicate AEs and adjudicate them for seriousness and relatedness. In addition, the Medical Monitor may advise the sponsor regarding the continuing safety of study subjects and those yet to be recruited. Sites will be expected to provide supporting source documentation, as requested, to assist the Medical Monitor with evaluation of safety-related events. Core Laboratory

A pathology core laboratory will be used to provide an unbiased assessment of debris samples collected for processing and analysis. The pathology core laboratory will provide shipping and processing instructions to the sites. The pathology core laboratory will follow its own charter or similar procedure to systematize their image review in compliance with the study protocol.

10.0 BENEFITS & RISK ANALYSIS

10.1 Potential Benefits of Study Participation

There are no guaranteed benefits from participation in this study; however, it is possible that treatment with a study device may have the following benefits:

- Reduced risk of stroke

10.2 Alternative Treatment

There is no obligation for a patient to take part in this study. Alternative treatments may include:

- TAVR without embolic protection
- TAVR with embolic protection using a commercially available device (e.g., Boston Scientific SENTINEL)

10.3 Potential Risks Associated with Study Participation

As with any percutaneous coronary procedure, use of the study devices during TAVR involves some risks. Risks associated with laboratory testing (i.e., blood draws) and the TAVR procedure will be listed in the site's procedure consent form used per their standard of care. Potential risks associated with the EmStop System may include but are not limited to:

- Acute kidney injury (AKI)
- Atrial fibrillation (new or worsening)
- Bleeding (life-threatening, major, minor)
- Death
- Periprocedural myocardial infarction (MI)
- Stroke
- Transient ischemic attack (TIA)
- Vascular or access-related complications

The frequency and severity of adverse events can vary, and may necessitate additional medical intervention, including surgery.

10.4 Methods to Minimize Risks

The EmStop System was subjected to a risk assessment as part of the design control process. Results of pre-clinical bench and laboratory testing have demonstrated that the device is likely to be safe and perform as intended in clinical use.

During this study, risks will be further minimized through careful subject screening and selection, training of investigators and study staff, adherence to the scheduled assessments, and regular monitoring visits.

10.5 Benefit-to-Risk Rationale

The results from risk analysis and risk mitigation measures support reasonable assurance of the safety and efficacy of the EmStop System when used in a manner consistent with its labeling and intended use. The evidence supporting safety and effectiveness of the EmStop System is based on robust pre-clinical bench and laboratory testing, as well as the clinical experience of similar TAVR embolic protection products, such as the market-released SENTINEL (Boston Scientific). The evidence supports a clinical benefit-to-risk determination that is favorable for the EmStop System.

11.0 ADVERSE EVENTS

11.1 Adverse Event Definitions

Adverse events will be adjudicated for seriousness and for relatedness to the investigational device and study procedure. Refer to **Section 13.0** for adverse event definitions.

11.2 Adverse Event Collection & Documentation

Collection of adverse events will start on the day of the procedure for enrolled subjects and will be assessed and reported throughout the study. Investigators must obtain all information available to determine the seriousness, relatedness, and outcome of the adverse event and to assess whether it meets the criteria for classification as an unanticipated adverse device effect (UADE) requiring immediate notification. All adverse events will be followed until resolution or investigator determination that the subject's condition is stable.

All reported adverse events will be documented on the Adverse Event CRF. Copies of de-identified source documentation that contain significant information related to the event, such as progress notes, consultations, nurse notes, operative reports, and subject summaries may be requested by the sponsor, CRO, Medical Monitor and/or core lab as needed for evaluation and adjudication.

The following are not considered reportable adverse events for this study:

- Any normal expected postoperative complaints or symptoms unless the event involves a clinically significant change in severity or duration of symptoms or requires clinical intervention that is different from ordinary postoperative care. Expected postoperative complaints and findings include, but are not limited to headache, edema, nausea, vomiting, and postoperative pain (excluding chest pain).
- Any condition that is recorded as pre-existing at baseline, unless there is a worsening of that condition in terms of nature, severity, or degree of incidence.
- Planned hospitalization for pre-existing conditions or a procedure required by the protocol, without serious deterioration in health.

In case of subject death, it is requested that a copy of the death certificate and a copy of the autopsy report, if applicable, be sent to the CRO. Any other source documents related to the death should also be provided to the CRO. If no source documents are available, the PI is required to describe the circumstances of the subject's death in written communication (e.g., letter, e-mail).

11.2.1 Device Deficiencies

Device performance, including deficiencies, will also be collected. If a device deficiency results in the subject experiencing any untoward medical occurrence, unintended disease or injury, or untoward clinical signs, these outcomes will be reported as an adverse event on an Adverse Event CRF. Any malfunctioning devices will be returned to the sponsor by the site for further evaluation.

11.3 Adverse Event Reporting Timeframes

The investigator is responsible for reporting serious adverse events to the IRB in accordance with the IRB's procedures. Unanticipated adverse device effects (UADEs) have special reporting requirements for both the investigator and sponsor, as described in 21 CFR 812.150:

- **Investigator Report:** If a subject experiences a UADE, the investigator must notify the sponsor/CRO and the reviewing IRB as soon as possible, but no later than 10 working days after the investigator first learns of the effect.
- **Sponsor Report:** UADEs will be reported to the FDA, all reviewing IRBs, and participating investigators as soon as possible, but no later than 10 working days after receiving notice of the UADE.

11.4 Adverse Event Relatedness

The investigator and the Medical Monitor will assess the relatedness of the adverse event to the investigational device and the study procedure using the categories listed below (see **Section 13.0** for definitions):

- Definitely
- Probably
- Possibly
- Unlikely
- Not Related

12.0 ADMINISTRATIVE PROCEDURES

12.1 Records & Reports

12.1.1 Case Report Forms

Worksheets may be used to collect subject data that is not readily available from the source documentation. An electronic data capture (EDC) system will be used to collect study-required data on electronic CRFs (eCRFs). The principal investigator (PI) at the site is responsible for ensuring the eCRFs are accurate and completed in a reasonable timeframe. The PI is required to review and approve the eCRF on the appropriate page(s) to verify the completeness, accuracy, and authenticity of the recorded data.

12.1.2 Sponsor / CRO Study Records & Reports

The sponsor and CRO are responsible for maintaining study records and reports per applicable ICH good clinical practices (GCPs), FDA regulations, ISO 14155, and applicable standard operating procedures and study specific plans (e.g., Monitoring Plan, Data Management Plan, Training Plan, and Statistical Analysis Plan).

Results on all pre-specified study outcomes will be released in interim reports, as needed, and in a final clinical study report that will be released within 6 months after study termination or completion. The release of this information, including negative outcomes, may be hastened if the study is terminated early.

12.1.3 Investigator Study Records

The investigator will securely maintain the following accurate, complete, and current records relating to their participation in the study:

- All essential correspondence that pertains to the investigation.
- Records of each subject's case history and exposure to the investigational device. Case histories include the CRFs and supporting data including, for example, signed and dated ICFs and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records will include:
  - Documents evidencing the informed consent process. The case history of each individual will document that informed consent was obtained at the appropriate time.
  - All relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
  - A record of the exposure of each subject to the investigational device, including the date and time of each use, and any other therapy.
- The protocol, with documents showing the dates and reasons for each deviation from the protocol.
- Signed investigator agreements, financial disclosure agreements, investigator signature pages, and curriculum vitae.
- IRB approval documents including approval of the protocol, protocol amendments and ICF.

12.1.4 Investigator Reporting Requirements

Investigator reporting requirements are noted in **Table 3** below.

Table 3: Investigator Reporting Requirements

Report	Submitted to	Description
Unanticipated Adverse Device Effects (UADE)	Sponsor/CRO & IRB	Notification as soon as possible, but no later than 10 working days after the investigator first learns of the effect.
Device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate	Sponsor/CRO	Notification without unjustified delay after the investigator first learns of the device deficiency that might have led to an SAE.
Serious Adverse Events (SAE)	IRB	Per IRB reporting requirements
Withdrawal of IRB approval	Sponsor/CRO	Notification within 5 working days of withdrawal.
Progress Report	Sponsor/CRO & IRB	Periodic report detailing the progress of the study, occurring at least annually.
Deviations from protocol (CFR 812.150)	Sponsor/CRO & IRB	**Emergency Use:** Notification must be made within 5 working days of the occurrence of an emergency deviation (made to protect the life or physical well-being of a subject). **Other:** If the deviation affects scientific soundness of the study or the rights, safety, or welfare of the subject (and is not an emergency), prior approval must be obtained from sponsor the reviewing IRB, and FDA when required.
Failure to obtain informed consent	Sponsor/CRO & IRB	Notification within 5 working days
Incomplete resheathing or retraction of the device or use of bail out procedure leading to device or procedure related adverse events	Sponsor/CRO	Notification within 24 hours following TAVR procedure; Sponsor must notify FDA within 5 working days
Final Report	IRB	Submitted within 3 months after termination or completion of the investigation.

12.1.5 Record Storage & Retention

Refer to the Clinical Trial Agreement for trial data storage, access, and retention requirements.

12.2 Data Management

Correction of missing or unclear data will be requested as necessary throughout the study. The CRO may request additional information including source documentation as needed. The CRO

will also be responsible for confirming the overall integrity of the data. Refer to the study Data Management Plan for more details.

12.3 Device Accountability

All EmStop System investigational devices will be labeled with reference (part or model) and lot numbers. Shipment and receipt records will be maintained, and upon receipt of the investigational devices, the site study coordinator (or delegate) will inventory the devices. As each subject receives treatment with the study device, the date of treatment, subject identifiers (site number/subject number), device performance assessment, and device traceability information will be recorded. If a study device is returned to the sponsor, the date of return and reason for the return shall be documented.

The EmStop System must be stored in a secure location at each clinical site to ensure use only in the study and unused devices must be returned promptly upon study completion or termination. Product labeled as “For Investigational Use Only” must only be used in the clinical investigation.

12.4 Site Qualification & Selection

The sponsor and/or CRO will assess each potential site to ensure the investigators and his/her staff meet the minimum following criteria:

- The site has an interventional cardiologist that can act as a principal investigator.
- The investigators are qualified by experience and training.
- The site has adequate research support staff with the availability to fulfill the clinical study requirements specified in the protocol.
- The site is not participating in another investigational study that is currently enrolling subjects with competing eligibility criteria; studies that have completed enrollment and are in the subject follow-up phase would not exclude the site from participation in this study.
- The investigators are not on the FDA disqualified or debarred list.

Additional details are specified in the study-specific Site Qualification Questionnaires used to select eligible sites.

12.5 Site Training

Training of the clinical site personnel will be the responsibility of the study sponsor and the CRO. Site personnel will be trained per the study-specific Training Plan, which will consider numerous requirements including inputs from the risk assessments described in this protocol. All site personnel will undergo training prior to performing any study-related procedures. All training will be documented. Existing site personnel who have been delegated new tasks and new site personnel will undergo training as designated in the Training Plan.

12.6 Site Monitoring

This clinical study will be monitored according to a study-specific Monitoring Plan that complies with GCP. Monitors will assess for appropriate study conduct and data integrity, including review of eCRFs and parity checks with the source documentation, worksheets, and hospital charts. Periodic site visits will be conducted (either on-site or remotely), including a site initiation visit, routine monitoring visits, and a study closeout visit upon completion of the study. At a minimum, the ICF and the ICF process, primary and secondary endpoint data, and adverse event data will be 100% monitored and compared to source documentation. Monitoring will include comparison of eCRFs to source documentation for accuracy and appropriateness, study device accountability, review for unreported adverse events, and prompt evaluation of potential UADEs.

12.7 Institutional Review Board (IRB)

At a minimum, the CRO must have documented IRB approval for the protocol and the site-specific ICF prior to site activation to enroll subjects. Identification of the study (study number, protocol title, and version), documents approved (e.g., protocol, ICF), and the date of IRB review should be clearly stated on the IRB approval documentation signed by the IRB. The site will not be activated until a copy of written and dated IRB approval has been received by the CRO and other applicable study activation requirements are complete.

The site must submit any protocol or ICF amendments to the IRB and is required to forward a copy of the written approval to the CRO. An IRB approval of the amended document(s) must be obtained before implementation and before new subjects are consented to participate in the study using the amended ICF, if applicable. The IRB should also be informed of any event likely to affect the safety of subjects or the conduct of the study. Any additional requirements imposed by the IRB or regulatory authority shall be followed, if appropriate.

The ICF must be reviewed by the CRO prior to submission to the IRB for approval.

12.8 Protocol Deviations

A protocol deviation is defined as a circumstance in which the investigator or other site personnel did not conduct the trial according to the protocol, applicable laws/regulations, or any study agreements (e.g., Clinical Trial Agreement, Investigator Agreement).

Every attempt will be made to adhere to the protocol. However, should an investigator be required to deviate from the protocol to protect the life or physical well-being of a study subject in an emergent circumstance, such notice will be given to the sponsor or CRO and IRB as soon as possible, but no more than 5 working days from the date the emergency occurred. Except for an emergent circumstance, prior approval from the sponsor, the IRB, and FDA (when applicable) is required for any change in, or deviation from, the protocol as such changes may affect the scientific soundness of the protocol or the rights, safety, and welfare of study subjects.

Protocol deviations will be documented on the Protocol Deviation CRF. Deviations are reportable to the central or the institution's governing IRB during the annual reporting process, unless otherwise directed by the governing IRB requirements.

Repeated protocol deviations will be closely monitored by the CRO/sponsor. If excessive deviations or a failure to reduce deviations is noted, the sponsor reserves the right to suspend study enrollment or terminate the site from the study until a sufficient system is in place at the site to reduce further deviations (21 CFR 812.46(a)).

12.9 Protocol Amendments

Changes to the protocol must be documented in a formal protocol amendment prior to implementation in the study. Amendments to the protocol will be initiated by the sponsor or CRO and must be approved by the IRB prior to implementation at the site.

12.10 Study Suspension or Termination

No formal statistical rule for early termination of this study for insufficient effectiveness of the study devices is defined.

The sponsor reserves the right to terminate or suspend the study for valid scientific reasons or reasons related to the protection of subjects (e.g., the discovery of an unexpected, significant, or unacceptable risk to the subjects). The sponsor also reserves the right to terminate the study for business reasons. Refer to the Clinical Trial Agreement for specific information regarding study termination (by IRB withdrawal of approval, by principal investigator, or by sponsor).

If the study is terminated prematurely or suspended, the sponsor will promptly inform all investigators of the termination or suspension and the reason(s). The IRB will also be informed, either by the sponsor or Investigator, and provided with the reasons(s) for the termination or suspension. Regulatory authorities will be informed, as required.

The IRB may choose to discontinue the study at any site for which they granted approval if the research study is not conducted in accordance with the IRB's requirements or the research study indicates unexpected serious harm to subjects.

12.11 Subject Confidentiality

All information and data sent to the CRO concerning a subject or their participation in this study will be considered confidential. The sponsor, CRO, monitors, IRB, and regulatory representatives will have access to these confidential files and have the right to inspect and copy all records pertinent to this study for data verification. All data used in the analysis and reporting of this study will be without identifiable references to a subject. Subject names and contact information will be available to the sponsor, CRO, and monitors during review of medical records. Subject names may be available to the core laboratory and Medical Monitor as they review study-related samples and source documentation. This information will be treated with adherence to professional standards of confidentiality. In addition, upon regulatory request, subject records shall be provided to regulatory agencies.

12.12 Audits & Inspections

Investigators and study sites are required to permit study-related monitoring, audits, IRB review, and regulatory inspection(s) and provide direct access to source data/documents.

12.13 Statements of Compliance

This study is to be conducted in compliance with the study protocol and in accordance with ethical principles that have their origin in the Declaration of Helsinki, as defined in the following U.S. and international standards for good clinical practice:

- International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice E6 (R2) (2016)
- U.S. Code of Federal Regulations (CFR) regarding clinical studies (21 CFR including parts 11, 50, 54 and 56 and 812) and HIPAA (45 CFR 164.508)
- ISO 14155: 2020

12.14 Finance & Agreements

For details on how the clinical investigation is financed and the agreement between the sponsor, investigators, and sites, refer to the Investigator Agreement and Clinical Trial Agreement.

12.15 Publications & Public Disclosure

Refer to the Clinical Trial Agreement for publications and public disclosure requirements and conditions.

12.16 Study Contacts

Refer to the Study Contact List for detailed contact information, including names, telephone numbers, and email addresses.

13.0 DEFINITIONS

13.1 Adverse Event Definitions

Adverse event (AE): Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated. [*ISO 14155 2020, 3.2*]

Adverse event relatedness: The relationship of an adverse event to the investigational device or the study procedure based on the categories defined below.

Relatedness	Description
Definitely	The adverse event follows a strong temporal sequence to the receipt (or attempted receipt) of the device treatment or procedure. This can include an adverse event that occurs after the study procedure.
Probably	The adverse event follows a reasonable temporal sequence to the receipt (or attempted receipt) of the device treatment or procedure, and the possibilities of other factors, such as underlying and concomitant illness, concomitant medications, or concurrent treatment can be excluded.
Possibly	The adverse event follows a reasonable temporal sequence from receipt (or attempted receipt) of the device treatment or procedure and the possibility of device treatment or procedure involvement cannot be excluded. However, other factors such as underlying or concomitant illness, concomitant medications, or concurrent treatment are presumable.
Unlikely	The adverse event has an improbable temporal sequence to the receipt (or attempted receipt) of the device treatment or procedure, or it can be reasonably explained by other factors, including underlying or concomitant illness, concomitant medications, or concurrent treatment.
Not related	The adverse event has no temporal sequence to the interventional procedure, the device treatment, or any user handling, or it can be explained by other factors, including underlying disease or concomitant illness, concomitant medication, or concurrent treatment.

Device deficiency: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance. [*ISO 14155 2020, 3.19*]

- Note: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. This definition includes device deficiencies related to the investigational medical device or the comparator.

Serious adverse event (SAE): An adverse event that led to any of the following:

- Death
- Serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
  - a life-threatening illness or injury
  - a permanent impairment of a body structure or a body function including chronic diseases
  - in-patient or prolonged hospitalization
  - medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function,
- Fetal distress, fetal death, a congenital abnormality, or birth defect including physical or mental impairment

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event. *[ref. ISO 14155:2020, 3.45]*

Note: An AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

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)*]

13.2 Other Study-Specific Definitions

Device interference: Interaction of the EmStop System with the TAVR system that leads to:

- Inability to advance or manipulate the TAVR system, or
- Inability to deploy the TAVR system, or
- Inability to retrieve the TAVR system

Device procedural success: Successful insertion, deployment, positioning, and removal of the EmStop System in the absence of device interference.

Major adverse cardiac and cerebrovascular events (MACCE): All-cause mortality, all stroke (disabling and non-disabling) and transient ischemic attack (TIA), and acute kidney injury (AKI) Stage 2 or 3 (including renal replacement therapy). MACCE events will be adjudicated by the Medical Monitor using VARC-2 definitions [*Kappetein 2013*].

Montreal cognitive assessment (MoCA): A highly sensitive tool for early detection of mild cognitive impairment that was validated in 2000. [https://www.mocatest.org/]

National Institutes of Health Stroke Scale (NIHSS): A systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit. [https://www.nihstrokescale.org/]

14.0 REFERENCES

Chakos, A, Wilson-Smith, A, Arora, S, Nguyen, T. C, et al. Long term outcomes of transcatheter aortic valve implantation (TAVI): a systematic review of 5-year survival and beyond. *Annals of cardiothoracic surgery*, 2017 *6*(5), 432–443. https://doi.org/10.21037/acs.2017.09.10

Kapadia S, Agarwal S, Miller DC, Webb J, et al. Insights into timing, risk factors, and outcomes of stroke and transient ischemic attack after transcatheter aortic valve replacement in the

PARTNER trial (Placement of Aortic Transcatheter Valves). *Circ Cardiovasc Interv*. 2016 Sep;9(9):e002981.

Kappetein A, Head S, Genereux P, Piazza N, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: The Valve Academic Research Consortium-2 consensus document. *J Thorac Cardiovasc Surg*. 2013;145:6-23.

Kleiman NS, Maini BJ, Reardon MJ, Conte J, et al. Neurological events following transcatheter aortic valve replacement and their predictors: a report from the CoreValve trials. *Circ Cardiovasc Interv*. 2016 Sep;9(9):e003551.

Shimamura J, Kuno T, Malik A, Yokoyama Y, et al. Safety and efficacy of cerebral embolic protection devices in patients undergoing transcatheter aortic valve replacement: a meta-analysis of in-hospital outcomes. *Cardiovasc Interv Ther*. 2021 Nove 13. Online ahead of print. https://link.springer.com/article/10.1007/s12928-021-00823-1

15.0 REVISION HISTORY

Rev.	Description of Changes	DCO #	Effective Date
A	Initial release.	2023-08-004	25Aug2023
B	Additional ancillary data collection measures were added to section 5.4. Table 3 was updated to include an additional investigator reporting requirement if there is incomplete filter resheathing or use of the bailout procedure, resulting in procedural or device related adverse events.	2023-10-001	10/10/2023