Clinical Investigational Plan (CIP) – The AMBULATE EXPAND Trial

A MULTI-CENTER, PROSPECTIVE, SINGLE ARM, PIVOTAL TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF THE VASCADE MVP® XL VENOUS VASCULAR CLOSURE SYSTEM (VVCS) FOR THE MANAGEMENT OF THE FEMORAL VENOTOMY AFTER CATHETER-BASED INTERVENTIONS UTILIZING 16-17F OUTER DIAMETER (OD) SHEATHS

Sponsor	Haemonetics Corporation 125 Summer Street Boston, MA 02110
Investigational Device Manufacturer	Cardiva Medical, Inc. 1615 Wyatt Dr Santa Clara, CA 95054 Cardiva Medical is a wholly owned subsidiary of Haemonetics Corporation
Study Responsibility	Haemonetics Corporation [redacted]
National Principal Investigator	[redacted]
Ultrasound Core Laboratory	[redacted]
Protocol Number	TP-CLN-100607
Protocol Revision	AB
Protocol Date	14 April 2025
Statistical Analysis Plan	[redacted]
IDE #	[redacted]
Clinicaltrials.gov ID	NCT06615154
This protocol contains confidential informaftion for use by the Investigators and their designated representatives participating in this clinical investigation. It should be held confidential and maintained in a secure location. *Do not copy or distribute without written permission.*	
This study will be conducted in compliance with the clinical study protocol (and amendments), 21 CFR Part 11, 50, 54, 56, 803, 812, 45 CFR Part 164.508(c), applicable parts of ISO 14155 and ICH E6(R2), and applicable regulatory requirements	

Signatures required per Haemonetics' document control process and document release date are documented in Agile.

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Revision History

Revision	Description
01	[redacted]
AA	[redacted]
AB	[redacted]

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Protocol Synopsis

Attribute	Description
Protocol Number	TP-CLN-100607
Study Title	A Multi-Center, Prospective, Single Arm, Pivotal Trial to Evaluate the Safety and Efficacy of the VASCADE MVP® XL Venous Vascular Closure System (VVCS) for the Management of the Femoral Venotomy After Catheter-Based Interventions Performed Utilizing 16-17F Outer Diameter (OD) Sheaths
Short Title	The AMBULATE EXPAND Trial
Study Overview	A multi-center, prospective, single arm, pivotal trial to evaluate the safety and efficacy of the VASCADE MVP XL Study Device for the management of the femoral venotomy after catheter-based interventions performed utilizing 16-17F OD sheaths
Study Objective	To establish the safety and efficacy of the VASCADE MVP XL Study Device when compared to performance goals (PG) and clinical acceptance criteria (CAC) for closing percutaneous femoral venous access sites at the completion of catheter-based procedures utilizing 16-17F OD procedural sheaths. This study will be considered a success if it meets the PG for both the primary safety endpoint and the primary efficacy endpoint.
Test Device	VASCADE MVP XL (800-1014XL) with 25F Disc (~8.3 mm) and 19 mg collagen implant For the purposes of the steps outlined in this protocol, the investigational VASCADE MVP XL device (model 800-1014XL), used for closure of 16-17F OD sheaths, is referred to as the VASCADE MVP XL Study Device. *Note that the commercial VASCADE MVP XL (800-1012XL) device may be used in the Non-Study Limb for its approved indication (10-12F Inner Diameter (ID), maximum 15F OD) and is identical to the study device, VASCADE MVP XL Study Device (800-1014XL), with the exception of labeling due to the difference in the indication; use of the study device for closure of 16-17F OD access sites is considered investigational use only).*
Indications for Use (Investigational)	The VASCADE MVP XL (800-1014XL) is indicated for the percutaneous closure of femoral venous access sites in patients who have undergone catheter-based procedures using a 16-17F OD procedural sheath.
Study Standardizations	Study Limb: The single Study Access Site must be standalone in one limb (i.e., not combined in the same limb with other access sites that may be part of the procedure) and must be closed last (i.e., after hemostasis is confirmed for all Non-Study Access Sites in the Non-Study Limb)
	Non-Study Limb (if additional access sites are required for the procedure): Non-Study Access Site(s) (i.e., 5-12F ID venous, max 15F OD) must be a venous access site(s) in the Non-Study Limb and closed with a commercial VASCADE Family device (in range of the commercial devices' indications) prior to Study Access Site closure.
Number of Roll-In Subjects	• Minimum 1 roll-in for first subject enrollment per site (recommend that deployer is an Investigator) • Up to 2 roll-ins per Enrolling Investigator and per Operator

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Attribute	Description
	The study is anticipating enrollment of up to 48 roll-in subjects.
Number of Pivotal Subjects (Non-Roll-In)	A minimum of 70 evaluable subjects (i.e., have completed all required visits through follow-up) will be part of the main study. *The study is expected to enroll up to 77 subjects to account for possible attrition of 10%. This includes the subset of subjects participating in the ultrasound sub-study.*
Number of Total Subjects	The enrollment limit is 125 subjects (maximum 77 pivotal subjects and maximum 48 roll-in subjects).
Number of Sites	5-12 sites, maximum 25% pivotal subject enrollment at a single site All sites will be in the United States.
Duration of Study	Each enrolled subject will have a follow-up visit at 30 days (± 7 days) post-procedure. Once all subjects have completed this visit, the study will be considered complete. The overall study enrollment duration (i.e., expected time to enroll and follow all subjects) will be approximately 5-10 months.
Ultrasound Sub-Study	A minimum of 25 subjects with evaluable images will be enrolled in the ultrasound sub-study from participating sites, which will require an ultrasound examination of the Study Access Site performed between when confirmed successful ambulation is documented and 5 calendar days post-procedure. Sites are encouraged to complete the exams prior to discharge if workflow allows. These minimum 25 subjects are part of the pivotal subject count.
Hypotheses	Primary Efficacy: The VASCADE MVP XL Study Device's TTA compares favorably to the TTA PG. Primary Safety: The VASCADE MVP XL Study Device's limb incidence rate of combined major venous access site closure-related complications compares favorably to the PG.
Primary Efficacy Endpoint	Time to ambulation (TTA), defined as elapsed time between Study Device removal and when subject stands and walks 20 feet without evidence of venous re-bleeding from the Study Access Site **(Per-subject analysis).** The outcome will be compared to a clinically relevant TTA of **6.1 hours** as the performance goal (PG).
Secondary Efficacy Endpoints	The following will be descriptively reported and compared to a Clinical Acceptance Criterion (CAC) with no required hypothesis testing: • Time to hemostasis (TTH), defined as elapsed time between Study Device removal and first observed and confirmed venous hemostasis, for the Study Access Site. **Per access site analysis | CAC: 9.8 minutes** • Time to discharge eligibility (TTDE), defined as elapsed time between Study Device removal and when subject is eligible for discharge based solely on the assessment of the Study Access Site. **Per-subject analysis | CAC: 4.4 hours** • Total Post-Procedure Time (TPPT): defined as elapsed time between removal of the last procedural device/catheter for the index procedure in Study Access Site and when subject is able to successfully ambulate based on the Study Access Site. **Per-subject analysis| CAC: 4.4 hours** For the following, the outcomes will be descriptively reported with no required hypothesis testing:

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Attribute	Description
	• Device Success, defined as the ability to deploy the delivery system, deliver the collagen, and achieve final hemostasis with the Study Device. **Per access site analysis** • Procedure Success, defined as attainment of final hemostasis at the Study Access Site and freedom from major access site closure-related complications at the Study Access Site through 30 days. **Per-subject analysis** • Time to discharge (TTD), defined as elapsed time between Study Device removal and when subject is discharged from the institution. **Per-subject analysis**
Primary Safety Endpoint	On a **per Study Limb basis**, the major access site closure-related complications, attributed directly to the investigational closure method (i.e., "device-related" with no other likely attributable cause) are: • Access site-related bleeding requiring transfusion • Vascular injury requiring repair (via surgery, transcatheter embolization, balloon angioplasty, or stent graft) • Access site-related infection confirmed by culture and sensitivity, requiring intravenous antibiotics and/or extended hospitalization • New onset permanent access site-related nerve injury in the ipsilateral lower extremity (i.e., persisting for 30 days) • Pulmonary embolism requiring surgical or endovascular intervention and/or resulting in death, to be confirmed by CT pulmonary angiography, lung ventilation/perfusion scan (VQ scan) or autopsy • Pulmonary embolism NOT requiring surgical or endovascular intervention and/or NOT resulting in death, to be confirmed by CT pulmonary angiography or lung ventilation/perfusion scan (VQ scan). The VASCADE MVP XL Study Device's limb incidence rate of combined major access site closure-related complications through the 30 +/- 7 day follow-up period will be compared to the primary safety performance goal (PG) of **10%**.
Secondary Safety Endpoint	On a **per Study Limb basis**, the minor access site closure-related complications, attributed directly to the investigational closure method (i.e., "device-related" with no other likely attributable cause) are: • Access site-related bleeding requiring greater than 30 minutes of continuous manual compression to achieve initial venous hemostasis • Access site-related hematoma $\geq$ 6 cm documented by ultrasound • Late access site-related bleeding requiring non-surgical intervention (following hospital discharge) • Ipsilateral deep vein thrombosis, confirmed by ultrasound/imaging • Access site-related vessel laceration • Localized access site infection confirmed by culture and sensitivity, treated with intramuscular or oral antibiotics • Arteriovenous fistula not requiring treatment, documented by ultrasound/imaging • Pseudoaneurysm requiring treatment (thrombin injection, fibrin adhesive injection, or ultrasound-guided compression), documented by ultrasound

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Attribute	Description
	• Pseudoaneurysm not requiring treatment, documented by ultrasound • New onset transient access site-related nerve injury in the ipsilateral lower extremity (i.e., persisting for < 30 days) As a secondary safety endpoint, the VASCADE MVP XL Study Device's limb incidence rate of combined minor access-site closure-related complications through the 30 +/- 7-day follow-up period will be compared to the clinical acceptance criterion (CAC) of **3%**. This comparison will be descriptive with no required hypothesis testing.
Additional Planned Analyses	Additional planned analyses for the VASCADE MVP XL Study Device include the following: • Major and minor access site closure-related complications: per-event summary • All other access site closure-related complications summary As commercial device data (For Non-Study Access Sites) will be collected, for completeness, these commercial data will be summarized descriptively: • Adverse event summary (by limb and by event) Additional analyses may be conducted as desired.
Follow-Up Schedule	The study will be considered complete after all subjects have completed the 30-Day +/- 7-Day follow-up visit or have been exited* from the study. **If subjects have been lost to follow-up, withdrawn, or have expired, they will be exited from the study.*
Pre-Operative Inclusion Criteria	All subjects are required to meet the following inclusion criteria in order to be considered eligible for participation in this trial: 1. 18 to 80 years of age (inclusive) 2. Capable and willing to give informed consent 3. Planned non-emergent catheter-based procedure via: a. Study Limb (Required): The common femoral vein using one 16-17F* OD introducer sheath i. *Minimum 10F ID b. Non-Study Limb (optional): The common femoral vein of the Non-Study Limb using up to three (3) 5-12F ID (max 15F OD) introducer sheaths 4. Able and willing to complete a 30 day +/- 7 days follow-up visit
Pre-Operative Exclusion Criteria	Subjects will be excluded from participating in this study if they meet any of the following criteria prior to initiation of the index procedure: 1. Currently involved in any other investigational clinical trial that may interfere with the outcomes of this study, in the opinion of the Investigator 2. Pre-existing immunodeficiency disorder and/or chronic use of high dose systemic steroids 3. Known history of bleeding diathesis, bleeding problems following medical procedures, or coagulopathy 4. Known baseline hemoglobin < 10 g/dl, hematocrit < 30%, platelet count < 100,000 cells/mm^3 5. Severe co-existing morbidities, with a life expectancy of less than 12 months in the opinion of the Investigator

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Attribute	Description
	6. Known history of deep vein thrombosis or pulmonary embolism in the last 12 months 7. Known allergy/adverse reaction to bovine derivatives 8. Active systemic infection, or cutaneous infection or inflammation in the vicinity of the groin 9. Unable to ambulate at least 20 ft at baseline 10. Pregnant (known or suspected) or lactating 11. Extreme morbid obesity (BMI greater than 45 kg/m^2) or underweight (BMI less than 20 kg/m^2) 12. Known planned procedures or known concomitant condition(s) that may extend ambulation attempts beyond 2-3 hours, and/or hospitalization time (e.g., staged procedure, serious co-morbidity), in the opinion of the Investigator 13. Femoral vessel closure in either limb with any of the following conditions: a. Planned femoral access in the next 60 days to reflect the device re-access period b. Any residual hematoma, significant bruising, or known associated vascular complications c. Use of an intra-vascular closure device within the previous 90 days d. Access within < 10 days 14. Currently known implanted vascular grafts/stents at the access site that would interfere with the planned closure procedure, in the opinion of the Investigator
Intra-Operative Exclusion Criteria	Subjects will be excluded from participating in this study if any of the following exclusion criteria occur prior to initiation of closure of the Study Access Site: 1. Administration of low molecular weight heparin (LMWH) within 8 hours before or planned after the procedure 2. Uncontrolled systolic hypertension (SBP > 180 mmHg) or hypotension (SBP < 90 mmHg) immediately prior to enrollment 3. Subject may be ineligible to ambulate per protocol for any reason, for example: a. Any procedural complications, medical conditions (e.g., extended diuresis required), or issues with Non-Study Access Site closure that may extend recovery, ambulation and discharge times b. The subject should not attempt ambulation according to the protocol requirements for any reason, in the opinion of the Investigator 4. Any attempted femoral arterial access in either limb during the procedure 5. The Investigator deems that a different method should be used to achieve hemostasis of the Study Access Site than stipulated per protocol (e.g., manual compression) 6. Disease state or other source of interference that would interfere with the use of the device, in the opinion of the Investigator (e.g., vascular grafts or surgery at the target vessel puncture site) 7. The following are exclusions for **ALL access sites** immediately prior to enrollment unless otherwise noted: a. Difficult insertion of procedural sheath or needle stick problems at the onset of the procedure (e.g., multiple stick attempts, unintentional vessel stick with hematoma, “back wall stick”) in any of the vessel punctures

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Attribute	Description
	b. Access site configurations and procedure sheath size outside of the protocol range: i. Study Limb (required) - MVP XL Study Device: 1. OD: < 16F or > 17F venous or 2. ID: < 10F or 3. More than one access site in the Study Limb ii. Non-Study Limb (optional) - VASCADE Family Commercial Device: 1. OD: > 15F or 2. ID: < 5F or > 12F venous or 3. More than 3 access sites in the Non-Study Limb or 4. Non-Study Access Site(s) are in the same limb as Study Limb c. Vessel access site location is noted to be “high” or not at the common femoral vessel (above the inguinal ligament, cephalad to lower half of the femoral head or the inferior epigastric vein origin from the external iliac vein) d. Intra-procedural bleeding around sheath, forming hematoma, and/or suspected vascular complications e. Length of the tissue tract, the distance between the anterior vessel wall and skin, is estimated to be less than 2.5 cm f. Femoral vessel diameter less than 6 mm at access site 8. The Non-Study Access Site(s) were not closed successfully with VASCADE commercial device(s) with final hemostasis confirmed prior to Study Access Site closure

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1 Introduction

1.1 Background

The VASCADE Family is a family of vascular closure devices designed to deliver a resorbable extravascular collagen patch to seal femoral vessel puncture sites at the completion of catheterization procedures. These devices are intended to assist physicians or catheter lab technicians in controlling bleeding from femoral access sites and achieving final hemostasis. Specifically, one subset of the VASCADE Family, the VASCADE MVP Family Group, contains the FDA approved[1] VASCADE MVP Venous Vascular Closure System (VVCS) (Model 800-612C) and VASCADE MVP XL VVCS (Model 800-1012XL), which are indicated for the percutaneous closure of femoral venous access sites while reducing time to ambulation, total post-procedure time, time to hemostasis, and time to discharge eligibility in patients who have undergone catheter-based procedures utilizing 6-12F inner diameter (ID) (15F maximum outer diameter (OD)) and 10-12F ID (max 15F OD) procedural sheaths, with single or multiple access sites in one or both limbs. VASCADE MVP VVCS (800-612C) and VASCADE MVP XL VVCS (800-1012XL) are also indicated for enabling same day discharge in patients who have undergone catheter-based cardiac arrhythmia ablation procedures utilizing 6-12F ID (max 15 OD) and 10-12F ID (max 15F OD) procedural sheaths, with single or multiple access sites in one or both limbs.

1.2 Unmet Clinical Need

There are a number of procedures that may require venous access sheaths larger than the currently marketed VASCADE MVP (800-612C) and VASCADE MVP XL (800-1012XL) indicated range, including but not limited to: Left Atrial Appendage Closure (LAAC) and cardiac ablation procedures. These procedures use the common femoral vein as the primary access site.

In these types of procedures, physicians currently have choices for post procedure hemostasis, including manual compression (standard of care (SOC)), suture, suture mediated closure (SMC), and vascular closure devices (VCDs). Based on previous experience with the VASCADE Family, the VASCADE MVP XL Study Device has the potential for improved outcomes over current standard of care and is being studied to address this unmet clinical need.

2 Information for the Investigator

The following summarizes the safety and performance data from prior pre-clinical and clinical investigations to justify human exposure to the investigational device.

[1] P120016

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2.1 Non-Clinical Testing

Non-clinical testing of the investigational device evaluated the following:

- Bench (Functional)
- Biocompatibility
- Packaging
- Shelf-life
- Sterilization

Conclusion: Based on testing completed and results evaluated, the VASCADE MVP XL Study Device successfully fulfilled the tests requirements.

2.2 Pre-Clinical Testing

Animal testing has been conducted using the VASCADE MVP XL Study Device and demonstrates that the device performs as intended and the collagen is completely resorbed by 60 days.

2.3 Previous Related Clinical Investigations

Multiple venous closure studies have been conducted by Cardiva Medical/Haemonetics. Pre-market studies for closure of venous femoral access sites were conducted between 2017-2018 for VASCADE MVP. These studies were used to support the FDA PMA approval (P120016/S024) in 2018. Post-market studies for closure of venous femoral access sites were conducted between 2020-2021 for VASCADE MVP. Additional information on the studies is provided in Section Appendix A: Previous Related Clinical Investigations Detail.

2.4 Risks and Benefits

2.4.1 Risks

Risks associated with endovascular procedures and/or VASCADE Family devices, including the investigational VASCADE MVP XL Study Device, include:

- Allergic response
- Arterio-venous fistula
- Bleeding from the puncture site
- Bruising at puncture site
- Death
- Deep vein thrombosis
- Device failure / malfunction
- Edema
- Embolization (of thrombus, air, calcific debris, or device)
- Hematoma
- Infection

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- Inflammatory response
- Intimal tear / dissection
- Laceration of the vessel wall
- Lower extremity ischemia
- Oozing from the puncture site
- Peripheral nerve injury
- Perforation of the vessel wall
- Pseudoaneurysm
- Pulmonary embolism
- Puncture site pain
- Retroperitoneal bleeding
- Superficial vein thrombosis
- Vasovagal response
- Vascular injury
- Vessel occlusion
- Vessel thrombus

2.4.2 Minimization of the Risks

Risks to the subjects participating in the study will be minimized to the extent possible. Potential sites will be screened to ensure current clinical use, availability, and familiarity with VASCADE Family devices in their practice. Qualification and selection of Investigators and clinical sites, along with proper site, Investigator, Co-Investigator, and Operator training per Section 14 will aid in minimization of study risks. A Data Safety Monitoring Committee (DSMC) will be in place per Section 16.

2.4.3 Potential Benefits and Rationale for Benefit/Risk Ratio

An evaluation of procedure types and environments, user types, alternative therapies, results of clinical investigations involving the VASCADE Family, pre-clinical data, and instruction for use was completed. This analysis demonstrated that the potential clinical benefits of the VASCADE MVP XL Study Device outweigh the potential clinical risks.

The potential benefits of the VASCADE MVP XL Study Device include a favorable time to ambulation and safety profile when compared to performance goals. Based on the review of clinical benefit-risk and overall risk acceptability, the benefit-risk ratio is acceptable for human trials.

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3 Device Description

The VASCADE MVP XL (800-1014XL) is comprised of a delivery catheter containing a resorbable collagen implant and is called the VASCADE MVP XL Study Device throughout this protocol. The device also contains a clip and is packaged with an Instruction for Use (IFU). The device is designed to deliver a resorbable extravascular collagen patch to seal femoral vessel puncture sites at the completion of a catheterization procedure. The VASCADE MVP XL Study Device is used in conjunction with 16-17F OD sheaths. The VASCADE MVP XL Study Device is introduced through a compatible sheath at the completion of a catheterization procedure.

The VASCADE MVP XL Study Device's technical specifications are provided in Table 1. The VASCADE MVP XL Study Device is the identical device as the previously approved VASCADE MVP XL (800-1012XL) and is part of the VASCADE MVP Family Group. The only difference between the VASCADE MVP XL Study Device (800-1014XL, max 17F OD) and the VASCADE MVP XL (800-1012XL, max 15 OD) is the range of the sheath size indication being investigated in this study. There are no new materials introduced in the VASCADE MVP XL Study Device, all components are comprised of the identical material as the VASCADE Family of products including the collagen implant. The identical manufacturing processes will be used as those currently used with VASCADE Family devices.

Table 1: VASCADE MVP XL Study Device Technical Specifications

Device	Model	Sheath Size Compatibility (French)		Sheath Length	Deployed Disc Diameter	Collagen Patch Length	Collagen Dry Weight	Device Working Length	Maximum OD (with collapsed Disc)
		Inner Diameter	Max Outer Diameter (approx)						
VASCADE MVP XL VVCS	800-1014XL	10F – 14F	17F	up to 12 cm	8.3 mm (25F)	15 mm	19 mg ± 3 mg	15 cm	2.5 mm

Figure 1 below shows the VASCADE MVP XL Study Device assembly.

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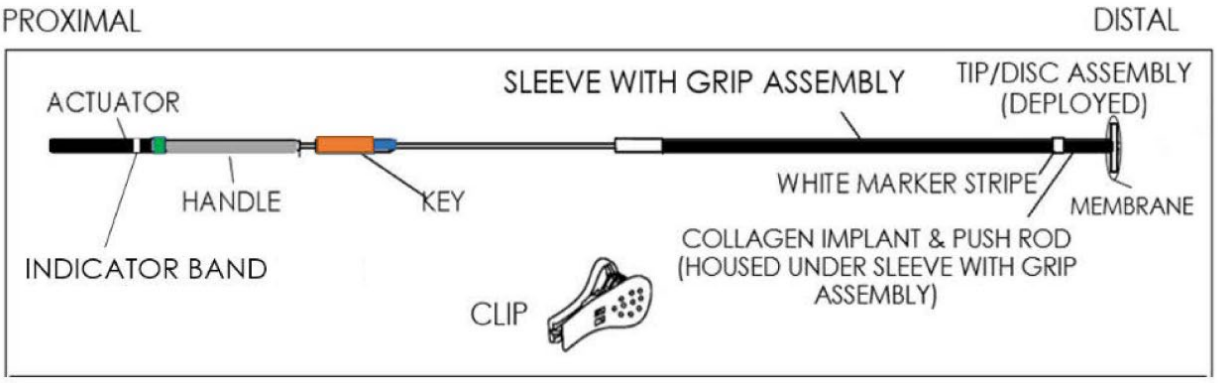


Figure 1. The VASCADE MVP XL Study Device

To use the VASCADE MVP XL Study Device with a sheath between 16-17F OD, the catheter is inserted into the femoral vessel through the previously placed closure sheath. After insertion, the distal tip of the catheter is deployed, opening and expanding a low-profile Nitinol (NiTi) disc within the lumen of the femoral vessel. The sheath is then removed from the vessel over the catheter and the low-profile disc is placed against the inner wall, locating the vessel wall and temporarily sealing the vessel. The position of the device disc against the vessel wall locates the collagen patch in the tissue tract immediately adjacent to the vessel site (extravascular). The collagen patch is then released. The clip is placed on the device shaft at the surface of the skin to hold the device in place during the procedure. The principle of operation is identical to that of the previously approved VASCADE Family devices.

3.1 Device Labeling

A copy of the IFU will be included with the devices. The labeling for the investigational device contains the following information:

1. Name and place of business of the manufacturer
2. Quantity of contents
3. Description of all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions
4. Statement: CAUTION-Investigational Device. Limited by Federal (or United States) Law to Investigational Use
5. Technical Specifications

3.2 MVP XL Study vs Commercial Device Differentiation

VASCADE MVP XL (800-1014XL) is the investigational device that will be used in this study. VASCADE MVP XL (800-1012XL) is a commercially available device that can be used in the Non-Study Limb in this study. See Table 2 below for differences between the two devices when used in this study.

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Table 2: MVP XL Study Device and Commercial Device Differentiation

VASCADE MVP XL (800-1014XL)	VASCADE MVP XL (800-1012XL)
Investigational device	Commercially available
Used in the Study Limb only	Use in the Non-Study Limb only, if applicable (Note: other commercially available VASCADE Family devices may be used in the Non-Study Limb as appropriate)
Investigational indication: 16-17F OD	Commercial indication: 10-12F ID, max 15F OD
Labeled "CAUTION—Investigational device. Limited by Federal (or United States) law to investigational use."	Commercial labeling
White box	Colored box

4 Study Objective

The objective of this study is to establish the safety and efficacy of the VASCADE MVP XL Study Device when compared to performance goals (PGs) and clinical acceptance criteria (CAC) for closing percutaneous femoral venous access sites at the completion of catheter-based procedures with 16-17F OD procedural sheaths.

Statistical Success Criteria: This study will be considered a success if it meets the PG for both the primary safety and the primary efficacy endpoints as defined in Sections 9.1 and Section 9.4 respectively.

5 Study Design

5.1 Overview

This is a multi-center, prospective, single arm, pivotal trial to evaluate the safety and efficacy of the VASCADE MVP XL Study Device for the management of the femoral venotomy after catheter-based interventions utilizing 16-17F OD sheaths. Measures of safety and efficacy will be assessed through 30 (+/- 7) days post-procedure.

5.2 Sample Size

A minimum of 70 evaluable subjects (i.e., have completed all required visits through follow-up) (see Section 8.5) will be enrolled. The study is expected to enroll up to 77 subjects to account for possible attrition of 10%. This 77 maximum includes the subset of subjects participating in the ultrasound sub-study. A minimum of 25 pivotal subjects with evaluable images will be enrolled in the ultrasound sub-study from participating sites. See Section 10.3.1 for sample size justification.

The sites selected will have previous experience with commercial VASCADE Family devices. A minimum of 1 roll-in for first subject enrollment per site is required (recommend that the deployer is an Investigator). In addition, up to 2 roll-ins per Enrolling Investigator and per Operator may be enrolled. The study is anticipating enrollment of up to 48 roll-in subjects.

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The enrollment limit is 125 subjects. This includes a maximum of 77 pivotal subjects (minimum of 70 evaluable pivotal subjects and approximately 7 pivotal subjects planned for attrition) and a maximum of 48 roll-in subjects.

5.3 Investigational Sites

This trial will enroll at a minimum of 5 sites and a maximum of 12 sites. A single site may not enroll more than 19 pivotal (non-roll-in) study subjects (25% target evaluable subject enrollment). All sites will be in the United States.

6 Study Population

The patient population for VASCADE Family devices are patients who undergo procedures requiring vessel closure. In the pivotal study for VASCADE MVP, AMBULATE, subject demographics including age, gender, race, ethnicity, and BMI were reported (Table 13). It is expected that the subject characteristics in AMBULATE will be similar in this study and consistent with the Medicare population in the US.

Sites should make an effort to recruit a population that is representative of the overall patient population meeting the inclusion/exclusion criteria.

6.1 Sheath Size Inclusion and Rounding

For the purposes of this study with respect to inclusion/exclusion criteria, sheath sizes will be rounded to the nearest whole number.

- Sheaths with sizes of 0.5, 0.6, 0.7, 0.8, and 0.9 will be rounded up (e.g. a 15.5F OD sheath would be rounded up to 16F and would be included in this study)
- Sheaths with sizes of 0.4, 0.3, 0.2, and 0.1 will be rounded down (e.g. a 15.1F OD sheath would be rounded down to 15F and would be excluded in this study)

6.2 Selection Criteria

The following pages outline the specific inclusion and exclusion criteria for the study; a patient must meet all eligibility criteria.

6.2.1 Pre-Operative Inclusion Criteria

All subjects are required to meet the following inclusion criteria in order to be considered eligible for participation in this trial:

1. 18 to 80 years of age (inclusive)[1]
2. Capable and willing to give informed consent

[1] The starting and ending numbers are included in the range (e.g. 18 and 80 are included)

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3. Planned non-emergent catheter-based procedure via:
    a. Study Limb (Required): The common femoral vein using one 16-17F* OD introducer sheath
        i. *Minimum 10F ID
    b. Non-Study Limb (optional): The common femoral vein of the Non-Study Limb using up to three (3) 5-12F ID (max 15F OD) introducer sheaths
4. Able and willing to complete a 30 day +/- 7 days follow-up visit

6.2.2 Pre-Operative Exclusion Criteria

Subjects will be excluded from participating in this study if they meet any of the following criteria prior to initiation of the index procedure:

1. Currently involved in any other investigational clinical trial that may interfere with the outcomes of this study, in the opinion of the Investigator
2. Pre-existing immunodeficiency disorder and/or chronic use of high dose systemic steroids
3. Known history of bleeding diathesis, bleeding problems following medical procedures, or coagulopathy
4. Known baseline hemoglobin < 10 g/dl, hematocrit < 30%, platelet count < 100,000 cells/mm^3
5. Severe co-existing morbidities, with a life expectancy of less than 12 months in the opinion of the Investigator
6. Known history of deep vein thrombosis or pulmonary embolism in the last 12 months
7. Known allergy/adverse reaction to bovine derivatives
8. Active systemic infection, or cutaneous infection or inflammation in the vicinity of the groin
9. Unable to ambulate at least 20 ft at baseline
10. Pregnant (known or suspected) or lactating
11. Extreme morbid obesity (BMI greater than 45 kg/m^2) or underweight (BMI less than 20 kg/m^2)
12. Known planned procedures or known concomitant condition(s) that may extend ambulation attempts beyond 2-3 hours, and/or hospitalization time (e.g., staged procedure, serious co- morbidity), in the opinion of the Investigator
13. Femoral vessel closure in either limb with any of the following conditions:
    a. Planned femoral access in the next 60 days to reflect the device re-access period
    b. Any residual hematoma, significant bruising, or known associated vascular complications

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c. Use of an intra-vascular closure device within the previous 90 days
d. Access within < 10 days

14. Currently known implanted vascular grafts/stents at the access site that would interfere with the planned closure procedure, in the opinion of the Investigator

6.2.3 Intra-Operative Exclusion Criteria

Subjects will be excluded from participating in this study if any of the following exclusion criteria occur prior to initiation of closure of the Study Access Site:

1. Administration of low molecular weight heparin (LMWH) within 8 hours before or planned after the procedure
2. Uncontrolled systolic hypertension (SBP > 180 mmHg) or hypotension (SBP < 90 mmHg) immediately prior to enrollment
3. Subject may be ineligible to ambulate per protocol for any reason, for example:
    a. Any procedural complications, medical conditions (e.g., extended diuresis required), or issues with Non-Study Access Site closure that may extend recovery, ambulation and discharge times
    b. The subject should not attempt ambulation according to the protocol requirements for any reason, in the opinion of the Investigator
4. Any attempted femoral arterial access in either limb during the procedure
5. The Investigator deems that a different method should be used to achieve hemostasis of the Study Access Site than stipulated per protocol (e.g., manual compression)
6. Disease state or other source of interference that would interfere with the use of the device, in the opinion of the Investigator (e.g., vascular grafts or surgery at the target vessel puncture site)
7. The following are exclusions for **ALL access sites** immediately prior to enrollment unless otherwise noted:
    a. Difficult insertion of procedural sheath or needle stick problems at the onset of the procedure (e.g., multiple stick attempts, unintentional vessel stick with hematoma, “back wall stick”) in any of the vessel punctures
    b. Access site configurations and procedure sheath size outside of the protocol range:
        i. Study Limb (required) – MVP XL Study Device
            1. OD: < 16F or > 17F venous or
            2. ID: < 10F or
            3. More than one access site in the Study Limb
        ii. Non-Study Limb (optional) – VASCADE Family Commercial Device:
            1. OD: > 15F or

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2. ID: < 5F or > 12F venous or
3. More than 3 access sites in the Non-Study Limb or
4. Non-Study Access site(s) are in the same limb as the Study Limb

c. Vessel access site location is noted to be “high” or not at the common femoral vessel (above the inguinal ligament, cephalad to lower half of the femoral head or the inferior epigastric vein origin from the external iliac vein)
d. Intra-procedural bleeding around sheath, forming hematoma, and/or suspected vascular complications
e. Length of the tissue tract, the distance between the anterior vessel wall and skin, is estimated to be less than 2.5 cm
f. Femoral vessel diameter less than 6 mm at access site

8. The Non-Study Access Site(s) were not closed successfully with VASCADE commercial device(s) with final hemostasis confirmed prior to Study Access Site closure

6.3 Withdrawal of Subjects

Subjects may withdraw from the study at any time, with or without reason and without prejudice to further treatment. In all cases of withdrawal, the reason(s) for withdrawal (if given) will be recorded upon study exit. In addition, the Investigator may withdraw the subject for any other reason determined by the Investigator to be in the best interest of the subject. If withdrawal is due to AE issues related to the device safety or performance, the Investigator should ask for the subject’s permission to follow his/her status outside of the clinical investigation until resolved.

Investigators are strongly encouraged to confer with the Sponsor prior to withdrawing any subjects from the study. Data already collected prior to subject withdrawal will not be removed from the study. Depending on when the subject was withdrawn from the study, this may make the subject non evaluable for specific endpoints (see Section 10.1). Subjects that withdraw from the study will not be replaced.

6.4 Ultrasound Sub-study

A sub-study of this pivotal clinical trial will be performed at select sites utilizing independent analysis of non-invasive duplex ultrasound (DUS) imaging, enrolling a minimum of 25 subjects with evaluable images in the study. These minimum 25 subjects are part of the pivotal subject count. Imaging is only required at the 16-17F OD puncture site (i.e., Study Access Site). Duplex ultrasound evaluation will be utilized to assess the local vascular impact of the VASCADE MVP XL Study Device, along with the development of any iatrogenic vascular complications. Any clinical site that is able to perform the required exams may be designated and trained as an

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ultrasound site. These sites will consent subjects for the ultrasound sub-study imaging until a minimum of 25 subjects with evaluable images have been enrolled across all ultrasound sub-study participating sites. Patients who are eligible to participate in the ultrasound sub-study will be asked to prospectively indicate their agreement by initialing on the informed consent form, thereby eliminating any potential enrollment bias. Any patient who is eligible (i.e., potential pivotal subject at a site that is still enrolling in the sub-study), but declines will have the stated reason documented. For any subject who does agree but doesn't receive the exam, a protocol deviation will be written.

Ultrasound will be performed at any point between when successful ambulation is documented (i.e., TTA) and 5 calendar days post-procedure. Sites are encouraged to conduct these exams prior to discharge if workflow allows. Ultrasound sub-study subjects should have their ultrasound appointments scheduled no later than 5 calendar days post-procedure to ensure compliance if not already completed at discharge.

All sub-study sites will be instructed on study requirements for duplex ultrasonography of the femoral vascular structures, and images will be uploaded for interpretation by a central core ultrasound laboratory with experience in multi-center vascular device trials.

7 Written Informed Consent

Written Informed Consent must be obtained for all subjects. Patients who meet pre-op inclusion/exclusion entry criteria will be invited to participate, and asked to sign the study-specific, Institutional Review Board (IRB) approved Informed Consent Form (ICF) before any study-specific tests or procedures are performed. Study personnel should explain that even if a patient agrees to participate in the study and signs an ICF, the Investigator may determine that the patient is not a suitable candidate for the study.

Patients will be asked to prospectively agree whether to participate in the Roll-in and/or Standard (pivotal) subject group(s) on the ICF by initialing next to the potential group(s) for which they could qualify. The patient will also be able to prospectively consent to the Ultrasound Sub-study, if applicable.

Subjects who are consented candidates and proceed through pre-operative and intra-operative screening will be documented on a Screening/Enrollment Log.

8 Study Procedures and Enrollment

8.1 Duration of Subject Participation

Subjects enrolled in the trial will participate for approximately 30 (+/- 7) days. The overall enrollment study duration (i.e., expected time to enroll and follow all subjects) will be approximately 5-10 months.

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The total expected duration of the clinical investigation is approximately 9-14 months. The clinical trial duration is defined as from the time of when the first site is activated through when the final clinical study report is filed, all sites are closed, and all operational activities are complete.

8.2 Enrollment

As a minimum of 70 evaluable subjects are required, up to 77 subjects will be enrolled to account for potential attritions of 10%. This includes the subset of 25 subjects with evaluable images participating in the ultrasound sub-study. Separate from the pivotal subject count, the study is anticipating enrollment of up to 48 roll-in subjects. The enrollment limit is 125 subjects (maximum 77 pivotal subjects and maximum 48 roll-in subjects).
Intraoperatively, any Non-Study Access Sites must be screened for eligibility and planned for closure with a VASCADE Family commercial device per the device's indications prior to enrollment.
To limit confounding factors related to intra-operative exclusions and endpoints, the closure for the venous 16-17F OD access site must be last (i.e., VASCADE MVP XL Study Device must be inserted after hemostasis is confirmed for all Non-Study Access Sites in the Non-Study Limb). At the completion of the procedure, including successful Non-Study Access Site closure with a commercial VASCADE Family device, patients that meet all of the pre- and intra-operative eligibility criteria may be enrolled in the study and are eligible to receive the VASCADE MVP XL Study Device for femoral venous hemostasis in a 16-17F OD access site, which is standalone in the Study Limb, as part of the study. If any Non-Study Access Site is NOT successfully closed with a VASCADE Family commercial device, the subject should not be enrolled and hemostasis should be achieved per Investigator's discretion.

The Investigator will acknowledge intention to enroll the patient prior to opening the investigational closure device package and insertion into the sheath. Once Investigator acknowledgement has been made and the VASCADE MVP XL Study Device has entered the body, the subject is considered enrolled into the study. At least one VASCADE MVP XL Study Device must be attempted to be inserted. If a subject did not have a VASCADE MVP XL Study Device inserted, he/she will not be considered enrolled in the study. If access is lost prior to Study Device insertion and an MVP XL Study Device is never inserted, the patient will not be enrolled and will be documented as an Intra-operative Screen Failure. Hemostasis should be achieved per Investigator's discretion.

Note: If a VASCADE MVP XL Study Device is removed from the packaging but not inserted (e.g. device opened and failed precheck, so it is replaced with an alternate Study Device), a Device

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Observations Form must be completed for the opened but unused Study Device to support accurate inventory control for investigational devices.

Documenting Enrollment & Subject Identification

Subject data will be captured according to the instructions below.

1. All consented patients must be entered on the Consent/Enrollment Log.
    a. All consented patients are documented by initials and date of consent on the Consent/Enrollment Log.
    b. Pre-op screen failures (if consented): The Consent/Enrollment Log documents the reason for pre-op exclusion. Keep the signed ICF for Monitor verification. These patients will not be entered in the Electronic Data Capture System (EDC).
2. If a consented patient's procedure has started and there is an exclusion (i.e., due to intra-op inclusion/exclusion), subjects will be assigned consecutively numbered Intra-operative Screen Failure (SF) ID's. The ID will be used to enter the subject in the EDC as a SF and will consist of a 2-digit study code (as provided by Sponsor), 2-digit site code (as assigned by Sponsor), and a 3-digit number code, as follows:
    a. Intra-op screen failures: AM-01-901, AM-01-902, etc.
    b. Intra-op screen failures only require completion of the specific logs, SWSs, and eCRFs as described in the Manual of Operations.
    c. Enter the SF ID on the Consent/Enrollment Log, keep the signed ICF and signed/dated SWSs as described in the Manual of Operations for monitor verification, and enter as screen failure in the EDC.
3. If a consented patient's procedure has started and there is not an exclusion (i.e., due to intra-op inclusion/exclusion), upon enrollment subjects will be assigned consecutively numbered Study ID's. The Study ID will be used to label any SWS and eCRFs. The Study ID will consist of a two-digit study code (as provided by Sponsor), 2-digit site code (as assigned by Sponsor), and a 3-digit number code, as follows:
    a. Roll-in subjects: AM-01-201, AM-01-202, etc.
    b. Pivotal subjects: AM-01-301, AM-01-302, etc.
    c. Enter the Study ID on the Consent/Enrollment Log, keep the signed ICF and signed/dated SWSs as described in the Manual of Operations for monitor verification, and register the subject in the EDC within one working day of Enrollment.

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8.3 Visit Schedule

The following table outlines the required study assessments.

Table 3. Study Event Schedule

	≤ 45 days before Procedure	**At time of Index Procedure**	**Post-Procedure/ Hospital Discharge**	**1-Month (30 days +/- 7 days)**
Demographics/ Medical History	X			
Groin / Access Site Assessment	X Pre-Op I/E	X Intra-Op I/E	X At discharge eligibility evaluation	X Follow-up general assessment (e.g., no infection, hematoma)
Complaints of neurologic injury in lower extremities[1]	X		X	X
Laboratory Tests[2]:	X			
Pre-op Inclusion / Exclusion Criteria Assessment	X			
Informed Consent	X			
Intra-operative Exclusion Criteria Assessment		X		
Pre-enrollment BP (SBP <180 and > 90 mmHg)		X		
Enrollment		X		
Study Device - Endpoint Data Collection:[3]				
TTH determination (clock/timer)		X		
TTA determination (clock/timer)			X	
TPPT determination (clock/timer)			X	
TTDE determination (clock/timer)			X	
TTD (source/medical record)			X	
Device Success		X		
Procedure Success				X
ACT (for heparinized subjects)		X		
Protamine use/indication		X		
Antiplatelet / anticoagulant regimen (SOC)	X	X	X	
Device Observations[4]		X		
Adverse Events[5]		X	X	X
Ultrasound Exam (sub-study)[6]			Between documented successful ambulation and 5 calendar days post-procedure.	

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	≤ 45 days before Procedure	At time of Index Procedure	Post-Procedure/ Hospital Discharge	1-Month (30 days +/- 7 days)
[1] Complaints of lower extremity discomfort will be evaluated by the Investigator for neuropathic etiology and clinical significance at 1) Baseline, 2) Hospital Discharge, and 3) 30 Day Follow-up to determine whether any symptoms are new or worsening from the Baseline evaluation and are of at least "moderate" severity for specific adverse event reporting. [2]Laboratory tests are collected according to standard of care for these procedures at each site. [3]Multiple study endpoints will require collection of specific clock times (i.e., on designated Source Worksheet using designated clock/timer), but results will be calculated within the database. [4]Reported according to 21 CFR 803, Medical Device Reporting and/or according to 21 CFR 812 on Device Observations eCRF, as applicable [5]Reported according to 21 CFR 803, Medical Device Reporting and/or according to 21 CFR 812 on the Adverse Event eCRF and/or Access Site Bleeding Evaluation eCRF, as applicable [6]The Ultrasound exam may be performed at any time between documented successful ambulation and 5 calendar days post-procedure. **Sites are encouraged to complete the exams prior to discharge if workflow allows.**				

8.4 Study Procedures

8.4.1 Pre-Operative

Prior to/during informed consent and prior to the patient's scheduled procedure, review the patient's medical history, demographic data (age, race, ethnicity, and gender), and baseline information (height, weight, BMI). Review the Pre-operative Inclusion and Exclusion criteria within 45 days prior to the planned procedure date, including screening laboratory draws (according to the institution's standard of care - e.g., platelet count, hemoglobin and hematocrit, pregnancy test, as applicable).

The patient's medical history and risk factors should be documented in the medical records. All subjects will be asked about any history of lower extremity discomfort in both lower limbs. If the Investigator determines the discomfort to be related to neuropathy, then any residual symptoms at enrollment, including frequency, severity and clinical significance will be evaluated by the Investigator and documented in the eCRF.

8.4.2 Intra-Operative – Data Collection for All Subjects

For consented subjects that continue to meet the Pre-operative Eligibility Criteria, record the following data regarding their procedure:

- Procedure type
  - Arrhythmia(s) treated (if applicable)
  - Ablation modality(ies) (if applicable)
- # of VASCADE Commercial devices used to close Non-Study Access Sites
- Techniques used to gain access at the Study Access Site, if any (e.g., type of imaging, puncture method)
- Procedural anti-coagulation administered
- Pre-enrollment blood pressure
- Final procedural ACT time and value for heparinized subjects
- Protamine administration, dose, and indication (if given)

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- Intubation status
- Urinary catheter usage

8.4.3 Intra-Operative – Access Site Requirements & Data Collection

The following procedural documentation requirements apply to all subjects enrolled in this study. Non-Study Access Sites must be closed first, and enrollment/closure of the Study Access Site may commence thereafter. Use the required Closure Source Worksheets to capture critical study data (must be complete, signed, dated by the designated Investigator) using the dedicated clock timer provided by Sponsor:

- Closure Procedure – Non-Study Access Sites (if applicable)
    - Non-Study Limb (Non-Study Access Site(s))
        - Requirements:
            - Up to 3 femoral venous access sites with a 5-12F ID (maximum 15 OD) procedural sheath (note: this can be 0 if the procedure only has a single access site, the Study Access Site)
            - Closed with commercial VASCADE Family Device; refer to commercial IFUs
            - Hemostasis must be achieved and confirmed in these access sites prior to enrollment
            - The Closure Procedure SWS documents these as Access Sites #C1-3
    - Document the following:
        - Number and location of femoral Non-Study Access Site(s); for each access site:
            - Closure device used (Model and Lot #)
            - Limb side (R or L)
            - Device success confirmed
            - Largest procedural sheath inner diameter
- Closure Procedure – Study Access Sites
    - Study Limb (Study Access Site)
        - Requirements:
            - Exactly one (1) femoral venous access site with a 16-17F OD procedural sheath, to be closed last
            - Closed with investigational device (VASCADE MVP XL Study Device); refer to the VASCADE MVP XL (800-1014XL) IFU for specific instructions on device use
            - No other access sites allowed in the Study Limb

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- Document the following:
  - Confirm Study Device use
  - Confirm only access site in the limb, R or L side, venous
  - Largest procedural sheath used (ID and OD)
  - **Clock Time Data** (*using calibrated study timer in hh:mm:ss)
    - **P0 Time:** Time of first index procedure sheath insertion
    - **P1 Time*:** Final procedural device/catheter removed from sheath in Study Access Site
    - **TX.1 Time*:** Time start hemostasis – time of study device removal
    - **TX.2 Time***: Time venous hemostasis is achieved
    - Confirmation of hemostasis
    - Adjunctive / light compression or other method applied for tissue tract ooze post final hemostasis confirmation in the lab (if yes, start/stop time)
  - Device Use
    - Investigator or Operator, last name
    - Closure device used/attempted (Model, Lot #, Study Serial # if applicable)
    - Device Success question (all must be Yes)
      - Device insertion was attempted
      - Deployed the delivery system
      - Delivered the collagen into the tissue tract
      - Achieved hemostasis with the device
      - If No, complete Device Observations Form and document method used to achieve final hemostasis
      - NOTE: Once the Study Device enters the body/sheath, the subject is enrolled and will complete all study follow-up requirements, including cases of failure to deliver the Study Device/achieve hemostasis with the Study Device. All Clock Times must be recorded.
    - Document opened/unused Study Devices

8.4.4 Access Site Closure Instructions

The investigational and commercial device(s) should be deployed according to their respective IFU. The investigational and commercial IFUs are provided in the device cartons. In addition, the investigational IFU is provided in the study materials, and commercial product IFUs are available at http://hospital.haemonetics.com/vascular-closure.

Table 4: Access Site Configurations

	Non-Study Limb	**Study Limb**
No. of Access Sites	0-3	1
Access Site Location	Common Femoral Vein	Common Femoral Vein

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	Non-Study Limb	**Study Limb**
Procedure Sheath Size	≤ 15 OD	16-17F OD
Closed with	Commercial VASCADE Family Device, per indications* *Closure must be completed prior to enrollment*	VASCADE MVP XL Study Device (Investigational Device) *Closed after hemostasis is confirmed on all Non-Study Access Sites*
*Commercial device information (e.g., lot number) will be collected to confirm device used is in range of indications.		

Study Access Site Closure Instructions

1. After deployment and compression, observe for hemostasis.
2. "First look" - Wipe away any blood with a 4x4. Assess for the following:
   - If no bleeding requiring pressure, document **Clock Time TX.2** – Time venous hemostasis achieved.
   - If venous bleeding is noted after deployment, manual compression can be used to achieve initial hemostasis at the Investigator's discretion. Venous bleeding requiring manual pressure prior to achieving initial venous hemostasis is not considered to be an adverse event and is not considered a Device Failure except in the case of requiring greater than 30 minutes of continuous manual compression to achieve initial venous hemostasis.
     - Re-assess after manual compression, and document **Clock Time TX.2** when venous hemostasis is confirmed.
   - If oozing (e.g., non-venous) is noted, document **Clock Time TX.2** (i.e., venous hemostasis has been achieved)**.** Then hold light/adjunctive pressure/compression methods as needed, documenting the time required, or add dressing/D-Stat as needed. Light pressure held to manage tissue tract oozing in the lab is not considered to be an adverse event and does not affect the Time to Hemostasis (Clock Time TX.2).
   - Wait 5 minutes after **Clock Time TX.2** to confirm that final venous hemostasis has been achieved. Repeat step for manual compression and hemostasis evaluation as needed until venous final hemostasis has been achieved and confirmed.
   - Note: *Formation of a hematoma post-sheath removal may indicate a back-wall or secondary venous or arterial puncture. If this situation is suspected, the closure device should be removed and the subject should be converted to manual compression at that location. The subject is still enrolled in the study since the Study Device was inserted, and all study times and follow-up requirements must be completed through the 30 +/- 7 day follow-up. These subjects will not be replaced.*

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3. Document any complications or device performance issues on the Device Observations eCRF for investigational product; refer to the Manual of Operations (MOP) for device return instructions in the case of any device performance issues.

- NOTE: Failure to retain any VASCADE MVP XL Study Device with a suspected malfunction for return to Sponsor is a protocol deviation and will be documented. Every effort to return Commercial devices with a suspected malfunction should be made.

8.4.5 Post-Operative

After hemostasis is achieved and confirmed, all access sites should be monitored every 15 minutes for the first hour for all subjects or based on institution's standard of care / documentation. Guidelines for assessments of ambulation, discharge eligibility, and discharge are provided below.

Time to Ambulation (TTA) Guidelines (all subjects):

Time to Ambulation is a primary efficacy endpoint of the study. Therefore, every effort must be made to ambulate the subjects within the timelines described below, providing that the subject is medically stable to do so.

- Recommended physician's bedrest orders are 2-3 hours, calculated from the time of Study Access Site hemostasis to time of the first attempted ambulation.
    - If medical circumstances require longer bedrest orders, the reason(s) will be documented. If longer bedrest orders were known prior to Study Access Site closure, this is an Intra-operative Exclusion Criteria protocol deviation.
- Check groin immediately post ambulation. If there is no evidence of venous re-bleeding at the Study Access Site, document **P2 Time (time of ambulation)** using the calibrated study timer.
- Any delay at attempted ambulation greater than 30 minutes beyond written ambulation order time OR greater than 3.5 hours after Study Access Site hemostasis time that is not related to a medical condition, will be documented as a Protocol Deviation (PD) (e.g., patient is sleeping, no staff available).
    - The 30-minute buffer period is provided to allow for minor workflow delays beyond the ordered bedrest period post final access site hemostasis.
- In the case of longer written bedrest orders, ambulation attempt must occur within 30 minutes of the bedrest order end (calculated between Study Access Site hemostasis time and ambulation time). If bedrest is extended due to a medical condition, the reason(s) will be documented. Any delay not related to a medical condition will be documented, and a Protocol Deviation will be written.

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NOTE: If the Study Access Site was not able to be closed with the VASCADE MVP XL Study Device (e.g., converted to manual compression after device had been inserted), subjects should be maintained on bedrest according to the Investigator's discretion and all study times will still be collected. This would not constitute a deviation from the protocol, however > 30-minute delay after ordered bedrest time without a medical justification will be documented as a Protocol Deviation.

Time to Discharge Eligibility (TTDE) Guidelines (all subjects):

- Approximately 10 (+/- 5) minutes (and at least 5 minutes) after the subject has successfully completed the ambulation assessment (**P2 Time**), the Study Access Site should be carefully assessed for the following:
    - Brisk venous bleeding or expanding hematoma (venous access sites)
    - Presence of any obvious vascular complications at the access site.
- If the subject does not exhibit any of these symptoms at the Study Access Site, he/she may be considered to be "Eligible for Hospital Discharge" based on this study definition of the Study Access Site assessment only. Document **P3 Time** (time of discharge eligibility) using the calibrated study timer.
- These are basic guidelines for this study-required assessment only which are not intended to impact actual hospital discharge assessments or times for these subjects. Using these guidelines, the Investigator may delegate this TTDE assessment to dedicated research members.
- Any significant delay in determination of this discharge eligibility (i.e., > 20 minutes after successful ambulation) that is not related to the Study Access Site assessment will be documented as a protocol deviation (e.g., no staff available, other condition unrelated to Study Access Site).
    - The 5-minute buffer period is provided to allow for minor workflow delays beyond the 10 (+/- 5) minute TTDE assessment.

NOTE: If there is any sign of active bleeding (not oozing) at the Study Access Site after ambulation and prior to TTDE, measures should be taken to re-achieve hemostasis and then the subject re-ambulated when the Investigator determines that it is appropriate to do so. In these cases, TTA and TTDE will be repeated and documented when successful as applicable, and the re-bleeding will be documented on the Access Site Bleeding Evaluation eCRF.

- Bleeding from Non-Study Access Sites will not impact TTA or TTDE times, unless it results in an inability to complete the 20-foot ambulation requirement.
- If tissue tract oozing requiring light compression methods is noted at the Study Access

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Site after ambulation (e.g., clearly not venous bleeding), then TTDE and P2 time will be documented, and ambulation considered to be successful.

Time to Discharge Guidelines (TTD) (all subjects):

Prior to hospital discharge, all subjects will be asked about any new or worsening symptoms of lower extremity discomfort in both lower limbs where femoral access was obtained. Any new or worsening symptoms will be evaluated by the Investigator for neuropathic etiology at Hospital Discharge to determine clinical significance and adverse event reporting requirements. Complaints that are not at least "moderate" in severity should be carefully evaluated for specific adverse event reporting, using the AE Code List to determine whether the event meets the threshold for a major or minor access site closure-related complication.

At select sites, a minimum of 25 subjects with evaluable images will have an ultrasound exam of the VASCADE MVP XL Study Device femoral access site performed, and a digital image recorded for the Study Limb. Refer to the Manual of Operations for complete instructions. The Core Lab will either complete a data transfer, or complete an eCRF in the EDC. Sites are encouraged to conduct the ultrasound prior to discharge for enrolled ultrasound sub-study subjects if workflow allows. However, conducting the ultrasound any time between when confirmed successful ambulation is documented and 5 calendar days post-procedure is acceptable. Ultrasound sub-study subjects should have their ultrasound appointments scheduled no later than 5 calendar days post-procedure to ensure compliance if not already complete at discharge.

Research personnel should attempt to confirm a date for the follow-up visit at 30 (+/-7) days with the subject prior to discharge to ensure compliance.

Use the guidelines above to complete the required Source Worksheets provided by the Sponsor to capture critical study data:

- Clock Time Data (*must use calibrated clock timer provided by Sponsor)
  - **P2 TIME*:** Record the date and time the subject was able to complete ambulation of 20 feet without venous re-bleeding from the Study Access Site.
    - NOTE: If the subject completes the 20 feet, and bleeding occurs from the Non-Study Access Site, the subject has successfully completed Ambulation and P2 Time is recorded, to be followed by the TTDE assessment. Return the subject to bedrest at the Investigator's discretion.
  - **P3 TIME*:** Record the date and time the subject was deemed eligible for discharge, based solely on the assessment of the Study Access Site after successful ambulation,

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(i.e., confirm the absence of Study Access Site venous bleeding or obvious complications).
    - The TTDE assessment should be conducted at least 10 +/-5 minutes after successful ambulation (P2 TIME).
    - NOTE: Re-bleeding from a Non-Study Access Site will not impact this assessment.
- **P4 TIME:** Record the date and time the subject was discharged from the facility. These data should be taken from the medical records.
- Adverse event(s) at femoral access site(s): Reference Section 15 for documentation of adverse events.

8.5 Follow-up Visit at 30 (+/- 7) Days

Subjects are required to be present for an in-person office visit 30 ± 7 days following their index procedure. If a subject is unable to return to the site during the visit window, a telephone or telemedicine visit may be performed and will be considered a follow-up contact, the reason for not having an in-person visit will be documented, and a protocol deviation will be documented. If Standard of Care in-person follow-up is within this time frame, this may be recorded as the study follow-up visit. If an in-person visit is conducted early, outside the 30 ± 7-day window, a telemedicine or telephone follow-up must be conducted within the study window to complete the safety assessment, and a protocol deviation will be documented. A subject will be considered an evaluable subject if a follow-up contact is performed even if there is a protocol deviation regarding the timing or location of follow-up.

A physical assessment of the Study Access Site, including auscultation for a femoral bruit, will be conducted during the 30-day follow-up. Any observations noted during the assessment will be captured in the CRFs. All subjects will be asked about any new or worsening symptoms of lower extremity discomfort in both lower limbs where femoral access was obtained. Any new or worsening symptoms will be evaluated by the Investigator for neuropathic etiology, and to determine clinical significance and adverse event reporting requirements. Complaints that are not at least “moderate” in severity should be carefully evaluated for specific adverse event reporting, using the AE Code List to determine whether the event meets the threshold for a major or minor access site closure-related complication. Potential neurologic injuries will need to be assessed at least 30 days post-procedure to determine whether they persist at 30 days, e.g., if the follow-up is done before 30 days and a neurologic injury event is “ongoing” at that time, the site will need to contact the subject at 30 + 7 days to determine if it resolved within 30 days.

The medical record must also be interrogated regarding any complications after hospital discharge through the follow-up period and documented as complete on the CRF, whether the

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subject completes the follow-up visit/contact or not.

At least 3 attempts to contact the subject within the study window should be made and documented before the subject is determined to be lost to follow-up or self-withdrawn. Continued efforts may be made beyond the 37-day window when feasible, in order to collect safety endpoint data on the subject.

8.6 Study Exit

Once the subject has completed the follow-up requirements, has been lost to follow-up or withdrawn, or has expired, they should be exited from the study. The date of exit and subject status will be recorded on the eCRF.

9 Efficacy and Safety Endpoint Definitions

Reference Section 10 for the Performance Goals (PGs) and Clinical Acceptance Criteria (CAC).

9.1 Primary Efficacy Endpoint

Time to ambulation (TTA), defined as elapsed time between Study Device removal and when subject stands and walks 20 feet without evidence of venous re-bleeding from the Study Access Site. | Per-subject analysis | Site reported in hours (hh): minutes (mm)

9.2 Secondary Efficacy Endpoints

The following will be descriptively reported and compared to a Clinical Acceptance Criterion (CAC) with no required hypothesis testing:

- Time to hemostasis (TTH), defined as elapsed time between Study Device removal and first observed and confirmed venous hemostasis, for the Study Access Site | Per access site analysis | Site reported in hours (hh): minutes (mm): seconds (ss).
- Time to discharge eligibility (TTDE), defined as elapsed time between Study Device removal and when subject is eligible for discharge based solely on the assessment of the Study Access Site. | Per-subject analysis | Site reported in hours (hh): minutes (mm)
- Total Post-Procedure Time (TPPT): defined as elapsed time between removal of the last procedural device/catheter for the index procedure in the Study Access Site and when subject is able to successfully ambulate based on the Study Access Site (Per-subject analysis) | Site reported in hours (hh): minutes (mm)

For the following, the outcomes will be descriptively reported with no required hypothesis testing:

- Device Success, defined as the ability to deploy the delivery system, deliver the collagen, and achieve final hemostasis with the Study Device. | Per access site analysis

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- Procedure Success, defined as attainment of final hemostasis at the Study Access Site and freedom from major access site closure-related complications at the Study Access Site through 30 days | Per-subject analysis
- Time to discharge (TTD), defined as elapsed time between Study Device removal, and when subject is discharged from the institution | Per-subject analysis | Site reported in hours (hh): minutes (mm)

9.3 Efficacy Endpoint Calculations

Table 5: Study-required Endpoint Calculations

<table>
<tr><th>Time Point</th><th>Reported Units</th><th>Procedure Step</th><th>TTH</th><th>TTA</th><th>TTDE</th><th>TTD</th><th>TPPT</th></tr>
<tr><td>P0</td><td>hh:mm</td><td>Index Procedure: First procedure sheath inserted</td><td rowspan="4"></td><td rowspan="4"></td><td rowspan="4"></td><td rowspan="4"></td><td></td></tr>
<tr><td>P1*</td><td>hh:mm</td><td>Index Procedure: Last procedural device/catheter removed for the index procedure in Study Access Site</td><td rowspan="4">P2-P1</td></tr>
<tr><td>-</td><td>-</td><td>Final Sheath Exchange, as applicable</td></tr>
<tr><td>-</td><td>-</td><td>Non-Study Access Site(s) hemostasis achieved and confirmed [may be prior to final sheath removal or exchange for Study Access Site, per Investigator's preferred workflow]</td></tr>
<tr><td>T1.1*</td><td rowspan="2">hh:mm:ss</td><td>Study Access Site (venous 16-17F OD) – Start hemostasis (Study Device removal)</td><td rowspan="2">T1.2-T1.1</td><td rowspan="3">P2-T1.1</td><td rowspan="4">P3-T1.1</td><td rowspan="5">P4-T1.1</td></tr>
<tr><td>T1.2*</td><td>Study Access Site (venous 16-17F OD) - Hemostasis achieved</td></tr>
<tr><td>P2*</td><td rowspan="3">hh:mm</td><td>Ambulation (Study Access Site)</td><td rowspan="3"></td></tr>
<tr><td>P3*</td><td>Discharge Eligibility (Study Access Site) - per attending medical team</td><td rowspan="2"></td></tr>
<tr><td>P4</td><td>Discharge</td><td></td></tr>
</table>

hh: hours; mm: minutes; ss: seconds
*Clock timer must be used
Endpoint Abbreviations:

- TTH: Time to Hemostasis
- TTA: Time to Ambulation (primary)
- TTDE: Time to Discharge Eligibility
- TTD: Time to Discharge
- TPPT: Total Post Procedure Time

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9.4 Primary Safety Endpoint

On a per Study Limb basis, the major access site closure-related complications, attributed directly to the investigational closure method (i.e., “device-related” with no other likely attributable cause) are:

- Access site-related bleeding requiring transfusion
- Vascular injury requiring repair (via surgery, transcatheter embolization, balloon angioplasty, or stent graft)
- Access site-related infection confirmed by culture and sensitivity, requiring intravenous antibiotics and/or extended hospitalization
- New onset permanent access site-related nerve injury in the ipsilateral lower extremity (i.e., persisting for 30 days)
- Pulmonary embolism requiring surgical or endovascular intervention and/or resulting in death, to be confirmed by CT pulmonary angiography, lung ventilation/perfusion scan (VQ scan) or autopsy
- Pulmonary embolism NOT requiring surgical or endovascular intervention and/or NOT resulting in death, to be confirmed by CT pulmonary angiography or lung ventilation/perfusion scan (VQ scan).

The VASCADE MVP XL Study Device’s limb incidence rate of combined major access site closure-related complications through the 30 +/- 7 day follow-up period will be compared to the primary safety performance goal (PG).

9.5 Secondary Safety Endpoint

On a per Study Limb basis, the minor access site closure-related complications, attributed directly to the investigational closure method (i.e., “device-related” with no other likely attributable cause) are:

- Access site-related bleeding requiring greater than 30 minutes of continuous manual compression to achieve initial venous hemostasis
- Access site-related hematoma $\geq$ 6 cm documented by ultrasound
- Late access site-related bleeding requiring non-surgical intervention (following hospital discharge)
- Ipsilateral deep vein thrombosis, confirmed by ultrasound/imaging
- Access site-related vessel laceration
- Localized access site infection confirmed by culture and sensitivity, treated with intramuscular or oral antibiotics
- Arteriovenous fistula not requiring treatment, documented by ultrasound/imaging

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- Pseudoaneurysm requiring treatment (thrombin injection, fibrin adhesive injection, or ultrasound-guided compression), documented by ultrasound
- Pseudoaneurysm not requiring treatment, documented by ultrasound
- New onset transient access site-related nerve injury in the ipsilateral lower extremity (i.e., persisting for < 30 days)

As a secondary safety endpoint, the VASCADE MVP XL Study Device's limb incidence rate of combined minor access-site closure-related complication through the 30 +/- 7 day follow-up period will be compared to the clinical acceptance criterion (CAC). This comparison will be descriptive with no required hypothesis testing.

10 Statistical Considerations

10.1 Analysis Populations and Data Handling Conventions

10.1.1 Safety Population

The Safety Population includes all enrolled subjects for whom the VASCADE MVP XL Study Device procedure has started (i.e., device insertion was at least attempted). All primary and secondary efficacy analyses and primary and secondary safety analyses will be performed on the Safety Population (i.e., Intent to Treat (ITT)).

10.1.2 Per Protocol Population

Primary endpoints will also be analyzed using the Per Protocol (PP) population. This is a subset of the safety population for subjects with no major protocol deviations (i.e. inclusion/exclusion violations and deviations related to capturing primary endpoint study assessments).

10.1.3 Missing Data

All efforts will be made to eliminate missing data for the primary efficacy endpoint of TTA and primary safety endpoint of major access site closure-related complications. Reference SAP for details on the impact of missing data.

10.1.4 Adjudication Data (Safety Endpoints)

Safety endpoints will be analyzed based on the adjudicated results. Both as reported and adjudicated results will be summarized.

10.2 Statistical Analysis Plan

A summary of the Statistical Analysis Plan (SAP) is provided below. See the SAP, [redacted] for full details.

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10.2.1 Roll-In Subjects

Results for roll-in subjects will be summarized separately and excluded from formal analysis. A summary of results for baseline characteristics, efficacy endpoints, and safety endpoints will be required.

10.2.2 Pivotal Subjects

10.2.2.1 Baseline Subject Characteristics

Subject demographics, baseline characteristics and medical history will be summarized descriptively.

10.2.2.2 Safety

Primary and secondary safety endpoints are based on a Performance Goal (PG) and a Clinical Acceptance Criterion (CAC), respectively. The current study's PG and CAC are summarized in the table below.

Table 6. Safety Endpoint PG and CAC

Type	Endpoint	Level	AMBULATE Trial (RPT 0508)		AMBULATE EXPAND Trial (Current)		
			VCD %	MC %	Performance Goal (PG)	Clinical Acceptance Criterion (CAC)	Goal
Primary	**Major Access Site Related Complications**	Limb	0.0%	0.0%	10%	-	Assess whether the Study Device meets the PG by being less than the PG (i.e., 10%).
Secondary	**Minor Access Site Related Complications**	Limb	1.0%	2.4%	-	3.0%	Assess whether the Study Device is similar to (or better than) the AMBULATE MC arm (i.e., CAC of 3.0%).
VCD = Vascular Closure Device | MC = Manual Compression							

Primary Safety Endpoint with PG

The primary safety endpoint for the AMBULATE EXPAND study is the Study Limb status for developing major access-site closure-related complications within 30 days post procedure. The PG for the primary endpoint is set to 10% for the VASCADE MVP XL Study Device.

To be acceptable, the major complication subject incidence observed in the study needs to be ≤ 2/70 = 2.9%.

Secondary Safety Endpoint with CAC

The secondary safety endpoint for the VASCADE MVP XL Study Device is the Study Limb's status for developing minor access-site closure-related complications within 30 days post procedure.

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The CAC for 30-day minor complication limb incidence rate is set at 3.0% for the VASCADE MVP XL Study Device. The study's observed minor complication limb incidence rate will be descriptively presented without hypothesis testing.

See SAP for additional details on the primary and secondary safety endpoint analyses.

Additional Adverse Events

All other reported adverse events will be descriptively summarized.

Reference Section 9 for endpoint definitions.

10.2.2.3 Efficacy

The primary efficacy endpoint is based on a Performance Goal (PG). The secondary efficacy endpoints are based on Clinical Acceptance Criteria (CAC). The current study's PG and CACs for efficacy are summarized in the table below.

Table 7. Efficacy Endpoint PGs and CACs

Type	Endpoint	Level	AMBULATE Trial (RPT 0508), VASCADE MVP Subjects		AMBULATE Expand Trial (Current)		
			VCD Mean (SD)	MC Mean (SD)	Performance Goal (PG)	Clinical Acceptance Criterion (CAC)	Goal
Primary	**Time to Ambulation (TTA) (hrs)**	Subject	2.8 (1.3)	6.1 (1.6)	6.1 hrs	-	Assess whether the Study Device meets the PG by being less than the PG (i.e., 6.1).
Secondary	**Time to Hemostasis (TTH) (mins)**	Access Site	6.1 (3.7)	13.7 (6.5)	-	9.8 min	Assess whether the Study Device is similar to (or better than) the AMBULATE VCD arm (i.e., mean + 1 SD).
Secondary	**Total Post-Procedure Time (TPPT) (hrs)**	Subject	3.1 (1.3)	6.8 (1.7)	-	4.4 hrs	
Secondary	**Time to Discharge Eligibility (TTDE) (hrs)**	Subject	3.1 (1.3)	6.5 (1.9)	-	4.4 hrs	
VCD = Vascular Closure Device | MC = Manual Compression							

Primary Efficacy Endpoint with PG

The primary efficacy endpoint for the AMBULATE EXPAND study is the time to ambulation. The PG for the primary endpoint is set to 6.1 hours for the VASCADE MVP XL Study Device.

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Using the AMBULATE MC mean of 6.1 hours the PG for the primary efficacy endpoint and assuming the true mean performance to be 2.8 hours (SD=1.3) based on the VCD arm of the AMBULATE trial, with N=70 in the current study (reference Section 10.3 regarding sample size), the power to demonstrate the Study Device meets the PG of 6.1 hours (i.e., with statistically significantly shorter time duration at a 1-sided $p < 0.025$ level) is >0.99 by a one sample t test.

Secondary Efficacy Endpoints with CAC

The secondary efficacy endpoints for the VASCADE MVP XL Study Device are performance for TTH, TPPT, and TTDE. The CACs for TTH, TPPT, and TTDE are 9.8 minutes, 4.4 hours, and 4.4 hours respectively for the VASCADE MVP XL Study Device. The results for the secondary endpoints will be compared to CACs and descriptively presented.

See SAP for additional details on the primary and secondary efficacy endpoint analyses.

Secondary Endpoints without CAC

Other outcomes will be descriptively reported with no required hypothesis testing or CAC (Procedure Success, Device Success, Time to Discharge (TTD)).

Reference Section 9 for endpoint definitions.

See SAP for details on the impact of missing data, assessment of site poolability, and subgroup analyses.

10.3 Sample Size

10.3.1 Justification

The study's power and sample size is provided by subject (as each subject will have only one Study Limb/Access Site involved and therefore one result for the primary safety endpoint as well as the primary efficacy endpoint).

With the sample size of 70, the power to demonstrate the Study Device meets the primary efficacy endpoint is acceptable by a one sample t test. For both the primary safety endpoint and primary efficacy endpoint, the sample size of 70 has an acceptable power > 0.80. Therefore, 70 is selected as the evaluable sample size.

See SAP for additional details on the sample size justification.

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10.3.2 Study Enrollment

As a minimum of 70 evaluable subjects are required, the study is expected to enroll up to 77 pivotal subjects to account for potential attritions of 10%. This does not include roll-ins. Up to 48 roll-in subjects may be enrolled.

11 Additional Planned Analyses

Additional planned analyses for VASCADE MVP XL Study Device include the following:

- Major and minor access site closure-related complications: per-event summary
- All other access site closure-related complications summary

As commercial device data (for Non-Study Access Sites) will be collected, for completeness, these commercial data will be summarized descriptively:

- Adverse event summary (by limb and by event)

Additional analyses may be conducted as desired. For example, additional analyses may be conducted such as:

- Same day discharge (SDD) next day Device Success, defined as subjects who were able to be sent home the same day and did not require next day hospital intervention due to Study Access Site closure-related complications

12 Data Management – Data Collection and Processing

Standardized eCRFs will be provided and required for use by all participating sites, refer to the Manual of Operations for specifications, instructions, and Source Worksheet information (see Section 13.1). Investigators are responsible for the accurate completion and timely submission of the data collected during the trial. All data from the trial will be entered into eCRFs via a secure, web-based system with password protection. Incoming data will be automatically reviewed to identify inconsistent or missing data and any adverse events. Any data issues are to be promptly addressed with the Investigator by the Sponsor. Quality assurance procedures will be established to ensure that complete, accurate and timely data are submitted, that protocol requirements are followed and that complications, adverse events and adverse device effects are correctly reported and investigated, as appropriate.

Study Exit will be documented for all enrolled subjects, regardless of whether they completed all study requirements (e.g., subject discontinuation, trial termination).

The database will be locked prior to the final analysis and records will be maintained as required per regulatory and contractual agreements (reference Section 20.3).

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13 Monitoring Procedures

13.1 Monitoring

Monitoring activities of clinical sites will be conducted periodically during the study, to ensure that all aspects of the current, approved protocol/amendment(s) are followed. Medical records and source documents will be reviewed for verification of data in the electronic database. The Investigator/institution guarantees direct access to original source documents by the Sponsor personnel, their designees, and appropriate regulatory authorities. In the event that the original medical records cannot be obtained for a patient that is seen by a non-study physician at a non-study institution, certified photocopies of the original source documents must be made available for review.

Mandatory source worksheets (SWS) will be provided by the Sponsor to be completed during the procedure to collect study-specific data that are not captured in standard medical records. All data should be entered completely, promptly and legibly with required signatures/initials/dates completed using Good Documentation Practices. Corrections should be made in a manner that does not obscure or eliminate the original error, by striking through the original data with one line, and initialing and dating the change.

Clinical monitoring will include a verification that Informed Consent was properly obtained and documented for all consented trial participants, a review of medical and study records for accuracy and completeness, resolution of missing or inconsistent results, and a review of source documents. The Monitor will verify that the Case Report Forms (eCRFs) are in agreement with the source documentation and other records. The Investigator will make available to the clinical Monitor for review all Informed Consent documents, Internet access to completed eCRFs, source documentation, original laboratory data, and other relevant records for all enrolled subjects at the site. It is important that relevant site personnel are available for consultation with the Monitors during the monitoring activities and that sufficient time is devoted at the site to the monitoring process.

Investigational device inventory and associated shipping/return records will be reconciled periodically during monitoring activities. Any discrepancies will be reviewed and reconciled with the Investigator.

Additionally, telephone and/or e-mail contact will be conducted on a regular basis with the Investigator and the site staff to ensure that the protocol is being followed and to address any issues that may occur during the course of the study. Remote monitoring and data cleaning may be performed between on-site activities.

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If a deficiency is noted during a monitoring activity (or at any other time during the course of the trial), the Monitor is required to communicate the situation with the Investigator and the Sponsor (if required) to secure compliance.

Investigators will be made aware of the results of monitoring activities in the form of follow-up correspondence and may be required to provide follow-up contact with the Monitors for issue clarification or resolution, if applicable. Risk-based monitoring may be utilized. The Monitoring Plan will include a combination of monitoring activities to oversee the study effectively.

The Sponsor or designee is responsible for the monitoring of the study. The site will be monitored by personnel qualified by training and experience to monitor the investigation. Names and addresses of individual study monitors will be documented in study documentation.

Any Investigator Site Files being stored electronically must be 21 CFR Part 11 compliant, otherwise the site will be asked to print/file all study file contents for Monitor's review and archiving. Study binders will be provided by the Sponsor. If Part 11 compliant and stored electronically, the Monitor will be provided direct access to inspect and reconcile the file contents during routine monitoring activities.

Refer to the Manual of Operations for a complete set of eCRFs and Source Worksheets and instructions on completion requirements.

13.2 Commercial Device Distribution and Accountability (VASCADE Family Commercial Devices)

13.2.1 Commercial Device Distribution

Each site will be responsible for ordering VASCADE Family commercial product to be used in the Study. The Investigator is responsible for ensuring that the devices are available at the site before the procedure date.

13.2.2 Commercial Device Accountability

Device information will be collected in the eCRF (e.g., lot#). Since the devices are commercially distributed, there are no device accountability requirements, however labels or other source data confirming the device information (e.g., lot #) should be kept with the subject's records for monitoring purposes.

13.3 Investigational Device Distribution and Accountability

13.3.1 Investigational Device Distribution VASCADE MVP XL Study Device

The Sponsor will provide and control the distribution of the investigational devices (VASCADE MVP XL Study Device (Model 800-1014XL), labeled for Investigational Use Only. One investigational device per subject is required (see Section 8.4) and an additional investigational

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device may be needed in specific cases (e.g. failing device pre-check, see Section 8.4). Device management instructions are provided in the Manual of Operations. The Investigator is responsible for ensuring that devices are requested for shipment in a time frame that enables the devices to arrive at the hospital before the procedure date.

13.3.2 Investigational Device Accountability

The Investigator shall maintain adequate records of the receipt and disposition of all investigational devices. The Investigator is responsible for ensuring that the investigational devices are used only under the Investigator's supervision by authorized users and are only used according to this protocol and any approved amendments. The Investigator will not supply an investigational device to any person not authorized to participate in the trial. The Investigator shall document in the operative notes and eCRF's the lot number of the devices used during a case. In addition, the Investigator shall keep complete and accurate records of all devices used or unused that have been returned to the Sponsor in a Device Accountability Log provided by the Sponsor.

13.3.3 Return of Materials Upon Study Termination

After the cases are completed, all unused investigational devices must be accounted for and shipped back to the Sponsor. Instructions for device return to the Sponsor will be reviewed at the site initiation visit and covered in the Manual of Operations.

NOTE: For any suspected malfunction of an investigational device, retain the device in a Biohazard bag and refer to the Manual of Operations for instructions on return requirements. Failure to retain/return these devices will be documented as a Protocol Deviation.

IMPORTANT: Please note that the devices must be labeled, packaged, and shipped according to the Manual of Operations for Device Return Instructions.

14 Quality Control and Quality Assurance

14.1 Site Training

To ensure accurate, complete, and reliable data, the Sponsor or its representatives will provide instructional material to the trial sites, as appropriate, and will:

- Instruct the Investigators and trial personnel on the protocol, consenting requirements, the completion of the eCRFs, Source Worksheets and other study documentation requirements, device use and accountability, device performance reporting and return, and trial procedures;
- Communicate regularly with site personnel via email or telephone;
- Conduct periodic monitoring activities of the trial sites (remote and/or on-site);
- Conduct periodic remote data cleaning and correspondence.

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14.2 Investigator, Co-Investigator & Operator Training

An Investigator is defined as the person responsible for the conduct of the clinical investigation at an investigational site. The Investigator is the responsible leader of the team and may be called the Principal Investigator. *"Enrolling Investigator" refers to any Investigator or Co-Investigator who enrolled a subject, who may then supervise an approved Operator to deploy the device (if applicable), make study assessments, and sign Source Worksheets related to that subject during the study.* For the purposes of this protocol, the term "Investigator" may be used interchangeably with "Enrolling Investigator".

A Co-Investigator is defined as an individual member of the clinical investigation team designated and supervised by the Investigator at an investigational site who performs critical investigation-related procedures and/or makes important investigation-related observations, including enrollment of subjects and deployment of the study device.

An Operator is defined as an individual member of the clinical investigation team who is qualified by training and experience (i.e., non-Investigator MD, certified vascular tech, etc.), and who is designated to deploy the study device in a study subject under the direction of, and the direct supervision of an Enrolling Investigator, but does not have authority to make decisions about enrollment. All participating sites are required to have VASCADE Family experience.

Prior to enrolling any subjects in the study, Investigators, Co-Investigators and Operators will be provided didactic training with a benchtop model to simulate the closure procedure with the VASCADE MVP XL Study Device, as needed. This training will be provided by a Sponsor-designated proctor. Roll-in cases will be performed after benchtop training, under the supervision of the Sponsor-designated proctor as follows:

- The first case enrolled at each site must be a roll-in case, and it is recommended that the deployer is an Investigator (practice study flow/requirements, data collection);
- Depending on the trainee's experience and comfort level with VASCADE Family devices and the VASCADE MVP XL (800-1012XL) commercial device, the Sponsor/proctor shall have the discretion to either approve or require additional training for each individual until all pre-specified training requirements have been met;
- A maximum of 2 roll-ins per Enrolling Investigator and per Operator.

An Investigator/Co-Investigator and Operator Training Record will be initiated by the Sponsor proctor to assess and ensure all skills and knowledge levels are satisfactory prior to written approvals by the Sponsor, as applicable.

Investigators and Co-Investigators will be notified in writing (i.e., "activated") when they have successfully completed the didactic and roll-in requirements (as applicable) and are eligible to

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enroll pivotal subjects into the trial, and to deploy the study device without a Sponsor proctor. The Principal Investigator will be notified in writing when an Operator has successfully completed or is not required to complete the roll-in requirements (i.e., “activated”) and is eligible to deploy the study device under the direct supervision of an active Investigator/Co-Investigator in a consented, qualifying study patient without a Sponsor proctor. An Operator will not have authority to make any decisions about enrollment, but only to deploy the device as directed; the Enrolling Investigator will oversee and make all study-related decisions and assessments for these subjects.

The roll-in subjects will be followed in the same fashion as the pivotal subjects but will be evaluated as a separate subject group.

14.3 Audits and Inspections

The Principal Investigator for the site will also allow representatives of the Sponsor and their designees, governing IRB, the United States Food and Drug Administration (FDA), and other applicable regulatory agencies (e.g., international regulatory authorities, Notified Bodies, etc.) to inspect all trial records, eCRFs, and corresponding portions of the subject’s office and/or hospital medical records at regular intervals throughout or after the study. These inspections are for the purpose of verifying adherence to the protocol, completeness and exactness of the data being transcribed to the eCRF, and compliance with FDA or other regulatory agency regulations.

The Principal Investigator for the site will inform the Sponsor or the Sponsor’s designee in advance if they are to be audited or inspected by any regulatory agencies. The Sponsor or the Sponsor’s designee will also inform the site if they are made aware of a pending audit or inspection by a regulatory agency.

15 Adverse Events (AEs)

15.1 General

Adverse events (AE) and serious adverse events (SAE) will be monitored from the time of enrollment through the 30 (± 7) day follow-up visit.

The Investigator should follow all unresolved serious adverse events until the events are resolved, the subject is lost to follow-up, the subject has withdrawn consent, or the adverse event is otherwise explained.

15.2 Adverse Event Definitions

Adverse Event (AE): Any untoward medical occurrence in a clinical investigation subject administered an investigational device and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign

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(including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigation product, whether or not related to the investigational product [ICH GCP].

The study definition of AE applies to any event with an onset post study procedure or to any underlying diseases present at baseline, that exacerbate in severity post study procedure. Therefore, an underlying disease that was present at the time of enrollment is not reported as an AE, but any increase in the severity of the underlying disease may be reported as an AE. This definition includes events occurring during the follow-up period.

Serious Adverse Event (SAE) [ICH GCP]: an untoward medical occurrence which:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

Unanticipated Adverse Device Effect (UADE) [21 CRF 812.3(s)]**:** 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 CRF 812.3(s)]. All UADE's shall be reported to Sponsor within 24 hours after the Investigator first learns of the event.

15.3 Adverse Event Relatedness Assessments

All reported AE's and SAE's will be assessed by the Investigator for "relatedness" to the closure device used, the procedure, and potential concomitant adverse events, conditions, interventions and/or medications using the following guidelines for assessment[1]:

Relatedness	Description
Not Related:	Relationship to the device can be excluded when: • The event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device • The serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible • The discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the adverse event • The event involves a body-site or an organ that cannot be affected by the device or procedure

[1] MDCG 2020-10/1 Rev 1 Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745 . (2022, October).

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Relatedness	Description
	• The serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors) • The event does not depend on a false result given by the investigational device used for diagnosis, when applicable In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the adverse event.
Possible Relation:	The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
Probable Relation:	The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.
Causal Relation:	The serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when: • The event is a known side effect of the product category the device belongs to or of similar devices and procedures • The event has a temporal relationship with investigational device use/application or procedures • The event involves a body-site or organ that ▪ the investigational device or procedures are applied to ▪ the investigational device or procedures have an effect on • The serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known) • The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the adverse event (when clinically feasible) • Other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out • Harm to the subject is due to error in use • The event depends on a false result given by the investigational device used for diagnosis, when applicable In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the adverse event

NOTE: *An Adverse Event Source Worksheet will need to be completed and signed by the Enrolling Investigator to document concurrence with data on the AE CRF.*

15.4 Adverse Event Severity Definitions

The following definitions for rating severity of adverse events will be used:

Mild:	Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs or symptoms are transient.
Moderate:	Interferes with the subject's usual activity and/or requires symptomatic treatment.
Severe:	Symptom(s) causing severe discomfort and significant impact of the subject's usual activity and requires treatment.

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15.5 Non-Events

For purposes of this study, the following events are not considered adverse events, because they are normally expected to occur in conjunction with catheter-based procedures / post-procedure, or are associated with customary, standard care of subjects undergoing these procedures:

- Early post-operative pain (within 24 hours post-index procedure) at the access site and/or related to position on procedure table
- Post-anesthesia/conscious sedation emesis, nausea, or headache (within 24 hours post-index procedure)
- Chest pain without associated ECG changes
- Hematocrit decrease from baseline not associated with hemodynamic changes, remaining above 30% and not requiring transfusion
- Electrolyte imbalance without clinical sequelae following endovascular procedure, even if requiring correction
- Low grade temperature increase ($\leq$38.3°C/$\leq$101°F)
- Sinus bradycardia/tachycardia that does not require treatment or intervention
- Systolic or diastolic blood pressure changes that do not require treatment or intervention
- Any pre-planned surgical procedures

This listing of events is intended to provide guidance to the investigational sites for purposes of adverse event reporting. The Investigator at the investigational site should utilize his/her own clinical judgment in evaluating adverse experiences for severity and clinical relevance and may decide that the above events should be reported as adverse events.

15.6 AE Reporting Requirements for the Trial

15.6.1 Reporting Requirements (Serious & Non-Serious Adverse Events)

A. Reportable Events (to Sponsor/CRFs)

All serious adverse events and all potentially device- and/or access site and/or procedure-related adverse events (e.g., “study-reportable events” for this study) must be recorded on the Adverse Event eCRF by the Investigator (or designee). The report should include: a description of the event, including start date, severity, duration, action taken, resolution date, treatment outcome, and the Investigator’s assessment of the relationship between the AE and the study/commercial device, procedure, concomitant medications, pre-existing condition, etc. AEs with an outcome of “ongoing” should be assessed at the follow-up evaluation to determine if the event has resolved. AEs ongoing at study completion/discontinuation should be left as “ongoing” on the AE CRF.

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See Section 15.6.2 for additional detail on AE reporting for Investigational vs Commercial devices.

All serious adverse events (including UADEs) must be reported by the Investigator (or designee) to the Sponsor within 24 hours of learning of the adverse event via eCRF. All other AEs should be entered in the AE eCRF as soon as practical after knowledge of the event.

In the case of reported safety endpoint adverse events or other events required for adjudication, medical record documentation (e.g., procedure notes, operative notes, discharge summary, relevant progress notes, imaging or lab studies) must be provided at Sponsor or its designee's request for adjudication of events.

B. Reportable Events (to IRB) – SAEs (including UADEs)

The following criteria must also be adhered to by the Investigator in the case of serious adverse events:

- It is the responsibility of the Investigator to inform their IRB of serious adverse events as required by their IRB's procedures and in conformance with FDA and local regulatory requirements.

C. Reportable Events (to Regulatory Authorities) - UADEs

The Sponsor or its designee, in cooperation with the Investigator, will assess all adverse events considered to be device-related for potential reportability to the FDA, IRBs and other regulatory authorities for UADEs. UADEs must be reported to FDA within 10 working days of Investigator's knowledge of the event [21 CRF 812.3(s)]. Sponsor requires the Investigator to report UADEs within 24 hours of knowledge of the event.

15.6.2 Reporting AE's related to Investigational vs. Commercial Device

Refer to the Manual of Operations for details on how to report specific events. Device-related AEs will be coded specifically to which device was used, if known. Refer to the AE Code List. AEs that cannot be attributable to either device (i.e., unable to determine due to multiple access sites in the case of a Protocol Deviation) will be reported the same way as an investigational device event as a conservative approach. Adverse events should be reported based on the information in Table 8.

Table 8: Reporting AEs - Investigational vs. Commercial Device

	AE Related To:	
Attribute	**VASCADE MVP XL Study Device (investigational device) / Study Access Site**	**VASCADE Family Commercial Device / Non-Study Access Site**
AE Code List	All VASCADE MVP XL Study Device device-related events will be coded with a "V", e.g., "V20" is for "Access site venous re-bleeding after initial hemostasis" in an access site that was closed with the VASCADE MVP XL Study Device.	Commercial device-related events will be coded with a "C", e.g., "C20" is for "Access site venous re-bleeding after initial hemostasis" in an access site that was closed with the commercial device.

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	AE Related To:	
Attribute	**VASCADE MVP XL Study Device (investigational device) / Study Access Site**	**VASCADE Family Commercial Device / Non-Study Access Site**
Adjudication	AE's that meet the major and minor access site closure-related endpoint definitions will be adjudicated by the DSMC. The DSMC will also adjudicate other AEs as necessary.	Not required
SAE Assessment	Assess seriousness using the ICH GCP reporting guidelines.	Assess seriousness using the ICH GCP reporting guidelines.
Applicable FDA Reporting Regulation (Investigational) (21 CFR 812) - Sponsor	Reported to FDA according to 21 CFR 812 Investigational Device Exemptions [including potential Unanticipated Adverse Device Effects (UADE) [1]]	Reported to FDA according to 21 CFR 812 Investigational Device Exemptions per protocol and required regulations
Applicable FDA Reporting Regulation (Commercial) (21 CFR 803) - Sponsor	The adverse event will be reviewed for input to the Sponsor's Complaint process and reported via the commercial regulations, as applicable.	The adverse event will be reviewed for input to the Sponsor's Complaint process and reported via the commercial regulations, as applicable.

15.6.3 Bleeding Events

Specifically for access site-related bleeding adverse events, the Access Site Bleeding Evaluation (ASBE) Source Work Sheet (SWS) and eCRF must be completed for both Study Access Sites and Non-Study Access Sites. Initial event data are collected to guide the site towards proper adverse event coding on the Adverse Event eCRF.

The most severe AE code should be used. For example, if access site bleeding requires a transfusion, then the AE Code would be escalated to "V01: Access site-related bleeding requiring transfusion", instead of "V20: Access site re-bleeding after initial hemostasis confirmed".

Alternately, if an event is determined to be mild in severity and not clinically significant (NCS) in the Investigator's opinion, the AE Code may be downgraded, or not reported at all.

15.7 Device Failures and Malfunctions

All suspected device malfunctions and device failures of the VASCADE MVP XL Study Device are required to be documented in the Device Observations eCRF. If a device was opened and either a) not inserted for any reason, or b) resulted in a failed closure/device failure or other suspected observation, the eCRF must be completed within 24 hours of observation and devices logged in on the Device Accountability Log.

In the event of a suspected observation or device problem, the investigational device shall be returned to the Sponsor for analysis. The Sponsor will assess for input to the Sponsor's Complaint process (i.e., for shared Product Family attributes for the Investigational device,

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device failures and malfunctions for commercial product). Instructions for returning the device are included in the Manual of Operations.

NOTE: Device failures or malfunctions are NOT to be reported as adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded in the usual way.

16 Data Safety Monitoring Committee (DSMC)

An independent combination Clinical Events Committee and Data Safety Monitoring Board, referred to as the Data Safety Monitoring Committee, or DSMC, shall be responsible for systematic review and adjudication of all site-reported deaths and major and minor access site-closure-related safety endpoint complications. All events meeting the definition of major and minor access site-closure related complications and adjudicated to be at least “moderate” in severity and clinically significant will be included in the safety endpoint analyses. All other adverse events reported to be at least possibly device- or procedure-related by the Investigator will be reviewed by an independent Safety Manager and/or a member of the DSMC to determine whether they meet criteria for adjudication. To enhance objectivity and reduce the potential for bias, the DSMC members shall be independent of the Sponsor as well as the investigational sites/ Investigators.

Members shall consist of at least three (3) independent physicians with experience in catheter-based procedures.

The methodology for performing these responsibilities shall be developed and outlined in the DSMC Adjudication Charter. Operational provisions shall be established to minimize potential bias.

The DSMC may recommend study termination if safety concerns warrant such action. The DSMC will establish guideline criteria for recommending study termination, including safety performance goal thresholds. The Safety Manager will maintain contact with the DSMC members to schedule event reviews to assure close and timely monitoring of potential safety endpoint adverse events and outcomes.

An Adjudication eCRF will be completed for each adjudicated event.

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17 Abbreviations and Definitions

17.1 Abbreviations

Abbreviation	Definition
ANCOVA	Analysis of Covariance
ASBE	Access Site Bleeding Evaluation
ACT	Activated Clotting Time
AE	Adverse Event
AF	Atrial Fibrillation
AV	Arteriovenous
BMI	Body Mass Index
BP	Blood Pressure
CAC	Clinical Acceptance Criterion
CAP	Continued Access Protocol
CI	Confidence Interval
CRO	Clinical Research Organization
CFR	Code of Federal Regulations
eCRF	Electronic Case Report Form
CT	Computed Tomography
CV	Curriculum Vitae
D/C	Discharge
DSMC	Data Safety Monitoring Committee
DUS	Duplex Ultrasound
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
EDC	Electronic Data Capture (database)
FAS	Failed Access Site
FDA	Food and Drug Administration
F	French
F/U	Follow-Up
GCP	Good Clinical Practice
GDP	Good Documentation Practice
GLP	Good Laboratory Practice
Hgb	Hemoglobin
Hct	Hematocrit
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
ICF	Informed Consent Form
ID	Inner Diameter
IDE	Investigational Device Exemption
I/E	Inclusion/Exclusion
IFU	Instructions for Use
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent to Treat
LAAC	Left Atrial Appendage Closure
LAR	Legally Authorized Representative
LMWH	Low molecular weight heparin
MC	Manual Compression
MDR	Medical Device Report (per 21 CFR 803, commercial)

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Abbreviation	Definition
MOP	Manual of Operations
OD	Outer Diameter
PAC	Premature Atrial Contraction
PD	Protocol Deviation
PE	Pulmonary Embolism
PFA	Pulse Field Ablation
PG	Performance Goal
PHI	Protected Health Information
PI	Principal Investigator
PMA	Premarket Approval
PP	Per Protocol
RC	Research Coordinator
RF	Radiofrequency
RGA	Return Goods Authorization
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDD	Same Day-Discharge
SF	Screen Failure
SMC	Suture Mediated Closure
SOC	Standard of Care
ST	Supraventricular Tachycardia
SWS	Source Worksheet
TPPT	Total Post-Procedure Time
TTA	Time to Ambulation
TTCE	Time to Closure Eligibility
TTH	Time to Hemostasis
TTDE	Time to Discharge Eligibility
TTD	Time to Discharge
UADE	Unanticipated Adverse Device Effect
VCD	Vascular Closure Device
VQ	Ventilation/Perfusion
VT	Ventricular Tachycardia
VVCS	Venous Vascular Closure System

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17.2 Definitions - Refer to AE Code List

SAFETY ENDPOINT DEFINITIONS

ACCESS SITE CLOSURE-RELATED COMPLICATIONS, ATTRIBUTED DIRECTLY TO THE CLOSURE METHOD PERIOD (I.E., "DEVICE-RELATED" WITH NO OTHER LIKELY ATTRIBUTABLE CAUSE):

- **MAJOR COMPLICATIONS:**
  - **ACCESS SITE-RELATED BLEEDING REQUIRING TRANSFUSION**
    Bleeding originating from the venous access site(s), which has occurred to the degree that transfusion of blood products is necessary to maintain hemodynamic stability.
  - **VASCULAR INJURY REQUIRING REPAIR (VIA SURGERY, TRANSCATHETER EMBOLIZATION, BALLOON ANGIOPLASTY, OR STENT GRAFT)**
    Access site closure-related injury to the venous wall or adjunct arterial vessel wall resulting in persistent bleeding and requiring surgical repair, transcatheter embolization, balloon angioplasty, or stent graft.
  - **ACCESS SITE-RELATED INFECTION CONFIRMED BY CULTURE AND SENSITIVITY, REQUIRING INTRAVENOUS ANTIBIOTICS AND/OR EXTENDED HOSPITALIZATION**
    Must meet at least one of the following criteria related to the access site(s): 1) positive wound culture requiring treatment with intravenous antibiotics; and/or 2) extended hospital discharge time directly related to complications of access site infection. Does not include administration of prophylactic antibiotic regimens.
  - **NEW ONSET PERMANENT ACCESS SITE-RELATED NERVE INJURY IN THE IPSILATERAL LOWER EXTREMITY**
    New onset access site closure-related nerve injury that persists for 30 days and is deemed to be clinically significant by the Investigator and is of at least "moderate" severity.
  - **PULMONARY EMBOLISM REQUIRING SURGICAL OR ENDOVASCULAR ITNERVENTION AND/OR RESULTING IN DEATH, TO BE CONFIRMED BY CT PULMONARY ANGIOGRAPHY, LUNG VENTILATION/PERFUSION SCAN (VQ SCAN) OR AUTOPSY**
    A blockage of an artery in the lungs by a substance that has traveled from elsewhere in the body through the bloodstream (i.e., embolism) that requires surgical or endovascular intervention and/or results in death, to be confirmed by CT pulmonary angiography, lung ventilation/perfusion scan (VQ scan) or autopsy.
  - **PULMONARY EMBOLISM NOT REQUIRING SURGICAL OR ENDOVASCULAR ITNERVENTION AND/OR NOT RESULTING IN DEATH, TO BE CONFIRMED BY CT**

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PULMONARY ANGIOGRAPHY, LUNG VENTILATION/PERFUSION SCAN (VQ SCAN) OR AUTOPSY

A blockage of an artery in the lungs by a substance that has traveled from elsewhere in the body through the bloodstream (i.e., embolism) that does not require surgical or endovascular intervention and/or does not result in death, to be confirmed by CT pulmonary angiography, lung ventilation/perfusion scan (VQ scan) or autopsy.

- **MINOR COMPLICATIONS:**
  - **ACCESS SITE-RELATED BLEEDING REQUIRING > 30 MINUTES OF CONTINUOUS MANUAL COMPRESSION TO ACHIEVE INITIAL VENOUS HEMOSTASIS**
    Bleeding from the venous access site(s) requiring greater than 30 continuous minutes of manual compression to achieve initial venous hemostasis at a single access site.
  - **ACCESS SITE-RELATED HEMATOMA ≥ 6 CM DOCUMENTED BY ULTRASOUND**
    A localized collection of extravasated blood in subcutaneous tissue at the access site measuring ≥ 6 cm at its widest point by ultrasound.
  - **LATE ACCESS SITE-RELATED BLEEDING REQUIRING NON-SURGICAL INTERVENTION (following hospital discharge)**
    Active re-bleeding from the venous access site(s) following hospital discharge, requiring non-surgical intervention, e.g. manual compression. See definition for "Oozing From the Access Site" and "Re-bleeding at Access Site" definitions to differentiate between venous and tissue tract bleeding.
  - **IPSILATERAL DEEP VEIN THROMBOSIS, CONFIRMED BY ULTRASOUND/IMAGING**
    Presence of a thrombus in the peripheral venous system of the ipsilateral limb. May be a complication of phlebitis or may result from injury to a vein or from prolonged bedrest. Symptoms include a feeling of heaviness, pain, warmth, or swelling in the affected part.
  - **ACCESS-SITE RELATED VESSEL LACERATION**
    An injury to the venous or arterial wall in which the tissue is torn or cut.
  - **LOCALIZED ACCESS SITE INFECTION CONFIRMED BY CULTURE AND SENSITIVITY, TREATED WITH INTRAMUSCULAR OR ORAL ANTIBIOTICS**
    Must meet BOTH of the following criteria related to the venous access site(s): 1) positive wound culture requiring treatment with intramuscular or oral antibiotics; and 2) no prolongation of hospital discharge time directly related to

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complications of access site infection. Does not include administration of prophylactic antibiotic regimens.

- **ARTERIOVENOUS (AV) FISTULA NOT REQUIRING TREATMENT, DOCUMENTED BY ULTRASOUND/IMAGING**
  A connection between the access vein and the adjacent artery that is demonstrated by arteriography or ultrasound, most often characterized by a continuous bruit that is mild to moderate in nature and does not require an intervention in the opinion of the Investigator. Note: An AV Fistula that is severe in nature and requires an interventional procedure (i.e., surgery) to mitigate further injury would fall under *Vascular Injury Requiring Repair (via Surgery)*.
- **PSEUDOANEURYSM REQUIRING TREATMENT, DOCUMENTED BY ULTRASOUND**
  A blood vessel abnormality resembling an aneurysm (localized abnormal dilatation of a blood vessel) but consisting of a collection of blood with persistent flow outside an artery, contained by surrounding tissue and due to a leaking hole through all layers of the arterial wall. The leaking hole is due to injury of (e.g., rupture of or trauma to) the arterial wall. The pseudoaneurysm is usually identified by angiography or ultrasound, and requires treatment (e.g., thrombin injection or fibrin adhesive injection).
- **PSEUDOANEURYSM NOT REQUIRING TREATMENT, DOCUMENTED BY ULTRASOUND**
  A blood vessel abnormality resembling an aneurysm (localized abnormal dilatation of a blood vessel) but consisting of a collection of blood with persistent flow outside an artery, contained by surrounding tissue and due to a leaking hole through all layers of the arterial wall. The leaking hole is due to injury of (e.g., rupture of or trauma to) the arterial wall. This pseudoaneurysm is usually identified by angiography or ultrasound, and does not require treatment.
- **NEW ONSET TRANSIENT ACCESS SITE-RELATED NERVE INJURY IN THE IPSILATERAL LOWER EXTREMITY**
  New onset access site closure-related nerve injury that persists for < 30 days and is deemed to be clinically significant by the Investigator and is of at least "moderate" severity.

ADVERSE EVENT (AE)

Any untoward medical occurrence in a clinical investigation subject administered an investigational device and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigation product, whether or not related to the investigational product [ICH GCP].

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The study definition of AE applies to any event with an onset post study procedure or to any underlying diseases present at baseline, that exacerbate in severity post study procedure. Therefore, an underlying disease that was present at the time of enrollment is not reported as an AE, but any increase in the severity of the underlying disease may be reported as an AE. This definition includes events occurring during the follow-up period.

ALLERGIC RESPONSE

A state of abnormal and individual hypersensitivity acquired through exposure to a particular allergen.

APPROVAL (IN RELATION TO INSTITUTIONAL REVIEW BOARDS (IRBs))

The affirmative decision of the IRB that the clinical investigation has been reviewed and may be conducted at the institutional site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

BRUISING AT PUNCTURE SITE

Subcutaneous escape of blood.

CO-INVESTIGATOR

Any individual member of the clinical investigation team designated and supervised by the Investigator at an investigational site who performs critical investigation-related procedures and/or makes important investigation-related observations, including enrollment of subjects and deployment of the study device. See also Investigator and Operator. *"Enrolling Investigator" refers to any Investigator or Co-Investigator who enrolled a subject, who may then supervise an approved Operator to deploy the device (if applicable), and make study assessments and sign Source Worksheets related to that subject during the study.*

COMPLAINT (in the context of Sponsor's Complaint process)

Complaint means any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution.

CONFIDENTIALITY

Prevention of disclosure, to other than authorized individuals, of a Sponsor's proprietary information or of a subject's identity / Protected Health Information (PHI) in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

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DATA SAFETY MONITORING COMMITTEE (DSMC)

An independent combination Clinical Events Committee and Data Safety Monitoring Board responsible for systematic review and adjudication of all site-reported deaths and major and minor access site closure-related complications, in Study Access Sites.

DEATH

Cease to live.

DEEP VEIN THROMBOSIS (DVT)

Blood clot formation in one or more deep veins (e.g., in the leg).

DEVICE FAILURE / MALFUNCTION

The device does not perform in accordance with the IFU.

DEVICE SUCCESS

Defined as the ability to deploy the delivery system, deliver the collagen, and achieve hemostasis with the device per IFU.

EDEMA

Swelling. Lower Extremity Edema is swelling in the lower extremity (such as occlusion of the common femoral vein resulting in blood pooling in the leg) requiring medical intervention.

ELECTRONIC CASE REPORT FORM (eCRF)

An electronic document designed to record all of the protocol-required information to be reported to the Sponsor on each subject.

EMBOLISM / EMBOLIZATION

The sudden blocking of an artery or vein by a clot or other material that has been brought to its site of lodgment by the blood current (embolus). Potential sources of emboli include thrombus, air, calcific debris, device components, or other material.

FAILED ACCESS SITE (FAS)

A femoral venous access site where hemostasis is not achieved by the intended device. In cases where access is lost prior to device insertion, where device is inserted but collagen is not successfully deployed, or when initial hemostasis time (TTH) requires > 30 minutes of manual compression to achieve, a Device Observations Form should be completed for each access site. The Device Observations Form will also be used for other device issues and for any device that was opened but not used for an access site during the case. Refer to the Manual of Operations (MOP) for instructions.

HEMATOMA

A stable, localized collection of extravasated blood in subcutaneous tissue, usually clotted. Measure the widest portion of the hematoma in centimeters.

HEMOSTASIS

Cessation of common femoral venous bleeding from the puncture site(s) (excluding cutaneous or subcutaneous oozing).

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INFECTION

Presence of pathogenic organisms in the blood or body

INFLAMMATORY RESPONSE

A localized protective response elicited by injury or destruction of tissues, not necessarily synonymous with infection.

INFORMED CONSENT

A process by which a subject voluntarily confirms in writing his or her willingness to participate in a particular investigation, after having been informed of all aspects of the investigation that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated Informed Consent form.

INTIMAL TEAR / DISSECTION

Disruption of a vessel wall resulting in splitting and separation of the intimal (subintimal) layers.

INVESTIGATIONAL SITE

The location(s) where investigation-related activities are actually conducted.

INVESTIGATOR

The person responsible for the conduct of the clinical investigation at an investigational site. If an investigation is conducted by a team of individuals at an investigational site, the Investigator is the responsible leader of the team and may be called the Principal Investigator. See also Co-Investigator and Operator. *"Enrolling Investigator" refers to any Investigator or Co-Investigator who enrolled a subject, who may then supervise an approved Operator to deploy the device (if applicable) and make study assessments and sign Source Worksheets related to that subject during the study.*

IPSILATERAL

Situated on or affecting the same side (e.g., same side of the body as the access site).

LACERATION OF THE VESSEL WALL

A deep cut or tear in the arterial or venous vessel wall.

LAST PROCEDURAL DEVICE

Refers to the final device removed from procedural sheaths used in the index procedure, e.g. the Ablation procedure prior to any sheath exchanges e.g. from long to short sheaths.

LIGHT/ADJUNCTIVE PRESSURE/COMPRESSION METHODS

Light, non-occlusive pressure to the venotomy site applied to stabilize non-venous bleeding at the access site (i.e., light digital pressure, mechanical compression devices used at low pressure to manage tissue tract ooze). This light, non-occlusive pressure is known as light/adjunctive compression.

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MANUAL COMPRESSION

Direct, digital pressure to the venotomy site applied to achieve venous hemostasis per Investigator discretion.

MANUAL OF OPERATIONS (MOP)

Study reference binder provided by Sponsor containing specific instructions for performing study-specific tasks. This confidential binder is part of the Investigator's Site File content for this study.

NON-STUDY ACCESS SITE(S)

The venous access site(s) made in the Non-Study Limb and closed using a commercial VASCADE Family device(s).

NON-STUDY LIMB

The limb in which the Non-Study Access Site(s) are located and closed using a commercial VASCADE Family device(s).

OOZING FROM THE ACCESS SITE

Minimal bleeding of a cutaneous or subcutaneous origin characterized by the absence of accumulated blood under the skin (e.g., hematoma) and controlled with the application of light compression methods (sand bags, pressure dressings, and/or light adjunctive pressure). Note: the occurrence of oozing will not be incorporated into the "time to hemostasis" measurement.

OPERATOR

Any individual member of the clinical investigation team who is qualified by training and experience (i.e., non-Investigator MD or certified vascular technician) and who is designated to deploy the study device in a study subject under the direct supervision of an Investigator or Co-Investigator, but does not have authority to make decisions about enrollment. See also Investigator and Co-Investigator.

PERFORATION OF VESSEL WALL

A hole or break in the venous or arterial wall (e.g., from insertion of a percutaneous device).

PROCEDURE SUCCESS

Defined as attainment of final hemostasis at the Study Access Site and freedom from major venous access site closure-related complications at the Study Access Site through 30 days.

PULMONARY EMBOLISM

A blockage of an artery in the lungs by a substance that has traveled from elsewhere in the body through the bloodstream (i.e., embolism), to be confirmed by CT pulmonary angiography, lung ventilation/perfusion scan (VQ scan) or autopsy.

PUNCTURE SITE PAIN

Local discomfort at the venous access site, which may range from mild to severe.

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RE-BLEEDING AT ACCESS SITE

Active venous bleeding from the puncture site occurring after initial hemostasis has been confirmed and requiring manual compression to re-achieve hemostasis.

RETROPERITONEAL BLEEDING

Bleeding from an injured vessel, with deposition of blood into the retroperitoneal space (between the peritoneum and the posterior abdominal wall).

SERIOUS ADVERSE EVENT (SAE)

Any untoward medical occurrence which results in death, is life threatening, requires in-patient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity.

SOURCE WORKSHEET (SWS)

A document provided by the Sponsor for collection of raw study data that is not routinely collected and/or summarized in the medical records. Several SWS are required by the Sponsor and may not be altered for use without Sponsor's permission – refer to the Manual of Operations for a list of required SWS. These completed SWS will require a printed name, signature, and date by the designee described on each SWS and will be used by the Monitor to verify key study data, e.g., Time to Hemostasis, device-relatedness for adverse events, etc. Any corrections must be clearly circled/ initialed/ dated with the old data crossed through according to Good Documentation Practice.

STUDY ACCESS SITE

The single venous access site made in the Study Limb and closed using the Study Device.

STUDY LIMB

The limb in which the Study Access Site is located and closed using the Study Device.

SUBJECT

An individual who participates in a clinical investigation.

SUPERFICIAL VEIN THROMBOSIS

Blood clot in vein close to the skin's surface. (e.g., in the leg).

UNANTICIPATED ADVERSE DEVICE EFFECTS (UADE) (definition per 21 CFR 812.3(s))

Any serious adverse effect on health or safety or any life-threatening problem or death *caused by, or associated with the study device,* if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the Investigational Plan or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

VASOVAGAL EPISODE / RESPONSE

A transient vascular and neurogenic reaction marked by pallor, nausea, and/or sweating symptoms, bradycardia and rapid fall in blood pressure, which may lead to a loss of consciousness and ECG changes.

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VESSEL OCCLUSION (ARTERIAL OR VENOUS)

Total obstruction of the vein or artery by thrombus or other emboli requiring surgical or interventional repair, thrombolysis or percutaneous thrombectomy.

VESSEL THROMBUS (ARTERIAL / VENOUS)

Formation or development of a blood clot or thrombus in the arterial or venous system of the ipsilateral distal extremity.

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17.3 Bibliography

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18 Appendix A: Previous Related Clinical Investigations Detail

18.1 Pre-Market Clinical Investigation: VASCADE MVP VVCS AMBULATE Study [RPT 0508]

The AMBULATE Trial was a prospective, randomized, controlled, multi-center clinical trial designed to evaluate the safety and effectiveness of the VASCADE MVP in sealing multiple femoral venous access sites and providing reduced times to ambulation compared with manual compression at the completion of catheter-based procedures performed through 6-12 F introducer sheaths. The trial was conducted at 13 sites in the United States and involved 204 subjects undergoing catheterization procedures, comparing VASCADE MVP VVCS (100 subjects) to Manual Compression (104 subjects). Only subjects with multiple access sites were enrolled to support the desired indication. Randomization was stratified to account for subjects with varying numbers of access sites in a 1:1 treatment device to control arm ratio to ensure treatment and control arms have the same proportion of access sites/subject, i.e., 3 access sites/subject vs. 4 access sites/subject. A subset of 25 subjects from each treatment arm was also enrolled in an Ultrasound Sub-Study, with exams performed at the 30-day follow-up visit.

The primary safety endpoint was major access site related complications on a per-limb basis and the primary effectiveness endpoint was time to ambulation. The secondary safety endpoint was minor access site related complications on a per-limb basis and the secondary effectiveness endpoints were time to hemostasis, total post-procedure time, time to discharge eligibility, time to discharge, time to closure eligibility, procedure success, and device success. The study was intended to demonstrate noninferiority with respect to the primary safety endpoint and superiority with respect to the primary effectiveness endpoint. There were no major access site related events reported in either randomized group. Table 9 provides a summary of results for minor access site related complications. Table 10 provides a summary of results for the primary and secondary effectiveness endpoints. Table 11 and Table 12 shows the proportion of subjects achieving device success and procedure success respectively. Table 13 provides a summary of the randomized subject demographics.

Table 9. AMBULATE Minor Venous Access Site Closure-Related Complications, As-Reported, Number of Limbs with Each Event

Access Site Closure-Related Complications at 30 Days by Event	VASCADE MVP (N=199)		MC (N=209)	
Any Minor Venous Access Site Closure-Related Complication	2	1.0%	5	2.4%
Bleeding from the access site requiring > 30 minutes of continual manual compression to achieve initial venous hemostasis	0	0.0%	0	0.0%

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Access Site Closure-Related Complications at 30 Days by Event	**VASCADE MVP** (N=199)		**MC** (N=209)	
Access site-related hematoma > 6 cm documented by ultrasound	0	0.0%	2	1.0%
Delayed bleeding from the access site (following hospital discharge)	0	0.0%	0	0.0%
Ipsilateral deep vein thrombosis, confirmed by ultrasound/imaging	0	0.0%	0	0.0%
Localized access site infection confirmed and treated with intramuscular or oral antibiotics	1	0.5%	1	0.5%
Arteriovenous fistula requiring treatment	0	0.0%	0	0.0%
Arteriovenous fistula not requiring treatment	0	0.0%	1	0.5%
Pseudoaneurysm requiring thrombin/fibrin adhesive injection or ultrasound-guided compression	1	0.5%	0	0.0%
Pseudoaneurysm not requiring treatment	0	0.0%	0	0.0%
Access site-related vessel laceration	0	0.0%	0	0.0%
Access site wound dehiscence	0	0.0%	0	0.0%
Transient access site-related nerve injury	0	0.0%	1	0.5%

Table 10. AMBULATE Summary of Primary and Secondary Effectiveness Endpoints

Outcome	**VASCADE MVP**			**Manual Compression**			**ANCOVA**	
	Total	**3 Access Sites**	**4 Access Sites**	**Total**	**3 Access Sites**	**4 Access Sites**	**Parameter Estimate** (95% CI)	***P* value**
TTA (hours)							-3.32 (-3.71, -2.92)	<0.0001
N	N=100	N=31	N=69	N=104	N=34	N=70		
Mean ± SD	2.8 ± 1.3	2.5 ± 0.8	2.9 ± 1.5	6.1 ± 1.6	5.9 ± 1.2	6.2 ± 1.7		
Median (min, max)	2.2 (2.0, 11.5)	2.2 (2.0, 5.6)	2.3 (2.0, 11.5)	6.1 (3.4, 15.7)	5.3 (4.2, 9.1)	6.2 (3.4, 15.7)		
TPPT (hours)							-3.69 (-4.10, -3.27)	<0.0001
N	N=100	N=31	N=69	N=104	N=34	N=70		
Mean ± SD	3.1 ± 1.3	2.7 ± 0.8	3.3 ± 1.5	6.8 ± 1.7	6.4 ± 1.3	6.9 ± 1.9		
Median (min, max)	2.6 (2.2, 11.8)	2.4 (2.2, 5.9)	2.7 (2.2, 11.8)	6.4 (4.2, 15.9)	6.2 (4.5, 9.8)	6.6 (4.2, 15.9)		

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Outcome	VASCADE MVP			Manual Compression			ANCOVA	
	Total	3 Access Sites	4 Access Sites	Total	3 Access Sites	4 Access Sites	Parameter Estimate (95% CI)	*P* value
TTH (minutes)							GEE Model -7.5 (-8.7, -6.3)	<0.0001
N	N=369	N=93	N=276	N=382	N=102	N=280		
Mean ± SD	6.1 ± 3.7	5.4 ± 2.0	6.3 ± 4.1	13.7 ± 6.5	11.4 ± 6.4	14.5 ± 6.4		
Median (min, max)	5.1 (0.4, 33.3)	5.1 (1.3, 23.3)	5.1 (0.4, 33.3)	11.7 (0.6, 37.1)	10.0 (2.9, 32.7)	12.5 (0.6, 37.1)		
TTDE (hours)							-3.41 (-3.87, -2.96)	<0.0001
N	N=100	N=31	N=69	N=104	N=34	N=70		
Mean ± SD	3.1 ± 1.3	2.7 ± 0.8	3.2 ± 1.5	6.5 ± 1.9	6.2 ± 1.3	6.6 ± 2.2		
Median (min, max)	2.5 (2.3, 11.7)	2.5 (2.3, 5.9)	2.6 (2.3, 11.7)	6.3 (4.3, 21.3)	5.7 (4.6, 9.4)	6.5 (4.3, 21.3)		
TTD (hours)							-0.04 (-3.25, 3.17)	0.98
N	N=100	N=31	N=69	N=104	N=34	N=70		
Mean ± SD	21.8 ± 13.4	20.5 ± 10.8	22.3 ± 14.5	21.8 ± 9.5	22.7 ± 10.6	21.4 ± 9.0		
Median (min, max)	22.3 (2.3, 96.1)	22.9 (2.3, 48.2)	22.3 (3.5, 96.1)	22.1 (5.7, 72.9)	22.8 (5.7, 71.5)	21.6 (5.8, 72.9)		
TTCE (minutes)							-27.23 (-33.86, -20.60)	<0.0001
N	N=100	N=31	N=69	N=104	N=34	N=70		
Mean ± SD	10.5 ± 6.0	9.0 ± 4.1	11.1 ± 6.6	37.6 ± 33.2	32.2 ± 27.6	40.3 ± 35.5		
Median (min, max)	10.1 (1.7, 47.5)	9.8 (1.7, 17.5)	10.2 (2.0, 47.5)	25.2 (1.8, 132.3)	21.1 (2.0, 108.9)	27.8 (1.8, 132.3)		

Table 11: VASCADE MVP Device Success (Device Arm Only) Per Access Site

Device Success	Number of Access Sites	Successes	Percent
Actual Devices Attempted	363	351	97%

Table 12: Proportion of Procedure Success

Procedure Success	VASCADE MVP (N=100)		Manual Compression (N=104)	
Yes	98	98%	103**	99%
Unknown*	2	2%	1	1%

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Procedure Success	VASCADE MVP (N=100)	Manual Compression (N=104)
*VASCADE MVP: One subject had final follow-up 20 days early (3 days post-procedure) and one subject was lost to follow-up |MC: One subject was lost to follow-up ** MC: One subject was lost to follow-up within the study period		

Table 13: AMBULATE Subject Demographics - Randomized Subjects

	VVCS (N=100)		Manual Compression (N=104)	
Age				
N	100	-	104	-
Mean	61.5	-	63.4	-
Std Dev	11.6	-	11.1	-
Median	62	-	65.5	-
Minimum	28	-	19	-
Maximum	80	-	79	-
Gender				
N	100	-	104	-
Female	33	33%	40	38%
Male	67	67%	64	62%
Ethnicity				
N	100	-	104	-
Hispanic or Latino	3	3%	6	6%
Not Hispanic or Latino	97	97%	95	91%
Unknown	0	0%	3	3%
Race				
N	100	-	104	-
White	86	86%	93	89%
Black or African American	6	6%	4	4%
American Indian or Alaska Native	3	3%	0	0%
Asian	2	2%	1	1%
Hispanic	1	1%	1	1%
Puerto Rican	1	1%	1	1%
Indian	0	0%	1	1%
Unknown	1	1%	2	2%

As a result, the primary study endpoints were met. The results from this clinical trial demonstrated that the rate of major venous access site closure-related complications for subjects treated with VASCADE MVP was non-inferior to the major access site closure-related

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complication rates of subjects treated with manual compression for sealing femoral venous access sites. The results also demonstrated superiority in the primary endpoint, time to ambulation, as compared to manual compression. The VASCADE MVP minor complication rate was numerically lower than for MC and clinically similar. VASCADE MVP also demonstrated superiority as compared to manual compression in the following secondary endpoints: total post-procedure time, time to hemostasis and time to discharge eligibility. Therefore, the AMBULATE Trial demonstrated that VASCADE MVP is safe and effective for its intended use when used in accordance with device labeling.

The results are documented in Natale A, et al. (2019).

18.2 Pre-Market Clinical Investigation: AMBULATE Continued Access Protocol (CAP) [RPT 0543]

The AMBULATE CAP study was a prospective multi-center single-arm clinical continued access protocol (CAP), designed to evaluate the safety and effectiveness of the study device in sealing multiple femoral venous access sites at the completion of catheter-based procedures performed through 6 - 12 F introducer sheaths, while allowing for one or more of the following: elimination of the urinary catheter, elimination of protamine and / or allowing same calendar day discharge for the appropriate patient population. A total of 168 subjects were enrolled. The primary safety endpoint was rate of major venous access site closure-related complications on a per-limb basis, and the primary effectiveness endpoint was procedure success. The secondary safety endpoint was rate of minor venous access site closure-related complications on a per-limb basis, and the secondary effectiveness endpoints were device success and study group success: no urinary catheter, no protamine, and same calendar day discharge.

There were no major venous access site closure-related complications. Table 14 provides a summary of results for minor access site-related complications.

Table 14: AMBULATE CAP Minor Venous Access Site Closure-Related Complications

Minor Venous Access Site Closure-Related Complications at 30 Days by Event	Limbs (N=325)	
	No.	Percent (%)
No Minor Venous Access Site Closure-Related	***318***	***97.8%***
Any Minor Venous Access Site Closure-Related Complication	***7***	***2.2%***
The specific complications are listed below.	*No.*	*Percent (%) of All Limbs*
V8: Access site-related bleeding requiring > 30 minutes of continual manual compression to achieve initial venous hemostasis	3	0.9%

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Minor Venous Access Site Closure-Related Complications at 30 Days by Event	Limbs (N=325)	
	No.	Percent (%)
V9: Access site-related hematoma > 6 cm documented by ultrasound	2	0.6%
V10: Late access site-related bleeding (following hospital discharge)	1	0.3%
V11: Ipsilateral deep vein thrombosis, confirmed by ultrasound/imaging	0	0.0%
V12: Localized access site infection confirmed and treated with intramuscular or oral antibiotics	0	0.0%
V13: Arteriovenous fistula requiring treatment	0	0.0%
V14: Arteriovenous fistula not requiring treatment	0	0.0%
V15: Pseudoaneurysm requiring thrombin/fibrin adhesive injection or ultrasound-guided compression	1	0.3%
V16: Pseudoaneurysm not requiring treatment	0	0.0%
V17: Access site-related vessel laceration	0	0.0%
V18: Access site-related wound dehiscence	0	0.0%
V19: Transient access site-related nerve injury	0	0.0%

Table 15 summarizes the primary effectiveness endpoints of the study for each study group and Table 16 summarizes the secondary effectiveness endpoints.

Table 15. AMBULATE CAP Summary of Primary Effectiveness Endpoints

Procedure Success	All Subjects (N=168)		No Urinary Catheter (N=164)		No Protamine (N=41)		Same Calendar Day Discharge (N=18)	
	No.	%	%	%	No.	%	No.	%
Yes	168	100%	164	100%	41	100%	18	100%
No	0	0%	0%	0%	0	0%	0	0%

Table 16: AMBULATE CAP Summary of Secondary Effectiveness Endpoints

	Device Success (N=622)*		No Urinary Catheter (N=164)		No Protamine (N=41)		Same Calendar Day Discharge (N=18)	
	No.	%	No.	%	No.	%	No.	%
Yes	612	98.4%	160	97.6%	39	95.1%	18	100%
No	10	1.6%	4	2.4%	2	4.9%	0	0%
*Total devices attempted. This does not include the four access sites in a single subject where closure was not attempted since the device was not used.								

The VASCADE MVP VVCS device was successful in demonstrating safety and effectiveness for the closure of femoral venous access sites in patients who had undergone catheter-based

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procedures utilizing 6 – 12 F procedural sheaths, with single or multiple access sites per limb, ranging from a single access site in one limb to multiple access sites in both limbs.
In addition, the low rate of pain medication use, high patient satisfaction for bedrest duration, and low scores for groin pain demonstrate additional patient benefits when VASCADE MVP is used in accordance with its indicated use.

The results are documented in Al-Ahmad, et al. (2021).

18.3 Post-Market Clinical Investigation: AMBULATE Same-Day Discharge Studies [RPT 0617, RPT 0601]

The AMBULATE Same Day-Discharge (SDD) Studies were multi-center, single arm registries to collect procedural outcomes data when the VASCADE MVP was used to seal femoral venous access sites at the completion of catheter-based ablation procedures for atrial fibrillation with or without another arrhythmia, performed through 6-12F ID (max 15F OD) introducer sheaths in patients who were discharged the same day as the procedure (retrospective study) or who were eligible for same-day discharge (prospective studies). These studies add to the body of knowledge for patient profiles subject to safe same-day discharge by focusing on patients who: 1) received VASCADE MVP for closure involving multiple access sites in one or both limbs; and 2) were being treated for atrial fibrillation (AF) with or without another arrhythmia. Ablation for atrial fibrillation, which is generally longer and/or more complex than for other arrhythmias, provides a greater challenge for establishing the safety profile for same-day discharge than ablation for other arrhythmias. Table 17 provides the safety and effectiveness results for the same-day discharge studies.

Table 17: Same-Day Discharge Studies Safety and Effectiveness Results

Study	Population	Performance			Safety	
		VASCADE MVP Success (Freedom from Access Site Complications)		Procedure Success (Freedom from Next Day Procedure-Related Complications)	Access Site Closure Related Complications	
		Next Day	Follow-Up		Major	Minor
Retrospective (AF All-Comers) Procedures: Dec 2018-Feb 2020 | 497 Patients | 4 sites | Standard of Care f/u	Discharged Same Day	99.8% (496/497)	99.8% (496/497)	99.6% (495/497)	0.0% (0/827)	0.1% (1/827)*
Prospective SDD#1 (Paroxysmal AF) June 2020-Nov 2020 | 151 Patients | 8 sites | 15-day f/u	Discharged Same Day	99.3% (137/138)	99.3% (137/138)	99.3% (137/138)	0.0% (0/193)	1.0% (2/193)**
	Discharged Same Day out of ITT	90.7% (137/151)	90.7% (137/151)	90.7% (137/151)		

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Study	Population	Performance			Safety	
		VASCADE MVP Success (Freedom from Access Site Complications)		Procedure Success (Freedom from Next Day Procedure-Related Complications)	Access Site Closure Related Complications	
		Next Day	Follow-Up		Major	Minor
	ITT	99.3% (150/151)	99.3% (150/151)	99.3% (150/151)		
Prospective SDD#2 (Persistent AF) Feb 2021-Jun 2021 | 203 Patients | 13 sites | 15-day f/u	Discharged Same Day	100.0% (185/185)	100.0% (185/185)	99.5% (184/185)	0.0% (0/272)	0.7% (2/272)***
	Discharged Same Day out of ITT	91.1% (185/203	91.1% (185/203	90.6% (184/203)		
	ITT	100.0% (203/203)	100.0% (203/203)	99.0% (201/203)		
*1 event occurred in 1 subject (1 limb) **3 events occurred in 2 subjects (2 limbs) ***2 events occurred in 2 subjects (2 limbs)						

The results from the AMBULATE VASCADE MVP Same-Day Discharge Retrospective and Prospective Registries demonstrate that VASCADE MVP is associated with same-day discharge in patients who underwent catheter-based procedures using 6–12F inner diameter procedural sheaths, with single or multiple access sites in one or both limbs and who were treated with the VASCADE MVP VVCS. This is demonstrated by the high success rate of all performance procedural outcomes and absence of major and low rate of minor access site closure-related complications. Additionally, the high success rates of the procedural performance outcomes indicate physicians were able to accurately assess patient eligibility for same-day discharge.

The results for the prospective registries are documented in Eldadah, et al. (2022).

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19 Appendix B: Ethical Considerations

19.1 Trial Conduct

The trial will be conducted in compliance with the clinical study protocol (and amendments), 21 CFR Part 11, 50, 54, 56, 803, 812, 45 CFR Part 164.508(c), applicable parts of ISO 14155 and ICH E6(R2), and applicable regulatory requirements. The clinical investigation shall be conducted in alignment with the ethical principles that have their origin in the Declaration of Helsinki.

19.2 Institutional Review Board/Independent Ethics Committee

A copy of the protocol, proposed Informed Consent form (ICF), other written patient information and any proposed patient-facing and/or advertising material must be submitted to the IRB for written approval per site-specific or central IRB procedures, as applicable. A copy of the written IRB approval of the protocol and ICF must be received by the Sponsor prior to recruitment of subjects into the study and shipment of investigational product.

The Investigator will be responsible for obtaining annual IRB approval and renewal throughout the duration of the study. Copies of the Investigator's reports and the IRB continuance of approval must be sent to Sponsor.

19.3 Informed Consent Form

An FDA-approved sample ICF is provided to be used for both Roll-In and Pivotal subjects in the study materials for the Investigator to prepare for use at his/her site. The Sponsor will review each site's redlines to the ICF and provide written approval prior to site submission of the documents to their respective IRBs. The reviewing IRB must then approve the ICF prior to use. If translations are required for specific populations, the Sponsor will provide certified translations for the site after IRB approval of the site template.

Prior to participation in the clinical trial, each patient must give written Informed Consent after the context of the study has been fully explained to the patient in language that is easily understood by the patient. The subjects must also be given the opportunity to ask questions and have those questions answered to their satisfaction.

The ICF will require the patient to indicate their agreement to be enrolled as a Roll-in and/or a Pivotal ("Standard") subject; Ultrasound sites will have a section requiring the patient to indicate their prospective agreement to be enrolled in the Ultrasound sub-study or not. If not, the subject will be asked to state a reason for not participating which will be documented in the eCRF.

Written Informed Consent must be recorded appropriately by means of the patient's dated signature on the ICF, and initials in any section where required. ICF signature/initial by a Legally Authorized Representative ("LAR") is not allowed in this study since the procedures are elective

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and the subject will have ample time to review and sign the consent form themselves. The person administering the Informed Consent shall also sign and date the ICF. The patient shall receive a copy of the ICF, and the informed consent process shall be documented in each subject's source record. Incomplete execution of the informed consent document shall be documented as a protocol deviation and the Investigator will need to determine reporting requirements of the deviation for their governing IRB.

19.4 Amending the Protocol

An Investigator may not make protocol changes without prior approval by the Sponsor. All significant protocol changes that may affect the following must be submitted and approved by the FDA before initiating the change:

- Validity of the data or information resulting from the completion of the approved protocol;
- Relationship of the likely subject risk to benefit relied upon to approve the protocol;
- Scientific soundness of the investigational plan, or;
- Rights, safety, or welfare of the human subjects involved in the investigation.

The change must be approved by the FDA and submitted and subsequently approved by the site IRB. The Sponsor will submit a copy of the protocol amendment to all Investigators for their IRB's to review and ensure the study continues to be conducted consistently across all sites. The investigative sites must send the Sponsor a copy of the IRB approval letter for the protocol amendment.

The Sponsor may make certain administrative changes to the protocol without prior approval of the FDA or IRB. The Sponsor will notify all investigative sites of such changes to ensure the study continues to be conducted consistently across all sites. The site IRB's will be notified of these changes by the Investigator when required by the Sponsor and/or IRB.

19.5 Emergency Actions

The Sponsor accepts the right of the Investigator to deviate from the protocol in an emergency when necessary to safeguard the life or the physical well-being of a study patient. The Investigator must give notice of any emergency deviations and justification for the deviation to the Sponsor and the IRB as quickly as possible after the episode, in any event no later than 24 hours after the emergency.

19.6 Protocol Deviations

A protocol deviation is defined as an event where the Clinical Investigator or site personnel did not conduct the study according to the protocol.

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Investigators shall be required to obtain prior approval from the Sponsor clinical study management before initiating deviations from the protocol, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval shall be documented in writing and maintained in clinical study management and Investigator files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control (e.g., subject was not available for scheduled follow-up office visit); however, the event is still considered a deviation and will be reported as a protocol deviation via the appropriate eCRF.

Deviations must be reported to the Sponsor as protocol deviations regardless of whether medically justifiable, pre-approved by the Sponsor or taken to protect the subject in an emergency. Subject specific deviations and non-subject specific deviations, (e.g., unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a physician who has not signed an Investigator agreement or not been trained in the use of the device, etc.), will be reported on the Protocol Deviation case report form. Investigators will also adhere to procedures for reporting study deviations to their IRB in accordance with their specific IRB reporting policies and procedures. The Sponsor will classify all protocol deviations as either important or not important.

Regulations require that Investigators maintain accurate, complete and current records, including documents showing the dates of and reasons for each deviation from the protocol. Refer to the Protocol Deviation eCRF/SWS for specific PD codes.

19.7 Coverage of Expenses

The treated subjects will not be reimbursed or compensated for participating in the trial, however provision of a modest stipend for travel expenses related to study-required follow-up is allowed and will be stated clearly in the informed consent form when applicable.

19.8 Confidentiality

Confidentiality of subjects will be maintained throughout the trial. A unique identification code will be assigned to each subject participating in this trial. Any data that may be published in abstracts, scientific journals, or presented at medical meetings will reference a unique subject code and will not reveal the subject's identity. The Sponsor and any other Sponsor representatives will make every reasonable effort to protect the confidentiality of the subjects participating in the trial.

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20 Appendix C: Study Administration

20.1 Pre-Study Documentation Requirements

Prior to shipment of investigational product, the following documents must be provided by the site to the Sponsor:

- Signed and dated Investigator Agreement, Protocol Signature Page and Financial Disclosure Form
- Fully executed Clinical Study Agreement and budget
- A copy of the written IRB approval of the protocol and ICF
- A copy of the IRB-approved ICF
- A copy of the curriculum vitae of the Principal Investigator, current medical license, and proof of current GCP training

20.2 Source Documentation

The Principal Investigator must maintain detailed source documents on all trial subjects who are enrolled in the trial. Source documents may include subject medical records, hospital charts, clinic charts, Investigator's subject study files/correspondence, results of diagnostic tests (e.g., laboratory tests), and study-specific source worksheets.

The following minimum information should be recorded in the subject's source records:

- The date the subject entered the study and the subject ID number
- The study name
- The date that informed consent was obtained
- Evidence that the subject meets trial eligibility requirements (e.g., medical history, trial procedures and/or evaluations)
- The dates of all trial related subject visits
- Evidence that required procedures and/or evaluations were completed, including completion of mandatory Source Worksheets provided by the Sponsor to collect study endpoint data (refer to Section 13.1)
- Documentation of specific investigational devices used, if any
- Documentation of specific commercial devices used, if any
- Occurrence and status of Adverse Events
- The date the subject exited the study, and a notation as to whether the subject completed the study or was discontinued, including the reason for discontinuation.

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20.3 Record Retention & Custody

The Investigator will maintain all essential trial documents and source documentation, in original format, that support the data collected on the study subjects in compliance with the ICH/GCP guidelines. Research Records must be maintained during the investigation and for the longest of the following:

A) A minimum of three years after the research is completed and the study closed with the IRB [1]

B) For a period of 2 years after the latter of the following two dates: the date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a premarket approval application [2] or other regulatory application

C) A longer period of time by agreement with the Sponsor or in compliance with other regulatory or site requirements.

When these documents no longer need to be maintained, it is the Sponsor's responsibility to inform the Investigator. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility. The Sponsor must receive written notification of this custodial change.

20.4 Criteria for Terminating Study

The Sponsor reserves the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators and associated IRBs will be notified in writing in the event of termination.

Possible reasons for study termination include:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- A decision on the part of the Sponsor to suspend or discontinue development of the device.

20.5 Criteria for Suspending/Terminating a Study Center

The Sponsor reserves the right to stop the enrollment of subjects at a study center at any time after the study initiation visit for the following possible reasons:

[1] OHRP Requirements: 45 CFR 46

[2] FDA IDE Requirements: 21 CFR 812

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- Repeated failure to complete electronic case report forms prior to scheduled monitoring visits
- No or slow enrollment
- Multiple protocol deviations without justification, or failure to follow remedial actions
- Any action that may negatively impact subjects' rights, safety or welfare
- Failure to obtain written Informed Consent prior to enrollment
- Failure to report serious device-related AEs and/or UADEs to Cardiva Medical, Inc. within study reporting timeline requirements
- Loss of (or unaccounted for) investigational product inventory
- Insufficient maintenance of study administrative and regulatory documentation
- Failure to fulfill Investigator Responsibilities.

20.6 Investigator Responsibilities

- Agree to sign and adhere to the Investigator Agreement, the Protocol Signature Page, and to protect the rights, safety and welfare of subjects under the Investigator's care
- Sign the Financial Disclosure form to disclose any significant financial interest according to 21 CFR 54, and promptly update this information if any relevant changes occur in the course of the investigation or for 1 year following completion of the study.
- Be willing to provide required assessments for analysis
- Be willing to perform and be capable of performing treatment procedures as outlined in this protocol and to delegate study responsibilities only to qualified personnel
- Comply with all required elements of this protocol and supply data suitable for quantitative analysis
- Agree to obtain and document proper written Informed Consent before any study specific procedures are performed
- Complete all electronic data modules prior to scheduled monitoring activities
- Keep study administration and regulatory documentation in an organized and current state using the Study Binders provided by the Sponsor; electronic records will be kept in compliance with 21 CFR Part 11
- Be willing to change hospital routine if required by protocol, as long as patient safety and well-being is not compromised
- Adhere to all relevant Ultrasound Core Laboratory requirements as applicable.
- Comply with all FDA and local regulatory and IRB reporting requirements, including 21 CFR 812.150:
    - Unanticipated adverse device effects – an Investigator shall submit to the Sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring

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during an investigation as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect. ***Sponsor requires notification within 24 hours of Investigator awareness to evaluate for reportability.***

- Withdrawal of IRB approval – an Investigator shall report to the Sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the Investigator's part of an investigation.
- Progress – an Investigator shall submit progress reports on the investigation to the Sponsor, the Monitor and the reviewing IRB at regular intervals, but in no event less often than yearly.
- Deviations from the investigational plan – an Investigator shall notify the Sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the Sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, prior approval by the FDA and IRB in accordance with 812.35(a) is also required.
- Informed consent – if an Investigator uses a device without obtaining informed consent, the Investigator shall report such use to the Sponsor and the reviewing IRB within 5 working days after the use occurs.
- Final report – an Investigator shall, within 3 months after termination or completion of the investigator or the investigator's part of the investigation, submit a final report to the Sponsor and reviewing IRB.
- Other – an Investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete and current information about any aspect of the investigation.

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21 Appendix D: Publication Policy

The existence of this clinical trial is confidential, and it should not be discussed with persons outside of the trial. Additionally, the information in this document and regarding this trial contains trade secrets and commercially sensitive information that is confidential and may not be disclosed unless such disclosure is required by regional or national law or regulations. Subject to the foregoing, this information may be disclosed only to those persons involved in the trial who have a need to know, but all such persons must be instructed not to further disseminate this information to others. These restrictions of disclosure will apply equally to all future information provided that it is indicated as confidential.

Sponsor is committed to honoring the principles of academic freedom while, at the same time, protecting its Confidential Information, the subjects, the integrity of this study and this study documentation all in compliance with Applicable Law. The first publication in a journal or presentation is planned to be a coordinated approach with results from all sites. With regard to this study, Site /Principal Investigator may publish the results based on data generated at the Site, provided that neither Site nor Principal Investigator shall publish or present these results from this study to any third parties until (a) Sponsor publishes the results from all sites participating in the Study; (b) Site receives notification from Sponsor that publication of the multi-site results is no longer planned; or (c) eighteen (18) months following the study closeout, whichever occurs first.

The study will be posted on ClinicalTrials.gov, as required by regulation.

Sites should reference the Clinical Study Agreement for site's agreement regarding confidentiality and publications.

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22 Appendix E: Regulatory Considerations

22.1 Role of the Sponsor

The Sponsor of this clinical study has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the FDA and other regulatory authorities, as applicable. In this study, the Sponsor will have certain direct responsibilities and will delegate other responsibilities to Consultants as deemed appropriate. Together, both the Sponsor and its Consultants, if applicable, will ensure adherence to the Sponsor's general duties (21 CFR 812.40), selection of Investigators (21 CFR 812.43), monitoring (21 CFR 812.46), supplemental applications (21 CFR 812.35 (a) and (b)), maintaining records (21 CFR 812.140 (b)), submitting reports (21 CFR 812.150 (b)), protection of human subjects (21 CFR 50), and Institutional Review Boards (21 CFR 56), along with complying to other relevant regulatory requirements as applicable.

22.2 Sponsor's General Duties

The Sponsor's general duties consist of submitting the IDE application to FDA, obtaining FDA and IRB approvals prior to shipping the devices, selecting qualified Investigators and Monitors, and shipping devices only to those qualified Investigators. The Sponsor is also required to obtain signed study agreements, to provide the Investigators with the information necessary to conduct the study and adequate on-site training to conduct the trial, to ensure proper clinical site monitoring, to provide the Investigators with this investigational plan (which includes the report of prior investigations), and to provide the required reports to the Investigators, IRBs, and FDA.

The Sponsor will be responsible for providing quality data that satisfies federal regulations and informing of serious unanticipated adverse events and deviations from the protocol as required. Written progress reports and a final report will be prepared, and the Sponsor will coordinate with the Ultrasound Core Laboratory.

22.3 Monitoring

The Sponsor and/or designee will conduct investigational site monitoring to ensure that all Investigators are in compliance with the protocol, Clinical Study Agreement, and the Investigators' agreements. The Sponsor and/or designee will monitor the sites to ensure that the completed CRFs match the medical records and resolve any differences. The Sponsor will retain the right to remove either the Investigator or the investigational site from the study.

The Sponsor will review significant new information, including unanticipated adverse device effects and ensure that such information is provided to the FDA, the Investigators and to all reviewing IRBs.

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22.4 Maintaining Records

The Sponsor will maintain copies of correspondence, data, shipment of devices, serious adverse device effects and other records related to the clinical trial. The Sponsor will maintain records related to the signed Investigator Agreements.

22.5 Submitting Reports

The Sponsor will submit the required FDA reports identified in this section of the regulation. This includes unanticipated serious adverse device effects, withdrawal of IRB or FDA approval, current 6-month Investigators lists (if applicable), annual progress reports, recall information, final reports, Investigators that use the device without obtaining informed consent, significant risk device determinations, and IRB records.

22.6 Site Record Retention Policy

The Sponsor, Ultrasound Core Lab, and clinical sites will maintain all records pertaining to this study for a period as defined in Section 18.3. Record retention dates will be provided to all concerned by the Sponsor.

22.7 Informed Consent & Institutional Review Board (IRB)

All subjects must provide written informed consent in accordance with the local clinical site's IRB. A copy of the consent form from each center must be forwarded to the Sponsor for review and approval prior to submitting it to the IRB. Each site must provide the Sponsor with a copy of the clinical site's IRB approval letter and the informed consent. Yearly approvals for the continuation of the trial at each clinical site must also be forwarded to the Sponsor.

All Protected Health Information (PHI) to be collected in the study will be described in the informed consent form, and all study data will be managed in accordance with the Privacy Law (HIPAA) and applicable IRB regulations.

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