



Clinical Investigation Plan (CIP) and Protocol
"AMBULATE CAP STUDY"
CONTINUED ACCESS PROTOCOL (CAP)

MULTI-CENTER, SINGLE ARM CONTINUED ACCESS PROTOCOL TO EVALUATE THE CARDIVA MID-BORE VENOS
VASCULAR CLOSURE SYSTEM (VVCS) FOR THE MANAGEMENT OF THE FEMORAL VENOTOMY AFTER CATHETER-
BASED INTERVENTIONS PERFORMED VIA 6- 12 FR PROCEDURAL SHEATHS WITH SINGLE OR MULTIPLE ACCESS SITES
PER LIMB

The trial will be performed in accordance with the relevant parts of Title 21 CFR Parts 812, 50, 54, and 56; and the ICH Guidelines for Good Clinical Practices (E6).

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Study Responsibility:	CARDIVA Medical, Inc. 2900 Lakeside Drive, Suite 160 Santa Clara, CA 95054
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Protocol Number:	PTL 0543
IDE:	G170144
Study Centers:	See the study manual for a list of study centers
Version:	Version 02

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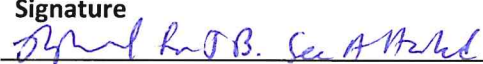
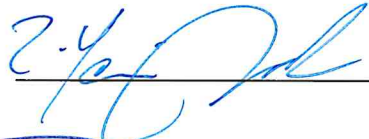
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Protocol Approval Page

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OR MULTIPLE ACCESS SITES PER LIMB

PROTOCOL PTL 0543
NUMBER:
VERSION NUMBER: 02

We, the undersigned, have read and approve the protocol specified above and agree on its content.

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Protocol Synopsis

“AMBULATE CAP STUDY” CONTINUED ACCESS PROTOCOL (CAP)

MULTI-CENTER, SINGLE ARM CONTINUING ACCESS PROTOCOL TO EVALUATE THE CARDIVA MID-BORE VENOUS VASCULAR CLOSURE SYSTEM (VVCS) FOR THE MANAGEMENT OF THE FEMORAL VENOTOMY AFTER CATHETER-BASED INTERVENTIONS PERFORMED VIA 6- 12 FR PROCEDURAL SHEATHS WITH SINGLE OR MULTIPLE ACCESS SITES PER LIMB

Primary Objective	The objective of the trial is to demonstrate the safety and effectiveness of the Cardiva Mid-Bore Venous Vascular Closure System (VVCS) in sealing femoral venous access sites at the completion of catheter-based procedures performed through 6-12 Fr introducer sheaths, while allowing for one or more of the following: elimination of the urinary catheter, elimination of protamine, or allowing same (calendar) day discharge for the appropriate patient population.
Test Device	Cardiva Mid-Bore Venous Vascular Closure System (VVCS) – 6-12 Fr device with 23 Fr Disc (~8 mm)
Indication for Use	The Cardiva Mid-Bore Venous Vascular Closure System (VVCS) is indicated for the percutaneous closure of femoral venous access sites while reducing times to ambulation and discharge eligibility in patients who have undergone catheter-based procedures utilizing 6 – 12 Fr procedural sheaths, ranging from a single access site in one limb to multiple access sites in both limbs.
Study Questions	<p>The Cardiva Mid-Bore VVCS meets its intended use while allowing for one or more of the following:</p> <ul style="list-style-type: none"> • Elimination of the urinary catheter • Elimination of protamine without compromising ambulation time, and / or • Allowing same calendar day discharge for the appropriate patient population without impacting the safety profile of the device
Study Design	A prospective multi-center single-arm clinical continued access protocol, 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 Fr 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.
Number of Patients	<p>Planned enrollment is approximately 300 individual subjects. Each subject can be co-enrolled in multiple study groups of the study and will contribute data to the study group(s) in which they are enrolled.</p> <p><i>A subject may <u>not</u> be enrolled in the No Protamine and Same Calendar Day Discharge arms simultaneously.</i></p>
Number of Sites	Up to 5 sites U.S., with a minimum of 2 sites enrolling subjects in the trial. Any one site will not enroll more than 60% of the subjects. The sites will be sites that participated in the AMBULATE Study [G170144].

Duration of Trial	Each enrolled subject will have follow-up contact at 30 days +/- 10 days post-procedure that will be either an office visit or a phone call. Once all subjects have completed this follow-up, the study will be considered complete.
Primary Effectiveness Endpoint	<u>Overall Procedure Success (pooled across all study groups)</u> Final hemostasis at all venous access sites and freedom from major venous access site closure-related complications through 30 day follow-up. (Per-patient analysis pooled across all study groups)
Secondary Effectiveness Endpoints	<ul style="list-style-type: none"> • <u>Study Group Success Rate</u> (defined for each study arm): <ul style="list-style-type: none"> ○ <u>No Urinary Catheter group</u>: No peri-procedural urinary catheter insertion required through successful Ambulation. (Per-patient analysis) ○ <u>No Protamine group</u>: No delay in Ambulation due to access site bleeding in subjects who receive heparin but are not reversed with protamine (Per-patient analysis) ○ <u>Same Calendar Day Discharge group</u>: Discharge within the same calendar day from the start of the procedure without the need for re-hospitalization within 72 hours of hospital discharge due to access site complications. (Per-patient analysis) • <u>Device Success</u>, defined as the ability to deploy the delivery system, deliver the collagen, and achieve hemostasis with the Mid-Bore VVCS. (Per-access site analysis)
Primary Safety Endpoint	On a per-limb basis , the rate of combined major venous access site closure-related complications through 30 days post-procedure +/- 10 days, attributed directly to the closure method (i.e., “device-related” with no other likely attributable cause): <ul style="list-style-type: none"> • Access site-related bleeding requiring transfusion; • Vascular injury requiring surgical repair; • Access site-related infection confirmed by culture and sensitivity, requiring intravenous antibiotics and/or extended hospitalization; • New onset permanent access site-related nerve injury (i.e., persisting for > 30 days); • New onset access site-related nerve injury in the ipsilateral lower extremity requiring surgical repair; • 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).

Secondary Safety Endpoint	<p>On a per-limb basis, the rate of combined minor venous access site closure-related complications through 30 days post-procedure +/- 10 days, attributed directly to the closure method (i.e., “device-related” with no other likely attributable cause):</p> <ul style="list-style-type: none">• Access site-related bleeding requiring greater than 30 minutes of continual manual compression to achieve initial venous hemostasis;• Access site-related hematoma > 6 cm documented by ultrasound;• Late access site-related bleeding (following hospital discharge);• Ipsilateral deep vein thrombosis confirmed by ultrasound/imaging;• Localized access site infection confirmed by culture and sensitivity, treated with intramuscular or oral antibiotics;• Arteriovenous fistula requiring treatment;• Arteriovenous fistula not requiring treatment;• Pseudoaneurysm requiring thrombin injection, fibrin adhesive injection or ultrasound-guided compression;• Pseudoaneurysm not requiring treatment.• Access site-related vessel laceration;• Access site-related wound dehiscence;• Transient access site-related nerve injury.
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Pre-Operative Inclusion Criteria	<p>All subjects are required to meet the following inclusion criteria in order to be considered eligible for participation in this trial:</p> <ol style="list-style-type: none"> 1. ≥18 years of age; 2. Capable and willing to give informed consent; 3. Acceptable candidate for an elective, non-emergent catheter-based procedure via the common femoral vein(s) using a 6 to 12 Fr inner diameter introducer sheath 4. Able and willing to complete a 30 (± 10) days post-procedure follow-up contact; 5. Acceptable candidate for emergent vascular surgery, and/or manual compression of the venous access site; 6. Study Group Criteria: The subject is eligible for at least one of the following study groups: <ol style="list-style-type: none"> a. <u>Same Calendar Day Discharge Candidate:</u> <ul style="list-style-type: none"> • The subject is expected to undergo an Atrial Fibrillation, Supraventricular Tachycardia, Ventricular Tachycardia or Atrial Flutter procedure. • If procedural heparin is planned to be used, it must be reversed at or before venous closure. • Physician or designee is expected to be on site for discharge evaluation. • Supraventricular Tachycardia (SVT) or Atrial Flutter Subjects: No Additional Criteria • Atrial Fibrillation or Ventricular Tachycardia Procedure Subjects: CHADS₂ Score must be ≤1: <p><u>CHADS₂ Score: Stroke Risk Assessment in Atrial Fibrillation</u></p> <table border="1"> <thead> <tr> <th>Score</th><th>CHADS₂ Risk Criteria</th></tr> </thead> <tbody> <tr> <td>1 point</td><td>C: Congestive heart failure</td></tr> <tr> <td>1 point</td><td>H: Hypertension</td></tr> <tr> <td>1 point</td><td>A: Age ≥ 75 years</td></tr> <tr> <td>1 point</td><td>D: Diabetes mellitus</td></tr> <tr> <td>2 points</td><td>S₂: Previous Stroke / transient ischemic attack / thromboembolism</td></tr> </tbody> </table> <ol style="list-style-type: none"> b. <u>No Urinary Catheter Candidate:</u> <ul style="list-style-type: none"> • The subject is a candidate to undergo the procedure and bedrest without a urinary catheter (i.e., indwelling, condom or straight catheter insertion). • No history of urinary retention due to e.g. anesthesia, prostate issues, etc. c. <u>No Protamine Candidate:</u> The subject is a candidate to receive procedural heparin for anti-coagulation management. <p>Note:</p> <p><i>Initial subject eligibility will be determined based on pre-operative screening.</i></p> <p><i>Final subject enrollment in one or more study groups will be determined at the end the procedure based on general intra-op exclusion criteria, as well as group-specific criteria.</i></p> <p><i>Enrollment is thus determined intra-operatively, at the end of the case.</i></p>	Score	CHADS ₂ Risk Criteria	1 point	C: Congestive heart failure	1 point	H: Hypertension	1 point	A: Age ≥ 75 years	1 point	D: Diabetes mellitus	2 points	S ₂ : Previous Stroke / transient ischemic attack / thromboembolism
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<p>Pre-Operative Exclusion Criteria</p>	<p>Subjects will be excluded from participating in this study if they meet any of the following criteria prior to initiation of the index procedure:</p> <ol style="list-style-type: none"> 1. Advanced refusal of blood transfusion, if it should become necessary; 2. Active systemic infection, or cutaneous infection or inflammation in the vicinity of the groin; 3. Pre-existing immunodeficiency disorder and/or chronic use of high dose systemic steroids; 4. Known history of bleeding diathesis, coagulopathy, hypercoagulability, or current platelet count < 100,000 cells/mm³; 5. Severe co-existing morbidities, with a life expectancy of less than 12 months; 6. Currently involved in any other investigational clinical trial that may interfere with the outcomes of this study in the opinion of investigator; 7. Femoral arteriotomy in either limb with any of the following conditions: <ol style="list-style-type: none"> a. access within < 10 days b. any residual hematoma, significant bruising, or known associated vascular complications c. use of a vascular closure device within the previous 30 days; 8. Femoral venotomy in either limb with any of the following conditions: <ol style="list-style-type: none"> a. access within < 10 days b. any residual hematoma, significant bruising, or known associated vascular complications c use of a vascular closure device 9. Any planned procedure involving femoral arterial or venous access in either limb within the next 30 days; 10. Any history of deep vein thrombosis, pulmonary embolism or thrombophlebitis; 11. Significant anemia with a hemoglobin level less than 10 g/dL or a hematocrit less than 30%; 12. Females who are pregnant, planning to become pregnant within 3 months of the procedure, or who are lactating; 13. Extreme morbid obesity (BMI greater than 45 kg/m²) or underweight (BMI less than 20 kg/m²); 14. Unable to routinely walk at least 20 feet without assistance; 15. Known allergy/adverse reaction to bovine derivatives; 16. Administration of low molecular weight heparin (LMWH) within 8 hours before or after the procedure; 17. Planned procedures or 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.
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Intra-Operative Exclusion Criteria	<p>Subjects will be excluded from participating in this study if any of the following exclusion criteria occur during the index procedure:</p> <p><u>General Intra-op Exclusion Criteria:</u></p> <ol style="list-style-type: none">1. Any attempt at femoral arterial access during the procedure;2. Any procedural complications that may extend routine recovery, ambulation and discharge times;3. If the physician deems that a different method should be used to achieve hemostasis of the venous access sites, or that the subject should not attempt ambulation according to the protocol requirements;4. All venous access sites must comply with the following exclusion criteria, assessed immediately prior to enrollment:<ol style="list-style-type: none">a. Difficult insertion of procedural sheath or needle stick problems at the onset of the procedure (e.g., multiple stick attempts, accidental arterial stick with hematoma, “back wall stick”, etc.) in any of the study veins;b. A procedural sheath < 6 Fr or > 12 Fr in inner diameter is present at time of closure;c. A procedural sheath > 12 Fr inner diameter at any time during the procedure.d. Venous access site location is noted to be “high”, above the inguinal ligament (cephalad to lower half of the femoral head or the inferior epigastric vein origin from the external iliac vein);e. Intra-procedural bleeding around sheath, or suspected intraluminal thrombus, hematoma, pseudoaneurysm, or AV fistula;f. Length of the tissue tract, the distance between the anterior venous wall and skin, is estimated to be less than 2.5 cm.
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Additional Intra-Operative Screening: Inclusion Criteria	<p>Study Group Criteria: The subject must be eligible for at least one of the following study groups:</p> <p>a) Same Calendar Day Discharge (all criteria apply):</p> <ul style="list-style-type: none"> • In the Investigator's opinion, the subject is a candidate for Same Calendar Day Discharge per protocol. • If procedural heparin is used, it was/will be reversed at or before venous closure. • Physician or designee must be on site for discharge evaluation. • Supraventricular Tachycardia (SVT) or Atrial Flutter Subjects: No Additional Criteria • Atrial Fibrillation or Ventricular Tachycardia Procedure Subjects: CHADS₂ Score is ≤1, as assessed pre-operatively. • The subject is not enrolled in the No Protamine Group. <p><u>CHADS₂ Score: Stroke Risk Assessment in Atrial Fibrillation</u></p> <table border="1"> <thead> <tr> <th>Score</th><th>CHADS₂ Risk Criteria</th></tr> </thead> <tbody> <tr> <td>1 point</td><td>Congestive heart failure</td></tr> <tr> <td>1 point</td><td>Hypertension</td></tr> <tr> <td>1 point</td><td>Age ≥ 75 years</td></tr> <tr> <td>1 point</td><td>Diabetes mellitus</td></tr> <tr> <td>2 points</td><td>Stroke / transient ischemic attack / thromboembolism</td></tr> </tbody> </table> <p>b) No Urinary Catheter:</p> <ul style="list-style-type: none"> • The subject does not have a urinary catheter inserted/indwelling at the end of the procedure, just prior to enrollment <p>c) No Protamine:</p> <ul style="list-style-type: none"> • The subject received procedural heparin for anti-coagulation management and did not/will not receive protamine. • The subject is not enrolled in the Same Calendar Day Discharge Group. <p><i>*a subject may not be co-enrolled in Same Calendar Day Discharge and No Protamine study groups.</i></p>	Score	CHADS ₂ Risk Criteria	1 point	Congestive heart failure	1 point	Hypertension	1 point	Age ≥ 75 years	1 point	Diabetes mellitus	2 points	Stroke / transient ischemic attack / thromboembolism
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Study Administration													
Clinical Research Organization (CRO)	Chellew Clinical Outsourcing, LLC (CCO) 7844 E. Riverdale St., Mesa, AZ 85207												

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1. Introduction

1.1. Background

While a variety of closure device options exist for femoral arterial closure, there are few closure device options for venous closure. Procedures requiring venous access such as venous stenting (single access site), cardiac ablation (multi-access site), DVT treatments (single access site), etc., are growing. Cardiva asserts that there is a need for developing percutaneous closure of venous access in patients.

Characteristics in the venous environment, such as lower blood velocity and pressure compared to arteries, can contribute to patient complications such as DVT due to reduced blood flow directly, e.g., manual compression, and indirectly e.g., prolonged bedrest. Vascular closure devices with intraluminal components could contribute to reduction in blood flow and/or increased risk of thrombosis.

The Cardiva Mid-Bore VVCS has no intraluminal components. It is based on the previously approved VASCADE® VCS arterial platform [P120016]¹ indicated for percutaneous closure of femoral arteries using 5 to 7F procedural sheaths. The Cardiva Mid-Bore Venous Vascular Closure System (VVCS, based on this proven design, are particularly promising in venous closure due to the following:

- Unimpeded, continual blood flow during closure and bedrest
- No intraluminal components post closure
- Naturally resorbed implant material

The VASCADE VCS arterial platform was evaluated in the RESPECT trial. The study was aimed at evaluating safety and efficacy of the extravascular, bioabsorbable closure system. This was a multicenter, randomized comparison of VASCADE VCS versus Manual Compression (MC) in Diagnostic (Dx) and Interventional (Ix) patients undergoing femoral access through 6/7 F introducer sheaths. Subjects were randomized 2:1, VASCADE versus MC.

Endpoints included:

- Time to Hemostasis (TTH)
- Time to Ambulation (TTA)
- Discharge Eligibility (TTDE)
- Time to Discharge (TTD)
- Device and Procedure Success
- Major and Minor Complications

A total of 420 patients were enrolled (211 Dx, 209 Ix). Mean age was 62 years with 29% of subjects being female. For Ix patients, 77%/69% (VASCADE/MC) received bivalirudin and 8%/3% received GP IIb/IIIa inhibitors. Patients were followed for 30 days.

The RESPECT trial demonstrated that the extravascular VASCADE closure device was safe and effective compared to manual compression in patients in whom 6 and 7 French femoral access was employed in Diagnostic and Interventional procedures. Despite high percentage of Bivalirudin use (77%), there were zero major access site related complications in either arm.

In addition, the use of VASCADE demonstrated a statistically significant reduction in minor access site related complications and significantly shortened TTH, TTA, and time to discharge eligibility (TTDE) when compared to MC.

VASCADE Arterial VCS Real World Experience for Venous Closure:

In the Dou et al (2016) publication, real world experience utilizing the VASCADE arterial VCS for venous closure suggests that venous access closure can be accomplished effectively and with minimal complications.

Results for device success were comparable to the Cardiva RESPECT study, where device success was defined as the ability to deploy the delivery system, deliver the collagen, and achieve hemostasis with the Cardiva VASCADE Vascular Closure System alone or with adjunctive compression:

- Dou (2016): 100% per RESPECT criteria
- RESPECT: 96% overall (94% diagnostic & 97% interventional)

With respect to complications, the Dou (2016) venous study had one device-related minor complication per RESPECT criteria and 1 major complication unrelated to the closure device.

It should be noted that the VASCADE arterial 6/7F device used in Dou (2016) was successful in achieving temporary and final hemostasis in venotomies up to 10F, three French sizes above the approved indication.

Mid-Bore Venous VVCS vs VASCADE VCS Device Design:

For the AMBULATE Study, the Cardiva Mid-Bore VVCS catheter's disc diameter was increased from ~19F (VASCADE arterial VCS) to ~21 initially and subsequently to ~23F¹ to mitigate the device pulling through the vessel wall in mid-bore venotomies as a function of venotomy size approaching the disc's diameter. The disc diameter increase anticipates use of procedure sheaths up to 12F inner diameter.

¹ G170144/S004 5 Day Notice of IDE Change

1.2. Unmet Clinical Need

Currently, the standard technique for venous closure is manual compression (MC). There are various procedures requiring venous access, including procedures that require a single venous access site in a single limb up to and including procedures that require multiple venous access sites in both limbs. Multi-access site / multi – limb procedures mainly include cardiac ablation. These cardiac ablation procedures account for both the fastest growing segment and majority of venous access procedures. Innovation in the field has progressed cardiac ablations from many hours to a short predictable procedure time, however the ongoing requirement for prolonged supine bedrest post-procedure still results in lengthy delays in time to patient ambulation (TTA).

According to Srivatsa (2015), there are certain limitations with the manual compression approach, including:

- 1) discomfort and pain for the patient;
- 2) postponement of sheath extraction post-procedure which could lead to more discomfort, increased bleeding risk and discontinuation of anti-coagulation post-procedure;
- 3) risk of deep venous thrombosis; and
- 4) risk of failed closure due to inaccurate location of the manual compression site.

1.3. AMBULATE, A Clinical Investigation for Venous Closure [PTL 0508]

The primary AMBULATE clinical investigational study was focused on multiple venous access site closure using the Cardiva Mid-Bore VVCS device for closure following venous catheterization procedures to address the greatest clinical need. Data collected during the clinical study suggest that there is additional potential for the use of Mid-Bore VVCS to impact other procedural and administrative practices to benefit the patient. Additional study is warranted to further evaluate the following unmet clinical needs:

- Elimination of Urinary Catheter
- Same Calendar Day Discharge
- Protamine Elimination

In addition, the AMBULATE study required Investigators to standardize their access practice as follows:

- 2-access site maximum per limb
- 3-access site minimum and 4-access site maximum per patient
- Placement of >9F sheaths in opposite legs

In real world procedures, there is a wide variety of configurations with respect to the number and location (i.e. limb) of femoral venous access sites.

Elimination of Urinary Catheter

Urinary catheters can contribute to patient discomfort and are associated with an increased risk of Urinary Tract Infection (UTI). Foley catheters which are not indicated for medical reasons (e.g. urinary retention or incontinence) are primarily indicated for patients who are expected to be placed on longer bedrest. In the AMBULATE Study we learned that there are a variety of practices at the site level regarding Foley Use including: exclusive use of urinary catheter; exclusive no urinary catheter; and Mixed Use.

Due to reduced expected bedrest period for VVCS subjects vs. MC subjects, it is expected that the use of the urinary catheter is unnecessary for most patients who are receiving the Cardiva Mid-Bore VVCS.

However, in the AMBULATE Study design where subjects were randomized intra-operatively at the end of the index procedure, urinary catheter use / non-use was not manipulated as part of the study and was dependent on Investigator's orders (prior to randomization of VVCS vs. MC).

The AMBULATE CAP Study is a single arm study, therefore Investigators will plan on bedrest orders consistent with Mid-Bore VVCS closure for all qualifying subjects. Based on this real-world study design, it is expected that a number of subjects not previously considered eligible for No Urinary Catheter due to expected prolonged bedrest may now be eligible for elimination of Foley catheter for their procedures.

Elimination of Protamine

In the AMBULATE study treatment arm, as indicated in the protocol¹, investigators did not wait for heparin reversal using Protamine or wait for target ACT levels in order to close using Mid-Bore VVCS. However, as randomization was intra-operative at the end of the index procedure, standard of care regarding heparin reversal was followed in the event the subject was randomized to manual compression.

In the AMBULATE CAP Study, however, the single arm study design will allow all qualifying subjects to receive Mid-Bore VVCS closure devices. Protamine is unnecessary with the use of Mid-Bore VVCS since heparin reversal will occur by natural decay during the bedrest period.

Same Calendar Day Discharge

In the AMBULATE Study, twenty-eight subjects were discharged on the same calendar day with nearly twice as many in the device arm versus the control arm. Specifically, 17/28 subjects (61%) for the VVCS arm and 11/28 subjects (39%) for the manual compression arm. Across the 204 study

¹ PTL 0508 AMBULATE Protocol Section 7.4.5 Access Site Closure Instructions

subjects, the majority (166) of subjects (81%) were discharged by the next calendar day for both device (76 subjects, 37%) and manual compression (90 subjects, 44%).

The AMBULATE CAP Study intends to gather additional data in a more defined study group populations to expand the potential for low risk patients (i.e. SVT, A-Flutter subjects, or A-Fib & VT subjects with CHADS₂ Score ≤ 1) to be discharged the same calendar day as their index procedure.

1.4. The AMBULATE Continued Access Protocol (CAP)

Overview:

The AMBULATE CAP study will continue to collect additional data on:

- Urinary Catheter Use
- Same Calendar Day Discharge
- Protamine Use

In contrast to the primary AMBULATE Study, the AMBULATE CAP study will allow investigators to follow their standard access practices rather than protocol-standardized sheath configurations. The CAP study design is intended to provide data to support typical clinical practice (e.g. sheath configuration) of the Mid-Bore VVCS devices for femoral venous closure in support of the CAP Study.

Objective:

The objective of the trial is to demonstrate the safety and effectiveness of the Cardiva Mid-Bore Venous Vascular Closure System (VVCS) in sealing femoral venous access sites at the completion of catheter-based procedures performed through 6-12 Fr introducer sheath, while allowing for one or more of the following: elimination of urinary catheter, elimination of protamine, and/or allowing same (calendar) day discharge for the appropriate patient population.

The AMBULATE CAP Study primary and secondary safety endpoints have the same complication definitions as the AMBULATE Study. The primary effectiveness endpoint of Procedure Success for this study has the same definition as AMBULATE Procedure Success, specifically, final hemostasis at all venous access sites and freedom from major venous access site closure-related complications through 30 days follow up.

Key differences between the randomized AMBULATE study and this CAP study include the following:

- Single Arm Study with prospectively assigned study groups
- No time-based endpoints or data collection
- No Ultrasound Sub-study
- Additional Inclusion/Exclusion Criteria for study groups
- No access site minimum or maximum per limb or per patient
- Allows placement of >9F sheaths in the same leg
- Allows ultrasound as an option to fluoroscopic imaging for disc location verification
- Follow up period is 30 days (+/-10) instead of 30 days (+/-7)

- Follow up can be completed as an office visit or a phone call

It should be noted that there was a development change conditionally approved in G170144/S004 Device Disc Size Change 5 Day Notice of IDE Change. The disc size manufacturing target was increased from 21F to 23F. There was no change to the product specification for disc diameter; the larger size is within the original specification range. This larger diameter device will continue to be used in the AMBULATE CAP Study.

Based on AMBULATE Study preliminary data¹, the Mid-Bore VVCS device was effective with no significant safety concerns. The differences between the AMBULATE Study and AMBULATE CAP Study reflect learning from the original study and are not expected to introduce additional risks to patients.

1.5. Real World Experience: VASCADE Arterial VCS Real World Experience for Venous Closure

In the Dou et al (2016) publication, real world experience utilizing the VASCADE arterial VCS for venous closure suggests that venous access closure can be accomplished effectively and with minimal complications.

Results for device success were comparable to the Cardiva RESPECT study, where device success was defined as the ability to deploy the delivery system, deliver the collagen, and achieve hemostasis with the Cardiva VASCADE™ Vascular Closure System alone or with adjunctive compression:

- Dou (2016): 100% per RESPECT criteria
- RESPECT: 96% overall (94% diagnostic & 97% interventional)

With respect to complications, the Dou (2016) venous study had one device-related minor complication per RESPECT criteria and 1 major complication unrelated to the closure device.

It should be noted that the VASCADE arterial 6/7F device used in Dou (2016) was successful in achieving temporary and final hemostasis in venotomies up to 10F, three French sizes above the approved indication.

The Cardiva Mid-Bore VVCS catheter's disc diameter has been increased from ~19F (VASCADE arterial VCS) to ~23F to mitigate the device pulling through the vessel wall in mid-bore venotomies as a function of venotomy size approaching the disc's diameter. The disc diameter increase anticipates use of procedure sheaths up to 12F inner diameter.

¹ RPT 0527 AMBULATE Sub-study Data Analysis Report for CE Mark

1.6. Design Verification Testing

1.6.1. Design verification testing including the following:

- Functional
- Mechanical
- Biocompatibility
- Packaging
- Shelf-life
- Sterilization

Conclusion: Based on testing performed, Mid-Bore Venous VCS 6 – 12F successfully fulfilled the tests requirements for design verification.

1.7. Pre-clinical Testing

Pre-clinical testing included the following two studies:

- Chronic GLP Animal Study [RPT 0503-01]: safety and efficacy
- Acute Animal Study [RPT 0533-01]: performance

1.7.1. Pre-clinical Chronic GLP Study Overview [RPT 0503]

The purpose of this chronic GLP study was to evaluate the *In-Vivo* safety and efficacy performance of the Cardiva VASCADE 6/7F Vascular Closure System (VCS) in percutaneous closure of femoral veins in the porcine model using 12F introducer sheaths.

- **High-level Protocol Summary:**

- 3 Animals with 6 Devices implanted bilaterally with 12F access sheaths
- ACT >300 seconds
- 30 Day Chronic Study
- Gross Pathology and histopathological analysis was completed on downstream organs and venotomy sites

- **Abbreviated High-level Results Summary**

- All sites achieved hemostasis within 2 minutes without any complication
- Vessel patency confirmed by ultrasound post collagen deployment
- No gross abnormalities indicative of complications or adverse effects
- Gross evaluation of end organs did not demonstrate any evidence of distal thromboembolic events

- Collagen patch was not associated with any type of intraluminal reaction or thrombus
 - No adverse effects or complications identified histologically
- **Conclusion:**
- Test article met the objectives set forth in study.
 - No gross abnormalities indicative of complications or adverse effects associated with the test procedure to implant site or organ system.
 - Test article sealed veins appropriately using a 12 French introducer sheath and was demonstrated to be safe for its intended use.

1.7.2. Pre-clinical Acute Study Overview [RPT 0533]

An acute animal study was performed in a porcine model to compare the larger disc device to the current device with respect to safety and effectiveness in achieving the intended use.

A total of 12 cases were performed, 6 per device type. A 9F indwelling sheath was in place for all procedures. A 14F sheath along with the 9F indwelling sheath was used for venous access to simulate the additional dilation that occurs during a cryo case procedure with 12F sheath access.

The study showed that the larger disc VVCS device offers a greater resistance to disc pull through. In this model, on average, the pull through forces were approximately 24% greater with the larger disc device. Additionally, the study showed that the larger disc VVCS device can be deployed with a 9F indwelling sheath with minimal or no distortion to the disc. Temporary hemostasis was obtained in all cases as was evident by lack of any extravasation of contrast in the surrounding tissue.

Therefore, design validation testing demonstrated that device was effective in achieving its intended use in venotomies using 14F access sheaths to simulate the 12F access sites with additional dilation as observed in the AMBULATE study. There were no safety issues observed in the study.

1.8. Clinical Studies

1.8.1. AMBULATE Study Mid-Bore VVCS Sub-study analysis for CE Mark [RPT 0527]

The AMBULATE trial was aimed at evaluating safety and efficacy of the extravascular, bioabsorbable closure system, Mid-Bore VVCS. This was a multicenter, randomized comparison of Mid-Bore VVCS versus Manual Compression (MC) patients undergoing femoral venous access through 6-12F introducer sheaths. Subjects were randomized 1:1, VVCS versus MC.

The AMBULATE Study Mid-Bore VVCS Sub-Study analysis was performed using interim data from the AMBULATE Study to assess a sub-set of subjects randomized to the treatment arm of the AMBULATE Study (PTL 0508-02) with respect to safety and performance of the Cardiva Mid-Bore Venous Vascular Closure System (VVCS) in support of CE marking.

Endpoints included:

- Time to Ambulation (TTA)
- Time to Hemostasis (TTH)
- Discharge Eligibility (TTDE)
- Time to Discharge (TTD)
- Device and Procedure Success
- Major and Minor Complications

Forty (40) consecutive subjects from 5 clinical sites were prospectively enrolled for treatment with Mid-Bore VVCS. Mean age was 63.8 years with 22.5% of subjects being female. Patients were followed for 30 days. Data Analysis results showed the following:

- Performance Endpoints: See Table 1
- Procedure Success and Device Success* : See Table 2
- Safety Endpoints: There were no major access site related complications and 1 minor access site related complication. See Table 3 and Table 4

**Definitions:*

Procedure Success: attainment of final hemostasis at all venous access sites and freedom from major venous access site closure-related complications through 30 days. This is a per-patient analysis.

Device Success: the ability to deploy the delivery system, deliver the collagen, and achieve hemostasis with the Mid-Bore VVCS. This is a per-access site analysis.

The performance and safety outcomes for the AMBULATE Study Mid-Bore VVCS Sub-analysis of the Cardiva Mid-Bore Venous Vascular Closure System (800-612C) demonstrate the performance and safety of the device. The Mid-Bore VVCS successfully closed femoral venous access sites in patients who have undergone catheter-based procedures utilizing 6 – 12 Fr 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. There were no major access site related complications and 1 minor access site related complication.

Table 1: Primary Performance Endpoint: TTA for CE Mark Sub Study [RPT 0527-03]

Time to Ambulation (hours)	Subjects with 3 Access Sites	Subjects with 4 Access Sites	All Subjects
N	11	29	40
Mean	2.36	2.75	2.65
Std Deviation	0.50	1.07	0.95
Median	2.17	2.24	2.21
Min	2.07	2.08	2.07
Max	3.68	6.32	6.32
95% Confidence Interval	2.03-2.70	2.35-3.16	2.34-2.95

Table 2: Secondary Performance Endpoint Analysis for CE Mark Sub Study [RPT 0527-03]

Description	N(40)
Total Post Procedure Time (hours)	
N	40
Mean	2.91
Std Deviation	0.99
Median	2.48
Min	2.25
Max	6.63
95% Confidence Interval	2.59-3.23
Time to Closure Eligibility (minutes)	
N	40
Mean	6.49
Std Deviation	3.00
Median	6.59
Min	1.60
Max	13.55
95% Confidence Interval	5.53-7.45
Time to Hemostasis (minutes)	
N	149
Mean	6.08
Std Deviation	3.40
Median	5.17
Min	3.00
Max	28.73
95% Confidence Interval	5.53-6.63

Description	N(40)
Time to Discharge Eligibility (hours)	
N	40
Mean	2.92
Std Deviation	0.94
Median	2.50
Min	2.30
Max	6.48
95% Confidence Interval	2.62-3.22
Time to Hospital Discharge (hours)	
N	40
Mean	21.6
Std Deviation	11.95
Median	22.52
Min	3.82
Max	75.75
95% Confidence Interval	17.78-25.42

Table 3: Major Access Site Related Complications - Total Number of Limbs with Any Number of Occurrences

(N=78)	Number	Percent
Combined major venous access site closure-related complications through 30 days post-procedure	0	0%
Individual major venous access site closure-related complications through 30 days post-procedure		
Access site-related bleeding requiring transfusion;	0	0%
Vascular injury requiring surgical repair;	0	0%
Access site-related infection confirmed by culture and sensitivity, requiring intravenous antibiotics and/or extended hospitalization;	0	0%
New onset permanent access site-related nerve injury (i.e., persisting for > 30 days)	0	0%
New onset access site-related nerve injury in the ipsilateral lower extremity requiring surgical repair;	0	0%
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;	0	0%

(N=78)	Number	Percent
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).	0	0%
Primary Safety 95% Confidence Interval	95.4%-100%	

Table 4: Minor Access Site Related Complications - Total Number of Limbs with Any Number of Occurrences

(N=78)	Number	%
Combined minor venous access site closure-related complications through 30 days post-procedure	1	1.3%
Individual minor venous access site closure-related complications through 30 days post-procedure		
Access site-related bleeding requiring greater than 30 minutes of continuous manual compression to achieve initial venous hemostasis;	0	0%
Access site-related hematoma > 6 cm documented by ultrasound	0	0%
Late access site-related bleeding (following hospital discharge)	0	0%
Ipsilateral deep vein thrombosis, confirmed by ultrasound/imaging	0	0%
Localized access site infection confirmed by culture and sensitivity, treated with intramuscular or oral antibiotics	1	1.3%
Arteriovenous fistula requiring treatment	0	0%
Arteriovenous fistula not requiring treatment	0	0%
Pseudoaneurysm requiring thrombin injection, fibrin adhesive injection or ultrasound-guided compression	0	0%
Pseudoaneurysm not requiring treatment	0	0%
Transient access site-related nerve injury	0	0%
Secondary Safety 95% Confidence Interval	93.1%-100%	

1.8.2. RESPECT Trial using VASCADE arterial VCS

VASCADE 6/7F VCS was evaluated in a prospective, multi-center, randomized (2:1) clinical trial (the RESPECT Trial) in 20 sites in the United States and one site in Australia, comparing VASCADE VCS to Manual Compression (MC). The trial involved 420 patients undergoing diagnostic (n = 211) or

interventional (n = 209) endovascular procedures, with 275 of those subjects receiving the VASCADE device.

The RESPECT trial was designed to evaluate the safety and effectiveness of the VASCADE 6/7 Fr VCS in sealing femoral arterial access sites. It was specifically designed to demonstrate a reduction in hemostasis, ambulation, and eligibility for hospital discharge in comparison to manual compression.

Table 3 and **Table 4** summarize safety and efficacy data from the RESPECT study.

Since commercial release in 2013, real-world experience with over 124,000 devices sold in the US, the data indicates the ongoing relevance of the clinical trial results (Tables 5, 6):

- 0.36% Reported Complaint Rate
- 0.1% Reported Patient Complication Rate

The VASCADE VCS platform has an established safety track record in controlled clinical settings and real world usage. VASCADE VCS's safety profile has been established in arterial vessel closure, which generally provides a more difficult closure environment compared to venous closure due to higher blood pressure.

Table 5: Access Site-Related Complications at 30 Days by Event

	Total (N=417)				
	VASCADE (N=275)		Manual Compression (N=142)		p-value*
Any Access Site-Related Major Complication	0	0.0%	0	0.0%	1.00
Access site-related bleeding requiring transfusion	0	0.0%	0	0.0%	1.00
Vascular injury requiring repair	0	0.0%	0	0.0%	1.00
New ipsilateral lower extremity ischemia causing a threat to the viability of the limb	0	0.0%	0	0.0%	1.00
Access site-related infection requiring intravenous antibiotics and/or extended hospitalization	0	0.0%	0	0.0%	1.00
New onset access site-related neuropathy in the ipsilateral lower extremity requiring surgical repair	0	0.0%	0	0.0%	1.00
Permanent access site-related nerve injury (> 30 days)	0	0.0%	0	0.0%	1.00
Any Access Site-Related Minor Complication	3	1.1%	10	7.0%	0.002
Access site-related bleeding requiring > 30 minutes to achieve hemostasis	1	0.4%	10	7.0%	0.0001
Access site-related hematoma > 6 cm	1	0.4%	0	0%	1.00
Late access site-related bleeding (following hospital discharge)	0	0%	0	0%	1.00
Ipsilateral lower extremity arterial emboli	0	0%	0	0%	1.00
Ipsilateral deep vein thrombosis**	4	1.5%	0	0%	NA
Access site-related vessel laceration	0	0%	0	0%	1.00
Access site wound dehiscence	0	0%	0	0%	1.00
Localized access site infection treated with intramuscular or oral antibiotics	0	0%	0	0%	1.00
Arteriovenous fistula not requiring treatment**	1	0.4%	0	0%	NA
Pseudoaneurysm requiring thrombin injection or fibrin adhesive injection**	1	0.4%	0	0%	NA

Pseudoaneurysm not requiring treatment**	4	1.5%	0	0%	NA
New onset access site-related neuropathy in the ipsilateral lower extremity not requiring surgical repair	1	0.4%	0	0%	1.00
Ipsilateral pedal pulse diminished by two grades or transiently lost	0	0%	0	0%	1.00

*Two-sided Fisher's exact test

**Due to different complication-detecting methods between study arms (100 VASCADE patients and no other study patients underwent a femoral ultrasound exam in an ultrasound sub-study), rates for pseudoaneurysm requiring or not requiring treatment, arteriovenous fistula not requiring treatment, and ipsilateral deep vein thrombosis (which were detected by ultrasound exam) are presented but not compared between arms, nor are they included in the computation of the VASCADE overall minor complication rate (top row).

Table 6: RESPECT Efficacy Endpoint Results

Total N=420	VASCADE (N=278)	Manual Compression (N=142)	p-value*
Time to Hemostasis (minutes)			
N	275	142	
Mean	4.8	21.4	< 0.0001
Std Deviation	5.4	12.4	
Median	3.0	20.0	< 0.0001
Min	0.6	0.0	
Max	31.6	97.0	
Time to Ambulation (hours)			
N	275	142	
Mean	3.8	5.8	< 0.0001
Std Deviation	5.1	3.1	
Median	3.2	5.2	< 0.0001
Min	1.0	1.7	
Max	78.0	22.8	
Time to Discharge Eligibility (hours)			
N	274	142	
Mean	4.8	6.5	0.001
Std Deviation	6.4	3.3	
Median	3.6	5.7	< 0.0001
Min	1.4	2.2	
Max	78.4	23.2	
Time to Hospital Discharge (hours)			
N	275	142	
Mean	18.3	13.7	0.04
Std Deviation	34.5	9.8	
Median	17.2	13.9	0.94
Min	1.7	2.4	
Max	432.9	55.6	
<i>*p-value from t-test for comparing means and Wilcoxon's test for comparing medians</i>			

1.9. Risks and Benefits

1.9.1. Risks

Risks associated with the Cardiva Mid-Bore VVCS are similar to those associated with other extravascular methods of achieving hemostasis at venotomy sites. Complications that may occur include:

- Allergic response
- Arterio-venous fistula
- Bleeding/oozing from the puncture site
- Bruising at puncture site
- Death
- Deep vein thrombosis
- Device failure / malfunction
- Edema
- Embolization (thrombus, air, calcific debris, device)
- Hematoma
- Infection
- Inflammatory response
- Intimal tear / dissection
- Laceration of the vessel wall
- Lower extremity ischemia
- 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
- Wound dehiscence

1.9.2. Benefits

The potential benefits of using the Cardiva Mid-Bore VVCS to achieve venous hemostasis include elimination of urinary catheter use, same calendar day discharge, and protamine elimination, which the trial is intended to evaluate, while maintaining an acceptable safety profile.

2. Device Description

The Cardiva Mid-Bore Venous Vascular Closure System (VVCS) is indicated for the percutaneous closure of femoral venous access sites while reducing times to ambulation and discharge eligibility in patients who have undergone catheter-based procedures utilizing 6 – 12 Fr 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.

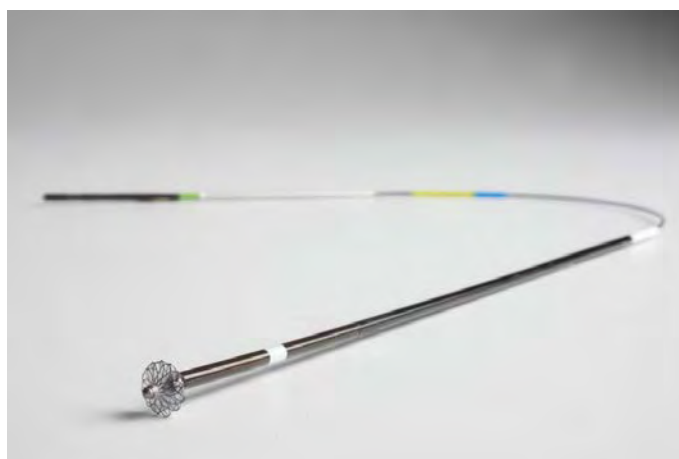
The Cardiva Mid-Bore VVCS is a disposable device based on the previously approved VASCADE 6/7F arterial VCS device. The only significant change with respect to the approved device is an increase in disc diameter from ~19F to ~23F to ensure temporary hemostasis and proper collagen deployment during closure of larger bore holes.

As in the previously approved device, the Mid-Bore VVCS device is designed to deliver a resorbable collagen patch extravascularly to block blood flow from the femoral venotomy site at the completion of a catheterization procedure. Cardiva's Mid-Bore VVCS devices are intended to assist physicians or catheter lab technicians in controlling bleeding from femoral venotomy sites and reduce time to ambulation.

The Mid-Bore VVCS device is used in conjunction with 6 – 12 Fr inner diameter introducer sheaths. The VVCS device is introduced through a compatible procedure sheath at the completion of a catheterization procedure.

The Mid-Bore VVCS is comprised of a catheter containing a resorbable collagen implant. Refer to Figure 1 below for an image of the device.

Figure 1: Cardiva Mid-Bore VVCS with Disc Deployed



To use the Cardiva VVCS, the catheter is inserted into the femoral vein through the previously placed introducer 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 vein. The introducer 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 venotomy. The position of the device disc against the vessel wall locates the collagen patch in the tissue tract immediately adjacent to the venotomy site (extravascular) and its location is verified using fluoroscopy prior to release. The clip is placed on the device shaft at the surface of the skin to hold the device in place during fluoroscopy.

Note, the principle of operation and the steps described below are identical to that of the previously approved device. Refer to the Instructions For Use document in **Attachment 3**.

Device Labeling

A copy of the Instructions for Use (IFU) will be included with the devices. The Cardiva Mid-Bore Venous Vascular Closure System (VVCS) labels contain the following information:

- Venous Vascular Closure System
- Lot number
- Expiration (use by) date
- For Investigational Use Only

3. AMBULATE CAP Study Objective

The objective of the trial is to demonstrate the safety and effectiveness of the Cardiva Mid-Bore Venous Vascular Closure System (VVCS) in sealing femoral venous access sites at the completion of catheter-based procedures performed through 6-12 Fr introducer sheath, 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.

4. Study Design

4.1. Overview

This is a prospective, multi-center, single-arm continued access clinical trial designed to evaluate the safety and effectiveness of the Cardiva Mid-Bore Venous Vascular Closure System (VVCS) in sealing multiple femoral venous access sites at the completion of catheter-based procedures performed through 6 - 12 Fr introducer sheaths. Measures of safety and effectiveness will be assessed through hospital discharge and 30 (± 10) days post-procedure.

4.2. Sample Size

Enrollment: 300 subjects will be included in this trial. Subjects will be considered enrolled in intra-procedural timeframe based on the inclusion/exclusion criteria previously identified.

Investigational Sites: This trial will be conducted at up to 5 sites in the United States, with a minimum of 2 sites enrolling subjects in the trial. Any one site will not enroll more than 60% of the subjects. The sites will be sites that participated in the AMBULATE Study.

5. Study Population

5.1. *Selection Criteria*

The following pages outline the specific inclusion and exclusion criteria for the study. Before the study randomization, a patient must meet all of the inclusion and exclusion criteria.

5.1.1. Pre-Operative Inclusion Criteria

Pre-Operative Inclusion Criteria	<p>All subjects are required to meet the following inclusion criteria in order to be considered eligible for participation in this trial:</p> <ol style="list-style-type: none"> 1. ≥ 18 years of age; 2. Capable and willing to give informed consent; 3. Acceptable candidate for an elective, non-emergent catheter-based procedure via the common femoral vein(s) using a 6 to 12 Fr inner diameter introducer sheath 4. Able and willing to complete a 30 (± 10) days post-procedure follow-up contact; 5. Acceptable candidate for emergent vascular surgery, and/or manual compression of the venous access site; 6. Study Group Criteria: The subject is eligible for at least one of the following study groups: <ul style="list-style-type: none"> • <u>Same Calendar Day Discharge Candidate:</u> • The subject is expected to undergo an Atrial Fibrillation, Supraventricular Tachycardia, Ventricular Tachycardia or Atrial Flutter procedure. • If procedural heparin is planned to be used, it must be reversed at or before venous closure. • Physician or designee is expected to be on site for discharge evaluation. • Supraventricular Tachycardia (SVT) or Atrial Flutter Subjects: No Additional Criteria • Atrial Fibrillation or Ventricular Tachycardia Procedure Subjects: CHADS₂ Score must be ≤ 1: <p><u>CHADS₂ Score: Stroke Risk Assessment in Atrial Fibrillation</u></p> <table border="1"> <thead> <tr> <th>Score</th><th>CHADS₂ Risk Criteria</th></tr> </thead> <tbody> <tr> <td>1 point</td><td>C: Congestive heart failure</td></tr> <tr> <td>1 point</td><td>H: Hypertension</td></tr> <tr> <td>1 point</td><td>A: Age ≥ 75 years</td></tr> <tr> <td>1 point</td><td>D: Diabetes mellitus</td></tr> <tr> <td>2 points</td><td>S: Stroke / transient ischemic attack / thromboembolism</td></tr> </tbody> </table> <ul style="list-style-type: none"> • <u>b) No Urinary Catheter Candidate:</u> • The subject is a candidate to undergo the procedure and bedrest without a urinary catheter (i.e., indwelling, condom or straight catheter insertion). • No history of urinary retention due to e.g. anesthesia, prostate issues, etc. • <u>c) No Protamine Candidate:</u> The subject is a candidate to receive procedural heparin for anti-coagulation management. <p>Note:</p> <p><i>Initial subject eligibility will be determined based on pre-operative screening.</i></p> <p><i>Final subject enrollment in one or more study groups will be determined at the end the procedure based on general intra-op exclusion criteria, as well as group-specific criteria. Enrollment is thus determined intra-operatively, at the end of the case.</i></p> 	Score	CHADS ₂ Risk Criteria	1 point	C: Congestive heart failure	1 point	H: Hypertension	1 point	A: Age ≥ 75 years	1 point	D: Diabetes mellitus	2 points	S: Stroke / transient ischemic attack / thromboembolism
Score	CHADS ₂ Risk Criteria												
1 point	C: Congestive heart failure												
1 point	H: Hypertension												
1 point	A: Age ≥ 75 years												
1 point	D: Diabetes mellitus												
2 points	S: Stroke / transient ischemic attack / thromboembolism												

5.1.2. Pre-Operative Exclusion Criteria

Pre-Operative Exclusion Criteria	<p>Subjects will be excluded from participating in this study if they meet any of the following criteria prior to initiation of the index procedure:</p> <ol style="list-style-type: none"> 1. Advanced refusal of blood transfusion, if it should become necessary; 2. Active systemic infection, or cutaneous infection or inflammation in the vicinity of the groin; 3. Pre-existing immunodeficiency disorder and/or chronic use of high dose systemic steroids; 4. Known history of bleeding diathesis, coagulopathy, hypercoagulability, or current platelet count < 100,000 cells/mm³; 5. Severe co-existing morbidities, with a life expectancy of less than 12 months; 6. Currently involved in any other investigational clinical trial that may interfere with the outcomes of this study in the opinion of investigator; 7. Femoral arteriotomy in either limb with any of the following conditions: <ol style="list-style-type: none"> a. access within < 10 days b. any residual hematoma, significant bruising, or known associated vascular complications c. use of a vascular closure device within the previous 30 days; 8. Femoral venotomy in either limb with any of the following conditions: <ol style="list-style-type: none"> a. access within < 10 days b. any residual hematoma, significant bruising, or known associated vascular complications c use of a vascular closure device 9. Any planned procedure involving femoral arterial or venous access in either limb within the next 30 days; 10. Any history of deep vein thrombosis, pulmonary embolism or thrombophlebitis; 11. Significant anemia with a hemoglobin level less than 10 g/dL or a hematocrit less than 30%; 12. Females who are pregnant, planning to become pregnant within 3 months of the procedure, or who are lactating; 13. Extreme morbid obesity (BMI greater than 45 kg/m²) or underweight (BMI less than 20 kg/m²); 14. Unable to routinely walk at least 20 feet without assistance; 15. Known allergy/adverse reaction to bovine derivatives; 16. Administration of low molecular weight heparin (LMWH) within 8 hours before or after the procedure; 17. Planned procedures or 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.
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5.1.3. Intra-Operative Inclusion Criteria

Intra-Operative Exclusion Criteria	<p>Subjects will be excluded from participating in this study if any of the following exclusion criteria occur during the index procedure:</p> <p><u>General Intra-op Exclusion Criteria:</u></p> <ol style="list-style-type: none">1. Any attempt at femoral arterial access during the procedure;2. Any procedural complications that may extend routine recovery, ambulation and discharge times;3. If the physician deems that a different method should be used to achieve hemostasis of the venous access sites, or that the subject should not attempt ambulation according to the protocol requirements;4. All venous access sites may must comply with the following exclusion criteria, assessed immediately prior to enrollment:<ol style="list-style-type: none">d. Difficult insertion of procedural sheath or needle stick problems at the onset of the procedure (e.g., multiple stick attempts, accidental arterial stick with hematoma, “back wall stick”, etc.) in any of the study veins;e. A procedural sheath < 6 Fr or > 12 Fr in inner diameter is present at time of closure;f. A procedural sheath > 12 Fr inner diameter at any time during the procedure.d. Venous access site location is noted to be “high”, above the inguinal ligament (cephalad to lower half of the femoral head or the inferior epigastric vein origin from the external iliac vein);e. Intra-procedural bleeding around sheath, or suspected intraluminal thrombus, hematoma, pseudoaneurysm, or AV fistula;f. Length of the tissue tract, the distance between the anterior venous wall and skin, is estimated to be less than 2.5 cm.
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5.1.4. Intra-Operative Inclusion Criteria

Additional Intra-Operative Screening: Inclusion Criteria	<p>Study Group Criteria: The subject must be eligible for at least one of the following study groups::</p> <p>a) Same Calendar Day Discharge (all criteria apply):</p> <ul style="list-style-type: none"> • In the Investigator's opinion, the subject is a candidate for Same Calendar Day Discharge per protocol. • If procedural heparin is used, it must be reversed at or before venous closure. • Physician must be on site for discharge evaluation. • Supraventricular Tachycardia (SVT) or Atrial Flutter Subjects: No Additional Criteria • Atrial Fibrillation or Ventricular Tachycardia Procedure Subjects: CHADS₂ Score is ≤1, as assessed pre-operatively. <ul style="list-style-type: none"> ○ The subject is not enrolled in the No Protamine Group. <p><u>CHADS₂ Score: Stroke Risk Assessment in Atrial Fibrillation</u></p> <table border="1"> <thead> <tr> <th>Score</th><th>CHADS₂ Risk Criteria</th></tr> </thead> <tbody> <tr> <td>1 point</td><td>Congestive heart failure</td></tr> <tr> <td>1 point</td><td>Hypertension</td></tr> <tr> <td>1 point</td><td>Age ≥ 75 years</td></tr> <tr> <td>1 point</td><td>Diabetes mellitus</td></tr> <tr> <td>2 points</td><td>Stroke/transient ischemic attack</td></tr> </tbody> </table> <p>b) No Urinary Catheter:</p> <ul style="list-style-type: none"> • The subject does not have a urinary catheter inserted/indwelling at the end of the procedure, just prior to enrollment. <p>c) No Protamine:</p> <ul style="list-style-type: none"> • The subject received procedural heparin for anti-coagulation management and did not/will not receive protamine. • The subject is not enrolled in the Same Calendar Day Discharge Group <p><i>*a subject may not be co-enrolled in Same Calendar Day Discharge and No Protamine study groups.</i></p>	Score	CHADS ₂ Risk Criteria	1 point	Congestive heart failure	1 point	Hypertension	1 point	Age ≥ 75 years	1 point	Diabetes mellitus	2 points	Stroke/transient ischemic attack
Score	CHADS ₂ Risk Criteria												
1 point	Congestive heart failure												
1 point	Hypertension												
1 point	Age ≥ 75 years												
1 point	Diabetes mellitus												
2 points	Stroke/transient ischemic attack												

5.2. Withdrawal of Subjects

While study withdrawal is discouraged, 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 termination. 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.

Subjects who are intended to receive VVCS and then never have any device(s) inserted, for any reason, will not be enrolled in the study. Screen failure data will be recorded on the log.

6. Written Informed Consent

Written Informed Consent must be obtained for all patients who are potential study candidates.

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 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 informed consent form, the Investigator may determine that the patient is not a suitable candidate for the study.

A Screening/Enrollment Log will be maintained to document select information about candidates who fail to meet the entry criteria.

7. Study Procedures and Enrollment

7.1. Duration of Subject Participation

Subjects enrolled in the trial will participate for approximately 30 days +/- 10 days.

7.2. Enrollment

Prior to the procedure, subjects will be screened for eligibility in each of the three study groups. Subjects must be eligible for at least one of the groups to be eligible for enrollment and may be eligible to participate in multiple groups. All subjects who are eligible for participation will undergo additional screening at the end of the procedure, prior to enrollment, to determine their participation in that study group. *Note that subjects may not participate simultaneously in the No Protamine and Same Calendar Day Discharge Groups for potential safety reasons.*

At the completion of the procedure, subjects that meet all the intra-operative eligibility criteria and who receive any portion of a Cardiva Mid-Bore VVCS are considered enrolled in the study. Subjects must have at least one device inserted into the sheath/body to be considered enrolled and subsequently must complete all study requirements. If a subject has all venous access sites closed with manual compression only for any reason, and did not ever have a Cardiva VVCS device inserted, he/she will not be enrolled in the study at all. Subjects who have at least one Cardiva VVCS device inserted should have as many venous access sites closed with VVCS as possible (i.e., “conversion” to manual compression should only occur when it is not feasible to close a site with VVCS). See Section 5.2 Withdrawal of Subjects.

7.3. Visit Schedule

The following outlines the required study assessments.

Table 7. Study Event Schedule

	≤ 45 days before Procedure	Procedure	Post- Procedure/ Successful Ambulation	Post- Procedure/ Hospital Discharge	30 days +/- 10 days Contact
Study Initiation:	X				
Demographics/ Medical History	X				
Groin assessment		X	X	X	X
Complaints of pain/nerve injury in lower extremities	X			X	X
Laboratory Tests*:	X				
Pre-op Inclusion / Exclusion Criteria Assessment	X	X			
Informed Consent	X				
Intra-procedural Inclusion Criteria		X			
Intra-procedural Exclusion Criteria Assessment		X			
Enrollment		X			
Data Collection:					
Hemostasis Confirmation		X			
Ambulation Date/Time			X		
PES - Pt. Experience Survey			X		
Same Calendar Day Discharge Eligibility Assessment			X		
Discharge Date/Time				X	
Pain Medication Use		X	X	X	
Anti-coagulant/Anti-platelet use	X	X			
Study Endpoint Data Collection:					
All groups: Procedure success		X			X
All groups: Device Success		X			
Same Calendar Day Discharge: Study group success				X	X ¹
No Urinary Catheter: Study group success		X	X		
No Protamine: Study group success		X	X		
Adverse Events		X	X	X	X

*For subjects on warfarin, document most recent INR prior to the procedure

¹ No re-admission for access site-related complications within 72 hours of discharge.

7.4. Study Procedures

7.4.1. Pre-Operative

Prior to the subject's scheduled procedure, obtain a medical history and record the subject's 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 collection of the following routine blood tests:

- platelet count
- hemoglobin and hematocrit

Review of the subject's medical history and risk factors will be documented. The subject will be asked about any pre-existing lower extremity nerve complaints in both lower limbs (i.e., symptoms, severity). Current medication regimen that may affect bleeding (e.g., anti-platelet, anti-coagulant, anti-thrombotic agents, etc.) will be documented.

7.4.2. 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: A-Fib, A-Flutter, SVT, VT, LAA, Other
- ablation modality (e.g., RF, Cryo)
- number and limb location of access sites (left/right)
- techniques used to gain venous access, if any (e.g., ultrasound, micropuncture)
- procedural anti-coagulation administered
- uninterrupted anti-coagulation protocol, if applicable
- final procedural ACT time and value, if applicable
- protamine administration, dose and time (if applicable per study group, and if given)
- Urinary catheter use

7.4.3. Intra-Operative – Access Site Requirements

The following procedural requirements apply to all subjects enrolled in this study:

- All access sites must have procedural sheaths with a minimum of a 6 Fr and a maximum of a 12Fr sheath inner diameter at the end of the case.
- Refer to the Cardiva Mid-Bore VVCS IFU for specific instructions on device use.

7.4.4. Intra-Operative - Subject Identification

At the end of the catheter-based procedure, with the procedural sheaths in place and under fluoroscopic¹ or ultrasound visualization, assess sheath placement and the anatomy of all venous access sites to verify the intra-operative eligibility criteria prior to randomization. Each

¹ Note: For fluoroscopy, an injection of contrast will be made.

venous access site must meet all intra-procedural access site-specific criteria for the subject to be eligible.

Once it has been determined that the subject does not meet any of the general intra-operative exclusion criteria, and that none of the venous access sites meet the specific access site exclusion criteria (i.e., all venous access sites must meet all study criteria for the subject to be eligible), then the subject is eligible for enrollment. The following hierarchal Study Group screening should be performed at this time, to ensure that a subject has met eligibility for enrollment into at least one of the Groups:

- **Study Group Assignment (in hierarchal order):**
 - **Same Day Calendar Discharge Group:** Final determination of eligibility for Same Calendar Day Discharge should be determined. These subjects require protamine administration, therefore cannot be simultaneously enrolled in the No Protamine Group.
 - **No Protamine Group:** If subject is NOT a candidate for Same Calendar Day Discharge, he/she should then be screened for eligibility in the No Protamine Group (i.e., no protamine administered for subjects who received anti-coagulants during the case).
 - **No Urinary Catheter Group:** If the subject was determined to have been a candidate for the No Urinary Catheter Group per Pre-procedural Inclusion Criteria, and the subject did not have a urinary catheter inserted pre-procedure, they will be enrolled in that Group when enrolled into the study. These subjects may be co-enrolled with either of the other 2 Study Groups.
- Once Study Group assignment has been determined, and a device has been inserted into the sheath, the subject is enrolled, and every femoral venous access site should be closed using the Mid-Bore VVCS.
- Study data will be captured according to the instructions below.
- ***NOTE: Any subject that meets final eligibility criteria and receives any portion of a Mid-Bore VVCS is considered to be enrolled, and all peri-procedural study data must be collected under the Intent to Treat principle. For this reason, it is imperative that final eligibility criteria are confirmed prior to first device insertion.***
- ***If the subject receives a Mid-Bore VVCS and it is subsequently discovered that one or more of the access sites is not able to be closed (e.g., complication), apply manual compression to the affected access sites and close all eligible access sites using Mid-Bore VVCS. All study data will still be collected for the subject. See Section 5.2 Withdrawal of Subjects.***

7.4.5. Access Site Closure Instructions

The following process will be used to collect procedural data:

The Mid-Bore VVCS, the device should be deployed according to procedure in the Instructions for Use (IFU) provided in **Attachment 3**.

Document device information:

- Device Lot #
- Device Success evaluation
- Document any complications or device performance issues on the Closure Procedure eCRF; refer to the Manual of Operations for device return instructions in the case of any device performance issues.

If the subject is unable to receive the Mid-Bore VVCS and instead must receive manual compression, it should be performed according to the institution's standard practice. If protamine is administered, the Investigator should follow institutional practice guidelines for re-checking ACT levels and/or waiting a specified time or for a target ACT value prior to removal of sheaths and application of manual compression.

Documenting Access Site Hemostasis:

While performing the procedure, record the following information¹:

- For each subject, record:
 - Number of femoral venous access sites on each side
 - Final introducer sheath size (inner diameter and length) at time of closure (i.e. after final sheath exchanges)
 - Hemostasis Confirmation: Document overall/final venous hemostasis was confirmed 5 minutes after final access site hemostasis. The bedrest timing begins at hemostasis confirmation (e.g., bedrest for 2 hours from this time).

Note: For VVCS, formation of a hematoma post-sheath removal may indicate a back-wall or secondary venous or arterial puncture. If this situation is suspected, the VVCS should be removed and the subject should be converted to manual compression at that location. Additional access sites may still be closed with Mid-Bore VVCS, as appropriate.

7.4.6. Post-Operative

After hemostasis is achieved and confirmed after 5 minutes, the access sites should be monitored for all subjects according to site's standard practices.

Post-procedure, record the following information between the time of transfer out of the lab and initial successful ambulation:

- Any medication administered for management of pain while the subject is on initial bedrest will be collected (up until time of successful ambulation).

¹ source worksheets will be provided by Sponsor

Ambulation Guidelines, all Subjects

Bed rest orders guidance for successful VVCS closure for subjects with 3 to 4 access sites is 2 to 2.5 hours after final venous hemostasis is achieved. Bedrest for other closure scenarios could be shorter (e.g., 1 VVCS access site) or longer (e.g., conversion to manual compression of one or more access sites, etc.) as ordered, per Investigator discretion. Following bedrest, the subject is ambulated if stable. Check the groin immediately post-ambulation. Re-check groin per institution's standard of care to verify status. Any delay in ambulation (i.e., >1 hour beyond physician's orders) and reason will be documented (e.g., pt. is sleeping, no staff available). After the subject has successfully completed the ambulation assessment, all access sites should be carefully assessed for the following and documented:

- Forming or expanding hematoma
- Presence of any obvious vascular complications at the access site.

If the subject does not exhibit any of these symptoms at any of the access sites within 20 minutes, he/she may be considered to have successfully ambulated.

If there is any sign of active bleeding at the access site(s) after ambulation, 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, ambulation will be repeated and documented when successful, and the re-bleeding will be documented as an adverse event.

NOTE: If one or more of the access sites are not able to be closed with the Mid-Bore VVCS (e.g., complication preventing use of the device, user error), subjects should be maintained on bedrest according to the Investigator's discretion. This would not constitute a deviation from the protocol.

Discharge Eligibility Guidelines (Same Calendar Day Discharge subjects only):

Subjects enrolled in the Same Calendar Day Discharge Group should be evaluated for potential same day discharge after successful ambulation has been achieved. If they are considered stable and eligible, attempts should be made to achieve discharge before midnight. If the subject is not deemed eligible, the reason will be documented and the subject should be discharged according to the physician's discretion. The Investigator may delegate this assessment to qualified medical personnel, based on institution's standard practices.

Patient Experience Survey Administration Guidelines [Attachment 4]

A Patient Experience Survey will be administered to all subjects after successful Ambulation, to characterize their experience while on bedrest post-procedure. The Research designee should confirm the responses are complete, according to the Instructions provide in the Manual of Operations. These data will be entered in the eCRF but will not be included in endpoint analyses.

Discharge Guidelines (all subjects):

Prior to hospital discharge, all subjects will be asked about any lower extremity nerve complaints in both lower limbs (i.e., symptoms, severity) that were not existing prior to the index procedure. The data will be captured in the Case Report Forms.

The discharge date and time will be recorded. Research personnel should attempt to confirm a date for a follow-up contact at 30 (+/-10) days with the subject prior to discharge to ensure compliance.

Any medication administered for management of pain between the time of successful ambulation and hospital discharge will be recorded.

Documentation of Venous Re-Bleeding at Femoral Access Site:

If a subject experiences venous re-bleeding at any of the femoral venous access sites after a) hemostasis had been confirmed for at least 5 minutes and b) prior to hospital discharge, document the following information on the Discharge eCRF:

- Location of bleed (indicate right or left groin)
- Date and time of re-bleed
- Complete adverse event form.

7.5. Follow-up at 30 (+/- 10) Days

Subjects should have follow-up by office visit or telephone call 30 ± 10 days following their index procedure. The subject should be queried regarding any complications they experienced after hospital discharge and the status of the access site wounds should be should be assessed by questioning and/or exam. All subjects will be asked about any lower extremity nerve complaints in both lower limbs (i.e., symptoms, severity) that were not existing prior to the index procedure.

In addition, the patient record will be reviewed regarding prescription of post-discharge pain medications related to their recovery. These data will be captured in the Case Report Forms, as applicable.

7.6. Study Exit

Once the subject has completed the follow-up contact or has withdrawn, they should be exited from the study provided they do not have any closure-related conditions that require continued follow-up. The date of exit and subject status should be recorded on the Study Exit CRF.

8. Assessment of Effectiveness and Safety

8.1. Primary Effectiveness Endpoint

Procedure Success, Final hemostasis at all venous access sites and freedom from major venous access site closure-related complications through 30 days follow up.
(Per-patient analysis, pooled across all study groups).

8.2. Secondary Effectiveness Endpoints

Study Group Success (defined for each study group)

- No Urinary Catheter: No peri-procedural urinary catheter insertion required through successful Ambulation. **(Per-patient analysis)**
- No Protamine: No delay in Ambulation due to access site bleeding in subjects who receive heparin but are not reversed with protamine **(Per-patient analysis)**
- Same Calendar Day Discharge: Discharge within the same calendar day from the start of the procedure without the need for re-hospitalization within 72 hours of hospital discharge due to access site complications. **(Per-patient analysis)**

Device Success, defined as the ability to deploy the delivery system, deliver the collagen, and achieve hemostasis with the Mid-Bore VVCS. **(Per-access site analysis).**

8.3. Primary Safety Endpoint

On a **per-limb basis**, the rate of combined major venous access site closure-related complications through 30 days post-procedure +/- 10 days, attributed directly to the closure method (i.e., “device-related” with no other likely attributable cause):

- Access site-related bleeding requiring transfusion;
- Vascular injury requiring surgical repair;
- Access site-related infection confirmed by culture and sensitivity, requiring intravenous antibiotics and/or extended hospitalization;
- New onset permanent access site-related nerve injury (i.e., persisting for > 30 days);
- New onset access site-related nerve injury in the ipsilateral lower extremity requiring surgical repair;
- 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).

8.4. Secondary Safety Endpoint

On a **per-limb basis**, the rate of combined minor venous access site closure-related complications through 30 days post-procedure +/- 10 days, attributed directly to the closure method (i.e., “device-related” with no other likely attributable cause):

- Access site-related bleeding requiring greater than 30 minutes of continual manual compression to achieve initial venous hemostasis;
- Access site-related hematoma > 6 cm documented by ultrasound;
- Late access site-related bleeding (following hospital discharge);
- Ipsilateral deep vein thrombosis, confirmed by ultrasound/imaging;

- Localized access site infection confirmed by culture and sensitivity, treated with intramuscular or oral antibiotics;
- Arteriovenous fistula requiring treatment;
- Arteriovenous fistula not requiring treatment;
- Pseudoaneurysm requiring thrombin injection, fibrin adhesive injection or ultrasound-guided compression;
- Pseudoaneurysm not requiring treatment.
- Access site-related vessel laceration
- Access site-related wound dehiscence
- Transient access site-related nerve injury

9. Statistical Considerations

9.1. *Analysis Populations and Data Handling Conventions*

9.1.1. Effectiveness

All subjects will be subject to all performance analyses and analyzed, regardless of actual treatment deviations.

9.1.2. Safety

All subjects who receive any portion of the Cardiva VVCS device treatment will be included in the analysis.

9.1.3. Missing Data

All efforts will be made to eliminate missing data for the primary effectiveness endpoint of procedure success and the primary safety endpoint of major access site closure-related complications. However, should missing data be non-trivial, the primary analyses will be based on complete cases with data and sensitivity analyses will be performed to assess robustness of the primary results. Multiple imputations strategy such as assuming missing at random and control based imputation will be employed for the primary effectiveness endpoint; worst case, best case and tipping point analyses will be performed for primary safety endpoint. Missing data for secondary endpoints will not be imputed by any method.

9.2. *Statistical Analysis Plan*

9.2.1. Baseline Subject Characteristics

Subject demographics, baseline characteristics and medical history will be summarized descriptively both combined and by study group. Mean, standard deviation, median, minimum, and maximum will be reported for continuous variables. Frequencies and proportions will be reported for categorical variables.

9.2.2. Effectiveness

Primary Effectiveness Analysis

The primary effectiveness analysis will be based on the procedure success rate of all subjects as defined in Section 8.1.

Secondary Effectiveness Analysis

The secondary effectiveness analysis will be based on the device success rate of all access sites and the study group success for each study group, as defined in Section 8.2.

Effectiveness Endpoint Confidence Intervals

The 95% confidence intervals for both primary and secondary effectiveness endpoints will be calculated using an exact binomial confidence interval.

9.2.3. Safety

Primary Safety Analysis

The primary safety analysis will be based on the 30-day limb incidence rate of combined major access site closure-related complications (see 8.3). Both the combined rate and individual complication incidence rates will be reported.

Secondary Safety Analysis

The combined incidence rate and individual complication incidence rates will also be reported for minor access site closure-related complications (see 8.4).

Additionally, all reported adverse events will be summarized by treatment regardless of relationship to access site closure.

Safety Endpoint Confidence Intervals

The 95% confidence intervals for both primary and secondary safety endpoints will be calculated using an exact binomial confidence interval.

9.3. Sample Size Justification

A sample size of 300 subjects is estimated based on expected enrollment during a 6-month period for 5 participating sites.

10. Data Management – Data Collection and Processing

Standardized eCRFs will be utilized by all participating sites, refer to the Manual of Operations for specifications and instructions. 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 CRO. 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. Investigators are to maintain all source documents as required by the protocol, including laboratory results, supporting medical records, and signed Informed Consent forms. The source documents will be used during the regular monitoring visits to verify information from the database against data contained on the completed eCRFs.

The Principal Investigator must maintain detailed records on all subjects who sign the Informed Consent and begin the pre-procedure evaluation. Data for enrolled subjects will be entered into eCRFs provided by the Sponsor. All data should be entered completely, promptly and legibly. For source documents, 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, along with the reason for the change (if not obvious).

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

11. Monitoring Procedures

11.1. Monitoring

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

It is important that the Investigator and relevant study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

Phone contacts and site visits will be conducted to ensure that the protocol is being followed and that any protocol deviations are properly documented. Clinical monitoring will include a verification that Informed Consent was properly obtained for all enrolled trial participants, a review of clinical 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 the Investigator and other relevant site personnel are available for consultation with the Monitors during the monitoring visits and that sufficient time is devoted at the site to the monitoring process.

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. In some cases, remote monitoring and data cleaning may be performed.

If a deficiency is noted during an on-site visit (or at any other time during the course of the trial), the Monitor is required to discuss the situation with the Investigator and the Sponsor (if required) to secure compliance.

11.2. *Investigational Device Distribution and Accountability*

11.2.1. Investigational Device Distribution

Cardiva Medical will provide and control the distribution of the investigational devices. Each investigational site will be responsible for ordering the investigational devices for the study. The Investigator is responsible for ensuring that the devices are ordered for shipment to arrive at the hospital before the procedure date.

Devices will be shipped with an Investigational Device Shipment Record. This form is to be used by Cardiva Medical and the investigational site to record any shipments of the investigational device. A copy is to be retained by the shipper and the recipient.

Sites will be responsible for payment of the investigational devices and will coordinate with Cardiva Medical to secure shipping and payment arrangements prior to shipment.

11.2.2. 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 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 Cardiva Medical in a Device Accountability Log provided by Cardiva Medical.

11.2.3. Return of Materials Upon Study Termination

After the cases are completed, all unused devices must be accounted for and shipped back to Cardiva Medical. Instructions for device return to Cardiva Medical will be reviewed at the site initiation visit.

IMPORTANT: Refer to the Manual of Operations for Device Return Instructions.

12. Quality Control and Quality Assurance

12.1. *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, the completion of the eCRFs, and trial procedures;
- Communicate regularly with site personnel via mail, email, telephone, and/or fax;
- Make periodic visits to the trial sites;
- Conduct periodic remote data cleaning and correspondence.

12.2. *Investigator and Co-Investigator 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.

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 or certified vascular tech), and who is designated to deploy the study device in a study subject under the direction of, and the direct supervision of an Investigator or Co-Investigator.

Site Investigators who have performed cases in the AMBULATE Randomized Study will not require additional training for the AMBULATE CAP Study. If a site adds a new Investigator, device training (IFU review, bench training, etc.) will be provided by a Sponsor-designated proctor prior to enrolling any subjects in the study. It is not anticipated that training cases (i.e., “Roll-ins”) will be required for this study. All Investigators will be trained to the CAP Study protocol and data collection requirements.

New Investigators and Co-Investigators will be notified in writing when they have successfully completed the training requirements and are eligible to enroll subjects into the trial, and to deploy the study device without a Sponsor proctor. Operators will be notified in writing when they have successfully completed the enrollment requirements and are eligible to deploy the study device under the direct supervision of an 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.

12.3. Audits and Inspections

The Principal Investigator for the site will also allow representatives of the governing IRB, the United States Food and Drug Administration (FDA), and other applicable regulatory agencies to inspect all trial records, eCRFs, and corresponding portions of the subject's office and/or hospital medical records at regular intervals throughout 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.

13. Adverse Events

General

All adverse events (AE) and serious adverse events (SAE) will be monitored from the time of randomization through the 30 days +/- 10 days follow-up contact.

An AE is defined as any undesirable clinical occurrence in a patient whether or not it is considered to be device related. In addition, the 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 is to be reported as an AE. This definition includes events occurring during the follow-up period.

All reported AEs must be recorded in the electronic database. A description of the event, including the start date, resolution date, action taken, and the outcome should be provided, along with the Investigator's assessment of the relationship between the AE, the study treatment and the study procedure.

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. |

A serious adverse event (SAE) is defined as an event which leads to:

- Death due to any cause
- Life-threatening condition
- Results in persistent or significant disability/incapacity
- Requires in-patient hospitalization or prolonged hospitalization
- Results in congenital abnormality

All SAE's will be reported.

Device-Related Adverse Event: an adverse event is considered to be device-related when, in the judgment of the Investigator, the clinical event has a reasonable time sequence associated with use of the investigational device and is unlikely to be attributed to concurrent disease or other procedures or medications. It is reasonable to believe that the device directly caused or contributed to the adverse event.

Procedure-Related Adverse Event: an adverse event is considered to be procedure-related when, in the judgment of the Investigator; it is reasonable to believe that the event is associated with the assigned study procedure and is not specific to the investigational device used. Other products, surgical techniques, or medications required specifically for the procedure are likely to have contributed to the occurrence of the event.

Concomitant Medication-Related Adverse Event: an adverse event is considered to be concomitant medication related when, in the judgment of the Investigator, it is reasonable to believe that the event is associated with concomitant medications used in conjunction with the investigational device and is not otherwise specific to the investigational device (e.g. bleeding associated with anticoagulation medication).

Pre-Existing Condition-Related Adverse Event: an adverse event is considered to be related to a pre-existing condition when, in the judgment of the Investigator, it is reasonable to believe that the event is associated with the subject's pre-existing condition and is not specific to the investigational device or procedure. Pre-existing conditions that are aggravated or become more severe during or after the procedure should be evaluated on a case-by-case basis to determine if the event may be more appropriately classified as device-related or procedure-related.

Cardiva Medical, Inc., or its designee, in cooperation with the Investigator, will assess all adverse events considered to be device-related for potential reportability to the FDA and other regulatory authorities as an Unanticipated Adverse Device Effect (UADE).

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.

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 48 hours post-index procedure) at the access site and/or related to position on procedure table and considered to be at least moderate in severity

- 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 or fluid imbalance without clinical sequelae following procedure, even if requiring correction
- Low grade temperature increase ($\leq 38.3^{\circ}\text{C}/\leq 101^{\circ}\text{F}$)
- Abnormal cardiac rhythms that do not require treatment or intervention or are considered to be expected and not clinically significant based on the procedure performed
- 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, and may decide that the above events should be reported as adverse events.

13.1. Reporting of Serious and Non-Serious Adverse Events

13.1.1. General Reporting Requirements (Serious & Non-Serious Adverse Events)

All serious and potentially device- and/or procedure-related adverse events must be recorded on the Adverse Event eCRF by the Investigator (or designee). The report should include: severity, duration, action taken, treatment outcome and relationship of the adverse experience to the study device, procedure, concomitant medications, pre-existing condition, etc. (i.e., unrelated, related or relationship unknown).

In the case of serious adverse events, procedure and/or device observations and malfunctions, medical record documentation (e.g. procedure notes, operative notes, discharge summary, relevant progress notes, imaging or lab studies) must be provided to Cardiva Medical or its designee.

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.

All serious device- and/or procedure-related adverse events must be reported by the Investigator (or designee) to the Sponsor within 24 hours of learning of the adverse event via eCRF. The Cardiva Medical contact information for questions is:

Sponsor: Cardiva Medical, Inc.
2900 Lakeside Drive, Ste. 160
Santa Clara, CA 95054
Telephone: 408-470-7170
Fax: 408-470-7134

Contact: Marlys Chellew, BSN
Clinical Consultant
Mobile: 916-303-0879
mchellew@chellewclinical.com

13.2. *Device Failures and Malfunctions*

All reported device malfunctions or failures of the Cardiva Mid-Bore VVSC are required to be documented in the eCRF. In the event of a suspected observation or device problem, the investigational device shall be returned to the Sponsor for analysis. Device failures and malfunctions should also be documented in the patient's medical record if a related adverse event occurs. Instructions for returning the investigational 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. See Manual of Procedures for specific reporting guidelines.

14. Study Committee

14.1. *Data Safety Monitoring*

All reported major and minor access site-closure related endpoint complications and any access-site closure related complications as reported by the Investigator will be submitted in a progress report to the FDA at 50% of planned enrollment.

15. Ethical Considerations

15.1. *Trial Conduct & the Declaration of Helsinki*

The trial will be performed in accordance with the relevant parts of Title 21 CFR Parts 812, 50, 54, 56; the ICH Guidelines for Good Clinical Practices (E6), and any regional and/or national regulations.

15.2. *Institutional Review Board/Ethics Committee*

The CAP Study is considered to be an amendment to the AMBULATE Randomized study, per IDE G170144, and will only utilize investigational sites that participated in the AMBULATE Study. A copy of the protocol, proposed Informed Consent form, other written patient information and any proposed advertising material must be submitted to the IRB for written approval. A copy of the written IRB approval of the protocol and Informed Consent form must be received by

Cardiva Medical, Inc. prior to recruitment of patients into the study and shipment of investigational product.

The Investigator must submit and, where necessary, obtain approval from the IRB as well as the FDA and Sponsor, for all subsequent significant protocol amendments and significant changes to the Informed Consent form. The Investigator should notify the IRB of deviations from the protocol or SAEs and UADEs occurring at the site and other SAE/UADE reports received from Cardiva Medical, Inc. in accordance with local procedures.

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 Cardiva Medical, Inc.

15.3. *Informed Consent Form*

Sample Informed Consent forms are provided for subjects in Attachment 2 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.

The reviewing IRB, the FDA and the Sponsor must first approve the Informed Consent form that is used. The Informed Consent forms must be in accordance with the current guidelines as outlined by the Good Clinical Practices (GCP) guidelines and 21 CFR Part 50.

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 patients must also be given the opportunity to ask questions and have those questions answered to their satisfaction.

Written Informed Consent must be recorded appropriately by means of the patient's dated signature on the ICF. 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.

15.4. *Amending the Protocol*

An Investigator may not make protocol changes without prior approval by Cardiva Medical. 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. Cardiva Medical 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 Cardiva Medical a copy of the IRB approval letter for the protocol amendment.

Cardiva Medical may make certain administrative changes to the protocol without prior approval of the FDA or IRB. Cardiva Medical 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.

15.5. *Emergency Actions*

Cardiva Medical, Inc. 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 Cardiva Medical, Inc. and the IRB as quickly as possible after the episode, in any event no later than 24 hours after the emergency.

15.6. *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.

Investigators shall be required to obtain prior approval from Cardiva Medical 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 contact, blood sample lost by laboratory, etc.); however, the event is still considered a deviation and will be reported via the appropriate CRF.

Deviations must be reported to Cardiva Medical regardless of whether medically justifiable, pre-approved by Cardiva Medical 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.

Regulations require that Investigators maintain accurate, complete and current records, including documents showing the dates of and reasons for each deviation from the protocol. For reporting purposes, Cardiva Medical classifies study deviations as major and minor:

Major deviation: Any deviation from subject inclusion and exclusion criteria, subject informed consent procedures or unauthorized device use.

Minor deviation: Deviation from a protocol requirement such as incomplete/inadequate subject testing procedures, follow-ups performed outside specified time windows, etc. Minor Deviations that continue to occur at an investigational site may be classified as Major Deviations if corrective action is not taken to secure future compliance to the protocol.

Major and/or recurring protocol deviations reported or identified by the monitor will be discussed with the investigative staff to identify root cause and corrective actions to be implemented to prevent recurrence. Investigators are expected to participate in this important activity in a serious and timely manner.

15.7. Coverage of Expenses

The treated subjects will not be reimbursed or compensated for participating in the trial.

15.8. 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 their CRO representative will make every reasonable effort to protect the confidentiality of the subjects participating in the trial.

16. Study Administration

This AMBULATE Continued Access Protocol (CAP) Study is a continued access protocol under the AMBULATE IDE Study¹ conducted per Clinical Investigation Protocol PTL 0508. Cardiva Medical, Inc. will make necessary efforts to ensure that this study is conducted in compliance with GCPs and all applicable regulatory requirements.

16.1. Pre-Study Documentation Requirements

Prior to shipment of investigational product, the following documents must be provided to Cardiva Medical, Inc.:

- Signed and dated Investigator Agreement and Financial Disclosure Form
- Fully executed Clinical Study Agreement and budget

¹ G170144 AMBULATE IDE

- Purchasing agreement for investigational devices
- A copy of the written IRB approval of the protocol and Informed Consent Forms
- A copy of the IRB-approved Informed Consent Forms
- A copy of the curriculum vitae of the Principal Investigator.

16.2. Source Documentation

The Principal Investigator must maintain detailed source documents on all trial subjects who are enrolled in the trial or who undergo screening. Source documents include subject medical records, hospital charts, clinic charts, Investigator's subject trial files, as well as the results of diagnostic tests (e.g., laboratory tests).

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
- Documentation of specific investigational devices used, if any
- Occurrence and status of any 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.

16.3. 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 patients in compliance with the ICH/GCP guidelines. Documents must be retained for at least 5 years after the last approval of marketing application or until at least 5 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with Cardiva Medical, Inc. or in compliance with other regulatory requirements. When these documents no longer need to be maintained, it is Cardiva Medical'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. Cardiva Medical, Inc. must receive written notification of this custodial change.

16.4. Criteria for Terminating Study

Cardiva Medical, Inc. 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 patients. 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 Cardiva Medical, Inc. to suspend or discontinue development of the device.
- Market approval of the study device.

16.5. Criteria for Suspending/Terminating a Study Center

Cardiva Medical, Inc. reserves the right to stop the enrollment of patients at a study center at any time after the study initiation visit if no patients have been enrolled or if the center has multiple or severe protocol violations without justification or fails to follow remedial actions.

Possible reasons for suspending/terminating a study center include:

- Repeated failure to complete electronic case report forms prior to scheduled monitoring visits.
- No or slow enrollment.
- Multiple or major protocol deviations without justification, or failure to follow remedial actions
- Failure to obtain written Informed Consent prior to enrollment
- Failure to report serious device-related AEs and/or UADEs to Cardiva Medical, Inc. within 24 hours of knowledge
- Loss of (or unaccounted for) investigational product inventory.

16.6. Investigator Responsibilities

- Agree to sign and adhere to the Investigator Agreement
- 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 material suitable for quantitative analysis
- Agree to obtain written Informed Consent before any study specific procedures are performed
- Complete all electronic data modules prior to scheduled monitoring visits

- Be willing to change hospital routine if required by protocol, as long as patient safety and well-being is not compromised

A full list of Investigator responsibilities is provided in **Attachment 1**.

17. 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 is indicated as confidential.

The data generated by this clinical trial are the property of the Sponsor, Cardiva Medical, Inc., and should not be disclosed without their prior written permission. These data may be used by the Sponsor now and in the future for presentation or publication at Sponsor's discretion or for submission to governmental regulatory agencies. The Principal Investigators may publish or present the trial results with prior consent of the Sponsor, but will not disclose confidential information. Prior to submission by a Principal Investigator for publication or presentation, the Sponsor will be provided with the opportunity to review the submission for confidential information and accuracy. The Sponsor will have the opportunity to a) approve the publication; b) require the removal of any Confidential Information (other than Study Data); and /or c) delay the proposed Publication for an additional ninety (90) days to enable Sponsor to seek patent protection.

The study will be posted on ClinicalTrials.gov prior to enrollment of the first subject, as required by regulation.

18. Regulatory Considerations

18.1. Role of Cardiva Medical

As the Sponsor of this clinical study, Cardiva Medical has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the Food and Drug Administration (FDA). In this study, Cardiva Medical will have certain direct responsibilities and will delegate other responsibilities to Consultants. Together, both Cardiva Medical and its Consultants 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)), and submitting reports (21 CFR 812.150 (b)).

18.2. General Duties [21 CFR 812. 40]

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 shipping devices only to those qualified Investigators. As the Sponsor, Cardiva Medical 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, and to provide the required reports to the Investigators, IRB's and FDA.

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

18.3. Monitoring [21 CFR 812. 46]

The Sponsor and/or designee will conduct investigational site monitoring to ensure that all Investigators are in compliance with the protocol and the Investigators' agreements. The Sponsor and/or designee will monitor the sites to ensure that the completed Case Report Forms 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 serious adverse events and ensure that such information is provided to the FDA, the Investigators and to all reviewing IRB's.

18.4. Supplemental Applications [21 CFR 812. 335 (A) and (B)]

As appropriate, the Sponsor will submit changes in the Investigational Plan to the FDA and Investigators to obtain IRB re-approval.

18.5. Maintaining Records [21 CFR 812. 140 (B)]

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.

18.6. Submitting Reports [21 CFR 812. 150 (B)]

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 list, annual progress reports, recall information, final reports, Investigators that use the device without obtaining informed consent, and significant risk device determinations.

18.7. Site Record Retention Policy [21 CFR 812. 140 (D)]

The Sponsor, Ultrasound Core Lab, and clinical sites will maintain all records pertaining to this study for a period of five years following: 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 pre-market approval application. Record retention dates will be provided to all concerned by the Sponsor.

18.8. Informed Consent & Institutional Review Board (IRB) [21 CFR Parts 50 & 56]

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).

19. Abbreviations and Definitions

19.1. Abbreviations

ACT	Activated clotting time
AE	Adverse Event
AV	Arteriovenous
CFR	Code of Federal Regulations
eCRF	Electronic Case Report Form
CV	Curriculum Vitae
DE	Discharge Eligibility
FDA	Food and Drug Administration
Fr	French
Hgb	Hemoglobin
Hct	Hematocrit
IDE	Investigational Device Exemption
IFU	Instructions for Use
INR	International Normalized Ratio
IRB	Institutional Review Board
LMWH	Low molecular weight heparin
MC	Manual Compression
PE	Pulmonary embolism
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Event

19.2. Definitions

ACCESS SITE-RELATED HEMATOMA > 6 CM (minor safety endpoint)

A localized collection of extravasated blood in subcutaneous tissue at the access site measuring > 6 cm at its widest point on visual inspection or palpation.

ACCESS SITE-RELATED BLEEDING REQUIRING TRANSFUSION (major safety endpoint)

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.

ACCESS SITE-RELATED BLEEDING REQUIRING > 30 MINUTES OF CONTINUAL MANUAL COMPRESSION TO ACHIEVE INITIAL VENOUS HEMOSTASIS (minor safety endpoint)

Bleeding from the venous access site(s) requiring greater than 30 consecutive minutes of manual compression to achieve venous initial hemostasis.

ACCESS SITE-RELATED INFECTION CONFIRMED BY CULTURE AND SENSITIVITY: REQUIRING INTRAVENOUS ANTIBIOTICS AND/OR PROLONGED HOSPITALIZATION (major safety endpoint)

Must meet at least one of the following criteria related to the venous access site(s): 1) positive wound culture requiring treatment with intravenous antibiotics; and/or 2) prolonged hospital discharge time directly related to complications of access site infection. Does not include administration of prophylactic antibiotic regimens.

ACCESS SITE-RELATED INFECTION CONFIRMED BY CULTURE AND SENSITIVITY: LOCALIZED AND REQUIRING INTRAMUSCULAR OR ORAL ANTIBIOTICS (minor safety endpoint)

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

ACCESS SITE-RELATED NERVE INJURY IN THE IPSILATERAL LIMB – NEW ONSET AND REQUIRING SURGICAL REPAIR (major safety endpoint)

New onset access site closure-related nerve injury that requires surgical intervention to mitigate symptoms or prevent permanent nerve damage.

ACCESS SITE-RELATED NERVE INJURY – NEW ONSET AND PERMANENT (major safety endpoint)

New onset access site closure-related nerve injury that persists for > 30 days and is deemed to be clinically significant by the Investigator.

ACCESS SITE-RELATED NERVE INJURY – TRANSIENT (minor safety endpoint)

New onset access site closure-related nerve injury that persists for \leq 30 days and is deemed to be clinically significant by the Investigator.

ACCESS SITE-RELATED VESSEL LACERATION (minor safety endpoint)

An injury to the venous or arterial wall in which the tissue is torn or cut.

ACCESS SITE-RELATED WOUND DEHISCENCE (minor safety endpoint)

A surgical complication in which the wound ruptures along a surgical incision.

ADVERSE EVENT SEVERITY RATING

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.

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.

ARTERIOVENOUS (AV) FISTULA NOT REQUIRING TREATMENT (minor safety endpoint)

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.

ARTERIOVENOUS (AV) FISTULA REQUIRING TREATMENT (minor safety endpoint)

A connection between the access artery and the adjacent vein that is demonstrated by arteriography or ultrasound, most often characterized by a continuous bruit that is severe in nature and requires an interventional procedure to mitigate further injury.

CHADS-2 SCORE

Clinical prediction rules for estimating the risk of stroke in patients with non-rheumatic atrial fibrillation (AF). Such a score is used to determine whether or not treatment is required with anti-coagulation or anti-platelet therapy, since AF can cause stasis of blood in the upper heart chambers, leading to the formation of a mural thrombus that can dislodge into the blood flow, reach the brain, cut off supply to the brain, and cause a stroke. A high score corresponds to a greater risk of stroke, while a low score corresponds to a lower risk of stroke.

	19.2.1. Condition	Points
C	Congestive Heart Failure	1
H	19.2.2. Hypertension, BP consistently above 140/90 mmHg (or on medication)	1
A	19.2.3. Age \geq 75 years	1
D	19.2.4. Diabetes mellitus	1
S ₂	19.2.5. Prior Stroke / TIA or Thromboembolism	2

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. See also Investigator and Operator.

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).

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 Cardiva Venous Vascular Closure System.

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

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.

HEMATOMA

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

HEMOSTASIS - VENOUS

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

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.

INTERNATIONAL NORMALIZED RATIO (INR)

A comparative rating of Prothrombin time (PT) ratios. Used to measure coumadin efficacy in subjects.

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.

IPSILATERAL

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

IPSILATERAL DEEP VEIN THROMBOSIS (minor safety endpoint)

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 bed rest. Symptoms include a feeling of heaviness, pain, warmth, or swelling in the affected part.

LATE ACCESS SITE-RELATED BLEEDING (i.e., following hospital discharge) (minor safety endpoint)

Active re-bleeding from the venous access site(s) following hospital discharge. See “Oozing From the Access Site” and “Re-bleeding at Access Site” definitions to differentiate between venous and tissue tract bleeding.

LIGHT PRESSURE 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).

MANUAL COMPRESSION

Direct digital non-occlusive pressure to the venotomy site applied to achieve hemostasis. Note: Mechanical compression devices, sandbags and other methods are to be used only following the achievement of hemostasis for management of non-venous oozing/bleeding.

LAST PROCEDURAL DEVICE

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

LOWER EXTREMITY ISCHEMIA

New (acute) onset of compromised peripheral blood flow, potentially causing a threat to the viability of the limb and requiring surgical or percutaneous intervention. This compromised blood flow is documented by subject symptoms, physical exam and/or a decreased or absent blood flow on lower extremity angiogram.

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 light manual pressure). Note: the occurrence of oozing will not be incorporated into the “time to hemostasis” measurement.

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 all venous access sites and freedom from major venous access site closure related complications through 30 days follow up.

PSEUDOANEURYSM AT ACCESS SITE WHICH MAY OR MAY NOT REQUIRE TREATMENT (minor safety endpoint)

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 may or may not require treatment (e.g., thrombin injection or fibrin adhesive injection).

PULMONARY EMBOLISM REQUIRING SURGICAL OR ENDOVASCULAR INTERVENTION AND/OR RESULTING IN DEATH (major safety endpoint)

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 INTERVENTION AND/OR NOT RESULTING IN DEATH (major safety endpoint)

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.

PUNCTURE SITE PAIN

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

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 that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

SUB-INVESTIGATOR / 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. See also Investigator.

SUBJECT

An individual who participates in a clinical investigation.

THROMBUS FORMATION

Blood clot formation.

UNANTICIPATED ADVERSE DEVICE EFFECTS (UADE)

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.

VASCULAR INJURY REQUIRING SURGICAL REPAIR (major safety endpoint)

Access site closure-related injury to the venous wall or adjunct arterial vessel wall resulting in persistent bleeding and requiring surgical repair.

VASOVAGAL EPISODE

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.

VASOSPASM

The sudden, but transitory constriction of a blood vessel, potentially causing discomfort and limitation of distal blood flow.

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.

19.3. Bibliography

1. Dou, E., Winokur, R.S., Sista, A.K. Venous access site closures using the VASCADE vascular closure system. *J. Vasc. Interv. Radiol.* 2016;27:1885–1888.
2. Srivatsa, S.S., Srivatsa, A., Spangler, T.A. Mynx vascular closure device achieves reliable closure and hemostasis of percutaneous transfemoral venous access in a porcine vascular model. *J Invasive Cardiol.* 2015 Feb; 27(2):121-7.

20. Attachment 1: Investigator Responsibilities, Records and Reports

20.1. Investigator Responsibilities

The Investigator is responsible for ensuring that this trial is conducted according to this protocol and that signed Informed Consent is obtained from each subject prior to their inclusion in this trial.

It is the Investigator's responsibility to ensure that all staff assisting with this trial have the appropriate qualifications and are fully instructed on the trial procedures and respect subject confidentiality, as specified in the Investigator Agreement with the Sponsor.

The Investigator is responsible for ensuring that the conduct of the trial conforms to the IRB/EC requirements and provides all necessary communication with the IRB/EC including, but not limited to, annual trial reports and required adverse event notifications.

20.2. Investigator Records

Case REPORT FORMS

The standardized electronic Case Report Forms (eCRFs) will be used to collect complete and accurate records of the clinical data from the trial according to the Good Clinical Practice (GCP) requirements. The Investigator is responsible for collecting and accurately recording the data generated for this trial.

SCREENING LOG

Investigators will maintain a screening log that will record the date of informed consent, the date of screening, the enrollment status (enrolled/excluded) and the reason for exclusion for all screen failures.

20.3. Investigator Reports

FINAL TRIAL REPORT

A summary of the final report will be prepared and provided to each Principal Investigator for submission to their respective IRB after completion of the trial.

SERIOUS ADVERSE EVENTS (SAEs)

The Investigators will report by eCRF any SAEs including serious, and/or potentially device- or procedure-related adverse events as soon as possible, within 24 hours of the Investigator becoming aware of the event, to the Sponsor and the Sponsor's CRO and to the IRB as per the committee's reporting requirements. The Serious Adverse Event eCRF is to be completed and submitted to the Sponsor as initial notification.

DEVICE MALFUNCTIONS

The Investigators will report by telephone, email or fax any Device Malfunctions as soon as possible, within 24 hours of the Investigator becoming aware of the event, to the Sponsor and the Sponsor's CRO.

WITHDRAWAL OF APPROVAL

If an IRB withdraws the approval to conduct this trial for any reason, the Investigator will notify the Sponsor and the Sponsor's CRO as soon as possible, but in no event later than five working days after the withdrawal of the approval.

21. Attachment 2: Sample Informed Consent Form

22. Attachment 3: Instructions For Use (IFU)

Participant Sample Consent Form

Title of Study: "THE AMBULATE CAP STUDY"

**MULTI-CENTER, SINGLE ARM CONTINUING ACCESS PROTOCOL TO EVALUATE THE CARDIVA MID-BORE
VENOUS VASCULAR CLOSURE SYSTEM (VVCS) FOR THE MANAGEMENT OF THE FEMORAL VENOTOMY
AFTER CATHETER-BASED INTERVENTIONS PERFORMED VIA 6- 12 FR PROCEDURAL SHEATHS WITH
SINGLE OR MULTIPLE ACCESS SITES PER LIMB**

Sponsor: Cardiva Medical, Inc., Santa Clara, CA

Principal Investigator:

Institution:

Your Consent

You are invited to take part in this research project at *(insert hospital / facility name)*. The purpose of this clinical study is to evaluate a new device designed to close the veins in your legs that will be punctured as part of your heart procedure. The devices are used at the end of the procedure. This consent form will provide you with information about the study, the procedures that will be performed, and your rights.

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home a copy of this form so that you can think and discuss with your family, friends, or local health care provider before making a decision to take part in this study.

Purpose & Background of the Study

Your doctor has explained to you that you need a procedure to treat your irregular heart beat. As part of this procedure, the doctor will put several holes in your leg veins in to order insert the medical equipment that is needed to perform the procedure. Once the doctor is finished with your procedure, these holes will need to be sealed (closed up) to prevent bleeding. You are being asked to participate in a research study to help evaluate the safety and effectiveness of a new vascular closure device developed by Cardiva Medical, called the Venous Vascular Closure System (VVCS). The device is used to close the leg vein holes that were punctured during your procedure. A small collagen (cotton-like) patch is placed just outside of the vein to plug the hole and stop the bleeding.

Cardiva Medical developed a similar version of this device that is used to close holes in leg *arteries* called the VASCADE Vascular Closure System. The VASCADE device was tested in a large clinical study and approved by the U.S. Food and Drug Administration (FDA) in 2012, and has been used and sold in the United States since that time.

The safety of the VASCADE device has been tested and proven in several previous research studies of over 350 human patients without serious problems or deaths. The collagen patch is similar to other collagen-based closure devices used in surgery to close small holes. In a large FDA approval study called RESPECT, a total of 417 subjects were enrolled. Two-thirds (275 patients) received the VASCADE device, and one-

third (142) received manual compression to close a single artery hole (femoral artery). Safety results were similar in both groups.

The new device for this study (“study device”) has some minor changes to it that make it more suitable for use in closing holes in veins, and has recently been tested in a new clinical study to show that it has similar results to the VASCADE device. The AMBULATE Study included 204 patients who were “randomized” (50:50 chance) to receive either the study device or manual pressure to stop the bleeding in the veins after procedures, when 3 or 4 punctures were needed. An additional 42 “Roll-in” patients were treated with the study device as part of the physicians’ initial training. A total of 141 patients received the study devices, in 486 venous puncture sites. The results of this study have been submitted to the U.S. Food and Drug Administration (FDA) for review and potential marketing approval. While this review is underway, the FDA allows enrollment of additional patients in order to collect specific information about how physicians utilize the device in their practices, for their patients.

If you choose to take part in the study, you will receive the study device to close off each of the leg vein holes. The collagen patch is still considered investigational for use in veins (not approved for sale).

The doctors will follow similar patient selection guidelines as they did in the AMBULATE Study, but will be looking at three specific groups of patients in this CAP Study:

- No urinary catheter: this means that when the study device is used to close the holes in the veins, a patient may not need a urinary catheter placed for the procedure or before hospital discharge because they may be able to get up and walk to the bathroom sooner.
- No Protamine: this means that when the study device is used to close the holes in the veins, a patient may not have to receive a medication that reverses the effect of the IV blood thinners used during your procedure. You should still be able to walk sooner when this medication is not used.
- Same Calendar Day Discharge: this means that when the study device is used, patients usually walk sooner and may be able to go home the same day as the procedure because of this. This will apply to specific types of procedures for safety reasons. The procedures included in this group are for treatment of atrial fibrillation, supraventricular tachycardia, ventricular tachycardia, atrial flutter or a combination of these procedures. You will not be able to enroll in the No Protamine and Same Calendar Day Discharge groups at the same time, to reduce the chance of bleeding complications.

This study will enroll about 300 patients at up to 5 hospitals in the United States. Your participation in this study will last 30 days (\pm 10 days). The expected total time for all patients to complete the study is about 6 months.

What happens if I say yes, I want to be in this research?

If you agree to be in this study, the first step is signing of this consent form. The following will then happen to you:

Pre-Procedure	Before the procedure you will have a medical interview to make sure you qualify for the study (are eligible to take part in the study) and you will have your blood drawn (approximately 1-2 teaspoons) for laboratory testing (creatinine, platelet count, hemoglobin, hematocrit, INR if on warfarin). These are normal blood tests that are drawn before a procedure like yours. Your doctor will review your chart to see if you will qualify for at least one of the 3 groups.
Procedure	<p>During the procedure your doctor will insert between 2 and 5 small plastic tubes to gain access to the large veins in both of your legs (femoral veins). He/she will then insert small tubes of various sizes into each of these access sites so that the medical equipment needed to perform your heart procedure can be inserted into your body for use. Since you will receive blood thinning medications as part of your regular procedure, your doctor will monitor your blood to determine how long it takes you to stop bleeding.</p> <p>When your doctor is finished with the procedure and your doctor feels it is okay for you to take part in the study, he/she will decide if you qualify for enrollment. If yes, then he/she will proceed to close all of the holes in the veins with the Cardiva device. You may qualify to be in more than one of the “groups” at a time, which means that data specific to that “group” will be collected but does not require any additional effort from you. If your doctor decides that you do not qualify for the study, you will not be enrolled and will be treated according to your doctor’s normal practice.</p>
Post-Procedure	<p>After the procedure, the puncture site (place where the hole was made for the heart catheters) will be checked often to make sure it is not bleeding.</p> <p>After you get up to walk, but before you are discharged from the hospital the Research Coordinator will give you a short “Patient Experience Survey” to complete. The survey will ask you how you feel about the time you were on bedrest after your procedure. This is for the study only and will not be part of your medical records.</p>
30 days	You will need to come in or have a telephone follow-up contact 30 (\pm 10) days after the procedure. You will be asked about the place where the holes were in your legs to make sure they have healed properly.

These are normal steps used in this type of heart procedure. The only difference is that your doctor will be using a device to close the venous holes to stop the bleeding instead of holding longer pressure on the holes to stop the bleeding.

Possible Risks

Possible side effects (problems) are similar to other closure devices and “manual compression”. Of the possible side effects listed below, there were no reports of these events occurring in the 275 VASCADE patients, except as noted for each event listed (i.e., % of patients experiencing an event):

- allergic response (to the material in the device or collagen)

- arterio-venous fistula (abnormal connection between artery and vein) (0.4%)
- bleeding/oozing from the puncture site (2.9%); bleeding requiring transfusion (0%)
- bruising at the puncture site (<0.05%)
- death
- deep vein thrombosis (thrombus formation in a vein in the leg) (1%)
- device failure / malfunction (4%)
- edema (swelling in the tissues)
- embolization (thrombus, air, calcific debris, device floating downstream)
- hematoma (bleeding under the skin) (2%)
- infection at the access site
- inflammatory response (inflammation)
- intimal tear / dissection (tear of the leg vein or artery wall)
- laceration of the vessel wall
- lower extremity ischemia (lack of oxygen to the leg)
- peripheral nerve injury (nerve damage to the leg) (<0.05%)
- perforation of the vessel wall (puncture of the vessel wall)
- pseudoaneurysm (abnormal collection of blood with persistent flow outside an artery due to a leaking hole in the artery due to injury) (1.8%)
- pulmonary embolism (blockage of an artery in the lungs)
- puncture site pain (1%)
- retroperitoneal bleeding (bleeding in the area behind the abdomen) (<0.05%)
- vasospasm (spasm of the artery)
- vasovagal response (slowed heart rate with possible fainting)
- vascular injury requiring repair (vessel damage requiring repair)
- vessel occlusion (blockage of the artery or vein)
- vessel thrombus (blood clot in the artery or vein)
- wound dehiscence (separation of wound edges)

There are other general risks that are associated with your entire procedure, and your doctor will tell you about those separately.

The risks to an unborn baby conceived during the study are unknown. Therefore, women in the study should practice acceptable pregnancy prevention methods during the study. Pregnant or lactating women cannot take part in the study. However, breastfeeding women may decide to stop nursing, after discussing it with their physician, in order to take part in the study.

Unknown risks: The risks of placing a vascular closure device are understood. However, there may be additional risks, which are unknown at this time.

Possible Benefits

There is no guarantee or promise that you will receive any benefits from the Cardiva VVCS. Potential benefits include rapid closure of the vein holes, which may increase your comfort after the procedure and may allow you to start walking sooner. The doctors may learn more about how this device performs in veins. There may also be other unexpected benefits that will be discovered as a result of this study, and any new significant information will be provided to you by your doctor.

Financial Responsibility

The study sponsor will pay the costs of tests, exams, and procedures that are performed only because you are in this study (are not part of your regular treatment). The cost for study devices used in this study will be billed by your hospital. You or your insurance company will be responsible for all costs of your usual ongoing medical care. This includes the cost of your procedure (including the study devices), hospital care and services, and any follow-up that would be performed as part of your medical care outside of this study. If your insurance company requires any co-payment or deductible, you will be responsible for making that payment. You will not be paid for your participation in this clinical trial, and there is no financial reward or compensation in any form.

Compensation for Injury

In the event that you become ill or injured as a result of your taking part in this research project, the Hospital will provide you with medical treatment. If you are in the “study” group, and it is determined that your illness or injury resulted from the collagen patch (VVCS) in your leg(s), this medical treatment, as well as other reasonable and customary medical expenses, will be paid for by the sponsor of the study (Cardiva Medical), but only to the extent that the costs and expenses are not covered by your health insurance or a government program. This agreement to provide free medical treatment does not include costs and expenses for an illness or injury that does not result from the collagen patch (VVCS). No funds have been set aside to compensate you for such injuries. In addition, the sponsor of the study has not set aside funds to compensate you for non-direct damages such as lost of wages, disability, or discomfort due to illness or injury. No compensation or reimbursement is available from (*insert institution*) or the Sponsor.

If you have any questions concerning the availability of medical care or if you think you have experienced a research related illness or injury, you should contact the research study doctor or other research study staff. The study doctor and sponsor will determine if the illness or injury may have resulted from the collagen patch you may have received.

You will not give up your legal rights by signing this document. For instance, your legal right to claim compensation for illness or injury where you can prove negligence or malpractice will not be affected when you sign this form.

Privacy, Confidentiality & Disclosure of Information

Your confidentiality will be maintained in accordance with the privacy and relevant health records laws of *(insert state/providence)*. You have a right of access to, and to request correction of, information held about you by *(insert facility name)* in accordance with the *(insert regulation)*. Any information obtained in connection with this research project that can identify you will remain confidential and will only be used for the purpose of this research project. It will only be disclosed to parties listed below with your permission, except as required by law.

During the study only your initials and a unique study number will be used to identify you. Your name, address and any other personal information will not appear on any documents that are collected in relation to this research. It will not be possible to identify you from information in any publication resulting from this study and every effort will be made to keep your own personal medical data confidential to the extent allowed by law.

By signing this consent form you agree that under direction of the study doctor, authorized representatives of the sponsor, Cardiva Medical, Inc. (the manufacturer of the study device), the Institutional Review Board, and the United States Food and Drug Administration (FDA) can access your health information in order to verify the accuracy of the data and verify compliance with the study procedures. By signing this Consent Form, you authorize release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

All records kept from the study may be destroyed after 15 years, unless Cardiva Medical requests otherwise.

New Information Arising During the Project

During the research study, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information.

Termination of the Study

This research study may be stopped for a variety of reasons. These may include reasons such as: discovery of an unexpected, significant, or unacceptable risk to patients or a decision on the part of Cardiva Medical to suspend or discontinue development of the device.

Right of Refusal and Alternative Treatments

Participation in this study is voluntary. You may refuse to participate in this study or discontinue participation at any time. If you refuse to participate in this study, it will not affect the care your doctor will provide to you or result in any penalty or loss of benefits to which you are otherwise entitled.

The only alternative to the Cardiva Medical VVCS device for closure of the vein puncture sites is use of another FDA-approved device, or manual compression (firm pressure).

Also, your Study doctor or the sponsor may terminate your participation in the Study at any time, for reason, including these:

- It would be dangerous for you to stay in the study
- You have not followed the instructions of your study doctor and/or study staff
- You become pregnant

- You need treatment not allowed in the study
- The Sponsor decides to end the study
- Other unexpected circumstances

Inquiries

There are some technical terms used in this consent form. If there is anything you do not understand, please ask your doctor or study nurse to explain.

In case of emergency, or if you have any questions during this study about your rights as a research participant or the procedure, please contact:

<i>(add investigator name)</i>	<i>(insert contact info)</i>
<i>(add sub-investigators)</i>	<i>(insert contact info)</i>
<i>(add coordinators)</i>	<i>(insert contact info)</i>

A description of this clinical trial will be available on <http://www.clinicaltrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Study Participant's Bill of Rights

Persons who participate in a medical experiment are entitled to certain rights. These rights include but are not limited to the subject's right to:

- Be informed of the nature and purpose of the experiment
- Be given an explanation of the procedures to be followed in the medical experiment, and any drug or device to be utilized
- Be given a description of any attendant discomforts and risks reasonably to be expected
- Be given an explanation of any benefits to the subject reasonably to be expected, if applicable
- Be given a disclosure of any appropriate alternatives, drugs, or devices that might be given advantageous to the subject, their relative risks, and benefits
- Be informed of the avenues of medical treatment, if any, available to the subject after the investigational procedure if complications should arise;
- Be given an opportunity to ask questions concerning the experiment or the procedures involved
- Be instructed that consent to participate in the medical experiment may be withdrawn at any time and the subject may discontinue participation without prejudice
- Be given a copy of the signed and dated consent form
- Be given the opportunity to decide to consent or not to consent to a medical experiment without the intervention of any element of force, fraud, deceit, duress, coercion, or undue influence on the subject's decision.

Consent

Your signature below indicates that:

- You have read and understood the above information.
- You have discussed the study with your study doctor.
- You have had a chance to ask all of your questions and have had them answered.
- You have decided to take part in the study based on the information aprovided.
- A copy of this form has been given to you.

Signature of Participant

____/____/____
Date

Printed Name of Participant

Signature, Person Conducting Informed Consent Discussion

____/____/____
Date

Printed Name, Person Conducting Informed Consent Discussion



VASCADE® MVP

MID-BORE Venous Vascular Closure System (VVCS) Model 800-612C

INSTRUCTIONS FOR USE

IFU 3972 Rev - B

For Investigational Use Only

CAUTION – Federal (USA) law restricts this device to sale by or on the order of a physician

DESCRIPTION

The MID-BORE Venous Vascular Closure System (VVCS) Model 800-612C is intended to seal the femoral vein access site(s) at the completion of the procedure. The system is designed to deliver a resorbable Collagen Patch, extra-vascularly, at the venotomy site to aid in achieving hemostasis. The device can be used in 6F to 12F, 12cm¹ introducer sheaths. The system consists of a sterile disposable Vascular Closure Catheter which houses a resorbable Collagen Patch, and the MID-BORE VVCS Clip (refer to Figure 1). The collagen patch is composed of type I Bovine collagen and is delivered in a compressed form that is approximately 15mm in length. The dry weight of the collagen is 12mg ± 3mg. The patch expands as a result of rehydration in the presence of blood in the tissue tract to provide an extravascular seal. A radiopaque proximal marker band on the Catheter provides means to aid in verifying placement of the patch in the tissue tract adjacent to the femoral venotomy site prior to the release of the patch. A second distal marker band locates the distal tip of the MID-BORE VVCS Disc. After completion of the procedure, the MID-BORE VVCS Catheter is inserted through the introducer sheath. The MID-BORE VVCS Disc is then deployed within the vessel and the introducer sheath is removed over the MID-BORE VVCS Catheter. After the introducer sheath is removed, the MID-BORE VVCS Disc is positioned against the intimal aspect of the venotomy, providing both temporary hemostasis and protection from intravascular placement of the Collagen Patch, and the MID-BORE VVCS Clip is applied at skin level to maintain the position of the Disc. After confirming the position of the Collagen Patch either fluoroscopically or by ultrasound, the Black Sleeve is unlocked and retracted to expose the Collagen Patch to the tissue tract. The system is left in place for a brief dwell period to allow the patch to swell, after which the Disc is collapsed and the MID-BORE VVCS Catheter is removed from the vein leaving the resorbable, extra-vascular, hemostatic Collagen Patch at the venotomy site providing hemostasis.

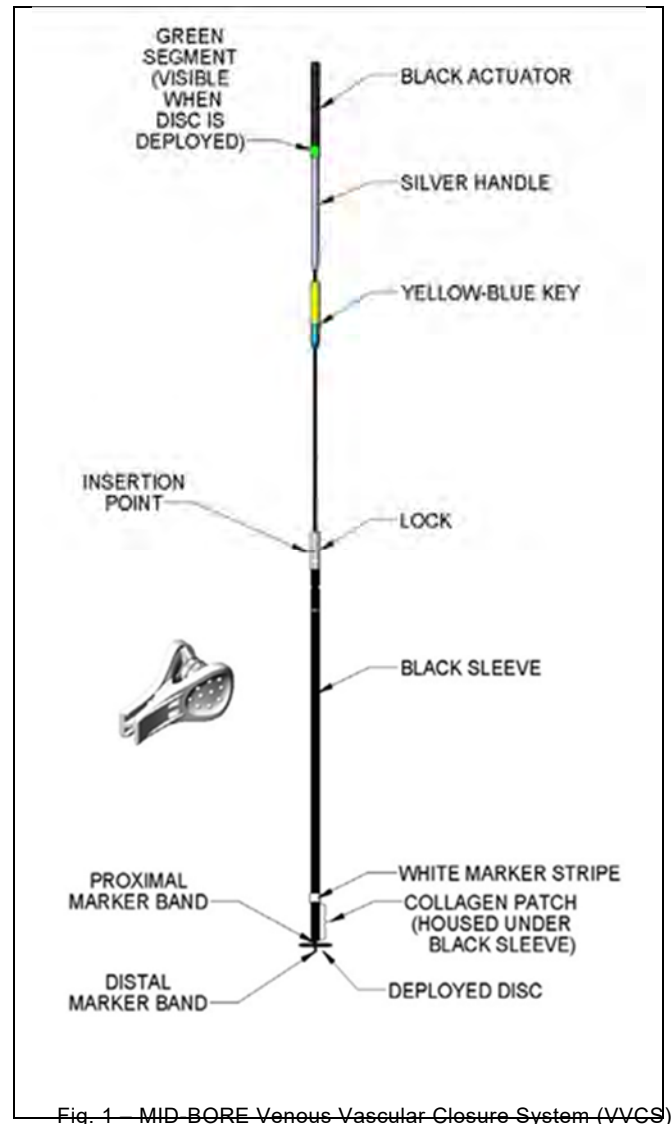


Fig. 1 MID-BORE Venous Vascular Closure System (VVCS)

INDICATIONS FOR USE

The MID-BORE Venous Vascular Closure System (VVCS) Model 800-612C is indicated for the percutaneous closure of femoral venous access sites while reducing times to ambulation and discharge eligibility in patients who have undergone interventional catheter-based procedures utilizing 6 – 12 F procedural sheaths with single or multiple access sites, ranging from a single access site in one limb to multiple access sites in both limbs.

CONTRAINDICATIONS

The MID-BORE VVCS should not be used in patients with a known allergy to bovine derivatives.

WARNINGS

- Do not reuse or re-sterilize. The MID-BORE VVCS is intended to be used once only for a single patient. Product reuse or re-sterilization, may result in transmission of infectious or blood borne diseases and/or death.
 - Do not use if components or packaging appear to be damaged or defective or if any portion of the packaging has been previously opened. Damaged or opened packages may compromise product functionality.
 - Do not use if product is beyond the expiration date. Product performance has not been established beyond the labeled shelf life.
 - Do not deploy the MID-BORE VVCS Disc in a stent. Do not pull the deployed MID-BORE VVCS disc through a stent. Damage to the product may occur.
 - Do not use MID-BORE VVCS if access is through a previously placed permanent closure device such as a metal clip. Interference between the two closure devices may result.
 - Do not deploy the Collagen Patch if there is a suspicion that the MID-BORE VVCS Disc is not seated against the intimal aspect of the venotomy site. Partial or complete obstruction of blood flow may result.
 - Do not deploy a second collagen patch at the same access site within 30 days. Safety has not been established.
-

PRECAUTIONS

- The MID-BORE VVCS should only be used by a trained licensed physician or healthcare professional.
 - Do not use in access sites where there is suspicion of a “backwall” stick. Increased bleeding risk may occur.
 - Do not use if venotomy is noted to be a “side stick.” Bleeding risk may increase.
 - Do not use if venotomy site is noted to be “high,” above the Inguinal Ligament (cephalad to lower half of the femoral head or the inferior epigastric artery origin from the external iliac artery). This may increase the risk of bleeding.
 - Do not use in a vein with suspected intraluminal thrombus, hematoma, pseudoaneurysm, or arteriovenous fistula. These conditions may complicate proper device use and performance.
 - Do not use if intra-procedural bleeding around the introducer sheath is noted including hematoma formation (sign of possible multiple wall stick). This may suggest problems with the access site.
 - Do not use in a procedural sheath > 12cm in length (or >15cm in overall length) or with a diameter other than 6-12F. This may complicate disk deployment.
-

SPECIAL PATIENT POPULATIONS

NOTE: The safety and effectiveness of MID-BORE VVCS have not been evaluated in the following patients who are/have:

- Less than 18 years of age;
- Pregnant and/or lactating women;
- Pre-existing immunodeficiency disorder and/or chronic use of systemic steroids;
- Known significant coagulopathy/bleeding disorder such as thrombocytopenia (platelet count <100,000/mm³), thrombasthenia, hemophilia, von Willebrand’s disease or anemia (Hemoglobin <10g/dL, Hematocrit <30%);
- Previous vascular grafts or surgery at the target vessel access site;
- Symptomatic ipsilateral lower extremity ischemia;
- Femoral venous lumen less than 6 mm;
- Length of the tissue tract, the distance between the anterior venous wall and skin, is estimated to be less than 2.5cm;
- INR ≥1.8 if patient received warfarin;
- Fibrinogen level < 150 mg/dl if patient received fibrinolytic agent;
- Extreme morbid obesity (BMI > 45 kg/m²) or underweight (BMI < 20 kg/m²);

Adverse Events

Complications may occur and may be related to the procedure or the vascular closure. They include, but are not limited to:

- Allergic response
- Vascular occlusion
- Venous thrombus
- Arterio-venous fistula
- Bleeding from the puncture site
- Oozing from the puncture site
- Bruising at the puncture site
- Death
- Device failure/malfunction
- Edema
- Embolization tissue, (thrombus, air, calcific debris device)
- Pulmonary Embolism
- Hematoma
- Infection
- Inflammatory response
- Intimal tear / dissection
- Lower extremity ischemia
- Perforation of the vessel wall
- Laceration of the vessel wall
- Peripheral nerve injury
- Pseudoaneurysm
- Retroperitoneal bleeding
- Deep vein thrombosis
- Vascular injury
- Vasovagal response
- Wound dehiscence
- Puncture site pain
- Superficial vein thrombosis

DEVICE PREPARATION AND PROCEDURE

At the time of initial access, if more than one sheath is planned to be placed in the same vein, the distance between the access sites should be kept at a minimum of 6 mm. Keep the stick separation at the skin level at a minimum of 6 mm and drive the needles to the vein at the same angle to keep the separation between the adjacent venotomies at a minimum of 6 mm. Imaging techniques such as ultrasound to confirm the separation is recommended.

At the time of initial introducer sheath placement, patient body habitus should be evaluated to provide reasonable assurance that the distance between the femoral venotomy and the skin surface is greater than 2.5cm. After introducer sheath placement, an anterior oblique fluoroscopic image with contrast or an ultrasound image may be digitally recorded and stored, so that the venotomy site location can be estimated and compared to the position of the proximal radiopaque marker just prior to Collagen Patch release. The proximal radiopaque marker is located immediately distal to the Collagen Patch. If more than one sheath is used in the same vein, it is recommended to close the proximal venotomy first to facilitate device placement and imaging prior to Collagen Patch release.

CAUTION: During access care should be taken so that the tissue tract is not pushed laterally or medially prior to accessing the vessel. This is to avoid misalignment of the tissue tract and the Collagen Patch relative to the venotomy site once the device is removed from the vessel which may result in prolonged time to hemostasis.

If more than one access is made in the vein, keep a minimum of 6 mm separation between the access sites. This is to allow the disc to track back to the vessel wall. Temporary hemostasis may not be achieved if the venotomies are too close to each other.

Not achieving temporary hemostasis may be an indication that the disc is not against the vessel wall. Releasing the collagen patch may result in all or a portion of the patch to be deployed in the vessel.

1. Use the Cardiva MID-BORE VVCS only as described below:

Device	Model	Sheath Size (French)	Sheath Length	Disc Size	Collagen Patch Length	Device Working Length	Maximum OD (with collapsed Disc)
Cardiva MID-BORE VVCS	800-612C	6F – 12F	up to 12 cm	7.7 mm	15 mm	15 cm	2.1 mm

2. Inspect the package for damage (breaks, tears, open seals, water damage, etc.) and verify that expiration date has not passed.
3. Using standard sterile technique, remove the tray containing the MID-BORE VVCS Catheter and Clip from the foil pouch. Carefully remove MID-BORE VVCS Catheter and Clip from the tray. Examine the device by first verifying that the Black Sleeve is locked in position and the Collagen Patch is not exposed. Also verify that the Yellow-Blue Key (**Figure 2**) is not engaged in the Lock (the Lock is located at the proximal aspect of the Black Sleeve), and the Yellow-Blue Key is located at the proximal end of the Catheter Shaft. Inspect the Catheter further by examining the deployed MID-BORE VVCS Disc. To deploy the Disc, hold the Silver Handle firmly and pull back

on the Black Actuator until it locks in place. When the Disc is locked in the deployed position, the Green Segment will become visible as shown in Figure 3. Examine the Disc, which should appear circular and symmetrical with an intact membrane. **Figure 4** shows the deployed and collapsed Disc. After examination, collapse the Disc by pressing the Black Actuator tip down (**Figure 5**). The tip of the MID-BORE VVCS Catheter should return to its original profile.



Fig. 2 – Verify Yellow-Blue Key is not engaged in the Lock and Black Sleeve is locked in position

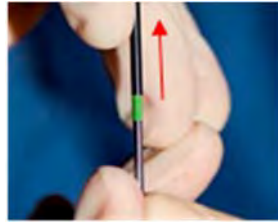


Fig. 3 – Pull back on Black Actuator Tip to deploy the Disc



Fig. 4 – Deployed & Collapsed Disc



Fig. 5 – Collapse Disc by pressing Black Actuator Tip like a ballpoint pen

4. Verify that the sheath is not positioned in a tortuous vessel, by examining the sheath placement images obtained earlier. If required, retract the sheath slightly to a non-tortuous location. Verify that the sheath is still positioned within the vein. If more than one sheath is in the vein, retract the most proximal sheath (top sheath) so that the distal opening of that sheath is proximal to the distal opening of other sheaths by 3-4 cm. This is to eliminate interference of a deployed disc with other indwelling sheaths during device deployment. **Care must be taken not to lose vessel access.** Deploy MID-BORE VVCS and obtain hemostasis in the most proximal sheath first (as per steps outlined below). Then move distally to repeat the steps to obtain closure for the other sheaths.

WARNING: Verify there is no vessel tortuosity or side branches within 3-4 cm from the distal opening of the sheath and the end of the sheath is not resting against the vessel wall. This is to prevent any vascular injury as a result of advancing the catheter. If required, retract the sheath slightly to a non-tortuous location, being careful not to lose vessel access.

5. Flush the sheath with sterile saline solution prior to insertion of the device.
6. Prior to insertion of device in the introducer sheath, momentarily insert the tip of the VVCS Catheter in saline solution up to the White Marker Stripe and quickly remove.

CAUTION: Do not soak the MID-BORE VVCS Catheter in saline. Momentarily insert only the Catheter tip in saline solution immediately before use to avoid over-hydration of the patch, which may result in difficulty of retracting the sleeve and causing Catheter pull through during the sleeve retraction step.

7. Gently insert the MID-BORE VVCS Catheter (with disc collapsed) into the introducer sheath hub as shown in **Figure 6**. Use short strokes to insert the device.
8. Insert the MID-BORE VVCS Catheter such that approximately half of the Lock is visible. Make certain that the Lock is NOT fully inserted into the sheath. See **Figure 7** for correct placement.

CAUTION: Do not advance MID-BORE VVCS Catheter into the patient if resistance is felt due to risk of vascular damage.



Fig. 6 – Insert device into hub of introducer sheath

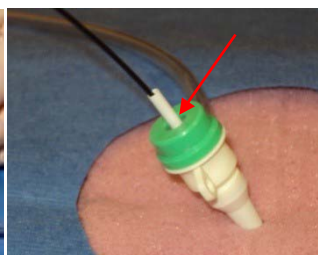


Fig. 7 – Insert device half way of the Lock

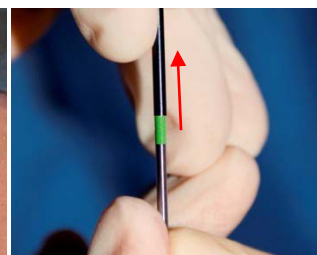


Fig. 8 – Pull back on Black Actuator Tip to deploy the MID-BORE VVCS Disc

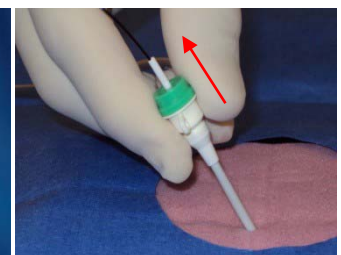


Fig. 9 – Grasp hub of sheath and remove over catheter

9. Deploy the Disc by holding the Silver Handle and pulling back the Black Actuator until it locks in place as shown in **Figure 8**.

CAUTION: Do **not** continue to pull on the Black Actuator once it is locked in place as this may damage the device.

NOTE: When the Disc is properly deployed, the Green Segment will become visible distal to the Black Actuator. If the catheter is not properly locked in place, the Black Actuator will slide back to its original position and the Green Segment will disappear indicating that the Disc is not properly deployed. In this case repeat the step for deploying the Disc by pulling the Black Actuator more firmly until it locks in place.

10. Gently remove sheath, without applying any compression at the access site or holding the MID-BORE VVCS Catheter, as shown in **Figure 9**. As the sheath slides over the MID-BORE VVCS Catheter, grasp the Catheter as the sheath exits the body. Continue sliding the sheath over the MID-BORE VVCS Catheter and discard sheath.

CAUTION: Compressing the access site during sheath removal may not allow the Disc to track back to the venotomy and may cause Disc deformation. This may lead to inability to achieve temporary hemostasis.

11. Apply gentle tension on the Black Actuator until temporary hemostasis is achieved. Note whether any portion of the White Marker Stripe, which is located near the distal aspect of the Black Sleeve, is visible above the skin. If it is, then the length of the tissue tract is less than 2.5 cm, indicating the tissue tract may not be long enough for the Collagen Patch.

WARNING: If any portion of the White Marker Stripe is showing DO NOT RELEASE the Collagen Patch as this may increase the risk of infection.

NOTE: If any portion of the White Marker Stripe is showing and the collagen patch is not to be deployed, the MID-BORE VVCS Catheter should be removed by collapsing the Disc and manual compression should be applied per institutional protocol.

12. Once temporary hemostasis is achieved, apply the Clip to the Black Sleeve at skin level as shown in **Figure 10**. Verify that deployed Disc is positioned against the intimal surface of the vessel at the venotomy site, either by fluoroscopy (to verify that the more proximal radiopaque marker is positioned at the venotomy), or by ultrasound. The Collagen Patch is located immediately proximal to the Proximal Marker Band. The Distal Marker Band locates the distal end of the Disc.

CAUTION: Applying too much upward tension on the Silver Handle may cause disc to pull out of vessel. Should this occur, convert to your **institution's manual compression protocol**.

WARNING: It is important to ensure that the Disc is in contact with the intimal aspect of the venotomy before deploying the extra-vascular Collagen Patch to avoid releasing the Collagen Patch in the vessel. **This is indicated by having temporary hemostasis and further verified by either fluoroscopy (Figure 11a) or ultrasound imaging (Figure 11b).**

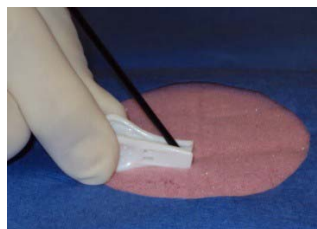


Fig. 10 – Apply Clip to Black Sleeve at skin level

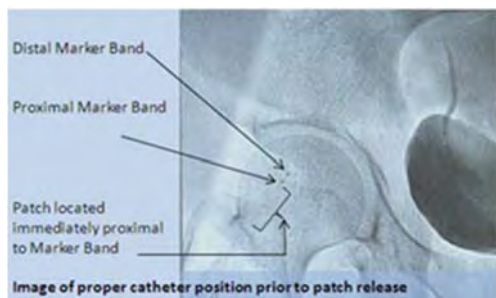


Fig. 11a – Fluoroscopic image demonstrating proper position of Disc



Figure 11b Ultrasound image demonstrating proper position of Disc

EXTRA-VASCULAR COLLAGEN PATCH DEPLOYMENT AND DEVICE REMOVAL

13. Once the Disc location is verified, expose the extra-vascular resorbable Collagen Patch by unlocking the Black Sleeve. This is done by grasping the Lock with the left hand, between the thumb and the index finger, and grasping the Yellow-Blue Key with the right hand and then sliding the Yellow-Blue Key into the Lock until no blue color is visible, as shown in **Figure 12**. Once the Sleeve is unlocked and while still holding on to the Lock, remove the Clip with the right hand, and gently slide the Lock back along the angle of entry to retract the Black Sleeve as shown in **Figure 13**. The Black Sleeve will move freely after some initial resistance. A second resistance point may be felt after the sleeve is moved approximately 1.6 cm (0.6 inch).

Proceed to fully retract the Black Sleeve proximally to the Silver Handle. This action exposes the Collagen Patch extra-vasculally, which will swell at the venotomy site. The Collagen Patch may be allowed to swell for up to 30 seconds prior to removal of the MID-BORE VVCS Catheter. The Clip may be reapplied during the Collagen Patch swell period with minimal tension on the Catheter (**Figure 14**).

NOTE: If the Black Sleeve does not retract easily, recheck that the blue end of the Yellow-Blue Key is fully engaged in the Lock.

NOTE: If the Collagen Patch is removed during sleeve retraction, collapse the Disc, remove the Catheter and apply manual compression, per institutional protocol.

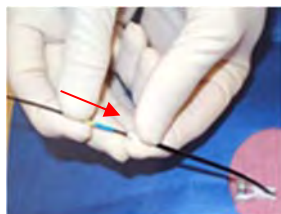


Fig. 12 – Unlock the Black Sleeve by sliding Yellow-Blue Key into the Lock

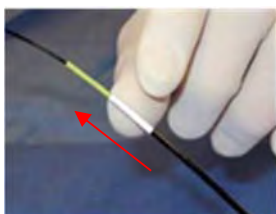


Fig. 13 – Retract the Black Sleeve by grasping the Lock and applying gentle upward tension toward the Silver Handle

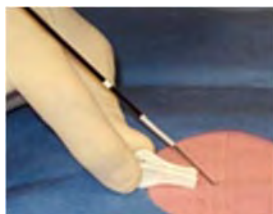


Fig. 14 – Reapply Clip during the Collagen Patch swell period



Fig. 15 – Grasp Green Tube prior to collapsing the Disc




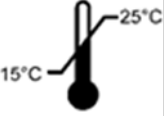











Fig. 16 – Collapse the Disc by pressing on the Black Actuator Tip

14. AFTER 15-30 seconds of patch swell time and PRIOR TO collapsing the Disc, remove the Clip. Rest the palm of the hand on the patient and grasp the green tube between the thumb and the index finger as shown in **Figure 15**. Push the green tube in the proximal direction approximately 1.5 cm while gently pulling back on the MID-BORE VVCS Catheter to maintain Disc position against vessel wall. The green tube may be slid back and forth 2-3 times in order to assure release of the Collagen patch from device. Upon completion of this step, leave the green tube in the forward position. Apply gentle compression at the site and collapse the Disc by pressing on the Black Actuator Tip as shown in **Figure 16**. Apply gentle manual compression at the site as the MID-BORE VVCS Catheter is removed. Continue to apply manual compression.
15. Observe for complete hemostasis. Manual compression can be used to decrease or stop any tract ooze until full hemostasis is achieved.

NOTE: Prior to the MID-BORE VVCS Catheter removal confirm that the Disc is completely collapsed by verifying that the Green Segment on the handle is no longer visible. Care should be taken not to compress too firmly over the VVCS catheter during the removal step of the device so that the catheter can be easily removed and without displacement of Collagen Patch. Note: The implanted Collagen Patch should not be affected by Magnetic Resonance Imaging (MRI).

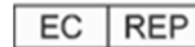
16. Apply sterile dressing to site per institution protocol. Maintain bed rest and periodically check site until patient is ready to ambulate.
17. Complete information on Patient Implant Card and provide to the patient.

GRAPHICAL SYMBOLS ON THE MID-BORE VVCS PACKAGING

Do not reuse		Store at room temperature		Manufacturer	
Sterilized using irradiation		Latex Free		Authorized representative in the European Community	
Use by		Lot Number		Keep Dry	
Caution, see Instructions for Use		Model Number		Do not use if the product sterilization barrier or its packaging is compromised	
Quantity of systems in package		Federal (USA) law restricts this device to sale by or on order of a physician	Rx Only		



Design *for* what's humanly possible



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LIMITED WARRANTY

Cardiva Medical, Inc. warrants that each Mid-Bore Venous Vascular Closure System (VVCS) is free from defects in workmanship and material under normal use and service, and provided it is used prior to the stated expiration date. Cardiva Medical, Inc. will not be liable for any incidental, special or consequential loss, damage or expense direct or indirect from the use of its product. Liability under this warranty is limited to refund or replacement of any device that has been found by Cardiva Medical, Inc. to be defective at the time of shipment. Damage to the device through misuse, alteration, improper storage or improper handling shall void this limited warranty. The remedies set forth in this warranty and limitation shall be the exclusive remedy available to any person. No employee, agent or distributor of Cardiva Medical, Inc. has any authority to alter or amend this limited warranty, or assume or bind Cardiva Medical, Inc. to any additional liability or responsibility with respect to this device. There is no express or implied warranty, including any implied warranty of merchantability or fitness for a particular purpose, on the Cardiva Medical, Inc. product(s) described herein.

23. Attachment 4: Patient Experience Survey

SUBJECT ID:

		-			
SITE #			SUBJECT #		

SUBJECT INITIALS:

F	M	L

Patient Experience Survey

Instructions to the Research Staff:

- For all subjects following successful ambulation, please provide the following survey pages to the subject under evaluation.
- The Survey should be read and answered in order.
- On completion of the survey, review for completeness and clarity. Make sure answers are logical and clearly answered.
- On completion of all applicable survey questions, enter the data in the eCRF and file source documents.

Instructions to the Patient:

- Enter the date and time that you completed the survey at the top of the form.
- INITIAL the bottom of each form when you complete it.
- Please read the questions and respond by circling only one number from 0-10 on the scale below each question, or by answering the specific question.

Examples:

<p>1. How do you feel about the <u>length of time</u> you spent lying on your back after the procedure?</p> <p>0 1 2 3 <u>4</u> 5 6 7 8 9 10</p> <p>Very Dissatisfied Very Satisfied</p> <p>Correct</p>	<p>2. How do you feel about the <u>length of time</u> you spent lying on your back after the procedure?</p> <p>0 1 2 3 <u>4 5</u> 6 7 8 9 10</p> <p>Very Dissatisfied Very Satisfied</p> <p>Incorrect</p>
--	--

Printed name of person providing survey to the subject

/

Signature

Date

SUBJECT ID:

		-			
SITE #			SUBJECT #		

SUBJECT INITIALS:

F	M	L

Patient Experience Survey

Time & Date Form Completed:	____/____/____ (dd-Mmm-yyyy)	
	Enter Time: ____:____	
1. Rate level discomfort in your groin at the catheter access site(s):		
1	2	3
4	5	6
7	8	9
10		
1- (No Discomfort)		5 - (Moderate Discomfort)
		10 - (Very Painful)
2. Which of the following best describes your bedrest experience?		<input type="checkbox"/> Bedrest was too short. I wasn't ready to walk yet. <input type="checkbox"/> Bedrest was just right <input type="checkbox"/> Bedrest was too long. I wanted to walk sooner.
3. Have you ever had an ablation procedure prior to this?		<input type="checkbox"/> Yes, complete a. – d. <input type="checkbox"/> No
a. How many ablation procedures have you had within: (Please answer all questions. Enter 0 if none.)		The last year: ____ 1-3 years ago: ____ 4-5 years ago: ____
b. The length of my current procedure's bedrest was: (select one)		<input type="checkbox"/> Longer <input type="checkbox"/> Shorter <input type="checkbox"/> Same <input type="checkbox"/> I don't recall
c. Which most closely describes my experience for my current procedure's bedrest? (select one)		<input type="checkbox"/> I prefer my current procedure's bedrest <input type="checkbox"/> I prefer my previous procedure's bedrest <input type="checkbox"/> No preference <input type="checkbox"/> I don't recall
d. My current procedure groin access site pain/discomfort is: (select one)		<input type="checkbox"/> Better <input type="checkbox"/> Worse <input type="checkbox"/> Same <input type="checkbox"/> I don't recall

SUBJECT ID:

		-			
SITE #			SUBJECT #		

SUBJECT INITIALS:

F	M	L

Patient Experience Survey

4. Provided your physician felt it was medically safe, which of the following do you prefer? (select one)

- ☐ Go home the same day
☐ Spend an additional night in the hospital
☐ No preference

a. If additional night, why? (select all that apply)

- ☐ No transportation
☐ Too late
☐ Still concerned about safety, despite physician's assurance
☐ Need additional support,
specify: _____

5. For post-procedure care, rate how important the following are to you:

a. Ability to walk within 2-3 hours post procedure and not be confined to bedrest

1	2	3	4	5	6	7	8	9	10
1- (Not Important)				5 - (Important)			10 - (Very Important)		

b. Ability to urinate post procedure unassisted (for example: no urinary catheter, bedpans, etc.):

1	2	3	4	5	6	7	8	9	10
1- (Not Important)				5 - (Important)			10 - (Very Important)		

c. Ability to go home within the same calendar day and not spend the night in the hospital:

1	2	3	4	5	6	7	8	9	10
1- (Not Important)				5 - (Important)			10 - (Very Important)		

6. If you require a future procedure, would you actively seek a facility:

a. That would allow you to walk within 2-3 hours post procedure and not be confined to bedrest?

☐ Yes ☐ No

b. That would not utilize a urinary catheter for urinary management?

☐ Yes ☐ No

c. That would allow you to be discharged within the same calendar day if medically appropriate?

☐ Yes ☐ No

Name:

Signature:

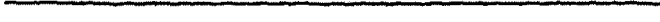



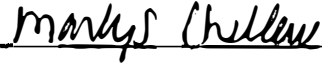
Date:

**CARDIVA MEDICAL, INC.
Protocol Approval Page**

STUDY TITLE: "AMBULATE CAP STUDY" CONTINUED ACCESS PROTOCOL (CAP)
MULTI-CENTER, SINGLE ARM CONTINUING ACCESS PROTOCOL TO EVALUATE THE
CARDIVA MID-BORE VENOUS VASCULAR CLOSURE SYSTEM (VVCS) FOR THE
MANAGEMENT OF THE FEMORAL VENOTOMY AFTER CATHETER-BASED
INTERVENTIONS PERFORMED VIA 6- 12 FR PROCEDURAL SHEATHS WITH SINGLE
OR MULTIPLE ACCESS SITES PER LIMB

PROTOCOL PTL 0543
NUMBER:
VERSION NUMBER: 02

We, the undersigned, have read and approve the protocol specified above and agree on its content.

Name/Title	Signature	Date
Justin Ballotta Chief Operating Officer		
Zia Yassinzadeh Chief Technology Officer		
Jennifer Lee Director, Quality & Engineering		
Terry Passarotti Director, Regulatory & Clinical Affairs		8/23/18
Mariys Chellew, BSN Independent Clinical Consultant		8/23/18

Rob Roland

From: Justin Ballotta
Sent: Thursday, August 23, 2018 3:43 PM
To: Rob Roland
Subject: Re: PTL 0543-02 ABULATE CAP Study Protocol
Attachments: image001.jpg

I approve. Please sign on my behalf.

Thank you,
Justin

> On Aug 23, 2018, at 3:39 PM, Rob Roland <Rob_Roland@cardivamedical.com> wrote:

>

> Marlys and Justin

>

> Attached is PTL 0543-02 which requires your approval. Please sign the

> 2nd page of the PTL and send it back to me. If you are unable to sign

> and scan please send back a email stating that you approve of the

> Document and authorize me to sign on your behalf

>

> thanks

>

>

> Rob Roland

> Sr. Quality Assurance and Compliance Specialist Cardiva Medical, Inc.

> 2900 Lakeside Dr. Suite 160

> Santa Clara, CA 95054

> Direct: 408-470-7131

> [cardivaMed_logo_color_vectorized]

>

> <PTL 0543-02 AMBULATE CAP Study Protocol + Attach Needing

> approval.pdf> <image001.jpg>