"ANTEGRADE-PVD" Post-Market Registry Protocol

A MULTI-CENTER, PROSPECTIVE, POST-MARKET REGISTRY TO EVALUATE PROCEDURAL OUTCOMES DATA USING THE CARDIVA VASCADE™ VASCULAR CLOSURE SYSTEM (VCS) FOR THE MANAGEMENT OF THE FEMORAL ARTERIOTOMY AFTER PERCUTANEOUS ENDOVASCULAR PROCEDURES VIA ANTEGRADE ACCESS

The registry will be performed in accordance with the relevant parts of Title 21 CFR Parts 50 and 803

Sponsor:	Cardiva Medical, Inc.
Registry Responsibility:	Cardiva Medical, Inc.
Principal Investigator:	Mehdi Shishehbor, DO
Study Centers:	Cleveland Clinic Foundation Cardiovascular Institute of the South San Antonio, Heart, Vascular and Rhythm Center North Mississippi Medical Center Coastal Surgery Specialists
Protocol Number:	PTL 0502-02
Date of Issue:	March 7, 2017 / Version 1.0

This protocol contains confidential information for use by the Investigators and their designated representatives participating in this clinical registry. It should be held confidential and maintained in a secure location.

Protocol Approval Page

STUDY TITLE: **ANTEGRADE-PVD Post-Market Registry Protocol**

A **MULTI-CENTER, PROSPECTIVE, POST-MARKET REGISTRY TO EVALUATE PROCEDURAL OUTCOMES DATA USING THE CARDIVA** VASCADE™ **VASCULAR CLOSURE SYSTEM (VCS) FOR THE MANAGEMENT OF THE FEMORAL ARTERIOTOMY AFTER PERCUTANEOUS ENDOVASCULAR PROCEDURES VIA ANTEGRADE ACCESS**

PROTOCOL NUMBER: PTL 0502-02

VERSION NUMBER: 1.0

DATE: March 7, 2017

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

Name/Title/Affiliation	Signature	Date
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Investigator's Agreement / Signature Page

STUDY TITLE: **ANTEGRADE-PVD Post-Market Registry Protocol**

A MULTI-CENTER, PROSPECTIVE, POST-MARKET REGISTRY TO EVALUATE PROCEDURAL OUTCOMES DATA USING THE CARDIVA VASCADE™ VASCULAR CLOSURE SYSTEM (VCS) FOR THE MANAGEMENT OF THE FEMORAL ARTERIOTOMY AFTER PERCUTANEOUS ENDOVASCULAR PROCEDURES VIA ANTEGRADE ACCESS

PROTOCOL NUMBER: PTL 0502-02

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DATE: March 7, 2017

STUDY CENTER: _____

(Print site name and number)

I, the undersigned, have read and understand the protocol specified above and agree on its content. I agree to perform and conduct the registry as described in the protocol.

_____

Print Investigator Name ☐ Principal Investigator ☐ Co-Investigator

_____

Signature Date

Protocol Synopsis

ANTEGRADE-PVD Post-Market Registry Protocol

A MULTI-CENTER, PROSPECTIVE, POST-MARKET REGISTRY TO EVALUATE PROCEDURAL OUTCOMES DATA USING THE CARDIVA VASCADE™ VASCULAR CLOSURE SYSTEM (VCS) FOR THE MANAGEMENT OF THE FEMORAL ARTERIOTOMY AFTER PERCUTANEOUS ENDOVASCULAR PROCEDURES VIA ANTEGRADE ACCESS

Primary Objective	The objective of the ANTEGRADE-PVD registry is to collect procedural outcomes data when the Cardiva VASCADE™ Vascular Closure System (VCS) is used to seal femoral arterial access sites at the completion of ipsilateral peripheral interventional procedures performed through 5-7 Fr introducer sheaths via an antegrade approach. Antegrade access is experiencing growing adoption in catheter-based procedures to treat peripheral artery disease, with many advantages for lower limb procedures in particular. This post-market registry is designed to capture data specific to this procedural technique, and is being conducted under an FDA-approved indication for use for this device.
Device	The Cardiva VASCADE™ Vascular Closure System (VCS) is an FDA-approved device (PMA P120016).
Approved Indication for Use	The Cardiva VASCADE™ Vascular Closure System (VCS) is indicated for femoral arterial access site closure while reducing times to hemostasis and ambulation in patients who have undergone diagnostic or interventional endovascular catheterization procedures utilizing a 5 Fr, 6 Fr or 7 Fr procedural sheath.
Study Design	A multi-center, prospective, single arm post-market registry
Number of Subjects	Up to 100 prospectively enrolled subjects
Number of Sites	Investigators experienced in antegrade access closure w/VASCADE VCS will enroll subjects at up to 7 U.S. sites
Study Duration	It is anticipated that enrollment will commence in December 2016, with final enrollment and 30 day follow-ups completed in Q3 2017. The registry will be considered complete after all enrolled subjects have completed the registry follow-up requirements.

Follow-up Schedule	Each enrolled subject will be followed for up to 30 +/-7 days post-procedure. There will be an office visit between 1-15 days; and a subsequent telephone follow-up will be done between 23-37 days as the final contact.
Primary Procedural Outcome – Performance	• Time to hemostasis (TTH), defined as elapsed time between device removal and first observed and confirmed arterial hemostasis.
Secondary Procedural Outcomes - Performance	• Time to ambulation (TTA), defined as elapsed time between device removal and when subject first stands and walks 20 feet without evidence of arterial re-bleeding from the access site. • Time to hospital discharge (TTD), defined as elapsed time between device removal and when subject is actually discharged from the facility. • Device Success, defined as the ability to deploy the delivery system, deliver the collagen, and achieve hemostasis with the Cardiva VASCADE™ VCS alone or with adjunctive compression • Procedure Success, defined as attainment of Device Success and freedom from major access site closure-related complications through 30 days
Primary Procedural Outcomes - Complications	Patient incidence rate of combined major access site closure-related complications through 30 days: • Access site closure-related bleeding requiring transfusion; • Vascular injury requiring repair (via surgery, ultrasound guided compression, transcatheter embolization or stent graft); • New ipsilateral lower extremity ischemia causing a threat to the viability of the limb and requiring surgical or additional percutaneous intervention; • Access site-related infection requiring intravenous antibiotics and/or extended hospitalization; • New onset neuropathy in the ipsilateral lower extremity requiring surgical repair • New onset permanent nerve injury in the ipsilateral lower extremity (> 30 days)

Secondary Procedural Outcomes - Complications	Patient incidence rate of combined minor access site closure-related complications through 30 days: • Access site-related bleeding requiring greater than 30 minutes to achieve initial arterial hemostasis; • Access site-related hematoma > 6 cm documented by ultrasound; • Late access site-related arterial bleeding requiring intervention (following hospital discharge); • Ipsilateral lower extremity arterial emboli documented by ultrasound/imaging; • Ipsilateral deep vein thrombosis documented by ultrasound; • Access site-related vessel laceration; • Access site wound dehiscence; • Localized access site infection treated with intramuscular or oral antibiotics; • Arteriovenous fistula not requiring treatment, documented by ultrasound/imaging; • Pseudoaneurysm requiring thrombin injection or fibrin adhesive injection; • New onset neuropathy in the ipsilateral lower extremity not requiring surgical repair.
Pre-Operative Inclusion Criteria	1. 18 to 80 years of age; 2. Capable and willing to give informed consent; 3. Acceptable candidate for an elective, non-emergent ipsilateral peripheral interventional endovascular procedure via antegrade access of the femoral artery using a 5, 6 or 7 Fr introducer sheath; 4. Acceptable candidate for post-procedural manual compression; 5. Able and willing to complete a follow-up office visit between 1-15 days post-procedure, and subsequent follow-up telephone assessment between 23-37 days; 6. Subject is able to ambulate at least 20 feet, with or without assistance (e.g., ambulatory amputee); 7. Acceptable candidate for emergent vascular surgery.

Pre-Operative Exclusion Criteria	Subjects will be excluded from participating in this registry if they meet any of the following criteria prior to initiation of the endovascular procedure: 1. Advanced refusal of blood transfusion, if necessary; 2. Active systemic or cutaneous infection or inflammation; 3. Pre-existing immunodeficiency disorder and/or chronic use of systemic steroids; 4. Known, significant history of bleeding diathesis, coagulopathy, or current platelet count < 100,000 cells/mm3, baseline INR ≥1.8, or fibrinogen level less than 150 mg/dl (if received a fibrinolytic agent within prior 24 hours) based on institution's standard pre-operative lab values; 5. Severe co-existing morbidities having a life expectancy of less than 90 days; 6. Currently involved in any investigational clinical trials that have not completed their primary endpoint and/or may interfere with the conduct of this registry, per Investigator's assessment; 7. Previous ipsilateral femoral arteriotomy with any of the following conditions: a. access within ≤ 10 days b. any residual hematoma, significant bruising, or known associated vascular complications; c. within ≤ 90 days, use of an intra-vascular closure device (i.e., Angioseal); 8. Planned / staged endovascular or surgical procedures within the next 10 days, prior to office visit (excluding planned/anticipated minor amputation); 9. Previous vascular grafts or surgery at the target vessel access site; 10. Known history of deep vein thrombosis in the ipsilateral limb within the past 30 days, unless confirmed to be resolved by ultrasound prior to enrollment; 11. Major amputation (i.e., above the ankle) of the ipsilateral lower extremity is planned/anticipated within next 30 (± 7) days, prior to study exit: 12. Large pannus, which may prevent antegrade access without significant tissue displacement, in the opinion of the investigator; 13. Significant anemia with a hemoglobin level less than 10 g/dL or

	a hematocrit less than 30% based on institution's standard pre-operative lab values; 14. Renal insufficiency (serum creatinine of > 2.5 mg/dl); 15. Females who are pregnant, planning to become pregnant within 3 months of the procedure, or lactating; 16. Extreme morbid obesity (BMI greater than 45 kg/m2) or underweight (BMI less than 20 kg/m2); 17. Known allergy/adverse reaction to bovine derivatives; 18. Administration of low molecular weight heparin (LMWH) within 8 hours of the procedure.
Intra-Operative Exclusion Criteria	Subjects will be excluded from participating in this registry if any of the following exclusion criteria occur <u>during the endovascular procedure, prior to enrollment</u> (i.e., prior to insertion of VASCADE VCS): 1. Use of a final introducer sheath > 12 cm (or > 15 cm in overall length), or not 5, 6 or 7 Fr diameter; 2. Contralateral femoral arterial access with > 5 Fr catheter that is not successfully closed with a closure device during the index procedure; 3. Index groin involves a previously placed permanent closure device (e.g., Starclose), where the device cannot be visualized to confirm that it is at least 1 cm proximal or distal to the puncture site; 4. Femoral artery diameter less than 6 mm at access site; 5. Angiographic evidence of moderate to severe calcium, > 50% stenosis, or a stent within 1 cm of the puncture site; 6. Overlapping Common Femoral Vein and Femoral Artery at access site; 7. Presence or placement of ipsilateral venous sheath during procedure; 8. Antegrade arterial access site: a. is a side stick b. is NOT a single anterior wall femoral puncture c. is NOT below the inguinal ligament / lower half of femoral head and not below the inferior epigastric artery origin from the external iliac artery; 9. More than one ipsilateral arterial access site is required in the

	index limb (e.g., femoral or other); 10. Intra-procedural bleeding around sheath, or suspected intraluminal thrombus, hematoma, pseudoaneurysm, or AV fistula; 11. Evidence of arterial insufficiency, emboli, or new stenosis / occlusion in the ipsilateral limb at the conclusion of the index intervention (i.e., complications occurring from untreated, or suboptimal treatment of disease); 12. Systemic hypertension (BP greater than 180/110 mmHg) or hypotension (BP less than 90/60 mmHg) just prior to enrollment; 13. Length of the tissue tract, the distance between the anterior arterial wall and skin, is estimated to be less than 2.5 cm; 14. If the physician deems that a different method should be used to achieve hemostasis of the arterial site; 15. Upon final angio/fluoro assessment of the final introducer sheath to be used for VASCADE delivery, documented evidence of: a. inadequate sheath placement (e.g., location, position, angle), and/or b. any kinking of the procedural sheath prior to enrollment and insertion of the VASCADE VCS.
Study Administration	
Sponsor	Cardiva Medical, Inc. 2900 Lakeside Drive, Suite 160 Santa Clara, CA 95054
Clinical CRO & Data Management	Chellew Clinical Outsourcing, LLC 7844 E. Riverdale St. Mesa, AZ 85207
Safety Monitoring	An Independent Physician Adjudicator (IPA) will review and adjudicate all serious device-related adverse event reports, deaths, and all minor and major access site closure-related complications for a determination of both seriousness and closure-relatedness. All adverse events and device failures will be evaluated as complaints and determinations made as to whether the complaint represents an event which is required to be reported to FDA under 21 CFR Part 803, Medical Device Reporting.

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1. Introduction

1.1. Background and Rationale

The Cardiva VASCADE Vascular Closure System (VCS) is designed to deliver a resorbable collagen patch, extravascularly at the arteriotomy site to aid in achieving hemostasis. The collagen patch is designed to seal the arteriotomy within minutes and be resorbed in approximately three months. There are two versions of the product; one is for use in 5 Fr 12 cm introducer sheaths and the other for use in in 6 or 7 Fr 12 cm introducer sheaths.

The safety and effectiveness of this device has been shown in several studies of retrograde access closure with very low complication rates and improved times to hemostasis and ambulation, compared to manual compression subjects (1). Results of the RESPECT Trial led to FDA's PMA approval of the Cardiva VASCADE™ VCS on Jan. 31, 2013, and it is currently commercially available in the U.S., and in Europe under the CE-mark.

The use of alternate approaches to arterial access for percutaneous transfemoral revascularization has been on the rise in the U.S. and abroad, as advances in technology have broadened treatment options for patients needing treatment in the lower extremity vasculature. Antegrade punctures of the femoral artery often require a steeper puncture angle and can be technically more challenging, especially in obese patients. However, antegrade femoral puncture is commonly performed in patients with infrainguinal vascular disease, and allows the operator to treat ipsilateral lower limb lesions with better manipulation, support and pushability of wires and catheters, when compared to femoral retrograde, cross-over access (2-5). Manual compression is still regarded as the gold standard for achieving hemostasis and is widely used in both antegrade and retrograde access, but it has long been associated with patient discomfort associated with groin pressure and prolonged immobilization (5).

Although most vascular closure devices have been routinely tested for safety and efficacy in retrograde access procedures, these same devices are being successfully used in antegrade access diagnostic and interventional peripheral procedures (6).

There have been many single-center and multi-center studies conducted to examine procedural outcomes when VCDs are used to close antegrade femoral access sites. Although the vast majority of these studies are limited to retrospective analyses, the major complication rates have been reportedly similar to those reported in retrograde evaluations with these commercial devices (4-10). However, due to major inconsistencies in study methods, definitions and reporting among currently published studies, it is difficult to make a meaningful comparison of outcomes across studies and devices (7).

Due to the growing adoption of antegrade femoral access and the use of VCDs to close these arteriotomies, it is important to collect performance and complication outcomes data related to this procedural variable. The aim of the ANTEGRADE-PVD registry is to consistently collect prospective data on procedural outcomes in antegrade access cases closed with the VASCADE VCS in a way that is consistent with the RESPECT Study design and the FDA-approved Instructions for Use (IFU).

1.2. *Risks and Benefits*

1.2.1. Risks

Risks associated with the VASCADE VCS are similar to those associated with other extravascular methods of achieving hemostasis at arteriotomy sites. Complications that may occur include:

- Allergic response
- Arterial occlusion
- Arterial thrombus
- Arterio-venous fistula
- Bleeding/oozing from the puncture site
- Bruising at wound site
- Death
- Device failure / malfunction
- Edema
- Embolization tissue (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
- Retroperitoneal bleeding
- Thrombus formation
- Vasovagal response
- Vasospasm
- Vascular injury
- Wound dehiscence
- Wound site pain

Previous evaluations have not shown any additional risks in comparison to those associated with other compression-based hemostasis methods.

1.2.2. Potential Benefits

In the RESPECT IDE Trial, demonstrated benefits of the VASCADE™

Vascular Closure System over manual compression alone to achieve hemostasis included reduced time to hemostasis and time to ambulation in both diagnostic and interventional subjects.

This registry is intended to evaluate the potential benefit of reduced time to hemostasis, time to ambulation and time to discharge in interventional subjects undergoing antegrade access, while also evaluating procedural complications. Although antegrade access is a procedural technique that is gaining favor among clinicians for the treatment of ipsilateral peripheral disease, prospective enrollment and evaluation of outcomes related to vessel closure is lacking. Data collected in this registry may benefit clinicians in decision-making related to these types of procedures.

2. Device Description

The Cardiva VASCADE Vascular Closure System (VCS) is designed to deliver a resorbable Collagen Patch, extravascularly at the arteriotomy site to aid in achieving hemostasis. The collagen patch is designed to seal the arteriotomy within minutes and be resorbed in approximately three months. There are two versions of the product; one is for use in 5 Fr 12 cm introducer sheaths and the other for use in in 6 or 7 Fr 12 cm introducer sheaths.

Refer to Attachment 2: Instructions for Use for a complete description of the device, warnings and precautions, and a summary of the PMA (P120016) Summary of Safety and Effectiveness Data.

2.1. Device Labeling

A copy of the Instructions for Use (IFU) will be included with the devices. The Cardiva VASCADE™ Vascular Closure Systems (VCS) are commercially labeled for sale in the United States and contain the following information:

- Product Name
- Part number
- Lot number
- Expiration (use before) date

2.2. Previous Clinical Experience

VASCADE 6/7 Fr 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.

VASCADE 5 Fr was evaluated in a prospective, single treatment, single-center study to confirm the safety and effectiveness of the scaled-down 5 Fr version of the VASCADE 6/7 Fr VCS.

Conclusions: The results from the RESPECT clinical trial demonstrated that patients who have undergone diagnostic or interventional cardiac or peripheral vascular endovascular procedures using a 6 or 7 Fr introducer sheath and were treated with VASCADE VCS have statistically and clinically significant decreased times to hemostasis and ambulation for diagnostic and interventional procedures, when compared to patients treated with manual compression. In addition, the trial demonstrated that patients treated with the VASCADE VCS were non-inferior to patients treated with manual compression with respect to major access site-related complications, with 0 (0%) major access site-related complications reported in both VASCADE and control cohorts. A confirmatory clinical study and engineering analysis demonstrated that the VASCADE 5 Fr VCS is equivalent to the VASCADE 6/7 Fr VCS in design and performance (1). Refer to Attachment 2: Instructions for Use for detailed study information.

3. Study Objective

The objective of the ANTEGRADE-PVD registry is to collect procedural outcomes data when the Cardiva VASCADE™ Vascular Closure System (VCS) is used to seal femoral arterial access sites at the completion of ipsilateral peripheral interventional procedures performed through 5-7 Fr introducer sheaths via an antegrade approach. Antegrade access is experiencing growing adoption in catheter-based procedures to treat peripheral artery disease, with many advantages for lower limb procedures in particular. This post-market registry is being conducted under an FDA-approved indication for use for this device.

4. Study Design

4.1. Overview

The ANTEGRADE-PVD registry is a multi-center, single arm post-market registry to evaluate procedural outcomes in subjects when the Cardiva VASCADE™ Vascular Closure System (VCS) is used to seal femoral arterial access sites at the completion of ipsilateral peripheral interventional procedures performed through 5-7 F introducer sheaths via an antegrade approach.

Procedural outcomes related to performance and complications will be assessed through hospital discharge and 30 (+/- 7) days post-procedure.

4.2. Sample Size

Up to 100 subjects will be prospectively enrolled in this registry.

4.3. Investigational Sites

This registry will be conducted at up to 7 clinical sites in the United States.

5. Subject Population

5.1. Selection Criteria

The following pages outline the specific inclusion and exclusion criteria for the registry. Before enrollment in the registry, a patient must meet all of the inclusion and exclusion criteria requirements.

5.1.1. Pre- Operative Inclusion Criteria

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

Pre-Operative Inclusion Criteria	1. 18 to 80 years of age; 2. Capable and willing to give informed consent; 3. Acceptable candidate for an elective, non-emergent ipsilateral peripheral interventional endovascular procedure via antegrade access of the femoral artery using a 5, 6 or 7 Fr introducer sheath; 4. Acceptable candidate for post-procedural manual compression; 5. Able and willing to complete a follow-up office visit between 1-15 days post-procedure, and subsequent follow-up telephone assessment between 23-37 days; 6. Subject is able to ambulate at least 20 feet, with or without assistance (e.g., ambulatory amputee); 7. Acceptable candidate for emergent vascular surgery.

5.1.2. Pre-Operative Exclusion Criteria

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

Pre-Operative Exclusion Criteria	1. Advanced refusal of blood transfusion, if necessary; 2. Active systemic or cutaneous infection or inflammation; 3. Pre-existing immunodeficiency disorder and/or chronic use of

	systemic steroids; 4. Known, significant history of bleeding diathesis, coagulopathy, or current platelet count < 100,000 cells/mm3, baseline INR ≥1.8, or fibrinogen level less than 150 mg/dl (if received a fibrinolytic agent within prior 24 hours) based on institution's standard pre-operative lab values; 5. Severe co-existing morbidities having a life expectancy of less than 90 days; 6. Currently involved in any investigational clinical trials that have not completed their primary endpoint and/or may interfere with the conduct of this registry, per Investigator's assessment; 7. Previous ipsilateral femoral arteriotomy with any of the following conditions: a. access within ≤ 10 days b. any residual hematoma, significant bruising, or known associated vascular complications; c. within ≤ 90 days, use of an intra-vascular closure device (i.e., Angioseal); 8. Planned / staged endovascular or surgical procedures within the next 10 days, prior to office visit (excluding planned/anticipated minor amputation); 9. Previous vascular grafts or surgery at the target vessel access site; 10. Known history of deep vein thrombosis in the ipsilateral limb within the past 30 days, unless confirmed to be resolved by ultrasound prior to enrollment; 11. Major amputation (i.e., above the ankle) of the ipsilateral lower extremity is planned/anticipated within the next 30 (+/- 7) days, prior to study exit; 12. Large pannus, which may prevent antegrade access without significant tissue displacement, in the opinion of the investigator; 13. Significant anemia with a hemoglobin level less than 10 g/dL or a hematocrit less than 30% based on institution's standard pre-operative lab values; 14. Renal insufficiency (serum creatinine of > 2.5 mg/dl); 15. Females who are pregnant, planning to become pregnant within 3 months of the procedure, or lactating; 16. Extreme morbid obesity (BMI greater than 45 kg/m2) or

	underweight (BMI less than 20 kg/m2); 17. Known allergy/adverse reaction to bovine derivatives; 18. Administration of low molecular weight heparin (LMWH) within 8 hours of the procedure.

5.1.3. Intra-Operative Exclusion Criteria

Subjects will be excluded from participating in this registry if any of the following exclusion criteria occur during the intravascular procedure, prior to enrollment (i.e., prior to insertion of VASCADE VCS):

Intra-Operative Exclusion Criteria	1. Use of a final introducer sheath > 12 cm (or > 15 cm in overall length), or not 5, 6 or 7 Fr diameter; 2. Contralateral femoral arterial access with > 5 Fr catheter that is not successfully closed with a closure device during the index procedure 3. Index groin involves a previously placed permanent closure device (e.g., Starclose), where the device cannot be visualized to confirm that it is at least 1 cm proximal or distal to the puncture site; 4. Femoral artery diameter less than 6 mm at access site; 5. Angiographic evidence of moderate to severe calcium, > 50% stenosis, or a stent within 1 cm of the puncture site; 6. Overlapping Common Femoral Vein and Femoral Artery at access site; 7. Presence or placement of ipsilateral venous sheath during procedure; 8. Antegrade arterial access site: a. is a side stick b. is NOT a single anterior wall femoral puncture c. is NOT below the inguinal ligament / lower half of femoral head and NOT below the inferior epigastric artery origin from the external iliac artery; 9. More than one ipsilateral arterial access site is required in the index limb (e.g., femoral or other); 10. Intra-procedural bleeding around sheath, or suspected intraluminal thrombus, hematoma, pseudoaneurysm, or AV fistula;

	11. Evidence of arterial insufficiency, emboli, or new stenosis / occlusion in the ipsilateral limb at the conclusion of the index intervention (i.e., complications occurring from untreated, or suboptimal treatment of disease); 12. Systemic hypertension (BP greater than 180/110 mmHg) or hypotension (BP less than 90/60 mmHg) just prior to enrollment; 13. Length of the tissue tract, the distance between the anterior arterial wall and skin, is estimated to be less than 2.5 cm; 14. If the physician deems that a different method should be used to achieve hemostasis of the arterial site; 15. Upon final angio/fluoro assessment of the final introducer sheath to be used for VASCADE delivery, documented evidence of: a. inadequate sheath placement (e.g., location, position, angle), and/or b. any kinking of the procedural sheath prior to enrollment and insertion of the VASCADE VCS.

5.2. Withdrawal of Subjects

While withdrawal is discouraged, subjects may withdraw from the registry 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 registry termination.

In addition, the Investigator may withdraw the subject due to any reason determined by the Investigator to be in the best interest of the subject.

Subjects withdrawn from the registry prior to hemostasis (e.g., after enrollment and prior to deployment of the collagen plug) should be converted to conventional means (manual compression) to achieve hemostasis.

6. Written Informed Consent – 21 CFR 50 Protection of Human Subjects

Patients who meet general entry criteria will be asked to sign the registry-specific, Institutional Review Board (IRB) -approved Informed Consent form before any registry-specific data are collected. The informed consent will be reviewed and approved by Cardiva Medical prior to IRB submission to ensure compliance with all applicable requirements of 21 CFR 50.

Since this is a post-market registry, subjects will be treated and followed according to the institution's accepted standard of care and in adherence with the protocol.

There are no additional tests. Standard of care for office visit follow-up timing for these subjects varies between sites and procedure-types, therefore a wide window for the office visit has been established to accommodate as many subjects as possible. The required office visit may be performed between 1-15 days post-procedure, followed by a telephone follow-up between 23-37 days for final assessment of any complications. These contacts are required so that Procedure Success can be evaluated at 30 days, and to ensure that outcomes are consistently reported according to industry standards.

Study personnel should explain that even if a patient agrees to participate in the registry and signs an informed consent form, the Investigator may still determine that the patient is not a suitable candidate for the registry.

A Screening/Enrollment Log will be maintained to document select information about candidates who are consented, but who are not enrolled due to failure to meet the entry criteria.

7. Study Procedures and Enrollment

7.1. Duration of Subject Participation

Subjects enrolled in the registry will participate for approximately 30 (+/- 7) days.

7.2. Enrollment

At the completion of the endovascular procedure, patients who meet all the pre- and intra-operative eligibility criteria may be enrolled in the registry and are eligible to receive the VASCADE VCS for access site hemostasis as part of the registry. The Investigator will acknowledge intention to enroll the patient prior to VASCADE VCS insertion into the procedural sheath, and it will be documented on a source worksheet. Once Investigator acknowledgement has been made and the device has entered the body, the subject is considered enrolled into the registry and should complete all evaluations and follow-up requirements. An Enrollment Notification eCRF must be completed and submitted within 24 hours to notify Sponsor of enrollment.

If a patient does not meet all eligibility criteria for the registry, the patient may receive one of the following to achieve arterial hemostasis, at the Investigator's discretion: 1) the VASCADE VCS as a commercial device, but the subject will not be enrolled in the registry; 2) another commercially available closure device; or 3) manual compression. These patients and the final reason for registry exclusion will be documented on the Screening/Enrollment Log.

7.3. Event Schedule

Table 1 outlines the required registry assessments.

Table 1. Registry Event Schedule

	Up to 8 Weeks Before Procedure	Procedure	Post-Procedure/ Hospital Discharge	1-15 Days Post-Procedure	23-37 Days Post-Procedure
Informed Consent[1]	X				
Demographics/ Medical History / Risk Factors	X				
Index limb assessment[2]	X		X	X	X
Femoral access site assessment (angiographic)		X	X	X	X
Anticoagulant/antiplatelet regimen[3]	X	X	X		
Pre-op Inclusion / Exclusion Criteria assessment	X				
Laboratory tests[4]	X				
Intra-procedural Exclusion Criteria assessment & acknowledgement of intent to enroll		X			
Treated with VASCADE VCS		X			
TTH determination		X			
TTA determination			X		
TTD determination			X		
Procedure Success		X			X
Adverse Events[5]		X	X	X	X
Office Visit				X	
Telephone follow-up					X

[1] If informed consent is obtained > 30 days prior to procedure, the subject's verbal re-confirmation of consent should be documented in the medical record prior to the procedure.

[2] Index limb assessment includes Rutherford Classification, assessment of peripheral pulses, any wounds, amputation history and/or planned amputation, existing neuropathy, and ambulatory status.

[3] Specific medication regimen within 24 hours prior to enrollment through completion of index procedure.

[4] For subjects on warfarin, INR should be taken within 24 hours before procedure. "Laboratory tests" refer to exclusion criteria requirements, according to standard of care for these procedures at each site.

[5] Required adverse event reports: serious, device-related injury or death; minor or major access site closure-related complications; any event that is deemed by Investigator to be clinically significant AND related to the device, the access site or the index limb (See Section 13).

7.4. Study Procedures

7.4.1. Pre-Operative (up to 8 weeks before procedure)

After informed consent and prior to the subject's scheduled procedure, obtain:

- Medical history and risk factors
- Surgical and interventional procedural history
- Demographics (age, race, gender, ht, wt)
- Index limb assessment (Rutherford Classification, pulses, wounds, previous amputation, existing neuropathy, ambulatory status)
- Screening laboratory draws (according to institution's standard of care):
    - Serum creatinine
    - Platelet count
    - Hemoglobin and hematocrit
    - Within 24 hours of the procedure, obtain an INR for subjects on warfarin
    - Pregnancy test, as applicable to institution's standard of care.
- Medication regimen: anticoagulant / antiplatelet agents taken within 24 hours prior to index procedure.

7.4.2. Intra-Operative

For consented subjects that meet the pre-operative eligibility criteria, record the relevant data regarding their endovascular procedure.

Prior to enrollment, record the following procedural information:

- ACT, if available based on institution's standard of care, (for subjects receiving unfractionated heparin)
- anticoagulants and/or antiplatelet agents administered
- access site information, including angiographic assessment and antegrade access techniques employed
- diameter and length of the introducer sheath
- vessels treated during intervention
- contralateral access information, if applicable (e.g., prior to antegrade access but during index procedure)
- known planned staging of procedure, including minor amputation and

additional interventions prior to study exit.

At the end of the endovascular procedure, with the procedural sheath in place and under fluoroscopic visualization, an injection of contrast will be made to assess the anatomy of the access site, the integrity of the procedural sheath (i.e., no kinking) and to verify the intra-operative eligibility criteria.

NOTE: This image must be recorded and printed for the subject's records.

7.4.3. Access Site Closure

The VASCADE Vascular Closure System should be deployed following the procedure in the Instructions for Use (IFU) provided in Attachment 2. While the procedure is being performed, record the following information on the Procedure Source Data Worksheet provided by the Sponsor (required):

- **T1:** time antegrade access achieved (i.e., time of stick)
- **T2:** time endovascular procedure is completed (i.e., last guide catheter removed and final sheath is in place)
- **T3:** time of sheath fluoro/angio to confirm that procedural sheath placement is correct and not kinked (print for subject's record)
- **T4:** time VASCADE VCS is inserted into the procedural sheath
- **T5:** time that VASCADE VCS was deployed and/or removed and adjunctive compression started*
- **T6:** time that arterial hemostasis was achieved
- Verification that arterial hemostasis was confirmed 5 minutes later
- Determination of Device Success
- Light compression methods implemented after TTH was achieved
- VASCADE VCS device specifications.

*Immediate formation of a hematoma post-sheath removal may indicate a back-wall or secondary arterial puncture. If this situation is suspected, the VCS should be removed and the subject should be converted to manual compression according to institution's standard guidelines.

Adjunctive Compression Guidelines:

Upon successful deployment of the VASCADE VCS, adjunctive compression at the site may be used until arterial hemostasis is achieved (i.e., no pulsatile bleeding or a forming hematoma). TTH will not be recorded until adjunctive compression is no longer applied and arterial hemostasis is achieved. These times will be recorded on the Procedure Source Data Worksheet provided by the Sponsor (required).

NOTE: Manual compression devices should not be used for achieving initial arterial hemostasis to ensure accurate recording of TTH.

Light Compression Guidelines:

If the subject experiences slight oozing from cutaneous or subcutaneous tissues, characterized by the absence of pulsatile arterial flow, light compression methods (i.e., sand bags, compression bandages/devices, and light manual pressure) may be used to manage oozing. Any light manual pressure applied to control oozing should be documented on the Source Document Worksheet.

7.4.4. Post-Operative

After hemostasis is achieved, the access site should be closely monitored at least every 15 minutes for the first hour, and then according to standard of care to confirm hemostasis.

Ambulation

Subjects should be ambulated according to institution's standard practice. Any incidents of delay in ambulation (> 1 hour beyond stated standard of care for each site) should be documented on the Ambulation eCRF and a Protocol Deviation eCRF should be completed for non-medical delays > 1 hour. Record the following information on the Post-Procedure Source Data Worksheet provided by the Sponsor (required):

- **T7** TTA: time that subject was able to stand and ambulate at least 20 feet without evidence of arterial re-bleeding at the access site.

Hospital Discharge

Prior to hospital discharge, all subjects will be evaluated for symptoms of lower extremity neuropathy in the ipsilateral limb that were not existing prior to the index procedure (i.e., paresthesias, numbness, weakness), including an assessment of severity. Record the following information on the Post-Procedure Source Data Worksheet provided by the Sponsor (required):

- **T8** TTD: time of discharge from the facility.

Subjects should be discharged according to institution's standard practice. Any incidents of access site arterial re-bleeding, or delay in time to discharge should be documented on the Discharge eCRF.

7.5. Follow-up

All enrolled subjects are required to complete an office visit between days 1-15, and a 30 (+/- 7) day telephone follow-up. Depending on each institution's

standard practice for follow-up visits, subjects may return to the office for access site assessment any time between 1 and 15 days post-procedure. The subject should be instructed that a follow-up telephone assessment will be conducted between day 23 and 37 to complete the study. It is important that all subjects are contacted within the 30 (+/- 7) day window to determine Procedural Success.

During both the office visit and telephone follow-up, the subject should be queried regarding any complications they experienced after hospital discharge and the status of the access site wound should be assessed. All subjects will be evaluated for symptoms of lower extremity neuropathy in the ipsilateral limb that were not existing prior to the index procedure (i.e., paresthesias, numbness, weakness), including an assessment of severity.

In the event of refusal to return to the clinic, a protocol deviation will be reported and a telephone follow-up will be completed.

7.6. Study Exit

Once the subject has completed the follow-up visit or has withdrawn, they should be exited from the registry provided they do not have any conditions that require continued follow-up. The date of exit and subject status will be recorded.

8. Assessment of Procedural Outcomes

8.1. Primary Procedural Outcomes - Performance

Time to hemostasis (TTH) is defined as the elapsed time between Cardiva VASCADE™ VCS removal and first observed and confirmed arterial hemostasis. The time to hemostasis will be measured in hour (hh):minutes (mm):seconds (ss). (TTH = T6 – T5).

8.2. Secondary Procedural Outcomes - Performance

Time to ambulation (TTA) is defined as elapsed time between device removal and when subject first stands and walks 20 feet without evidence of arterial re-bleeding from the access site. The time to ambulation will be measured in hour (hh):minutes (mm). (TTA = T7 – T5).

Time to discharge (TTD) is defined as elapsed time between device removal and when subject is actually discharged from the facility. The time to ambulation will be measured in hour (hh):minutes (mm). (TTA = T8 – T5).

Device Success is defined as the ability to deploy the delivery system, deliver the collagen, and achieve hemostasis with the Cardiva VASCADE™ VCS alone or with adjunctive compression.

Procedure Success is defined as attainment of Device Success and freedom from major access site closure-related complications through 30 days.

8.3. Primary Procedural Outcomes - Complications

The primary procedural complication composite to be evaluated is the 30-day patient incidence rate of combined major access site closure-related complications. Major complications include:

- Access site closure-related bleeding requiring transfusion;
- Vascular injury requiring repair (via surgery, ultrasound guided compression, transcatheter embolization or stent graft);
- New ipsilateral lower extremity ischemia causing a threat to the viability of the limb and requiring surgical or additional percutaneous intervention;
- Access site-related infection requiring intravenous antibiotics and/or extended hospitalization;
- New onset neuropathy in the ipsilateral lower extremity requiring surgical repair;
- New onset permanent nerve injury in the ipsilateral lower extremity. (> 30 days).

8.4. Secondary Procedural Outcomes - Complications

The secondary procedural complication composite to be evaluated is the 30-day patient incidence rate of combined minor access site closure-related complications. Minor complications include:

- Access site-related bleeding requiring greater than 30 minutes to achieve initial arterial hemostasis;
- Access site-related hematoma > 6 cm documented by ultrasound;
- Late access site-related arterial bleeding requiring intervention (following hospital discharge);
- Ipsilateral lower extremity arterial emboli documented by ultrasound/imaging;
- Ipsilateral deep vein thrombosis documented by ultrasound;
- Access site-related vessel laceration;
- Access site wound dehiscence;
- Localized access site infection treated with intramuscular or oral antibiotics;
- Arteriovenous fistula not requiring treatment, documented by ultrasound/imaging;
- Pseudoaneurysm requiring thrombin injection or fibrin adhesive injection;
- New onset access site-related neuropathy in the ipsilateral lower extremity not requiring surgical repair.

9. Statistical Considerations

9.1. Analysis Populations and Data Handling Conventions

9.1.1. Intent to Treat (ITT) Population

All subjects who receive any portion of the Cardiva VASCADE™ VCS device treatment under this protocol (i.e., intention to enroll acknowledged by Investigator prior to introduction of the device; subject is then enrolled at time of device introduction) will be included in the primary, ITT performance and complication analyses.

Subjects who do not receive any portion of the VASCADE™ VCS but instead receive manual compression, a VASCADE VCS commercial device (i.e., outside of the registry), or another approved closure device instead (i.e., by error or by Investigator choice), will not be enrolled and are therefore excluded from all analyses.

9.1.2. Per Protocol (PP) Population

As secondary analyses, all subjects who have the collagen deployed and meet all I/E criteria will be included in the PP performance and complication analyses.

9.1.3. Missing Data

Missing data will not be imputed by any method.

9.2. Statistical Analysis Plan

9.2.1. General Analysis Principles

As a descriptive study, mean, standard deviation, median, minimum and maximum will be reported for continuous variables. Frequencies and proportions will be reported for categorical variables. Ninety-five percent confidence intervals will be reported for outcome summaries, e.g. mean and median for time to hemostasis (TTH), time to ambulation (TTA), and time to discharge (TTD), and Wilson score confidence intervals for proportions of device success and procedure success.

Since the critical limb ischemia population encompasses a broad spectrum of disease severity and comorbidities, both performance and complication outcomes will be presented overall and by the following subgroups: Rutherford score $\leq$ 5 vs. 6 (i.e., tissue loss), index intervention above knee v. at/below knee, gender, presence vs. absence of diabetes mellitus, BMI $\leq$ 30 vs. > 30, and inpatient vs. outpatient facility procedures. Additionally, TTA and TTD will also be presented overall and by no delay vs. delays related to the access site vs. delays due to other causes, as reported by the Investigator.

9.2.2. Performance Outcomes

9.2.2.1. Primary Performance Outcome Analysis (TTH)

The primary performance outcome to be described is time to hemostasis (TTH) as defined in Section 8.1. Summary statistics for TTH (mean, standard deviation, median, minimum, and maximum) will be reported for the ITT and PP subject cohorts, and as described in Section 9.1. Ninety-five percent confidence intervals will be presented for means and medians. The proportions of enrolled Cardiva VASCADE™ VCS subjects converted to manual compression will also be reported.

9.2.2.3 Secondary Performance Outcomes Analyses

Secondary performance outcomes to be reported include time to ambulation (TTA), time to discharge (TTD), and proportions of device success and procedure success as defined in Section 8.2 in both the ITT and PP cohorts. The analyses will be as described in Section 9.2.1.

9.2.3. Complication Outcomes

9.2.3.1. Primary Complication Outcome Analysis

The primary complication outcome analysis will be based on the 30-day patient incidence rate of combined major access site closure-related complications for the ITT and PP cohorts, as described in Section 9.1. The proportion of subjects with any major access site closure-related complications will be reported with 95% Wilson core confidence intervals. For each particular major complication listed in Section 8.3, the proportion of subjects reporting it will also be summarized.

9.2.3.2. Secondary Complication Outcome Analysis

The secondary safety analysis will be based on the 30-day patient incidence rate of combined minor access site closure-related complications for the ITT and PP cohorts. The proportion of subjects with any minor access site closure-related complications will be reported with 95% Wilson core confidence intervals. For each particular minor complication listed in Section 8.4, the proportion of subjects reporting it will also be summarized.

Additionally, all reported adverse events will be summarized, and will be mapped to standard terms. The number and proportion of subjects reporting any given adverse event will be tabulated according to the worst severity reported up to the 30 day follow-up. Separate tables will be constructed for (a) all reported adverse events, (b) device related adverse events, (c) serious device-related adverse events, and (d) all serious adverse events.

9.3. Sample Size Estimation

As a descriptive study, the sample size was not derived for statistical comparisons. It is judged that 100 subjects will provide sufficient precision for the outcome parameters of interest.

10. Data Management – Data Collection and Processing

Standardized eCRFs will be utilized by all participating sites using an EDC platform. Investigators are responsible for the accurate completion and timely submission of the data collected during the registry. All data from the registry 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.

The Principal Investigator must maintain detailed records on all subjects who sign the Informed Consent and begin the pre-procedure evaluation. 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 if they did or did not complete the registry (e.g., subject discontinuation, registry termination).

11. Monitoring Procedures

11.1. Monitoring

Remote and on-site monitoring visits to the clinical sites will be made periodically during the registry, to ensure that all aspects of the current, approved protocol/amendment(s) and 21 CFR 50 requirements 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 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.

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

11.2. Commercial Device Distribution and Accountability

11.2.1. Commercial Device Distribution

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

11.2.2. Device Accountability

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

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;

- Instruct the Investigators and site personnel on the protocol, the completion of the eCRFs, and registry procedures
- Communicate regularly with site personnel via mail, email, telephone, and/or fax

12.2. Physician Training

Investigators with significant experience in performing antegrade access and subsequent closure with VCDs were chosen to participate in this registry, therefore "roll-in" cases will not be performed in the registry. A Cardiva Medical representative may be present for the first several cases. All enrolling Investigators will be approved by Cardiva Medical, in writing, prior to their participation in the registry.

13. Adverse Events and Device Failure Reporting Requirements

13.1. Regulatory Requirements – 21 CFR 803 Medical Device Reporting for Commercially Available Devices

Cardiva Medical, Inc., or its designee, in cooperation with the Investigator, will assess all reported adverse events considered to be serious and device-related for potential reportability to the FDA according to 21 CFR 803 requirements.

MDR reportable events are incidents that reasonably suggest that the VASCADE VCS, a) may have caused or contributed to a death or serious injury; or b) has malfunctioned and that the device or a similar device marketed by Cardiva Medical would likely cause or contribute to a death or serious injury if the malfunction were to recur.

"*Caused or contributed to*" means that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of:

- failure;
- malfunction, defined as the failure of a device to meet its performance specifications or otherwise perform as intended, according to approved labeling;
- improper or inadequate design;
- manufacture;
- labeling (i.e., IFU);
- user error.

A "serious injury" means that an injury or illness which:

- Is life-threatening – substantial risk of dying at the time of the AE, or use or continued use of the device might have resulted in the death of a patient;
- Results in permanent impairment of a body function or damage to a body structure, excluding trivial impairment or damage ("permanent" means irreversible impairment, excluding trivial impairment or damage).
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Incidences requiring surgery to remove malfunctioned device will be considered a serious injury. Retrieval of a fracture piece from a body cavity without the need for additional medical intervention will not be considered a serious injury.

13.2. Reporting Guidelines

13.2.1. Serious Adverse Events or Injuries

- Complete Adverse Event eCRF within 24 hours of knowledge of any Serious Adverse Event.
    - Events will be categorized for seriousness by both Good Clinical Practice Guidelines (GCP), and by 21 CFR 803 MDR Reporting requirements.
- Complete device-related questions on AE eCRF. IF AE is marked as "Related to VCS", an email notification will then be sent to Cardiva Medical Complaint Handling and to the CRO for follow-up. You may be prompted to complete a Device Performance/Complaint eCRF.
- Follow institution's IRB adverse event reporting requirements, as applicable.

13.2.2. Device Failures or Malfunction

- For any device performance issues occurring in this registry, whether an adverse event resulted or not, complete the Device Performance/Complaint eCRF within 24 hours of the observation. An email notification will then be sent to Cardiva Medical and to the CRO for follow-up.
- 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 reported.
- For questions, contact:

Cardiva Medical Customer Service

Toll Free: (in the U.S.) 1-866-602-6099

Toll Free Fax: (in the U.S.) 1-866-602-1795

Email: complaint@cardivamedical.com

13.3. Registry Reporting Requirements for Adverse Events

The following adverse events must be reported in this post-market registry:

- serious, device-related adverse events (i.e., "reportable")
- major or minor access site closure-related complications (serious and non-serious), as defined in Section 8
- any adverse event that, in the Investigator's opinion, is clinically significant AND is any one of the following:
    - device-related
    - access site-related
    - access limb-related.

1. Complete an Adverse Event eCRF within 24 hours of knowledge of a reportable event. Medical records (e.g., procedure notes, operative notes, discharge summary, relevant progress notes, imaging or lab studies) may be requested by Cardiva Medical or its designee for event review and potential adjudication.

2. For questions, contact Marlys Chellew at 916-303-0879.

All required adverse events (AE) (serious and non-serious) will be recorded on the eCRF and monitored from the time of enrollment through study exit.

In addition to 21 CFR 803 seriousness definitions, the following definitions for Serious Adverse Events will be used for consistency with published comparative data (per GCP, E6).

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
- Necessitates an intervention to prevent a permanent impairment of a body function or permanent damage to a body structure
- Results in congenital abnormality

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.

14 Ethical Considerations

14.1 Institutional Review Board Approval

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. before the site initiation visit and recruitment of patients into the registry.

The Investigator must submit and, where necessary, obtain approval from the IRB for all subsequent significant protocol amendments and significant changes to the Informed Consent form. Cardiva Medical may make certain administrative changes to the protocol without prior approval of the IRB. Cardiva Medical will notify all investigative sites of such changes to ensure the study continues to be conducted consistently across all sties. The Investigator should notify the IRB of deviations from the protocol and/or SAEs occurring at the site in accordance with local requirements.

The Investigator will be responsible for obtaining annual IRB/IEC approval and renewal throughout the duration of the study. Copies of the Investigator's reports and the IRB/IEC continuance of approval must be sent to Cardiva Medical, Inc.

14.2 Informed Consent Form – 21 CFR 50 Protection of Human Subjects

A sample Informed Consent form is provided in Attachment 1 for the Investigator to prepare for use at his/her site. The written Informed Consent documents should be prepared in the language(s) of the potential patient population, and the final template approved by Cardiva Medical prior to IRB submission, to ensure compliance with applicable parts of 21 CRF 50.

The reviewing IRB must first approve the Informed Consent forms that are used. 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).

Prior to participation in the registry, each patient must give written Informed Consent after the context of the registry 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. The patient will receive a copy of the Informed Consent form.

14.3 Protocol Deviations

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

Due to the post-market nature of this registry, no waivers will be granted for inclusion/exclusion criteria. Subjects who do not meet all criteria may be treated commercially with the VASCADE VCS at the Investigator's discretion, but shall not be enrolled in the registry.

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. Protocol deviations will be reported on the Protocol

Deviation case report form. Investigators will adhere to procedures for reporting study deviations to their IRB in accordance with their specific IRB reporting policies and procedures.

14.4 Coverage of Expenses

Subjects will not be reimbursed or compensated for participating in the registry.

14.5 Confidentiality

Confidentiality of subjects will be maintained throughout the registry. A unique identification code will be assigned to each subject participating in this registry. 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 registry.

15 Administration

15.1 Pre-Enrollment Documentation Requirements

Prior to enrollment of subjects, the following documents must be provided to Cardiva Medical, Inc.:

- Fully executed Clinical Study Agreement
- Signed and dated Investigator Agreement/Protocol Signature Page for approved Investigators
- A copy of the written IRB approval of the protocol
- A copy of the written IRB approval of the Informed Consent Form
- A copy of the curriculum vitae of the Principal Investigator and Co-Investigator (if applicable)

15.2 Source Documentation

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

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

- The date the subject entered the registry and the subject number
- The date that informed consent was obtained
- Evidence that the subject meets registry eligibility requirements (e.g., medical history, trial procedures and/or evaluations)
- The dates of all registry related subject visits
- Evidence that required procedures and/or evaluations were completed

- Use of specified concurrent medications
- Documentation of specific device used
- Occurrence and status of applicable Adverse Events
- The date the subject exited the registry, and a notation as to whether the subject completed the registry or was discontinued, including the reason for discontinuation.

15.3 Criteria for Terminating Study

Cardiva Medical, Inc reserves the right to terminate the registry but intends only to exercise this right for valid scientific or administrative reasons. Investigators and associated IRB will be notified in writing in the event of termination.

15.4 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 site initiation visit if no patients have been enrolled or if the center has multiple or serious protocol violations without justification or fails to follow remedial actions.

Possible reasons for suspending/terminating a center include:

- Repeated failure to complete electronic case report forms prior to scheduled monitoring visits.
- Failure to obtain written Informed Consent.
- Failure to report serious device-related injuries or device failures to Cardiva Medical, Inc. in accordance with 21 CFR 803.
- Failure to comply with the requirements of the protocol.
- Misuse of the VASCADE VCS (i.e., IFU not adhered to).

15.5 Investigator Responsibilities

- Agree to sign and adhere to the Investigator Agreement
- Agree to obtain IRB approval of the protocol and consent form prior to enrolling subjects
- Agree to report serious, device-related injuries and deaths, as well as device failures in accordance with 21 CFR 803 (See Section 13)
- Comply with all required elements of this protocol (e.g., perform testing and follow-up as specified, compliance) and supply data suitable for quantitative analysis
- Agree to obtain written Informed Consent before any registry specific procedures are performed
- Complete all electronic data modules prior to scheduled monitoring visits

16 Publication Policy

The data generated by this registry 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, if applicable. The Principal Investigators may publish or present the registry 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.

17 Responsibilities

17.1 Role of Cardiva Medical

As the Sponsor of this registry, Cardiva Medical has the overall responsibility for the conduct of the study, including adherence to applicable sections of Title 21 CFR Part 50 - Human Subject Protection and for Medical Device Reporting according to Title 21 CFR Part 803 for commercial devices.

Cardiva Medical is also responsible for obtaining signed study agreements, for providing the Investigators with adequate information and on-site training to conduct the registry, to ensure proper clinical site monitoring, and to provide the required reports to the Investigators and IRB's, as applicable for this registry.

In this registry, 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 these responsibilities.

17.2 Monitoring

The Sponsor and/or designee will conduct remote and on-site monitoring to ensure that all Investigators are in compliance with the protocol. 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.

17.3 Maintaining Records

The Sponsor and clinical sites will maintain copies of correspondence, data, serious adverse device effects and other records related to the registry for a period of two years after the registry is terminated or completed.

18 Abbreviations and Definitions

18.1 Abbreviations

ACT	Activated clotting time

AE	Adverse Event
AV	Arteriovenous
CFR	Code of Federal Regulations
eCRF	Electronic Case Report Form
CV	Curriculum Vitae
FDA	Food and Drug Administration
Fr	French
Hgb	Hemoglobin
Hct	Hematocrit
IFU	Instructions for Use
INR	International Normalized Ratio
IRB	Institutional Review Board
LMWH	Low molecular weight heparin
MDR	Medical Device Reporting (21 CFR 803)
SAE	Serious Adverse Event
TTA	Time to Ambulation
TTD	Time to Discharge
TTH	Time to Hemostasis

18.2 Definitions

ACCESS SITE-RELATED HEMATOMA > 6 CM
A localized collection of extravasated blood in subcutaneous tissue at the access site measuring > 6 cm at its widest point, documented on ultrasound.

ACCESS SITE CLOSURE-RELATED BLEEDING REQUIRING TRANSFUSION
Bleeding originating from the index arteriotomy site, which has occurred to the degree that transfusion of blood products is necessary to maintain hemodynamic stability.

ACCESS SITE-RELATED BLEEDING REQUIRING > 30 MINUTES TO ACHIEVE INITIAL HEMOSTASIS
Bleeding from the arterial access site requiring greater than 30 consecutive minutes of standard compression to achieve initial arterial hemostasis.

ACCESS SITE-RELATED INFECTION REQUIRING INTRAVENOUS ANTIBIOTICS AND/OR PROLONGED HOSPITALIZATION
Must meet one of the following: 1) wound opened with excision of tissue (I&D); 2) positive wound culture requiring treatment with intravenous antibiotics; 3)

administration of intravenous antibiotics for access site-related infection based on medical judgement, even if wound culture is negative or not done, or 4) prolonged hospital discharge time directly related to complications of arteriotomy site infection. Does not include administration of prophylactic antibiotic regimens.

ACCESS SITE CLOSURE-RELATED NERVE INJURY
New onset of functional disturbance and pathologic change in the ipsilateral peripheral nervous system. May include transient loss of sensation, pain, numbness or tingling in the extremity; or transient loss of motor function.

ACCESS SITE CLOSURE-RELATED VESSEL LACERATION
A cut or tear to an arterial or venous vessel wall, requiring surgical or interventional repair.

ACCESS SITE WOUND DEHISCENCE
A separation of all layers of the access site wound.

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.

ADJUNCTIVE COMPRESSION
Moderate manual compression at the arteriotomy site immediately after VASCADE VCS deployment, applied as an adjunctive measure to facilitate TTH. Adjunctive compression time will be included in TTH; any light manual pressure held for tissue tract oozing should be documented separately.

ALLERGIC REACTION
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 registry has been reviewed and may be conducted at the institutional site within the constraints set forth by the IRB, the institution, and the applicable regulatory requirements.

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

ARTERIAL / VENOUS THROMBOSIS
Formation or development of a blood clot or thrombus, specifically in the arterial or venous system of the ipsilateral distal extremity.

ARTERIOVENOUS (AV) FISTULA
A connection between the access artery and the adjacent vein that is demonstrated by arteriography or ultrasound, most often characterized by a continuous bruit; diagnosis should be confirmed by angiographic or ultrasound imaging.

CO-INVESTIGATOR / SUB-INVESTIGATOR
An individual member of the investigation team designated and supervised by the Investigator at a registry site who enrolls subjects into the registry. Sub-Investigators must be qualified by training and experience to participate, and must be approved by Cardiva Medical prior to enrolling subjects. See also Investigator.

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 failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed.

DEVICE SUCCESS
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.

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 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 blood clots, fat globules, air bubbles, tissue, clumps of bacteria, thrombus or foreign material.

EMBOLIZATION OF DEVICE COMPONENTS
Accidental deployment or dislodgement of any component of the Cardiva VASCADE™ VCS into the bloodstream.

HEMATOMA
A localized collection of extravasated blood in subcutaneous tissue, usually clotted. A metric ruler should be used to measure the widest portion of the hematoma.

HEMOSTASIS
Cessation of common femoral artery bleeding (excluding cutaneous or subcutaneous oozing).

INDEPENDENT PHYSICIAN ADJUDICTOR (IPA)
An independent physician, qualified by training and experience in the field of interventional cardiology or radiology, who will review and adjudicate all reported adverse events that are both serious and device-related; and all reported major and minor access site closure-related complications. The IPA is not a participant in the trial and is independent of Cardiva Medical.

INFLAMMATION
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 an arterial wall resulting in splitting and separation of the intimal (subintimal) layers.

INVESTIGATIONAL SITE
The location(s) where registry-related activities are actually conducted.

INVESTIGATOR
The person responsible for the conduct of the registry at a clinical site. The responsible leader of the team and may be called the Principal Investigator. See also Co-Investigator.

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

IPSILATERAL DEEP VEIN THROMBOSIS
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; diagnosis should be confirmed by ultrasound imaging.

IPSILATERAL LOWER EXTREMITY ARTERIAL EMBOLI
Presence of emboli in the peripheral arterial system of the ipsilateral limb; diagnosis should be confirmed by angiographic or ultrasound imaging.

LATE ACCESS SITE-RELATED ARTERIAL BLEEDING REQUIRING INTERVENTION (i.e., following hospital discharge) Re-bleeding from the puncture site following hospital discharge and up to 30 days post procedure that requires manual compression or other intervention to prevent a life-threatening event.

LIFE-THREATENING ADVERSE EVENT
A device-related injury in which the patient was at substantial risk of dying at the time of the adverse event, or use or continued use of the device might have resulted in the death of the patient.

LOCALIZED ACCESS SITE INFECTION
Infection occurring at the access site requiring treatment with oral or intramuscular antibiotic therapy. Does not include administration of prophylactic antibiotic regimens.

MANUAL COMPRESSION
Direct digital non-occlusive pressure to the arteriotomy site applied to achieve hemostasis. Note: C-clamp, FemoStop®, Sandbags and other methods are to be used only following the achievement of hemostasis for management of non-arterial oozing/bleeding.

MEDICAL DEVICE REPORTING REQUIREMENTS (MDR)

21 CFR 803 Medical Device Reporting are the regulations that establish requirements for medical device reporting for device user facilities (i.e., hospital), manufacturers, importers and distributors regarding incidents where applicable commercially available devices may have caused or contributed to serious injury and death, and/or when the device malfunctions. The following definitions relate to 21 CFR 803 MDR requirements, also see Section 13:

> Caused or contributed:
> Means that a death or serious injury was or may have been attributed to a medical device, or that a medical device was or may have been a factor in a death or serious injury, including events occurring as a result of failure, malfunction, improper or inadequate design, manufacture, labeling, or user error.

Malfunction:
Means the failure of a device to meet any of its performance specifications or otherwise to perform as intended. Performance specifications include all claims made in the labeling of the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed through means such as labeling claims, advertising matter, and oral or written statements of Cardiva representatives.

Medical Device Report (MDR):
Means a report mandated by the FDA to be completed on FDA Form 3500A regarding a reportable event.

MDR Reportable Event:
Any incident about which a Cardiva Medical employee receives or becomes aware of information that reasonably suggests that a Cardiva Medical device; (1) may have caused or contributed to a death or serious injury; or (2) has malfunctioned and that the device or a similar device marketed by Cardiva Medical would likely cause or contribute to a death or serious injury if the malfunction were to recur.

Permanent:
Means irreversible impairment or damage to a body structure or function excluding trivial impairment or damage.

Reasonably Suggests:
Means that a "reasonable" person considering the information would conclude that a reportable event has occurred. Information which leads a person qualified to make a medical judgment (e.g. a physician, nurse, risk manager, clinical engineer, etc.) to reach a reasonable conclusion that a device-related event is or is not reportable is to be documented in the MDR event files.

Serious illness or injury:

Means an injury or illness that (1) is life-threatening; (2) results in permanent impairment of a body function or permanent damage to body structure; or (3) necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure. Incidences requiring surgery to remove a malfunctioned device will be considered a serious injury. Retrieval of a fracture piece from a body cavity without the need for additional medical intervention will not be considered a serious injury.

NEW IPSILATERAL LOWER EXTREMITY ISCHEMIA

New (acute) onset of compromised peripheral blood flow, 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.

NEW ONSET ACCESS SITE CLOSURE-RELATED NEUROPATHY IN THE IPSILATERAL LOWER EXTREMITY REQUIRING SURGICAL REPAIR
New onset access site closure-related nerve injury that requires surgical intervention to mitigate symptoms or prevent permanent nerve damage.

NEW ONSET ACCESS SITE CLOSURE-RELATED NEUROPATHY IN THE IPSILATERAL LOWER EXTREMITY NOT REQUIRING SURGICAL REPAIR
New onset access site closure-related nerve injury that does not require surgical intervention to mitigate symptoms or prevent permanent nerve damage, however is evaluated to be moderate to severe in nature by the Investigator (see "Adverse Event Severity Rating").

OOZING
Minimal bleeding of a cutaneous or subcutaneous origin characterized by the absence of pulsatile arterial flow 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 arterial wall (e.g., from insertion of a percutaneous device).

PERIPHERAL PULSE ASSESSMENT SCALE
0 = absent; not palpable; 1 = diminished; 2 = expected; 3 = full, increased; 4 = bounding.

PERIPHERAL VASCULAR DISEASE
Damage to or dysfunction of the arteries outside the heart resulting in reduced blood flow; *especially*: narrowing or obstruction (as from atherosclerosis) of an artery (as the iliac artery or femoral artery) supplying the legs that is marked chiefly by intermittent claudication and by numbness and tingling in the legs.

PERMANENT ACCESS SITE CLOSURE-RELATED NERVE INJURY (> 30 DAYS)
New onset access site closure-related nerve injury that persists for > 30 consecutive days following device removal and is evaluated to be moderate to severe in nature by the Investigator (see "Adverse Event Severity Rating").

PROCEDURE SUCCESS
Defined as attainment of Device Success and freedom from major vascular complications through 30 days.

PSEUDOANEURYSM
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 should be confirmed by angiography or ultrasound.

- 2 levels of severity:
    - Requiring thrombin injection or fibrin adhesive injection to contain the leak
    - Not requiring treatment

RE-BLEEDING
Arterial bleeding from the puncture site occurring after initial hemostasis has been confirmed.

REPORTABLE EVENT
See SERIOUS ADVERSE EVENT

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

RUTHERFORD CLASSIFICATION
A commonly used clinical staging system for describing peripheral arterial disease, similar to the Fontaine classification. There are seven stages:

1. Stage 0 – Asymptomatic
2. Stage 1 – Mild claudication
3. Stage 2 – Moderate claudication
4. Stage 3 – Severe claudication
5. Stage 4 – Rest pain
6. Stage 5 – Ischemic ulceration not exceeding ulcer of the digits of the foot
7. Stage 6 – Severe ischemic ulcers or frank gangrene

SERIOUS ADVERSE EVENT (SAE)
A "serious injury" which must be reported to FDA is a device-related death or a device-related injury as defined in 21 CFR 803, which:

- Results in death;
- Is life-threatening – substantial risk of dying at the time of the AE, or use or continued use of the device might have resulted in the death of a patient;
- Results in permanent impairment or damage to a body structure of function, excluding trivial impairment or damage

- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

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.

VASCULAR INJURY REQUIRING REPAIR
Injury to the access site arterial wall or adjunct venous vessel wall resulting in persistent bleeding and requiring repair (via surgery, angioplasty, ultrasound-guided compression, transcatheter embolization or stent graft).

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.

WOUND SITE PAIN
Local discomfort at the arteriotomy site which may range from mild to severe.

18.3 Bibliography

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19 Attachment 1: Sample Informed Consent Form

20 Attachment 2: Instructions For Use (IFU)

Participant Sample Consent Form

Title of Study: ANTEGRADE-PVD Post-Market Registry

A MULTI-CENTER, PROSPECTIVE, POST-MARKET REGISTRY TO EVALUATE PROCEDURAL OUTCOMES DATA USING THE CARDIVA VASCADE™ **VASCULAR CLOSURE SYSTEM (VCS) FOR THE MANAGEMENT OF THE FEMORAL ARTERIOTOMY AFTER PERCUTANEOUS ENDOVASCULAR PROCEDURES VIA AN ANTEGRADE APPROACH**

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

Principal Investigator: [add]

Institution: [add]

Your Consent

You are invited to take part in this registry at *(insert hospital / facility name)*. A "registry" is a place where official records are collected and kept. The purpose of this "registry" is to collect procedural data when the Cardiva Medical VASCADE™ Vascular Closure System (VCS) device is used to close the artery that will be punctured using a specific technique, as part of your upcoming procedure.

This device was approved by the U.S. Food and Drug Administration (FDA) in January, 2013, and has been used and sold in the United States since that time. The Cardiva Medical VASCADE VCS is *not investigational*.

This consent form will provide you with information about the registry, 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.

Purpose & Background of the Registry

Your doctor has explained to you that you need a procedure to look at the arteries (blood vessels) in your legs and possibly treat them. At the beginning of this procedure, the doctor will puncture a hole in an artery in your groin area, in order to look at the arteries in your leg on x-ray. The doctor will make the hole on the same side of your body as the leg that needs to be treated. This is a technique called "antegrade access", which means "in the direction of the blood flow". This is one of several techniques that your doctor can decide to use for your procedure, based on his/her medical opinion about risks and benefits specific to your case. Your doctor's decision that you need the procedure and use of an antegrade technique is made based on your medical needs and independent of this registry.

Once the doctor has finished any treatment of your leg arteries this hole will need to be sealed (closed up) to prevent bleeding. There are several FDA approved devices that could be used to close the hole, and the Cardiva Medical VASCADE VCS is one such device..

Your doctor already uses this device to close holes in both "antegrade" and other types of cases, but there have not been many studies to collect data about antegrade procedures. The purpose of this registry is to collect data about your procedure so that the results can be provided for other health care professionals to use when making decisions about what procedures and devices to use in their patients.

If you choose to take part in the registry, you will receive the Cardiva Medical device, providing your doctor feels you meet the study criteria. A small collagen (cotton-like) patch is placed just outside of the artery to plug the hole and stop the bleeding. The patch is absorbed by the body (dissolves) in about three months.

Your doctor will do everything the same way he/she would if you were not in a study, except he/she will collect specific information about your procedure and information about how your are doing for about 30 days afterwards.

If your doctor decides that you do not meet registry criteria, you may still receive a Cardiva Medical VCS outside of the registry, but you would not be enrolled in the registry. Your doctor may also decide that using an antegrade approach and/or using a Cardiva Medical VCS is not the best option for you. In those cases, you will not be enrolled in the registry and may receive another commercially available device, or you may have firm pressure placed on the leg artery hole for the amount of time it takes for the artery to clot and stop bleeding. This is known as "manual compression" and is also a usual way of treatment.

This study will enroll about 100 patients at up to 7 hospitals in the United States.

Procedures

This study will last 30 days (± 7 days). The expected total time for all patients to complete the study is about 9 months. If you agree to be in this registry, the following will happen to you:

Pre-Procedure Before the operation you will have a medical interview and physical to make sure you qualify for the registry (are eligible to take part). Any blood that is taken will be done as part of your standard care, and there are no tests done specifically for the registry.

Procedure During the operation your doctor will insert a small plastic tube to gain access to the large artery in your leg (femoral artery) using the "antegrade" technique. He/she will then insert a small tube and inject dye to evaluate any blockages in your arteries on the same side of the body. It is possible that he/she might open a blocked

artery if he/she feels this is necessary during your procedure. He/she will also monitor your blood to determine how long it takes you to stop bleeding.

When your doctor is finished with the operation and your doctor feels it is okay for you to take part in the registry, he/she will use the VASCADE™ VCS to close the hole in the artery. This is when you would be "enrolled" as a subject in the registry and details about your procedure will be collected for the registry.

Post-Procedure

After the procedure, the puncture site (place where the hole was made for the tube) will be checked often to make sure it is not bleeding. Your doctor will determine how long you need to stay in bed, when you can walk and when you can be discharged based on his/her normal care for this type of procedure.

Office Visit between 1-15 Days

You will need to come in to your doctor's office some time between 1 – 15 days after the procedure to be checked. Your doctor will check the place where the hole was in your leg to make sure it has healed properly, and will ask you questions about any problems you may have had.

This type of visit is normal care for your procedure, and will be scheduled according to your doctor's preferred timing for the visit.

Phone Visit between 23 - 37 days

You will be called on the phone by your doctor's office within about 23 – 37 days after the procedure to check if you have any problems and that your leg has continued to heal properly. This is done to make sure that all patients in the study are followed for at least 23 days, according to the protocol.

Possible Risks

The safety of this 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, a total of 417 subjects were enrolled. Two-thirds (275 patients) received the VASCADE device, and one-third (142) received manual compression to close the artery hole. Safety results were similar in both groups. Of the possible side effects listed below, there were no reports of these occurring in the 275 VASCADE patients, except for the following:

*Reported in < 1% of patients receiving VASCADE
**Reported in < 2% of patients receiving VASCADE

***Reported in < 2.5% of patients receiving VASCADE

Possible side effects (problems) are similar to other closure devices and "manual compression" and can include:

- allergic response (to the material in the device or collagen)
- arterial occlusion (blockage of the leg artery)
- arterial thrombus (blood clot in the leg artery)
- arterio-venous fistula (abnormal connection between artery and vein)*
- death
- device failure / malfunction***
- edema (swelling in the tissues)
- embolization (thrombus, air, tissue, device floating downstream)
- groin bruising*
- groin hematoma (bleeding under the skin)**
- groin inflammatory response (inflammation)
- groin wound dehiscence (separation of wound edges)
- intimal tear / dissection (tear of the leg artery wall)
- limb ischemia (lack of oxygen to the leg)
- mild infection or infection of the groin requiring extended hospital stay and IV antibiotic administration
- minor bleeding* and/or bleeding requiring transfusion
- peripheral nerve injury (nerve damage to the leg)*
- 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)**
- retroperitoneal bleeding (bleeding in the pelvis)*
- thrombus formation (blood clot in an artery or a vein)**
- vasospasm (spasm of the artery)
- vasovagal response (slowed heart rate with possible fainting)
- vascular injury requiring repair (vessel damage requiring repair)
- Wound site pain***

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

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 this registry. Potential benefits include rapid closure of the artery hole, 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 cases where an "antegrade" technique is used. There may also be other unexpected benefits that will be discovered as a result of this registry, and any new significant information will be provided to you by your doctor.

Financial Responsibility

You are not expected to pay any costs associated with participation in this registry. The registry does not require any tests that are not part of normal care. The Sponsor will pay your doctor for his/her time required to collect the data for the purpose of this registry. You or your insurance will be responsible for all costs for regular treatment. 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 registry, the Hospital will provide you with medical treatment. If it is determined that your illness or injury resulted from the collagen patch (VASCADE™ VCS) in your leg, this medical treatment, as well as other reasonable and customary medical expenses, will be paid for by the Sponsor of the registry (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 (VASCADE™ VCS). No funds have been set aside to compensate you for such injuries. In addition, the Sponsor of the registry has not set aside funds to compensate you for non-direct damages such as lost 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 waive 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 laws of the United States and 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)*. Any information obtained in connection with this registry project that can identify you will remain confidential and will only be used for the purpose of this registry. It will only be disclosed to parties listed below with your permission, except as required by law.

During the registry 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 registry. It will not be possible to identify you from information in any publication resulting from this registry 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 registry device), and the Institutional Review Board can access your health information in order to conduct the registry. Although this registry is not governed by the United States Food and Drug Administration (FDA), the FDA may request access to your health information related to this registry at any time.

Cardiva Medical or its representative may also send health information about you to its data management unit located in the U.S.A. By signing the attached Consent Form, you authorize release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as noted above.

A description of this registry will be available on http://www.ClinicalTrials.gov. This web site will not include information that can identify you. At most, the Web site will include a summary of results. You can search the Web site at any time.

All records kept from the registry may be destroyed after 2 years, unless Cardiva Medical requests otherwise.

New Information Arising During the Project

During the registry, 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 Registry

This registry may be stopped for a variety of reasons. These may include reasons such as unacceptable side effects, or decisions made in the commercial interests of the Sponsor.

Right of Refusal and Alternative Treatments

Participation in this registry is voluntary. You may refuse to participate in this registry or discontinue participation at any time. If you refuse to participate in this registry, it will not affect the care your doctor will provide to you. There are other treatments that are available to you including other closure devices and standard manual compression.

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

- You have not followed the instructions of your study doctor and/or study staff
- You become pregnant
- You need treatment not allowed in the registry
- The Sponsor decides to end the registry
- 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 registry about your rights as a registry participant or the procedure, please contact:

(add investigator name)	*(insert contact info)*
(add sub-investigators)	*(insert contact info)*
(add coordinators)	*(insert contact info)*

Consent

Your signature below indicates that:

- You have read and understood the above information.
- You have discussed the registry 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 registry based on the information aprovided.
- A copy of this form has been given to you.

_____ _____/_____/_____
Signature of Participant Date

_____
Printed Name of Participant

_____ _____/_____/_____
Signature of Person Conducting Informed Consent Date

_____
Printed Name of Person Conducting Informed Consent

CARDIVA MEDICAL, INC.

VASCADE™ Vascular Closure System (VASCADE VCS)

INSTRUCTIONS FOR USE
5F and 6/7F

IFU 2611 Rev N

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

DESCRIPTION

The VASCADE VCS is intended to seal the femoral arterial access site at the completion of an endovascular procedure. The system is designed to deliver a resorbable Collagen Patch, extra-vascularly, at the arteriotomy site to aid in achieving hemostasis. There are two versions of products in the VASCADE product family. One is for use in 5F 12cm[1] introducer sheaths, and the other device is for use in 6F or 7F 12cm[1] introducer sheaths. The system consists of a sterile disposable Vascular Closure Catheter which houses a resorbable Collagen Patch, and the VASCADE 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 in VASCADE 5F is 8.5mg ± 2mg and in VASCADE 6/7F it 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 verify placement of the patch in the tissue tract adjacent to the femoral arteriotomy site prior to the release of the patch. A second distal marker band locates the distal tip of the VASCADE Disc. After completion of the catheterization procedure, the VASCADE VCS Catheter is inserted through a commercially available 5F, 6F, or 7F introducer sheath. The VASCADE Disc is then deployed within the vessel and the introducer sheath is removed over the VASCADE VCS Catheter. After the introducer sheath is removed, the VASCADE Disc is positioned against the intimal aspect of the arteriotomy, providing both temporary hemostasis and protection from intravascular placement of the Collagen Patch, and the VASCADE Clip is applied at skin level to maintain the position of the VASCADE Disc. After confirming the position of the Collagen Patch fluoroscopically, 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 VASCADE Disc is collapsed and the VASCADE VCS Catheter is removed from the artery leaving the resorbable, extra-vascular, hemostatic Collagen Patch at the arteriotomy site providing arterial hemostasis.

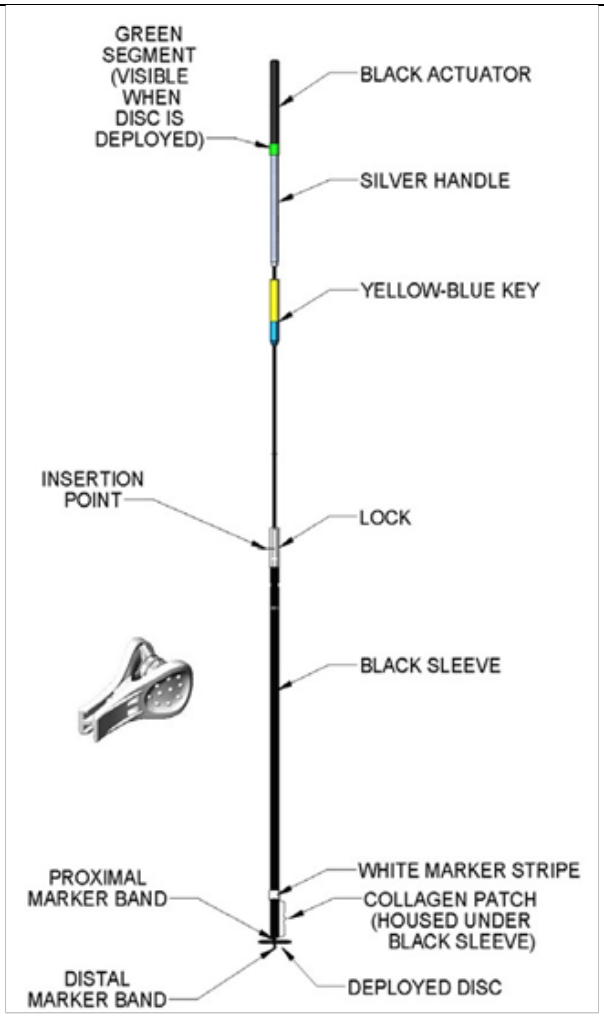

Fig. 1 – VASCADE Vascular Closure System (VCS)

INDICATIONS FOR USE

The VASCADE™ Vascular Closure System (VCS) is indicated for femoral arterial access site closure while reducing times to hemostasis and ambulation in patients who have undergone diagnostic or interventional endovascular procedures using a 5F, 6F, or 7F procedural sheath. The VASCADE VCS is also indicated to reduce time to discharge eligibility in patients who have undergone diagnostic endovascular procedures using a 5F, 6F, or 7F procedural sheath.

[1] Overall length of the sheath (including the hub) needs to be less than 15cm.

CONTRAINDICATIONS

The VASCADE VCS should not be used in patients with a known allergy to bovine derivatives.

WARNINGS

- Do not reuse or re-sterilize. The VASCADE VCS 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 VASCADE Disc in a stent. Do not pull the deployed VASCADE disc through a stent. Damage to the product may occur.
- Do not use VASCADE 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 VASCADE Vascular Closure Disc is not seated against the intimal aspect of the arteriotomy site. Partial or complete obstruction of blood flow may result.
- Do not deploy a second collagen patch at the same access site within 90 days. Safety has not been established.

PRECAUTIONS

- The VASCADE VCS 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 arteriotomy is noted to be a “side stick.” Bleeding risk may increase.
- Do not use if arteriotomy 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 an artery 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 5F for VASCADE 5F, or 6F or 7F for VASCADE 6/7F. This may complicate disk deployment.

SPECIAL PATIENT POPULATIONS

NOTE: The safety and effectiveness of VASCADE VCS 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/mm!), 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;
- Fluoroscopically visible calcium or atherosclerotic disease within 1 cm of the puncture site;
- Femoral artery lumen less than 6 mm;
- Length of the tissue tract, the distance between the anterior arterial 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/m");
- Uncontrolled hypertension (BP > 180/110);

Adverse Events

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

- Allergic response
- Arterial occlusion
- Arterial 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)
- 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
- Vasospasm
- Wound dehiscence
- Puncture site pain

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. **Table 1**, **Table 2**, and **Table 3** summarize the reported major and minor complications in the trial for all patients, diagnostic patients, and interventional patients, respectively.

Table1: Reported Major and Minor Complications - All Patients

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).

Table2: Reported Major and Minor Complications Diagnostic Patients

Access Site-Related Major Complications at 30 Days by Event	Diagnostic (N=210)				
	VASCADE (N=136)		Manual Compression (N=74)		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	**2**	**1.5%**	**2**	**2.7%**	**0.61**
Access site-related bleeding requiring > 30 minutes to achieve hemostasis	0	0%	2	2.7%	0.12
Access site-related hematoma > 6 cm	1	0.7%	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**	3	2.2%	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**	0	0%	0	0%	NA
Pseudoaneurysm requiring thrombin injection or fibrin adhesive injection**	0	0%	0	0%	NA
Pseudoaneurysm not requiring treatment**	1	0.7%	0	0%	NA
New onset access site-related neuropathy in the ipsilateral lower extremity not requiring surgical repair	1	0.7%	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).

Table3: Reported Major and Minor Complications
Interventional Patients

Access Site-Related Major Complications at 30 Days by Event	Interventional (N=207)				
	VASCADE (N=139)		Manual Compression (N=68)		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	**1**	**0.7%**	**8**	**11.8%**	**0.001**
Access site-related bleeding requiring > 30 minutes to achieve hemostasis	1	0.7%	8	11.8%	0.001
Access site-related hematoma > 6 cm	0	0%	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**	1	0.7%	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	0.7%	0	0%	NA
Pseudoaneurysm requiring thrombin injection or fibrin adhesive injection**	1	0.7%	0	0%	NA
Pseudoaneurysm not requiring treatment**	3	2.2%	0	0%	NA
New onset access site-related neuropathy in the ipsilateral lower extremity not requiring surgical repair	0	0%	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).

VASCADE 6/7F VCS Clinical Trial

The RESPECT Study was a prospective, randomized, controlled multi-center clinical trial designed to evaluate the safety and effectiveness of the study device in sealing common femoral arterial access sites and providing reduced times to hemostasis and ambulation compared with Manual Compression (MC) at the completion of diagnostic or interventional endovascular procedures (cardiac or peripheral vascular catheterizations) performed through 6F or 7F introducer sheaths. Patients were randomized in a 2:1 treatment device to control ratio. The trial was conducted at 20 sites in the United States and one site in Australia. In an ultrasound sub-study, images of the access site were obtained from 100 consecutively randomized, treated, VASCADE patients at 5 sites prior to hospital discharge.

To be eligible for the trial, patients were required to be between 18 and 80 years of age; able and willing to sign an Informed Consent Form; acceptable candidates for an elective, non-emergent diagnostic or interventional endovascular procedure via the common femoral artery using a 6F or 7F introducer sheath who were also acceptable candidates for post-procedure manual compression; and able and willing to complete a 30-day ± 7 days follow-up evaluation. Patients were excluded if they had clinically significant peripheral vascular disease; bleeding disorder; ipsilateral femoral arteriotomy within the previous 30 days; planned endovascular procedure within the next 30 days; previous vascular grafts at target access site; extreme morbid obesity (BMI greater than 45 kg/m2) or were underweight (BMI less than 20 kg/m2); known allergy/adverse reaction to bovine derivatives; planned extended hospitalization; administration of low molecular weight heparin (LMWH) within 8 hours of the procedure; femoral artery diameter less than 6mm at access site; multi arterial sticks; received unfractionated heparin with an ACT greater than 300 seconds in the absence of a glycoprotein (GP) IIb/IIIa inhibitor or greater than 250 seconds in the presence of a glycoprotein IIb/IIIa inhibitor; intra-procedural bleeding around sheath or suspected intraluminal thrombus, hematoma, pseudoaneurysm, or AV fistula; uncontrolled hypertension; or length of tissue tract estimated to be less than 2.5cm.

A total of 420 patients, 211 diagnostic and 209 interventional patients, were enrolled. The mean age was 62 years and mean BMI was 30kg/m2. Twenty-nine percent (29%) of patients were female. The study also included 69 roll-in cases, consisting of 45 diagnostic and 24 interventional patients. The randomized VASCADE arm included 137 diagnostic and 141 interventional patients, while the manual compression arm included 74 diagnostic and 68 interventional patients. Seventy-seven percent (77%) of the VASCADE interventional patients received bivalirudin, 27% received heparin, 60% received clopidogrel, and 8% received GP IIb/IIIa inhibitors. The mean Activated Clotting Time (ACT) in patients receiving unfractionated heparin for diagnostic patients was 221 seconds vs. 172 seconds in the VASCADE and manual compression groups, respectively. The mean ACTs in interventional patients were similar among groups, with the VASCADE group reporting 289.5 ± 136.9 seconds vs. 289.0 ± 100.7 seconds in the manual compression group.

Enrolled patients were followed for 30±7 days. Four hundred fifteen (415) randomized patients (98.8%) completed 30-day follow-up. Three patients were prematurely randomized and immediately withdrawn from the study due to ineligibility; one was lost to follow-up and one withdrew consent to participate prior to 30-day follow-up.

Effectiveness Results

Table 4 summarizes the primary efficacy endpoint, Time to Hemostasis (TTH), and secondary efficacy endpoints, Time to Ambulation (TTA), Time to Discharge Eligibility (TTDE), and Time to Discharge (TTD). The primary efficacy endpoint, TTH, was defined as elapsed time between device removal, i.e., device removal for Cardiva VASCADE VCS and sheath removal for manual compression, and first observed and confirmed arterial hemostasis (no or minimal subcutaneous oozing and the absence of expanding or developing hematoma). TTA was defined as the elapsed time between device removal, i.e., device removal for Cardiva VASCADE VCS and sheath removal for manual compression, and when ambulation was achieved (patient standing and walking at least 20 feet without re-bleeding). TTDE was defined as the elapsed time between device removal, i.e., device removal for Cardiva VASCADE VCS and sheath removal for manual compression, and when the patient was eligible for hospital discharge based upon an assessment of the access site.

Table 4: Primary and Secondary Effectiveness

	Diagnostic (N=211)			Interventional (N=209)			Total (N=420)		
	VASCADE (N=137)	Manual Compression (N=74)	p-value*	VASCADE (N=141)	Manual Compression (N=68)	p-value*	VASCADE (N=278)	Manual Compression (N=142)	p-value*
Time to Hemostasis (minutes)									
N	136	74		139	68		275	142	
Mean	4.0	18.2	< 0.0001	5.5	24.9	< 0.0001	4.8	21.4	< 0.0001
Std Deviation	4.2	8.1		6.3	15.1		5.4	12.4	
Median	2.6	18.5	< 0.0001	3.3	20.5	< 0.0001	3.0	20.0	< 0.0001
Min	0.6	4.3		0.8	0.0		0.6	0.0	
Max	24.7	64.6		31.6	97.0		31.6	97.0	
Time to Ambulation (hours)									

	Diagnostic (N=211)			Interventional (N=209)			Total (N=420)		
	VASCADE (N=137)	Manual Compression (N=74)	p-value*	VASCADE (N=141)	Manual Compression (N=68)	p-value*	VASCADE (N=278)	Manual Compression (N=142)	p-value*
N	136	74		139	68		275	142	
Mean	2.6	4.6	< 0.0001	5.0	7.2	0.003	3.8	5.8	< 0.0001
Std Deviation	2.0	1.6		6.7	3.7		5.1	3.1	
Median	2.2	4.4	< 0.0001	4.1	6.4	< 0.0001	3.2	5.2	< 0.0001
Min	1.0	1.7		2.2	2.5		1.0	1.7	
Max	20.1	11.0		78.0	22.8		78.0	22.8	
Time to Discharge Eligibility (hours)									
N	136	74		138	68		274	142	
Mean	3.1	5.0		6.6	8.2		4.8	6.5	
Std Deviation	2.1	1.6		8.4	4.0		6.4	3.3	
Median	2.6	4.8		4.6	7.0		3.6	5.7	
Min	1.4	2.2		2.6	3.0		1.4	2.2	
Max	20.5	11.3		78.4	23.2		78.4	23.2	
Time to Hospital Discharge (hours)									
N	136	74		139	68		275	142	
Mean	12.0	7.3		24.5	20.8		18.3	13.7	
Std Deviation	45.4	7.3		16.2	6.7		34.5	9.8	
Median	3.4	5.3		23.4	19.9		17.2	13.9	
Min	1.7	2.4		3.4	4.9		1.7	2.4	
Max	432.9	55.6		147.6	45.7		432.9	55.6	

*p-value from t-test for comparing means and Wilcoxon's test for comparing medians

Table 5 summarizes the secondary effectiveness endpoint of Procedure Success. Procedure Success was defined as attainment of final hemostasis using any method and freedom from major vascular complications through 30 days. The Procedure Success Rate was 100% for VASCADE and Manual Compression.

Table 5: Secondary Effectiveness, Procedure Success

Procedure	Treatment Assignment	Number of Patients	Number of Successes	Success Rate	95% Confidence Interval*	
Diagnostic	VASCADE	136	136	100%	97%	100%
	Manual Compression	74	74	100%	95%	100%
Interventional	VASCADE	139	139	100%	97%	100%
	Manual Compression	68	68	100%	95%	100%
Total	Cardiva VCS	275	275	100%	99%	100%
	Manual Compression	142	142	100%	97%	100%

*95% Exact Binomial Confidence Interval
**Two-sided Fisher's exact test.

Table 6 summarizes the results of Device Success. Device Success was defined as the ability to deploy the delivery system, deliver the collagen, and achieve hemostasis with the VASCADE Vascular Closure System alone or with adjunctive compression. The overall Device Success Rate for the total patients was 96%.

Table 6: Secondary Effectiveness, Device Success

Procedure	Number of Patients**	Number of Successes	Success Rate	95% Confidence Interval*	
Diagnostic	136	128	94%	88.7%	97.4%
Interventional	139	135	97%	92.8%	99.2%

*95% Exact Binomial Confidence Interval
** Includes 6 instances of failure to follow written Instructions for Use. Excluding these 6 instances, Device success rates are 96% (Diagnostic), 99% (Interventional) and 98% (Total)

Table 7, **Table 8**, **Table 9**, and **Table 10** summarize the cumulative data for TTH, TTA, TTDE, and TTD, respectively.

Table 7: Cumulative Time to Hemostasis (TTH) All Patients

Time point	Total (N=420)			
	VASCADE (N=278)		Manual Compression (N=142)	
N	275		142	
≤ 1 minute	8	3%	1	1%
≤ 2 minutes	51	19%	1	1%
≤ 3 minutes	136	49%	1	1%
≤ 4 minutes	195	71%	1	1%
≤ 5 minutes	221	80%	5	4%
≤ 10 minutes	246	89%	16	11%
≤ 20 minutes	263	96%	85	60%
≤ 30 minutes	274	100%	132	93%

Table 8: Cumulative Time to Ambulation (TTA) All Patients

Time point	Total (N=420)			
	VASCADE (N=278)		Manual Compression (N=142)	
N	275		142	
≤ 1 hour	0	0%	0	0%
≤ 2 hours	22	8%	1	1%
≤ 3 hours	122	44%	12	8%
≤ 4 hours	179	65%	31	22%
≤ 5 hours	255	93%	68	48%
≤ 10 hours	268	97%	131	92%
≤ 15 hours	270	98%	138	97%

Table 9: Cumulative Time to Discharge Eligibility (TTDE) All Patients

Time point	Total (N=420)			
	VASCADE (N=278)		Manual Compression (N=142)	
N	274		142	
≤ 2 hours	10	4%	0	0%
≤ 4 hours	152	55%	20	14%
≤ 6 hours	247	90%	79	56%
≤ 8 hours	257	94%	117	82%
≤ 12 hours	262	96%	131	92%
≤ 24 hours	270	99%	142	100%
≤ 48 hours	272	99%	142	100%

Table 10: Cumulative Time to Discharge (TTD) All Patients

Time point	Total (N=420)			
	VASCADE (N=278)		Manual Compression (N=142)	
N	275		142	
≤ 2 hours	1	0%	0	0%
≤ 4 hours	86	31%	12	8%
≤ 6 hours	123	45%	50	35%
≤ 8 hours	131	48%	66	46%
≤ 12 hours	134	49%	69	49%
≤ 24 hours	207	75%	129	91%
≤ 48 hours	265	96%	141	99%

Evaluation of VASCADE 5F VCS

A. VASCADE 5F Confirmatory Trial

The purpose of the VASCADE 5F study was to confirm the safety and effectiveness of the scaled-down 5F version of the VASCADE 6/7F VCS. The 5F device is virtually identical to the slightly larger 6/7F VCS. The study population was defined as patients undergoing cardiac or peripheral vascular catheterization procedures via the femoral artery approach when using a standard 5F introducer sheath. The study was conducted at a single-center in Australia, and was a prospective, non-randomized, non-blinded, single treatment trial. The inclusion and exclusion criteria were identical to the U.S. IDE RESPECT trial with the exception that patients had to be undergoing a catheterization procedure utilizing a 5F introducer sheath.

Thirty (30) patients were enrolled into the study. All of the patients enrolled in the study underwent diagnostic procedures. Patient demographic characteristics at baseline, such as gender, age, and BMI were comparable between the U.S. IDE trial and the 5F Australian confirmatory study. The safety and effectiveness endpoints for the 5F confirmatory study were identical to the 6/7F study. Identical to the pivotal RESPECT trial, the primary safety endpoint was the rate of combined major access site-related complications within 30 ± 7 days following the catheterization procedure. The secondary safety endpoint was the rate of combined minor access site-related complications within 30 ± 7 days following the procedure. Identical to the IDE RESPECT trial, the primary effectiveness endpoint was TTH. The secondary effectiveness endpoints were TTA, TTDE, TTD, procedure success, and device success.

Results of 5F trial

Table 1: Access Site-Related Major Complications

Access Site-Related Major Complications	**5-French (N=30)**	
Any access-site-related major complication	**1**	**3.3%**
Access site re-bleeding requiring transfusion	1*	3.3%
Vascular injury requiring repair	0	0.0%
New ipsilateral lower extremity ischemia causing a threat to the viability of the limb	0	0.0%
Access site-related infection requiring intravenous antibiotics and/or extended hospitalization	0	0.0%
New onset access site-related neuropathy in the ipsilateral lower extremity requiring surgical repair	0	0.0%
Permanent access site-related nerve injury (> 30 days)	0	0.0%

One occurrence only.

Table 2: Access Site-Related Minor Complications

Access Site-Related Minor Complications	**5-French (N=30)**	
Any Access Site-Related Minor Complication	**1**	**3.3%**
Access site-related bleeding requiring > 30 minutes to achieve hemostasis	0	0.0%
Access site-related hematoma > 6 cm	0	0.0%
Late access site-related bleeding (following hospital discharge)	0	0.0%
Ipsilateral lower extremity arterial emboli	0	0.0%
Ipsilateral deep vein thrombosis	0	0.0%
Access site-related vessel laceration	0	0.0%
Access site wound dehiscence	0	0.0%
Localized access site infection treated with intramuscular or oral antibiotics	0	0.0%
Arteriovenous fistula not requiring treatment	0	0.0%
Pseudoaneurysm requiring thrombin injection or fibrin adhesive injection	0	0.0%
Pseudoaneurysm not requiring treatment	0	0.0%
New onset access site-related neuropathy in the ipsilateral lower extremity not requiring surgical repair	1*	3.3%
Ipsilateral pedal pulse diminished by two grades or transiently lost	0	0.0%

*One occurrence only.

Table 3: TTH, TTA, TTDE, and TTD Effectiveness Endpoints

	5 French (N=30)
Time to Hemostasis (minutes)	
N	30
Mean	3.0
Std Deviation	2.4
Median	2.3
Min	0.2
Max	11.8
Time to Ambulation (hours)	.
N	30
Mean	4.1
Std Deviation	5.9
Median	2.3
Min	1.5
Max	25.9
Time to Discharge Eligibility (hours)	.
N	30
Mean	5.6
Std Deviation	9.0
Median	3.1
Min	2.0
Max	46.9
Time to Hospital Discharge (hours)	.
N	30
Mean	11.9
Std Deviation	16.0
Median	3.5
Min	2.0
Max	73.0

B. VASCADE 5F Engineering Analysis

Engineering analysis for the scaled down VASCADE 5F VCS included Collagen Patch size calculations resulting in a proportionally smaller Collagen Patch as compared with the VASCADE 6/7F VCS device. These analyses confirmed equivalent tissue-tract space-filling capability between the 5F and 6/7F versions of the VASCADE device. In addition, fundamentally the same verification and validation testing was completed for the 5F VASCADE VCS device as was completed for the 6/7F VASCADE VCS device.

Conclusions

The results from the RESPECT clinical trial demonstrate that patients who have undergone diagnostic or interventional cardiac or peripheral vascular endovascular procedures using a 6F or 7F introducer sheath and were treated with VASCADE VCS have statistically and clinically significant decreased times to hemostasis and ambulation for diagnostic and interventional procedures, and statistically and clinically significant decreased time to discharge eligibility for diagnostic procedures, when compared to patients treated with manual compression. In addition, the trial demonstrated that patients treated with the VASCADE VCS were noninferior to patients treated with manual compression with respect to major access site-related complications.

A confirmatory clinical study and engineering analysis demonstrated that the VASCADE 5F VCS is equivalent to the VASCADE 6/7F VCS in design and performance.

DEVICE PREPARATION AND PROCEDURE

At the time of initial introducer sheath placement, patient body habitus should be evaluated to provide reasonable assurance that the distance between the femoral arteriotomy and the skin surface is greater than 2.5cm. After introducer sheath placement, an anterior oblique fluoroscopic image may be digitally recorded and stored, so that the arteriotomy site location can be compared to the position of the radiopaque marker just prior to Collagen Patch release. The radiopaque marker is located immediately distal to the Collagen Patch. A single wall, common femoral arteriotomy should also be confirmed at this time.

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 arteriotomy site once the device is removed from the vessel which may result in prolonged time to hemostasis.

1. Use the Cardiva VASCADE VCS only as described below:

Device	Model	Sheath Size	Sheath Length	Disc Size	Collagen Patch Length	Device Working Length	Maximum OD
Cardiva VASCADE 5F VCS	700-500DX	5 French	up to 12 cm	6.5 mm	15 mm	15 mm	1.80 mm
Cardiva VASCADE 6/7F VCS	700-580I	6 or 7 French	up to 12 cm	6.5 mm	15 mm	15 mm	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 VASCADE VCS Catheter and Clip from the foil pouch. Carefully remove VASCADE VCS 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 VASCADE 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 VASCADE VCS 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

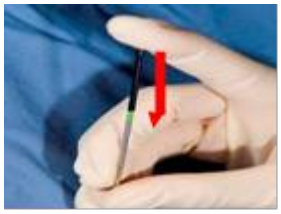

Fig. 5 – Collapse Disc by pressing Black Actuator Tip like a ballpoint pen

4. Verify that the sheath is not positioned in a tortuous vessel. If required, retract the sheath slightly to a non-tortuous location. Verify that the sheath is still positioned within the artery.

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 VCS Catheter in saline solution up to the White Marker Stripe and quickly remove.

CAUTION: Do not soak the VASCADE VCS 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 Catheter pull through during the sleeve retraction step.

7. Gently insert the VASCADE VCS Catheter (with disc collapsed) into the introducer sheath hub as shown in **Figure 6**. Insert the VASCADE VCS 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 VASCADE VCS Catheter into the patient if resistance is felt due to risk of vascular damage.

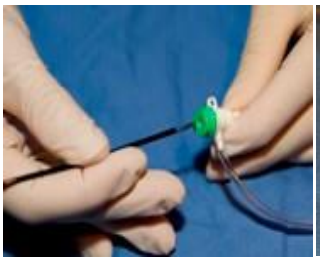

Fig. 6 – Insert device into hub of introducer sheath

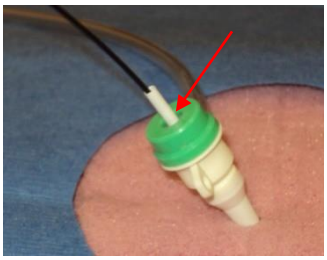

Fig. 7 – Insert device half way of the Lock

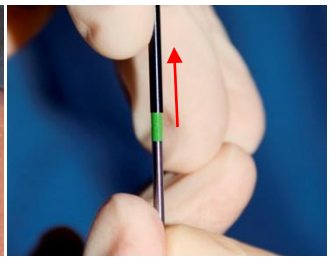

Fig. 8 – Pull back on Black Actuator Tip to deploy the Vascade Disc

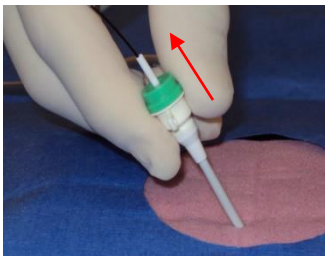

Fig. 9 – Grasp hub of sheath and remove over catheter

8. 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 (in VASCADE 5F approximately 1mm of the Green Segment remains visible when disc is collapsed) 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.

9. Gently remove sheath, without applying any compression at the access site or holding the VASCADE VCS Catheter**,** as shown in **Figure 9**. As the sheath slides over the VASCADE VCS Catheter, grasp the Catheter proximal to the LOCK as it exits the distal end of the introducer sheath. Continue sliding the sheath over the VASCADE VCS Catheter and discard sheath.

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

10. 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 continue the procedure as follows:

For diagnostic cases: the VASCADE VCS Catheter should be removed by collapsing the Disc and then manual compression can be applied per institutional protocol.

For anti-coagulated patients: the Clip may be applied to the VASCADE VCS Catheter on the skin surface as shown in **Figure 10** to maintain temporary hemostasis. The device may then stay in dwelling to allow time for the ACT level to normalize. The device can then be removed followed by application of manual compression per institutional protocol to achieve final hemostasis.

11. Once temporary hemostasis is achieved, apply the Clip to the Black Sleeve at skin level as shown in **Figure 10.** Utilize fluoroscopy to verify that the deployed Disc is positioned against the intimal surface of the arteriotomy by noting the position of the more proximal radiopaque marker. The marker should be at the arteriotomy site which can be verified by comparing its location with the location of the arteriotomy documented at the time of the introducer sheath insertion. The Collagen Patch is immediately proximal to this Marker Band. The Distal Marker Band locates the distal end of the Disc.

CAUTION: Applying too much upward tension on the Black Actuator 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 arteriotomy before deploying the extra- vascular Collagen Patch to avoid releasing the Collagen Patch in the vessel**.** This step requires fluoroscopy **(Figure 11)**.

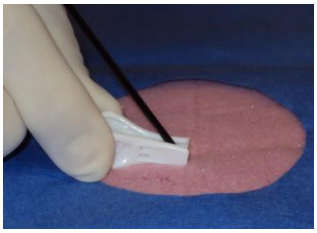

Fig. 10 – Apply Clip to Black Sleeve at skin level

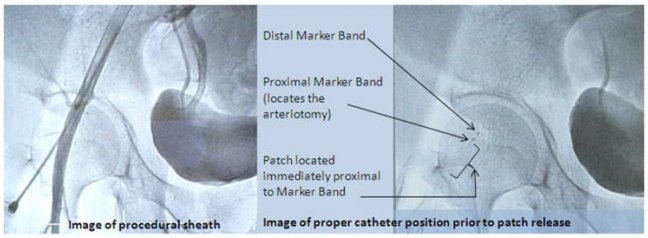

Fig. 11 – Fluoroscopic image demonstrating proper position of Disc against the arteriotomy

EXTRA-VASCULAR COLLAGEN PATCH DEPLOYMENT AND DEVICE REMOVAL

12. 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-vascularly, which will swell at the arteriotomy site. The Collagen Patch may be allowed to swell for up to 30 seconds prior to removal of the VASCADE VCS Catheter. The Clip should 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, for non-anti-coagulated patients, collapse the Disc, remove the Catheter and apply manual compression, per institutional protocol. If the patient is anti-coagulated, the Clip may be applied to the VASCADE VCS Catheter on the skin surface to maintain temporary hemostasis. The device may then stay in dwelling in order to allow time for the ACT level to normalize. The device can then be removed followed by application of manual compression to achieve final hemostasis.

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

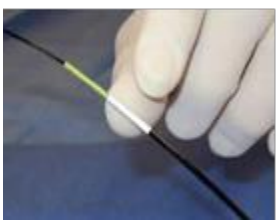

Fig. 13 – Retract the Black Sleeve by grasping the Lock and applying gentle upward tension toward the Silver Handle

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

13. After patch swell time (≤ 30 seconds) has elapsed, 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**. With slack in the catheter, collapse the Disc by pressing on the Black Actuator Tip as shown in **Figure 16**. When the Disc is fully collapsed, the Green Segment should not be visible for 6/7F device, or only a small portion, approximately 1mm, may be visible for the 5F device. While keeping the green tube stationary pull back the VASCADE VCS Catheter proximally. The Catheter Handle will move approximately 1.5cm while the green portion of the catheter remains stationary. This action slides the collapsed catheter Disc by the Collagen Patch while maintaining the position of the Collagen Patch. Once this initial movement has occurred, let go of the Green Tube. Gentle manual compression may be applied at the arteriotomy site. Remove the VASCADE VCS Catheter, and apply manual compression.

    Alternative Technique: AFTER 15-30 seconds of patch swell time and PRIOR TO collapsing the Disk, 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 VASCADE VCS Catheter to maintain Disk position against artery 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, apply proximal compression, collapse the Disc by pressing on the Black Actuator Tip as shown in **Figure 16**. Gentle manual compression may be applied at the arteriotomy site. Remove the VASCADE VCS Catheter, and apply manual compression.

14. Observe for arterial hemostasis. Manual compression can be used to decrease or stop any tract ooze until full hemostasis is achieved.

NOTE: Prior to the VASCADE VCS Catheter removal confirm that the Disc is completely collapsed by verifying that the Green Segment is no longer visible for 6/7F device and only a small portion approximately 1mm is visible for the 5F device. Care should be taken not to compress directly over the 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).

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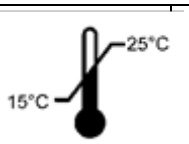
15. Apply sterile dressing to site per institution protocol. Maintain bed rest and periodically check site until patient is ready to ambulate.
16. Complete information on Patient Implant Card and provide to the patient.

GRAPHICAL SYMBOLS ON THE VASCADE VCS 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		

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