# RESPECT Trial

**(Rapid Extravascular Sealing via PercutanEous Collagen ImplanT)**

**A MULTI-CENTER, PROSPECTIVE, RANDOMIZED, CONTROLLED, TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF THE CARDIVA VASCULAR CLOSURE SYSTEM (VCS) VS. MANUAL COMPRESSION FOR THE MANAGEMENT OF THE FEMORAL ARTERIOTOMY AFTER PERCUTANEOUS ENDOVASCULAR PROCEDURES**

Prepared By: _____ 7/21/11
Michael Daniel — Date

**Approval:**

The approvals below indicate that this document has been reviewed.

_____ 7/21/11
Zia Yassinzadeh, Research & Development (R&D) — Date

_____ 7/21/11
Justin Ballotta, Operations — Date

_____ 7-21-11
Viet Le, Quality Assurance — Date

Signed Electronically for M. Chellew 7/21/11
Marlys Chellew, Clinical Affairs — Date

_____ 7/21/11
Michael Daniel, Regulatory Affairs — Date

# CARDIVA MEDICAL, INC. RESPECT Trial

## IDE G100246 – Unconditionally Approved by FDA 12/9/2010

## Protocol Amendment #01

**STUDY TITLE:** **RESPECT Trial**

**Rapid Extravascular Sealing via PercutanEous Collagen ImplanT**

**A MULTI-CENTER, PROSPECTIVE, RANDOMIZED, CONTROLLED TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF THE CARDIVA VASCADE™ VASCULAR CLOSURE SYSTEM (VCS) VS. MANUAL COMPRESSION FOR THE MANAGEMENT OF THE FEMORAL ARTERIOTOMY AFTER PERCUTANEOUS ENDOVASCULAR PROCEDURES**

**PROTOCOL:** Protocol No.: PTL 0243

**VERSION:** 6.0

**DATE:** July 21, 2011

**AMENDMENT:** Device design and process modifications were implemented by the sponsor. These modifications were fully evaluated via design verification and validation testing. To prevent any issues related to poolability of study data, the sponsor has decided to start the study enrollment over with 420 randomized patients. Patients previously enrolled in the randomized portion of the study will be evaluated separately. The primary analysis will include only patients enrolled from this point forward. Patient numbering conventions have been modified to clearly differentiate between the first cohort and the re-start group.

PROTOCOL IS OTHERWISE UNCHANGED (excluding date/revision corresponding to this amendment)

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

Marlys Chellew, BSN, MBA

Consulting Vice President, Clinical Affairs Cardiva Medical, Inc.

Diana Espinoza 7/21/11

Date:

Zia Yassinzadeh

Vice President Research and Development Cardiva Medical, Inc.

Z. Yassinzadeh 7/21/11

Date:

Michael A. Daniel, MS, MBA

Consulting Vice President Regulatory Affairs Cardiva Medical, Inc.

7/21/11

Date:

CARDIVA MEDICAL, INC.

# Clinical Investigation Plan (CIP) and Protocol

# RESPECT Trial

**(Rapid Extravascular Sealing via PercutanEous Collagen ImplanT)**

**A MULTI-CENTER, PROSPECTIVE, RANDOMIZED, CONTROLLED, TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF THE CARDIVA VASCADE™ VASCULAR CLOSURE SYSTEM (VCS) VS. MANUAL COMPRESSION FOR THE MANAGEMENT OF THE FEMORAL ARTERIOTOMY AFTER PERCUTANEOUS ENDOVASCULAR PROCEDURES**

**(PTL 0243)**

*The trial will be performed in accordance with the relevant parts of Title 21 CFR Parts 812, 50, 54, 56 and ISO 14155-1 / 14155-2.1; the ICH Guidelines for Good Clinical Practices (E6), the Declaration of Helsinki, and any regional and/or national regulations*

| | | |
|---|---|---|
| Sponsor: | CARDIVA Medical, Inc<br>888 West Maude Avenue<br>Sunnyvale, CA 94085 | |
| Study Responsibility: | Marlys Chellew, BSN, MBA<br>Consulting Vice President,<br>Clinical Affairs<br>Cardiva Medical, Inc.<br>888 West Maude Avenue<br>Sunnyvale, CA 94085 | Michael A. Daniel, MS, MBA<br>Consulting Vice President<br>Regulatory Affairs<br>Cardiva Medical, Inc.<br>888 West Maude Avenue<br>Sunnyvale, CA 94085 |
| Principal Investigators: | James B. Hermiller, MD, FACC, FSCAI<br>Director, Cardiovascular Interventional Fellowship<br>St Vincent Hospital<br>The St Vincent Heart Center of Indiana<br>10590 North Meridian Street, Suite 300<br>Indianapolis, Indiana 46290 | |
| Study Centers: | See the study manual for a list of study centers | |
| Date of Issue: | July 21, 2011 / Version 6.0 | |

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

# CARDIVA MEDICAL, INC. RESPECT Protocol Approval Page

**STUDY TITLE:** **RESPECT Trial**

**Rapid Extravascular Sealing via PercutanEous Collagen ImplanT**

**A MULTI-CENTER, PROSPECTIVE, RANDOMIZED, CONTROLLED TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF THE CARDIVA VASCADE™ VASCULAR CLOSURE SYSTEM (VCS) VS. MANUAL COMPRESSION FOR THE MANAGEMENT OF THE FEMORAL ARTERIOTOMY AFTER PERCUTANEOUS ENDOVASCULAR PROCEDURES**

**PROTOCOL NUMBER:** Protocol No.: PTL 0243

**VERSION NUMBER:** 6.0

**DATE:** July 21, 2011

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

Marlys Chellew, BSN, MBA

Consulting Vice President, Clinical Affairs
Cardiva Medical, Inc.

Signed electronically 7/21/11

Date:

Zia Yassinzadeh

Vice President Research and Development
Cardiva Medical, Inc.

Z. Yassinzadeh 7/21/11

Date:

Michael A. Daniel, MS, MBA

Consulting Vice President Regulatory Affairs
Cardiva Medical, Inc.

7/21/11

Date:

# Investigator's Signature Page

**STUDY TITLE:** **RESPECT Trial**

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**STUDY CENTER:**

_____

(Print name of study center)

We, the undersigned, have read and understand the protocol specified above and agree on its content. We agree to perform and conduct the study as described in the protocol. In addition, when applicable, we agree to enlist sub-investigators who also agree to perform and conduct the study as described in the protocol.

_____

SITE PI – Print Name

_____

SITE PI – Signature

_____

DATE

# Protocol Synopsis

# RESPECT Trial

## Rapid Extravascular Sealing via PercutanEous Collagen ImplanT

### A MULTI-CENTER, PROSPECTIVE, RANDOMIZED, CONTROLLED TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF THE CARDIVA VASCADE™ VASCULAR CLOSURE SYSTEM (VCS) VS. MANUAL COMPRESSION FOR THE MANAGEMENT OF THE FEMORAL ARTERIOTOMY AFTER PERCUTANEOUS ENDOVASCULAR PROCEDURES

| | |
|---|---|
| **Primary Objective** | The objective of the trial is to demonstrate the safety and effectiveness of the Cardiva VASCADE™ Vascular Closure System (VCS) in sealing femoral arterial access sites and providing reduced times to hemostasis (TTH), time to ambulation (TTA) and time to discharge eligibility (TTDE) compared with manual compression at the completion of diagnostic or interventional endovascular procedures performed through 6Fr or 7Fr introducer sheaths. |
| **Test Device** | Cardiva VASCADE™ Vascular Closure System (VCS) |
| **Indication for Use** | The Cardiva VASCADE™ Vascular Closure System (VCS) is indicated for the percutaneous closure of common femoral artery access sites while reducing times to hemostasis and ambulation in patients who have undergone diagnostic or interventional endovascular catheterization procedures utilizing 6 Fr or 7 Fr procedural sheaths. |
| **Hypothesis** | The Cardiva VASCADE™ Vascular Closure System (VCS) provides TTH and TTA results that are less than manual compression by a clinically meaningful and statistically significant margin. The rate of major access site-related complications with the Cardiva VASCADE™ Vascular Closure System (VCS) is non-inferior to the major complication rates of manual compression for sealing femoral arterial access sites. |
| **Study Design** | A prospective, randomized, controlled multi-center clinical trial designed to evaluate the safety and effectiveness of the study device in sealing femoral arterial access sites and providing reduced times to hemostasis and ambulation compared with manual compression at the completion of diagnostic or interventional endovascular procedures performed through 6 Fr or 7 Fr introducer sheaths. Subjects will be randomized in a 2:1 treatment device to control ratio. |
| **Number of Patients** | 420 randomized subjects, and up to 100 roll-in Cardiva VASCADE™ VCS subjects |
| **Number of Sites** | Up to 20 U.S. sites. Up to 5 New Zealand & Australia sites may be added. |

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| **Duration of Trial** | Each enrolled subject will be followed for 30 days (± 7 days) post-procedure |
| **Primary Effectiveness Endpoint** | Time to hemostasis (TTH), defined as elapsed time between device removal, i.e. device removal for Cardiva and sheath removal for manual compression, and first observed and confirmed hemostasis.<br>(See Study Flow Chart on page 18) |
| **Secondary Effectiveness Endpoints** | • Time to ambulation (TTA), defined as elapsed time between device (Cardiva) or sheath (manual compression) removal and when subject stands and walks 20 feet without evidence of arterial re-bleeding from the access site<br>• Time to discharge eligibility (TTDE), defined as elapsed time between device (Cardiva) or sheath (manual compression) removal and when subject is medically able to be discharged based solely on the assessment of the access site, as determined by the medical team<br>• Time to hospital discharge (TTHD), defined as elapsed time between device (Cardiva) or sheath (manual compression) removal and when subject is actually discharged from the hospital<br>• 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<br>• Procedure Success, defined as attainment of final hemostasis using any method and freedom from major vascular complications through 30 days |
| **Primary Safety Endpoint** | Rate of combined major access site-related complications |
| **Secondary Safety Endpoint** | Rate of combined minor access site-related complications |
| **Follow-Up Schedule** | The study will be considered complete (with regard to the primary endpoint) after all randomized patients have completed the 30-Day +/- 7 day follow-up. |
| **Pre-Operative Inclusion Criteria** | 1. 18 to 80 years of age;<br>2. Capable and willing to give informed consent;<br>3. Acceptable candidate for an elective, non-emergent diagnostic or interventional endovascular procedure via the common femoral artery using a 6 Fr or 7 Fr introducer sheath who are also acceptable candidates for post-procedure manual compression;<br>4. Able and willing to complete a 30 day +/- 7 days follow-up evaluation;<br>5. 100 subjects willing to undergo ultrasound prior to discharge;<br>6. Acceptable candidate for emergent vascular surgery. |

| | |
|---|---|
| **Pre-Operative Exclusion Criteria** | Subjects will be excluded from participating in this trial if they meet any of the following criteria prior to initiation of the endovascular procedure<br>1. Advanced refusal of blood transfusion, if necessary;<br>2. Active systemic or cutaneous infection or inflammation;<br>3. Pre-existing immunodeficiency disorder and/or chronic use of systemic steroids;<br>4. Known, significant history of bleeding diathesis, coagulopathy, von Willebrand's disease 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);<br>5. Severe co-existing morbidities having a life expectancy of less than 30 days;<br>6. Currently involved in any other investigational clinical trials;<br>7. Ipsilateral femoral arteriotomy within the previous 30 days;<br>8. Planned endovascular procedure within the next 30 days;<br>9. Previous ipsilateral femoral artery closure using a permanent implant-based closure device;<br>10. Previous vascular grafts or surgery at the target vessel access site;<br>11. History of symptomatic peripheral arterial disease, revascularization or deep vein thrombosis in the ipsilateral limb;<br>12. Unilateral or bilateral lower extremity amputation(s);<br>13. Significant anemia with a hemoglobin level less than 10 g/dL or a hematocrit less than 30%;<br>14. Renal insufficiency (serum creatinine of > 2.5 mg/dl);<br>15. Females who are pregnant, planning to become pregnant within 3 months of the procedure, or lactating;<br>16. Extreme morbid obesity (BMI greater than 45 kg/m2) or underweight (BMI less than 20 kg/m2);<br>17. Unable to routinely walk at least 20 feet without assistance (see protocol);<br>18. Known allergy/adverse reaction to bovine derivatives, sodium hyaluronate or hyaluronan preparations;<br>19. Procedures that extend hospitalization (e.g., staged endovascular procedure, CABG);<br>20. Administration of low molecular weight heparin (LMWH) within 8 hours of the procedure. |

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|---|---|---|
| **Intra-Operative Exclusion Criteria** | Subjects will be excluded from participating in this trial if any of the following exclusion criteria occur during the endovascular procedure:<br>1. An introducer sheath with an overall length greater than 11 cm, or not 6 Fr or 7 Fr diameter;<br>2. Femoral artery diameter less than 6 mm at access site;<br>3. Difficult insertion of procedural sheath or needle stick problems at the onset of the procedure (e.g., multiple stick attempts, "back wall stick", etc.);<br>4. Angiographic evidence of more than minimal calcium, atherosclerotic disease, or stent within 1 cm of the puncture site;<br>5. Overlapping Common Femoral Vein and Femoral Artery at access site;<br>6. Placement of ipsilateral venous sheath during procedure;<br>7. Arterial access site located not at common femoral artery (e.g., on or below the bifurcation, above the lower border of the inferior epigastric artery, or above the pelvic brim);<br>8. More than one access site required;<br>9. Loss of distal pulses in the ipsilateral extremity during the procedure;<br>10. Subjects receiving unfractionated heparin with an ACT greater than 300 seconds in the absence of a glycoprotein IIb/IIIa inhibitor or greater than 250 seconds in the presence of a glycoprotein IIb/IIIa inhibitor (may wait to remove introducer sheath until ACT level reaches the target value);<br>11. Intra-procedural bleeding around sheath, or suspected intraluminal thrombus, hematoma, pseudoaneurysm, or AV fistula;<br>12. Systemic hypertension (BP greater than 180/110 mmHg) or hypotension (BP less than 90/60 mmHg) prior to randomization;<br>13. Length of the tissue tract, the distance between the anterior arterial wall and skin, is estimated to be less than 2.5 cm;<br>14. If the physician deems that a different method should be used to achieve hemostasis of the arterial site or that the subject should not attempt ambulation according to the protocol requirements. | |
| **Ultrasound Sub-Study** | | |
| | 100 randomized, treated, diagnostic and/or interventional subjects at 4-6 sites will be enrolled at in an ultrasound sub-study to image access site prior to hospital discharge. | |
| **Study Administration** | | |
| **CRO, United States (Clin / Reg)** | Chellew Clinical Outsourcing, LLC<br>310 Elan Village Lane, Ste. 310<br>San Jose, California 95134 | Daniel & Daniel Consulting<br>8 Snowberry Court<br>Orinda, California 94563 |
| **CRO Australia / N. Zealand** | Pacific Clinical Research Group (PCRG)<br>P.O. Box 1600 / North Sydney NSW 2059<br>Australia | |
| **Ultrasound Core Lab** | M.R. Jaff, MD / VasCore, Massachusetts General Hospital, Boston, Mass. | |
| **Data Management** | Innoventz, Inc., 800 E. Colorado Blvd, Ste. 120, Pasadena, California 91101 | |

**Table of Contents**

# 1. Introduction

## 1.1. Background and Rationale

In 2008, approximately 6.5 million diagnostic and therapeutic interventional cardiology procedures were performed in the U.S. It is expected that the number of interventional cardiology procedures performed in the U.S. will climb to approximately 8.1 million in the year 2013.[1] In most of these procedures, the common femoral artery is used as the cardiac access site. For each of these cases, post-procedure vascular access management is the most critical aspect to determining a successful subject outcome without complications.[2-4] For many decades, manual compression has been the "gold standard" for post-procedure vascular access management[5-6] despite the close observation, prolonged immobilization and bed rest that are required for this method. In the past decade, a variety of closure devices have been developed to facilitate access site management and to increase patient comfort. Although a number of new devices have been introduced in the last several years, there remain concerns about the safety, efficacy and ease-of-use with these closure devices. With the development of interventional coronary procedures, larger sheaths and more intense anticoagulation measures are now routinely employed.[2,5,7-8] Additionally, advances in peripheral vascular procedures place greater demands on the vascular access sites, resulting in higher rates of access site complications, primarily related to bleeding. In addition, many patients are likely to undergo repeated angiographic procedures over time, most frequently using the femoral artery as the vascular entry point. This growing vascular access site usage signals a need for more awareness and more diligence in protecting that site, since it is so critical to these procedures and the endovascular specialist's practice.

Many factors relating to the patient, physician, staff, and hospital impact access management for patients. Arterial puncture site recovery remains the single-most important impediment to early ambulation, early hospital discharge (both outpatient and inpatient), and risk of post-procedure complications like bleeding, arterial injury, infection, hematoma, pseudoaneurysm, and A-V fistula.[2,3] Complication rates range from 0.1-12%[3,5,7]. Moreover, certain complications such as bleeding can be predictors of early mortality which increases the importance of managing vascular access sites to avoid certain complications.[9] In addition, more complicated post-intervention antiplatelet regimes heighten the need for optimal vascular site management.[7] To improve the outcomes of endovascular and interventional procedures, a number of vascular closure devices (VCD) have been introduced.

Since 2004, Cardiva Medical, Inc. ("Cardiva") has developed medical devices that promote the hemostasis process following femoral artery catheterization procedures. Starting with FDA clearance of the VasoStasis Vascular Closure System in 2004 (K041486), Cardiva has introduced a number of devices that have helped further promote hemostasis as an adjunct to manual compression (i.e., K051817, K061075, K070458, K072297, and K082930). Compared to standard manual compression, these marketed products have demonstrated decreased sheath dwell, manual compression, and where

applicable, ambulation and discharge times. With the development of the VASCADE™ Vascular Closure System ("VCS"), Cardiva intends to improve on the Cardiva family of devices' hemostatic potential by placing an extravascular collagen patch within the tissue tract to further promote faster hemostasis.

Based on this previous experience, it is hypothesized that the VCS will be more effective than the Cardiva predecessor devices because the VCS utilizes a collagen patch at the arteriotomy site external to the femoral artery lumen. The hydrophilic collagen patch promotes hemostasisand has the potential to reduce time to hemostasis and time to ambulation in patients undergoing diagnostic or interventional catheterization procedures, as compared to manual compression alone.

## 1.2. Summary of Findings from Previous Studies

### 1.2.1. Pre-clinical Studies

Testing on the device included comprehensive design verification and validation testing. The following testing was completed on the device:

- Biocompatibility testing
- Mechanical testing
- Packaging testing
- Shelf-life testing
- Sterilization validation
- Preclinical GLP animal study

These tests were successfully completed and are described in more detail in the Investigator Brochure.

The Pre-clinical GLP study was performed to demonstrate the safety of the Cardiva VASCADE™ Vascular Closure System to seal an arteriotomy created by a 7F introducer in the ovine femoral artery.

The test model was based on utilization of mature Suffolk sheep with a minimal weight of 100kg that provided adequate femoral arterial size for demonstration of the impact of Cardiva VASCADE™ Vascular Closure System. Femoral arterial penetration is carried out on both left and right sides of each animal studied. Twelve animals are utilized and were divided into four test groups with three sheep in each group. The time end points are 7 days +/- 1 day, 30 days +/- 3 days, 60 days +/- 5 days, and 90 days +/- 7 days. The procedure provided for a total of 24 femoral artery closure sites studied at varying times post procedure.

The final procedure involved anesthesia followed by Doppler examination to determine femoral arterial patency. The anesthetized animals were heparinized and euthanatized with harvest of tissues carried out by an *en bloc* resection of the femoral artery with the tissue immersion fixed in 10% neutral buffered formalin

(NBF). In addition, samples were collected from two areas of the gastrocnemius muscle and quadriceps muscle from each limb.

In summary all animals had effective coagulation following catheterization. Further there was no evidence of ischemic or embolic change identified in the gastrocnemius and quadriceps muscles with two areas examined histologically from each lower limb area. Similarly there was no evidence that the collagen patches ever gained entry into the arterial system and no areas of distal embolism were observed. The impact of the collagen patch once deposited is to promote rapid integration of the patch material into the surrounding tissues with tight fixation ensured by the invading fine vascular network and the prominent internal patch fibroplasia. It can be concluded that deployment of the patch does not pose a hazard to intravascular penetration and once exposed to the surrounding tissues the collagen patch is rapidly fixed in situ. There is minimal inflammatory cell reaction to the collagen itself and the host reaction is one of dissolution and consolidation.

### 1.2.2. Clinical Studies

An earlier version of the VASCADE™ Vascular Closure System, known as the Catalyst VI Vascular Closure System, was tested in a clinical trial at 2 sites in New Zealand. The VCS was utilized to promote hemostasis at 34 femoral access sites for 31 subjects. None of the subjects experienced a major complication. Three minor complications were reported: one hematoma, one pseudoaneurysm, and one access site-related infection. None of the complications were determined to be device related and all of the complications were resolved with no further clinical sequelae.

Hemostasis was successfully achieved for all access sites. The VCS was used to successfully promote hemostasis without a major complication at 32 of the 34 access sites (94.1%). The remaining two access sites were crossed-over to manual compression without incident. The mean time to hemostasis (with adjunctive manual compression), 3.6 ± 2.3 minutes, and mean time to eligibility for ambulation, 1.8 ± 0.5 hours, compare favorably to reported times for manual compression in studies of other vascular closure devices.

This first-in-man trial of the VCS demonstrated the initial feasibility for the safety and performance of the device.

A feasibility study utilizing the final VASCADE™ device was undertaken at two (2) sites in New Zealand. As of November 11, 2010 there were a total of 21 subjects enrolled in the study, 13 subjects + 1 roll-in at Auckland City Hospital, and 7 subjects at Middlemore Hospital.

A total of 20 subjects between 51 and 83 years of age were enrolled in this study. Four (4) of the enrolled subjects were women (20%) and sixteen (16) were men (80.0%). The mean age of the participants was 67.30 ± 9.95 years and their mean body mass index (BMI) was 29.44 ± 3.50 kg/m$^2$. Time to hemostasis was the

primary effectiveness endpoint for the study. The table below provides the mean time to hemostasis (TTH) for all patients, and also stratified by type of procedure. The overall mean time to hemostasis was 1 minute, 7 seconds.

Time to Hemostasis

| Measure | Mean ± SD (n) |
|---|---|
| Time to Hemostasis – Overall (min) | 1:07 ± 1:02 (20) |
| Time to Hemostasis – Diagnostic (hr) | 1:16 ± 1:25 (10) |
| Time to Hemostasis – Intervention (hr) | 0:57 ± 0:29 (10) |

Hemostasis was achieved in less than one (1) minute for 16 subjects (80%); less than or equal to two (2) minutes for two subjects (10%); and less than five (5) minutes for the remaining two subjects (10%).

Secondary effectiveness endpoints included time to ambulation, time to eligibility for hospital discharge, and time to hospital discharge. The mean time to ambulation for all patients was 4 hours, 52 minutes. The mean time to ambulation was 2 hours, 34 minutes for diagnostic patients, and 7 hours, 11 minutes for interventional patients.

Several subjects experienced prolonged times to eligibility for hospital discharge and hospital discharge. None of the reasons for extended eligibility for discharge or actual discharge was related to the Cardiva VASCADE™ VCS device or the closure procedure.

The primary safety endpoint was the incidence of major complications, as defined in the investigational plan. There have been no major complications related to the endpoints reported in the study to date. The incidence of minor complications was a secondary safety endpoint for the study. There were no minor vascular complications reported in the study to date.

Adverse events were also evaluated in the study. There have been six adverse events reported in the study to date. A single serious adverse event (hospitalization for musculoskeletal pain due to falling off a bicycle) was reported. Five minor adverse events were reported including slight groin discomfort (1), minor access site subcutaneous ooze (1), access site hematoma (1), skin lesion removed from nose (1), and superficial bruising around groin area (1).

Ultrasound images were collected post-operatively prior to discharge. Images were obtained for all subjects prior to hospital discharge. There were no major or minor vascular complications noted.

The interim results from this study demonstrated the initial safety and effectiveness of the device. Hemostasis was successfully achieved at all access sites. The mean time to hemostasis was 1 minute, 7 seconds and the mean time to ambulation was 4 hours, 52 minutes. There were no major complications and no minor complications reported.

## 1.3. Risks and Benefits

### 1.3.1. Risks

Risks associated with the Vascular Closure System 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 (air, tissue, device)
- Hematoma
- Infection
- Inflammatory response
- Intimal tear / dissection
- 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.

### 1.3.2. Benefits

The potential benefits of the VASCADE™ Vascular Closure System over manual compression alone to achieve hemostasis include reduced time to hemostasis, time to ambulation, and to hospital discharge eligibility. The trial is intended to evaluate these benefits

## 1.4. Rationale for Ultrasound Sub-study

A sub-study of this pivotal U.S. clinical trial will be performed utilizing independent analysis of noninvasive duplex ultrasound (DUS) imaging in treated subjects who

underwent either diagnostic and/or interventional procedures. DUS evaluation will be utilized to assess the local vascular impact of the Cardiva VASCADE™ Vascular Closure System (VCS), along with the development of iatrogenic vascular complications at the time of discharge. Specific investigational sites will be designated as ultrasound sites. These sites will perform ultrasound imaging on sequentially randomized patients in the treatment group until a total of 100 patients have been evaluated. Ultrasound will be performed prior to hospital discharge. All sub-study sites will be instructed in performance of duplex ultrasonography of the femoral vascular structures at the time of discharge, and images will be interpreted by a central core ultrasound laboratory with experience in multicenter vascular device trials (VasCore, Massachusetts General Hospital, Boston, MA).

## 2. Device Description

The Cardiva 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 supplied by Kensey Nash that is 15mm in length and 12mg +/- 3mg in dry weight. The patch is deployed extra-vascularly and expands as a result of rehydration, at the arteriotomy site to aid in achieving hemostasis. The system consists of a sterile disposable Vascular Closure Catheter which houses the resorbable **Collagen Patch**, and the **Clip** (Fig 1).

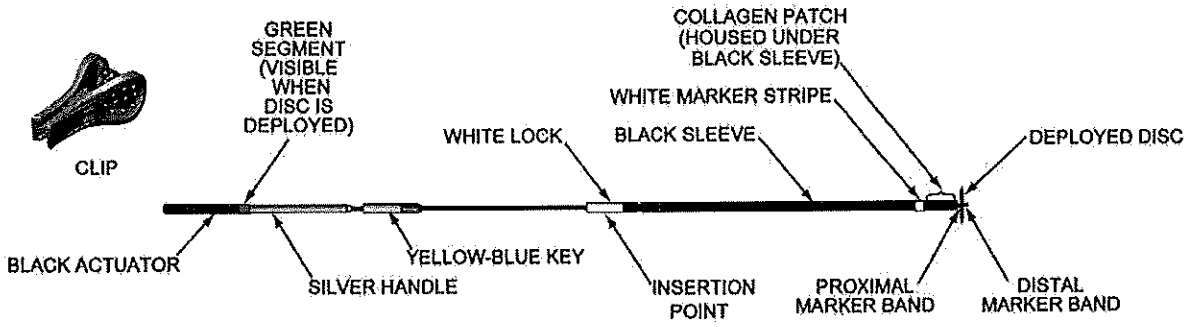


Figure 1: VASCADE™ Vascular Closure System

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 Disc. After completion of the catheterization procedure, the Cardiva VASCADE™ VCS Catheter is inserted through a commercially available 6F or 7F introducer 11 cm sheath. The 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 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 Clip is applied at skin level to maintain the position of the 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 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. Used in this way, the VASCADE™ VCS assists in blocking blood flow from the arteriotomy via an occlusion mechanism. The collagen patch is designed to seal the arteriotomy within minutes and be resorbed in approximately three months.

### 2.1. Device Labeling

A copy of the Instructions for Use (IFU) will be included with the devices. The Cardiva VASCADE™ Vascular Closure System (VCS) labels contain the following information:

- Vascular Closure System
- Lot or Serial number (for randomization)
- Expiration (use before) date
- For Investigational Use Only

## 3. Study Objective

The objective of the trial is to demonstrate the safety and effectiveness of the Cardiva VASCADE™ Vascular Closure System (VCS) in sealing femoral arterial access sites and providing reduced times to hemostasis (TTH) and time to ambulation (TTA) compared with manual compression at the completion of diagnostic or interventional endovascular procedures performed through 6 Fr or 7 Fr introducer sheaths. This study will be considered a success (from a statistical perspective) if it meets "both the Cardiva VASCADE™ VCS superiority goal for the primary effectiveness analysis and the Cardiva VASCADE™ VCS non-inferiority goal for the primary safety analysis as stated in Sections 9.2.2.2 and 9.2.3 respectively.

## 4. Study Design

### 4.1. Overview

A prospective, randomized, controlled, multi-center clinical trial to evaluate the safety and efficacy of the VASCADE™ Vascular Closure System compared to manual compression. Subjects will be randomly assigned in a 2:1 scheme to vascular closure with the Vascular Closure System or manual compression following percutaneous vascular access for diagnostic or interventional procedures. Measures of safety and efficacy will be assessed through hospital discharge and 30 (+/- 7) days post-procedure. See Figure 2 for a flow chart of the study design.

### 4.2. Sample Size

420 subjects will be randomized in this trial. In addition, up to 100 roll-in subjects will be enrolled.

### 4.3. Investigational Sites

This trial will be conducted at up to 20 clinical sites in the United States with up to 5 additional sites in New Zealand and Australia.

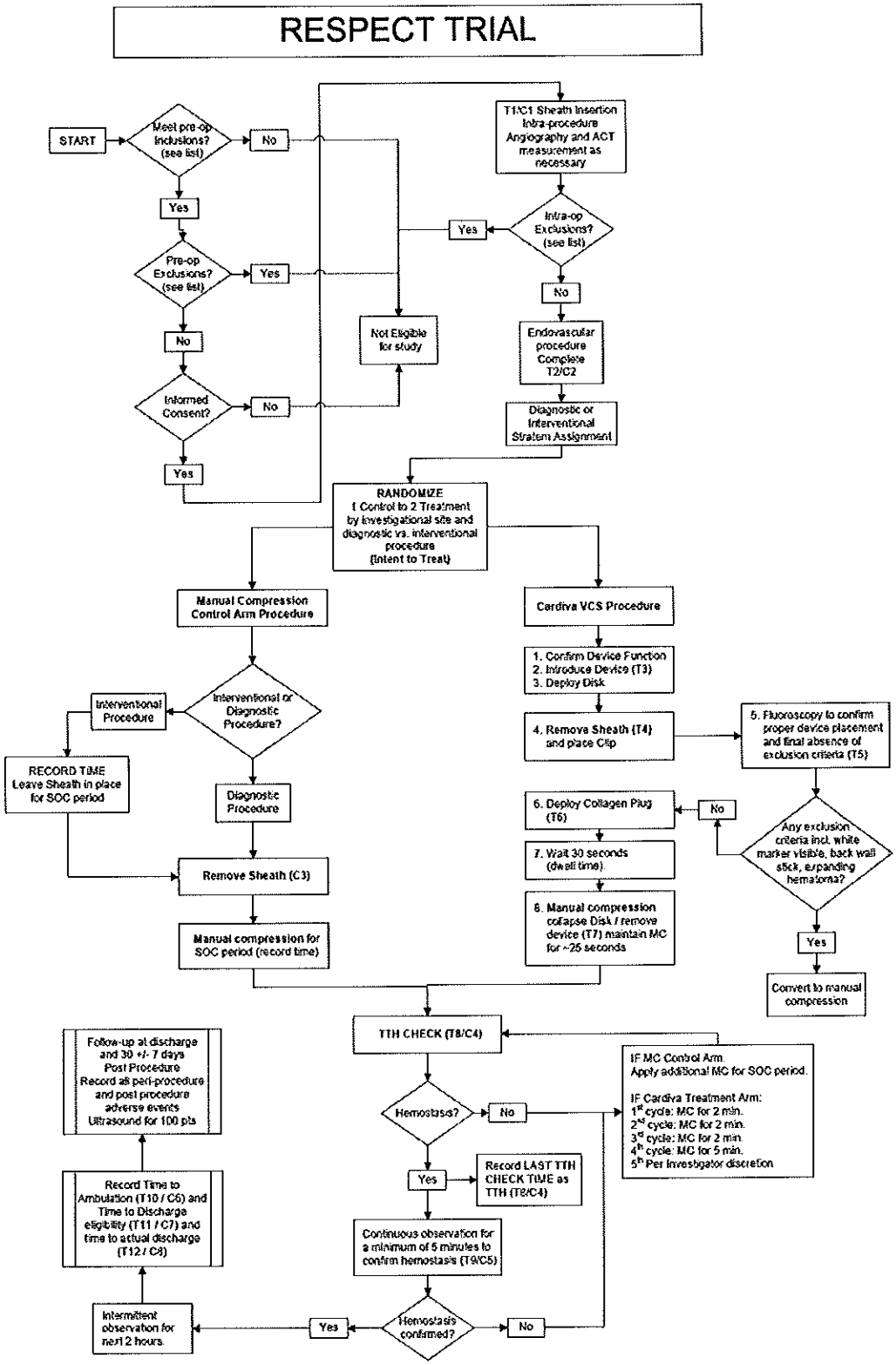


Figure 2. Schematic of Study Design

# 5. Study Population

## 5.1. *Selection Criteria*

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

### 5.1.1. Pre- Operative Inclusion Criteria

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

| | |
|---|---|
| **Pre-Operative Inclusion Criteria** | 1. 18 to 80 years of age;<br>2. Capable and willing to give informed consent;<br>3. Acceptable candidate for an elective, non-emergent diagnostic or interventional endovascular procedure via the common femoral artery using a 6 Fr or 7 Fr introducer sheath who are also acceptable candidates for post-procedure manual compression;<br>4. Able and willing to complete a 30 day +/- 7 days follow-up evaluation;<br>5. 100 subjects willing to undergo ultrasound prior to discharge;<br>6. Acceptable candidate for emergent vascular surgery. |

### 5.1.2. Pre-Operative Exclusion Criteria

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

SEE TABLE ON NEXT PAGE.

| | |
|---|---|
| **Pre-Operative Exclusion Criteria** | Subjects will be excluded from participating in this trial if they meet any of the following criteria prior to initiation of the endovascular procedure<br>1. Advanced refusal of blood transfusion, if necessary;<br>2. Active systemic or a cutaneous infection or inflammation;<br>3. Pre-existing immunodeficiency disorder and/or chronic use of systemic steroids;<br>4. Known, significant history of bleeding diathesis, coagulopathy, von Willebrand's disease 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);<br>5. Severe co-existing morbidities having a life expectancy of less than 30 days;<br>6. Currently involved in any other investigational clinical trial;<br>7. Ipsilateral femoral arteriotomy within the previous 30 days;<br>8. Planned endovascular procedure within the next 30 days;<br>9. Previous ipsilateral femoral artery closure using a permanent implant-based closure device;<br>10. Previous vascular grafts or surgery at the target vessel access site;<br>11. History of symptomatic peripheral arterial disease, revascularization or deep vein thrombosis in the ipsilateral limb;<br>12. Unilateral or bilateral lower extremity amputation(s);<br>13. Significant anemia with a hemoglobin level less than 10 g/dL or a hematocrit less than 30%;<br>14. Renal insufficiency (serum creatinine of > 2.5 mg/dl);<br>15. Females who are pregnant, planning to become pregnant within 3 months of the procedure, or lactating;<br>16. Extreme morbid obesity (BMI greater than 45 kg/m2) or underweight (BMI less than 20 kg/m2);<br>17. Unable to routinely walk at least 20 feet without assistance (see protocol);<br>18. Known allergy/adverse reaction to bovine derivatives, sodium hyaluronate or hyaluronan preparations;<br>19. Procedures that extend hospitalization (e.g., staged endovascular procedure, CABG);<br>20. 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 trial if any of the following exclusion criteria occur during the intravascular procedure:

| | |
|---|---|
| **Intra-Operative Exclusion Criteria** | Subjects will be excluded from participating in this trial if any of the following exclusion criteria occur during the intravascular procedure:<br>1. An introducer sheath with an overall length greater than 11 cm, or not 6 Fr or 7 Fr diameter;<br>2. Femoral artery diameter less than 6 mm at access site;<br>3. Difficult insertion of procedural sheath or needle stick problems at the onset of the procedure (e.g., multiple stick attempts, "back wall stick", etc.);<br>4. Angiographic evidence of more than minimal calcium, atherosclerotic disease, or stent within 1 cm of the puncture site;<br>5. Overlapping Common Femoral Vein and Femoral Artery at access site;<br>6. Placement of ipsilateral venous sheath during procedure;<br>7. Arterial access site located not at common femoral artery (e.g., on or below the bifurcation, above the lower border of the inferior epigastric artery, or above the pelvic brim);<br>8. More than one access site required;<br>9. Loss of distal pulses in the ipsilateral extremity during the procedure;<br>10. Subjects receiving unfractionated heparin with an ACT greater than 300 seconds in the absence of a glycoprotein IIb/IIIa inhibitor or greater than 250 seconds in the presence of a glycoprotein IIb/IIIa inhibitor (may wait to remove introducer sheath until ACT level reaches the target value);<br>11. Intra-procedural bleeding around sheath, or suspected intraluminal thrombus, hematoma, pseudoaneurysm, or AV fistula;<br>12. Systemic hypertension (BP greater than 180/110 mmHg) or hypotension (BP less than 90/60 mmHg) prior to randomization;<br>13. Length of the tissue tract, the distance between the anterior arterial wall and skin, is estimated to be less than 2.5 cm;<br>14. If the physician deems that a different method should be used to achieve hemostasis of the arterial site or that the subject should not attempt ambulation according to the protocol requirements. |

## *5.2. Withdrawal of Subjects*

While study withdrawal is discouraged, patients may withdraw from the study at any time, with or without reason and without prejudice to further treatment. In all cases of withdrawal, the reason(s) for withdrawal (if given) will be recorded upon study termination.

In addition, the investigator may withdraw the subject due to any of the following situations:

- adverse event
- any other reason determined by the investigator to be in the best interest of the subject.

Subjects withdrawn from the trial prior to hemostasis (e.g., after randomization and prior to deployment of the collagen plug) should be converted to conventional means (manual compression) to achieve hemostasis. Subjects withdrawn due to an adverse event should be followed until the event has been resolved or is stable, if at all possible.

# 6. Written Informed Consent

Written Informed Consent must be obtained for all patients who are potential study candidates before any study-specific tests or procedures are performed.

Patients who meet general entry criteria will be asked to sign the study-specific, Institutional Review Board (IRB) -approved Informed Consent form before any study-specific tests or procedures are performed. Study personnel should explain that even if a patient agrees to participate in the study and signs an informed consent form, the Cardiva VASCADE™ Vascular Closure System may demonstrate that the patient is not a suitable candidate for the study.

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

# 7. Study Procedures and Enrollment

## *7.1. Duration of Subject Participation*

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

## *7.2. Enrollment*

Subjects that meet the pre-operative inclusion/exclusion criteria will be invited to participate in the trial and sign the Institutional Review Board (IRB) or Ethics Committee (EC) approved informed consent form. All subjects must provide written informed consent before undergoing any trial related activity.

At the completion of the endovascular procedure, subjects that meet all the intra-operative eligibility criteria will be enrolled in the trial and randomized to use either the Vascular Closure System or manual compression for access site hemostasis. Once a subject has been randomized, he or she is considered enrolled into the study. An Enrollment Notification eCRF must be completed and submitted within 24 hours to notify Sponsor of enrollment.

## 7.3. Visit Schedule

The following page outlines the required study assessments.

**Table 1. Study Event Schedule**

| | Within 1 month Before Procedure | Within 1 week Before Procedure | Procedure | Post-Procedure/ Hospital Discharge | 1-Month (30 days) ± 7 days |
|---|---|---|---|---|---|
| Study Initiation: | X | | | | |
| Demographics/ Medical History | X | | | | |
| Physical Examination | X | | | | |
| Clinical Status evaluation | X | | | | |
| Groin assessment | | | X | X | X |
| Neurologic assessment of ipsilateral limb | X | X | | X | X |
| Laboratory Tests*: | | X | | | |
| Inclusion / Exclusion Criteria Assessment | | X | | | |
| Informed Consent | | X | | | |
| Intra-procedural exclusion | | | X | | |
| Randomization and Intent to Treat | | | X | | |
| TTH determination | | | | X | |
| TTA determination | | | | X | |
| TTDE determination | | | | X | |
| Adverse Events | | | X | X | X |
| Ultrasound (100 subjects) | | | | X | |

*For subjects on warfarin, INR should be taken within 24 hours before procedure

## 7.4. Study Procedures

### 7.4.1. Pre-Operative

Prior to the subject's scheduled procedure, obtain a medical history and record the subject's demographic (age, race, sex and date of birth) and baseline information (height, weight, and systolic/diastolic blood pressure,). In addition, the presence/absence of previous arterial puncture site in ipsilateral groin > 30 days before procedure, and the presence/absence of non-severe peripheral vascular disease will be recorded. Subjects will be evaluated for any significant previous history of lower extremity neuropathy in the ipsilateral limb, including an assessment of etiology, existing symptoms and severity. Within 7 days prior to the planned procedure date, obtain serum blood tests:

- Creatinine
- Platelet count
- Hemoglobin and hematocrit

Within 24 hours of the procedure, obtain an INR for subjects on warfarin.

### 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 randomization, record the blood pressure, heart rate and any pre-operative anticoagulants or antiplatelet agents administered. Record the following procedure information:

- procedure type (diagnostic or interventional)
- procedure target (coronary, peripheral or other)
- access site location
- diameter, length and manufacturer of the introducer sheath
- intra-operative anticoagulants or antiplatelet agents
- assessment of peripheral pulses
- activated clotting time (ACT) at the end of the of the catheterization procedure for subjects receiving heparin

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 to verify the intra-operative eligibility criteria. For subjects receiving heparin, obtain an activated clotting time (ACT) and record the results prior to sheath removal. (SEE FLOW CHART ON PAGE 18.)

### 7.4.3. Intra-Operative Randomization

Once it has been determined that the subject does not meet any of the intra-operative exclusion criteria, the subject is eligible for randomization.

Randomizations will be stratified by investigational site and procedure type: diagnostic vs. interventional. The same approximate number of diagnostic and interventional procedures are planned. At least 50% of the patients enrolled will be undergoing interventional procedures. At each investigational site, variable block randomizations will be performed separately for each procedure type via sealed envelopes. There will be a 2:1 randomization ratio for Cardiva VASCADE™ VCS vs. manual compression for access site closure.

### 7.4.4. Access Site Closure

Treatment Arm Guidelines

If the subject is randomized to receive the Vascular Closure System, it should be deployed following the procedure in the Instructions for Use (IFU) provided in Attachment 3. While performing the procedure, record the following information:

- **T1:** time of sheath insertion

- **T2:** time endovascular procedure is completed (i.e., last guide catheter removed)
- **T3:** device insertion
- **T4:** time of the introducer sheath removal*
- **T5:** time that disc is assessed by fluoroscopy
- **T6:** time the covering sleeve was removed exposing the collagen patch
- **T7:** time the device (VCS) is removed
- **T8:** time that hemostasis was achieved
- **T9:** time that hemostasis (T8) was confirmed for 5 minutes

- Any complications that were observed.

*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 as described below.

Manual Compression Guidelines:

- Apply manual compression per institutional standard of care. While performing the procedure, record the following information:
- **C1:** time of sheath insertion
- **C2:** time endovascular procedure is completed (i.e., last guide catheter removed)
- **C3:** time of introducer sheath removal
- **C4**: time that hemostasis was achieved
- **C5:** time that hemostasis (C4) was confirmed for 5 minutes

- Any complications that were observed.

Adjunctive Compression Guidelines (both treatment arms):

- 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, pressure dressings, and light manual pressure) may be used to manage oozing. All methods to control oozing should be documented on the appropriate electronic case report form.

### 7.4.5. Post-Operative

After hemostasis is achieved, the access site should be monitored every 15 minutes for the first hour (for both interventional and diagnostic subjects) and then every 30 minutes for the second hour to confirm hemostasis in the interventional arm.

Post-procedure, record the following information:

- **T10:** Time to ambulation
- **T11:** Time to eligibility for hospital discharge based upon access closure site
- **T12:** Time to hospital discharge
- **C6:** Time to ambulation
- **C7:** Time to eligibility for hospital discharge based upon access closure site
- **C8:** Time to hospital discharge

Record the date and time the subject was able to ambulate 20 feet without assistance (T10 & C6). Record the date and time the subject was eligible for discharge (T11 & C7) and the date and time the subject was discharged (T12 & C8). Record any post-operative anticoagulants or antiplatelet agents administered.

VASCADE™ VCS Ambulation Guidelines:

- Diagnostic cases: Bed rest for 1-2 hours, then ambulate if stable. Re-check groin after 20 minutes to verify bleeding status.
- Interventional cases: Bed rest for 3-4 hours, then ambulate if stable. Re-check groin after 20 minutes to verify bleeding status.

Manual Compression Ambulation Guidelines:

- Follow institutional guidelines for ambulation. Re-check groin after 20 minutes to verify bleeding status.

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. These data will be captured in the Case Report Forms.

## 7.5. Follow-up

A subset of 100 subjects at selected sites will have an ultrasound of the femoral access site performed and a digital image recorded prior to hospital discharge.

Subjects should return to the clinic 30 ± 7 days following their endovascular procedure. 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. These data will be captured in the Case Report Forms.

In the event of refusal to return to the clinic, a telephone follow-up may be completed. Subjects withdrawn due to an adverse event should be followed until the event has been resolved or is stable.

### 7.6. Study Exit

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

## 8. Assessment of Effectiveness and Safety

### 8.1. Primary Effectiveness Endpoint

Time to hemostasis (TTH): 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 (see flow chart). The time to hemostasis will be measured in hour (hh):minutes (mm):seconds (ss). (TTH = T8 – T7 for treatment arm and TTH = C4 – C3 for control arm)

### 8.2. Secondary Effectiveness Endpoints

Time to ambulation (TTA): Elapsed time between device removal, i.e. device removal for Cardiva VASCADE™ VCS and sheath removal for manual compression, and when subject stands and walks 20 feet without evidence of arterial re-bleeding from the access site. The time to ambulation will be measured in hh:mm. (TTA = T10 – T7 for treatment arm and TTA = C6 – C3 for control arm)

Time to discharge eligibility (TTDE): Elapsed time between device removal, i.e. device removal for Cardiva VASCADE™ VCS and sheath removal for manual compression, and removal and when subject is medically able to be discharged based solely on access site assessment. Time to discharge eligibility will be measured in hh:mm. (TTDE = T11 – T7 for treatment arm and TTDE = C7 – C3 for control arm)

Time to hospital discharge (TTHD): Elapsed time between device removal, i.e. device removal for Cardiva VASCADE™ VCS and sheath removal for manual compression, and when subject is actually discharged from the hospital discharge, as recorded on the discharge order. Time to discharge will be measured in hh:mm. (TTHD = T12 – T7 for treatment arm and TTHD = C8 – C3 for control arm)

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.

Procedure Success: defined as attainment of final hemostasis using any method and freedom from major vascular complications through 30 days.

## 8.3. Primary Safety Endpoint

The primary safety endpoint is the 30-day rate of combined access site-related major complications. Major complications include:

- Access site-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. This compromised blood flow is documented by subject symptoms, physical exam and/or a decreased or absent blood flow on lower extremity angiogram.;
- Access site-related infection requiring intravenous antibiotics and/or extended hospitalization;
- New onset access site-related neuropathy in the ipsilateral lower extremity requiring surgical repair;
- Permanent access site-related nerve injury. (> 30 days)

## 8.4. Secondary Safety Endpoint

The secondary safety endpoint is the 30-day rate of combined access site-related minor complications. Minor complications include:

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

# 9. Statistical Considerations

## *9.1. Analysis Populations and Data Handling Conventions*

### 9.1.1. Effectiveness

According to the Intent-to-Treat (ITT) principle, all randomized subjects will be included in all effectiveness analyses and analyzed according to the randomization treatment assignment, regardless of actual treatment deviations.

### 9.1.2. Safety

All subjects who receive any portion of the Cardiva VASCADE™ VCS device treatment or manual compression control treatment as randomized will be included in safety analysis for between-arm comparisons according to the randomized treatment assignment. Subjects who do not receive any portion of the randomized treatment, i.e. randomized to Cardiva VASCADE™ VCS but receive manual compression instead (e.g. by error or investigator choice) or vice versa, will be excluded from between-arm safety comparisons. Adverse events experienced by such subjects and roll-in-subjects will be described separately.

### 9.1.3. Missing Data

Missing data will not be imputed by any method. However sensitivity analyses using the best-case, neutral, and worst-case imputations, i.e. assuming all missing data for VCS are 'failures' and all for manual compression are 'successes', for missing data will be performed for the primary safety and effectiveness analyses. If results of the worst case imputations differ qualitatively from those with available data only in terms of statistical significance, 'Tipping Point' analyses will be performed. That is, all possible imputations will be attempted to identify the 'change point' scenarios.

## *9.2. Statistical Analysis Plan*

### 9.2.1. Baseline Subject Characteristics

Subject demographics, baseline characteristics and medical history will be summarized descriptively by treatment groups. Mean and standard deviation will generally be reported for continuous variables; median and range may be reported instead if the data distribution is skewed. Frequencies and proportions will be reported for categorical variables.

### 9.2.2. Effectiveness

#### 9.2.2.1. Primary Effectiveness (TTH) Analysis

The primary effectiveness endpoint is time to hemostasis (TTH) as defined in Section 8.1. Non-randomized roll-in patients will not be included in this analysis. Summary statistics

for TTH (mean, standard deviation, median, minimum, and maximum) will be reported by treatment arm for the entire randomized study sample (ITT) and by the randomization stratification factor (i.e. procedure type: diagnostic vs. interventional). The proportions of Cardiva VASCADE™ VCS subjects converted to manual compression will also be reported.

The main effectiveness analysis will be based on the mean TTH. A regression analysis will be performed with TTH as the outcome and treatment arm and procedure type indicators as the independent variables. A 1-sided $p<0.025$ for the treatment indicator favoring the Cardiva VASCADE™ VCS (i.e. shorter TTH) will be regarded as a successful demonstration of the superiority of the Cardiva VASCADE™ VCS' overall effectiveness over manual compression.

9.2.2.2 Secondary TTH Analysis

Mean TTH will be further compared between the two treatment groups separately for diagnostic and interventional procedures. This comparison will be done by the t test. Symbolically, the statistical hypotheses to be tested for each of the two procedure types are:

$H_0$: Cardiva VASCADE™ VCS mean TTH $\geq$ manual compression mean TTH

$H_A$: Cardiva VASCADE™ VCS mean TTH $<$ manual compression mean TTH

For each procedure, the rejection of $H_0$ in favor of Cardiva VASCADE™ VCS at an overall 1-sided 0.025 significance level using the Hochberg multiple testing approach[1] (see 9.2.2.3) will be considered evidence for Cardiva VASCADE™ VCS' superior effectiveness over manual compression.

In addition, without hypothesis testing, the proportions of subjects achieving arterial hemostasis will be descriptively reported by treatment arm at fixed time points both overall and for each type of procedure (e.g. 1 minute, 5 minutes, 10 minutes, 15 minutes, etc.).

9.2.2.3 Secondary Effectiveness Endpoints Analyses

Besides TTH, other secondary effectiveness endpoints include time to ambulation (TTA), time to discharge eligibility (TTDE), time to hospital discharge (TTHD), and proportions of device success and procedure success as defined in 8.2.

Analyses and statistical hypothesis testing for TTA will be the similar to those for the primary effectiveness endpoint TTH as specified in 9.2.2.1. TTDE, TTHD, and proportions of patients achieving device and procedure success will be descriptively reported for Cardiva VASCADE™ VCS and manual compression arms without hypothesis testing.

As described in 9.2.2.2, statistical significance evaluations of the three secondary efficacy analyses, i.e. TTH separately for diagnostic and interventional procedures and

[1] Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance, 1988. Biometrika 75: 800-802.

TTA for the entire ITT sample, will follow the Hochberg approach with an overall 1-sided type I error rate of 0.025.

### 9.2.3. Safety

Primary Safety Analysis

The primary safety analysis will be based on the 30-day incidence rate of combined major access site closure complications (see 8.3) for the entire safety study sample per 9.1.2. The statistical hypotheses are as follows.

$H_0$: Cardiva VASCADE™ VCS rate – manual compression rate $\geq$ 5%

$H_A$: Cardiva VASCADE™ VCS rate – manual compression rate < 5%

A 95% confidence upper limit based on the Wilson score intervals for individual proportions[10] will be constructed for the VCS – manual compression rate difference. The VCS' major complications rate will be considered non-inferior to that of the manual compression if this 95% confidence upper limit is <5%, i.e. if $H_0$ is rejected.

Though multiple occurrences of major complications in the same subject are unlikely, the following event-based safety analysis will also be conducted. For each access site closure related major complications, (a) the total numbers of event occurrences, (b) numbers and proportions of subjects with 0, 1, 2, 3 or more event occurrences, and (c) number and proportion of subjects with any event occurrence, will be tabulated by treatment arms. The same will be done for the combined occurrences of all access site closure related major complications. For each major complication and the combined occurrences of all closure related major complications, the incidence rates in (b) will be compared between treatment arms by both the exact Mantel-Haenszel test for ordinal data[1] and the exact Wilcoxon's test using SAS® 9.1. Scores of 0, 1, or 2 will be assigned to patients with 0, 1, or 2 event occurrences respectively. A score of 3 will be assigned to those with 3 or more event occurrences; such occurrences are expected to be rare, if any. In this application, the Mantel-Haenszel test amounts to comparing the mean scores between the two treatment groups. Two-sided p values from both Mantel-Haenszel and Wilcoxon's tests will be provided for information purposes only and not as pass/fail criteria.

The rates in (c) will be compared by the Fisher's exact test.

In addition, the numbers and proportions of subjects with 0 major access site closure complications, 1 major complication, 2 different major complications, 3 different major complications, etc, will also be tabulated. The incidence rates will be similarly compared between treatment arms by the exact Mantel Haenszel and Wilcoxon tests. A by-patient listing of the actual events reported will be provided in conjunction.

[1] Mantel N and Haenszel W. *Statistical aspects of the analysis of data from retrospective studies of disease.* Journal of the National Cancer Institute 22, 719-748.

Secondary Safety Analysis

Event-based analysis will also be conducted on access site closure related minor complications as described in 8.4. Reporting and analyses (p values) of the minor complications will be similar to those for the major complications. Non-inferiority testing will not be conducted for minor complications.

Serious Adverse Events (SAEs) will be reported on a per patient basis; comparisons will be made between treatment groups when the number of events warrants an analysis.

Due to the multiplicity of hypothesis testing in secondary safety analyses (both major and minor complications and potentially the SAE's), the overall false positive identifications of event rate differences would be inflated if statistical significance is defined by the typical $\alpha<0.05$. However, the Bonferroni type of corrections assuming test independence would result in under-detection of differences because the comparisons will be highly correlated, e.g. between (b) and (c) above and between related complications. Because of these reasons and the difficulty in pre-specifying the between-comparison correlation values, we propose to use $p<0.01$ as a rough guideline of statistical significance. This approach would still result in an overall $\alpha$ that is greater than 0.05, but the higher false positive identification rate would be conservative and the bias would be towards more patient protection.

Additionally, patient-based rates will be reported by treatment group for all reported adverse events regardless of relationship to access site closure. The Fisher's exact p value will be presented for each event. Non-inferiority analyses will not be conducted.

### 9.2.4. Interim Analysis

When 50% of the safety results are available, i.e. with approximately 140 evaluable VCS subjects, an interim safety analysis will be performed for futility assessment only. Early termination due to results in favor of Cardiva VASCADE™ VCS will not be considered, therefore there will be no inflation of false positive error rate due to this interim analysis. Assuming no manual compression major complications, if $\geq$ 6/140 (4.3%) VCS subjects experience major access site-related complications, early study termination will be considered. If the true underlying complication rate is 2%, there is only a 0.06 chance of such an occurrence. Assuming the observed interim rate of 4.3% to be more representative of the true major complication rate, the chance of a successful demonstration of non-inferiority to manual compression at planned study completion is 6% or less.

## *9.3. Sample Size Justification*

Effectiveness

The following estimates are based on previous studies.

| Procedure Type | Estimated Mean ± SD TTH (min) | |
|---|---|---|
| | VCS | Manual Compression |
| Diagnostic | 4 ± 6 | 15 ± 6 |
| Interventional | 5 ± 17 | 27 ± 30 |

Combining the two types of procedures in a 1:1 ratio, the overall mean TTH difference between the two treatments is approximately 17. Roughly assuming the overall effect over standard deviation ratio to be 1, with an evaluable sample size of 420 (280 VCS, 140 manual compression) the power to detect a statistical significant difference at a 1-sided 0.025 level is >0.99.

Safety

Based on previous experience the VCS' overall major complication rate is estimated to be 2% or lower and the corresponding manual compression rate is close to 0%. With these assumptions, simulations were conducted using the R software for an evaluable sample size of 280 VCS subjects and 140 manual compression subjects. The power for the Newcombe 95% confidence upper limit to exclude 5% is approximately 0.89.

## 10. Data Management – Data Collection and Processing

Standardized eCRFs will be utilized by all participating sites using the Medrio platform. Conventional paper-based CRFs may also be used depending upon sites, eCRF availability and timing. Investigators are responsible for the accurate completion and timely submission of the data collected during the trial. All data from the trial will be entered into eCRFs via a secure, web-based system with password protection. Incoming data will be automatically reviewed to identify inconsistent or missing data and any adverse events. Any data issues are to be promptly addressed with the investigator by the CRO. Quality assurance procedures will be established to ensure that complete, accurate and timely data are submitted, that protocol requirements are followed and that complications, adverse events and adverse device effects are correctly reported and investigated, as appropriate. Investigators are to maintain all source documents as required by the protocol, including laboratory results, supporting medical records, and signed Informed Consent forms. The source documents will be used during the regular monitoring visits to verify information from the database against data contained on the completed eCRFs.

The Principal Investigator must maintain detailed records on all subjects who sign the Informed Consent and begin the pre-procedure evaluation. Data for enrolled subjects will be entered into eCRFs provided by the Sponsor. All data should be entered completely, promptly and legibly. For source documents, corrections should be made in a manner that does not obscure or eliminate the original error, by striking through the original data with one line, and initialing and dating the change, along with the reason for the change (if not obvious).

Study Exit eCRFs are completed for all enrolled subjects, regardless if they did or did not complete the trial (e.g., subject discontinuation, trial termination).

# 11. Monitoring Procedures

## *11.1. Monitoring*

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

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

Phone contacts and site visits will be conducted to ensure that the protocol is being followed and that any protocol deviations are properly documented. Clinical monitoring will include a verification that Informed Consent was properly obtained for all enrolled trial participants, a review of clinical records for accuracy and completeness, resolution of missing or inconsistent results and a review of source documents. The clinical monitor will verify that the Case Report Forms (eCRFs) are in agreement with the source documentation and other records. The investigator will make available to the clinical monitor for review all Informed Consent documents, Internet access to completed eCRFs, source documentation, original laboratory data and other relevant records for all enrolled subjects at the site. It is important that the investigator and other relevant site personnel are available for consultation with the clinical monitors during the monitoring visits and that sufficient time is devoted at the site to the monitoring process.

Additionally, telephone and/or e-mail contact will be conducted on a regular basis with the investigator and the site staff to ensure that the protocol is being followed and to address any issues that may occur during the course of the trial.

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

## *11.2. Investigational Device Distribution and Accountability*

### 11.2.1. Investigational Device Distribution

Cardiva Medical will control the distribution of the investigational devices. Each investigational site will be responsible for ordering the investigational devices for the

study. The Investigator is responsible for ensuring that the devices are ordered for shipment to arrive at the hospital before the procedure date.

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

### 11.2.2. Device Accountability

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

### 11.2.3. Return of Materials Upon Study Termination

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

IMPORTANT: Please note that the devices must be labeled with a "BIOHAZARD" sticker if there is reasonable belief that the device has come in contact with blood or infectious substances that are known or are believed to cause disease in animals or humans.

# 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 trial personnel on the protocol, the completion of the eCRFs, and trial procedures
- Communicate regularly with site personnel via mail, email, telephone, and/or fax
- Make periodic visits to the trial sites.

During those visits, the Sponsor or its representatives will monitor the subject data recorded in the eCRFs against source documents at the trial site.

### 12.2. Physician Training

Prior to enrolling subjects in the trial, investigators will be provided didactic training on the procedural steps required to use the Vascular Closure System. Physicians who have not previously used the device will receive training with a Sponsor-designated proctor using a benchtop model to simulate the closure procedure. In addition, physicians may enroll up to two (2) roll-in subjects prior to commencement of randomization. Investigators will be notified in writing when they have successfully completed the roll-in requirements and are eligible to randomize subjects into the trial. These roll-in subjects will be followed in the same fashion as the randomized subjects and evaluated for safety as a separate subject cohort.

### 12.3. Audits and Inspections

The Principal Investigator for the site will also allow representatives of the governing IRB or EC, the United States Food and Drug Administration (FDA), and other applicable regulatory agencies to inspect all trial records, CRFs, and corresponding portions of the subject's office and/or hospital medical records at regular intervals throughout the trial. These inspections are for the purpose of verifying adherence to the protocol, completeness and exactness of the data being transcribed onto the CRF, and compliance with FDA or other regulatory agency regulations.

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

## 13. Adverse Events

### 13.1. General

All adverse events (AE) and serious adverse events (SAE) will be monitored from the time of randomization through the 1-month follow-up visit.

An AE is defined as any undesirable clinical occurrence in a patient whether or not it is considered to be device related. In addition, the definition of AE applies to any event with an onset post study procedure or to any underlying diseases, present at baseline, that exacerbate in severity post study procedure. Therefore, an underlying disease that was present at the time of enrollment is not reported as an AE, but any increase in the severity of the underlying disease is to be reported as an AE. This definition includes events occurring during the follow-up period.

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

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

Mild: Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs or symptoms are transient.

Moderate: Interferes with the subject's usual activity and/or requires symptomatic treatment.

Severe: Symptom(s) causing severe discomfort and significant impact of the subject's usual activity and requires treatment.

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

- Death due to any cause
- Life-threatening condition
- Results in persistent or significant disability/incapacity
- Requires in-patient hospitalization or prolonged hospitalization
- Necessitates an intervention to prevent a permanent impairment of a body function or permanent damage to a body structure
- Results in congenital abnormality

All SAE's will be reported.

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

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

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

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

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

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

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

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

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

## *13.2. Reporting of Serious and Non-Serious Adverse Events*

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

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

In the case of serious adverse events, procedure and/or device observations and malfunctions, medical record documentation (e.g. procedure notes, operative notes,

discharge summary, relevant progress notes, imaging or lab studies) must be provided to Cardiva Medical or its designee.

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

- The Adverse Event eCRF must be electronically signed by the Investigator or Co-Investigator.
- It is the responsibility of the Investigator to inform their IRB/EC of serious adverse events as required by their IRB/EC procedures and in conformance with FDA and local regulatory requirements.

All serious adverse events must be reported by the Investigator (or designee) to the sponsor, within 24 hours of learning of the adverse event via eCRF. The Cardiva Medical contact information for questions is:

| | |
|---|---|
| Sponsor: | Cardiva Medical, Inc.<br>888 West Maude Avenue<br>Sunnyvale, CA 94085<br>**Telephone: 408-470-7100**<br>Fax: 408-212-9889 |
| Contact: | Marlys Chellew, BSN, MBA<br>Consulting Vice President, Clinical Affairs<br>**Mobile: 916-303-0879** |

### 13.3. Device Failures and Malfunctions

All reported device observations, malfunctions or failures of the Cardiva VASCADE™ VSC are required to be documented in the eCRF. In the event of a suspected observation or device problem, the investigational device shall be returned to the Sponsor for analysis. Device failures and malfunctions should also be documented in the patient's medical record. Instructions for returning the investigational device are included in the Study Reference Manual.

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

## 14. Study Committee

### 14.1. Clinical Events Committee / Data Safety Monitoring Board

An independent combination Clinical Events Committee (CEC) and Data Safety Monitoring Board (DSMB) (the same group) shall be responsible for systematic review and adjudication of all reported deaths, major and minor vascular complications, and all potentially device- or procedure-related adverse events. In order to enhance objectivity

and reduce the potential for bias, the CEC/DSMB members shall be independent of the Sponsor as well as the investigational sites/ investigators.

Members shall consist of at least three (3) independent physicians, with experience in interventional cardiology procedures and a statistician.

The methodology for performing these responsibilities shall be developed and outlined in the Adjudication Charter. Operational provisions shall be established to minimize potential bias. In the case of an SAE with associated imaging, the CEC/DSMB may review imaging assessments to assess the reported event.

The CEC/DSMB will recommend study termination if safety concerns warrant such action. The DSMB will establish guideline criteria for recommending study termination, to the extent that it is possible for the DSMB to predict adverse events or outcomes, before the proposed study begins. The DSMB will meet at least 2 times during the study in order to assure close and timely monitoring of adverse events and outcomes.

# 15. Ethical Considerations

## *15.1. Trial Conduct & the Declaration of Helsinki*

The trial will be performed in accordance with the relevant parts of Title 21 CFR Parts 812, 50, 54, 56 and ISO 14155-1 / 14155-2.1; the ICH Guidelines for Good Clinical Practices (E6), the Declaration of Helsinki, and any regional and/or national regulations.

## *15.2. Institutional Review Board/Ethics Committee*

A copy of the protocol, proposed Informed Consent form, other written patient information and any proposed advertising material must be submitted to the IRB/IEC for written approval. A copy of the written IRB/IEC approval of the protocol and Informed Consent form must be received by Cardiva Medical, Inc before recruitment of patients into the study and shipment of investigational product.

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

The Investigator will be responsible for obtaining annual IRB/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.

## 15.3. Informed Consent Form

A sample Informed Consent form is provided in Section 21 Attachment 2 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.

The reviewing IRB/IEC and the sponsor must first approve the Informed Consent forms that are used. The Informed Consent forms that are used should be in accordance with the current guidelines as outlined by the Good Clinical Practices (GCP) guidelines, Declaration of Helsinki and the International Conference on Harmonization (ICH).

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

Written Informed Consent must be recorded appropriately by means of the patient's, or their legal representative's dated signature. The patient will receive a copy of the Informed Consent form.

## 15.4. Amending the Protocol

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

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

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

Cardiva Medical may make certain administrative changes to the protocol without prior approval of the FDA or IRB. Cardiva Medical will notify all investigative sites of such changes to ensure the study continues to be conducted consistently across all sties. The site IRB's will be notified of these changes.

## 15.5. Emergency Actions

Cardiva Medical, Inc accepts the right of the Investigator to deviate from the protocol in an emergency when necessary to safeguard the life or the physical well being of a study patient. The Investigator must give notice of any emergency deviations and justification

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

## 15.6. Protocol Deviations

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

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

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

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

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

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

## 15.7. Coverage of Expenses

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

## 15.8. Confidentiality

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

that may be published in abstracts, scientific journals, or presented at medical meetings will reference a unique subject code and will not reveal the subject's identity. The Sponsor and their CRO representative will make every reasonable effort to protect the confidentiality of the subjects participating in the trial.

# 16. Study Administration

Cardiva Medical, Inc will make necessary efforts to ensure that this study is conducted in compliance with GCPs and all applicable regulatory requirements.

## *16.1. Pre-Study Documentation Requirements*

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

- Signed and dated Investigator Agreement
- A copy of the written IRB/IEC approval of the protocol
- A copy of the written IRB/IEC approval of the Informed Consent Form
- A copy of the curriculum vitae of the Principal Investigator and Co-Principal Investigator (if applicable)

## *16.2. Source Documentation*

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

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

- The date the subject entered the trial and the subject number
- The trial protocol number and the name of the Sponsor
- The date that informed consent was obtained
- Evidence that the subject meets trial eligibility requirements (e.g., medical history, trial procedures and/or evaluations)
- The dates of all trial related subject visits
- Evidence that required procedures and/or evaluations were completed
- Use of any concurrent medications
- Documentation of specific device used, if any
- Occurrence and status of any Adverse Events
- The date the subject exited the trial, and a notation as to whether the subject completed the trial or was discontinued, including the reason for discontinuation.

## *16.3. Record Retention*

The Investigator will maintain all essential trial documents and source documentation, in original format, that support the data collected on the study patients in compliance with

the ICH/GCP guidelines. Documents must be retained for at least 2 years after the last approval of marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with Cardiva Medical, Inc or in compliance with other regulatory requirements. When these documents no longer need to be maintained, it is Cardiva Medical's responsibility to inform the Investigator. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility. Cardiva Medical, Inc must receive written notification of this custodial change.

## 16.4. Criteria for Terminating Study

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

Possible reasons for study termination include:

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

## 16.5. Criteria for Suspending/Terminating a Study Center

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

Possible reasons for suspending/terminating a study center include:

- Repeated failure to complete electronic case report forms prior to scheduled monitoring visits.
- Failure to obtain written Informed Consent.
- Failure to report CEC Events/SAE/UADE to Cardiva Medical, Inc. within 24 hours of knowledge.
- Loss of (or unaccounted for) investigational product inventory.

## 16.6. Investigator Responsibilities

- Agree to sign and adhere to the Investigator Agreement
- Agree to participate in Investigator meetings as scheduled by Cardiva Medical, Inc
- Be willing to provide required assessments for analysis

- Be willing to perform and be capable of performing treatment procedures as outlined in this protocol
- Comply with all required elements of this protocol (e.g., perform testing and follow-up as specified, especially during personnel transitions) and supply material suitable for quantitative analysis
- Agree to obtain written Informed Consent before any study specific procedures are performed in accordance with GCP
- Complete all electronic data modules prior to scheduled monitoring visits
- Be willing to change hospital routine if required by protocol (as long as patient safety and well-being is not compromised)
- Adhere to all relevant Ultrasound Core Laboratory requirements

# 17. Publication Policy

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

The data generated by this clinical trial are the property of the Sponsor, Cardiva Medical, Inc., and should not be disclosed without their prior written permission. These data may be used by the Sponsor now and in the future for presentation or publication at Sponsor's discretion or for submission to governmental regulatory agencies. The Principal Investigators may publish or present the trial results with prior consent of the Sponsor, but will not disclose confidential information. Prior to submission by a Principal Investigator for publication or presentation, the Sponsor will be provided with the opportunity to review the submission for confidential information and accuracy.

# 18. Regulatory Considerations

## *18.1. Role of Cardiva Medical*

As the sponsor of this clinical study, Cardiva Medical has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the Food and Drug Administration (FDA). In this study, Cardiva Medical will have certain direct responsibilities and will delegate other responsibilities to Consultants. Together, both Cardiva Medical and its Consultants will ensure adherence to the sponsor's general duties (21 CFR 812.40), selection of Investigators (21 CFR 812.43), monitoring

(21 CFR 812.46), supplemental applications (21 CFR 812.35 (a) and (b)), maintaining records (21 CFR 812.140 (b)), and submitting reports (21 CFR 812.150 (b)).

## 18.2. General Duties [21 CFR 812. 40]

The sponsor's general duties consist of submitting the IDE application to FDA, obtaining FDA and IRB approvals prior to shipping the devices, selecting qualified Investigators and shipping devices only to those qualified Investigators. As the sponsor, Cardiva Medical is also required to obtain signed study agreements, to provide the Investigators with the information necessary to conduct the study and adequate on-site training to conduct the trial, to ensure proper clinical site monitoring, and to provide the required reports to the Investigators, IRB's and FDA.

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

## 18.3. Monitoring [21 CFR 812. 46]

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

The sponsor will review significant new information, including unanticipated serious adverse events and ensure that such information is provided to the FDA, the Investigators and to all reviewing IRB's.

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

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

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

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

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

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

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

The sponsor, Ultrasound Core Lab, and clinical sites will maintain all records pertaining to this study for a period of two years following: the date on which the investigation is terminated or completed, or the date that the records are no longer required for purposes of supporting a pre-market approval application. Record retention dates will be provided to all concerned by the sponsor.

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

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

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

## 19. Abbreviations and Definitions

### 19.1. Abbreviations

| | |
|---|---|
| ACT | Activated clotting time |
| AE | Adverse Event |
| AV | Arteriovenous |
| CABG | Coronary Artery Bypass Graft Surgery |
| CEC | Clinical Events Committee |
| CFR | Code of Federal Regulations |
| eCRF | Electronic Case Report Form |
| CV | Curriculum Vitae |
| DSMB | Data Safety Monitoring Board |
| FDA | Food and Drug Administration |
| Fr | French |
| Hgb | Hemoglobin |
| Hct | Hematocrit |
| IDE | Investigational Device Exemption |

| | |
|---|---|
| IFU | Instructions for Use |
| INR | International Normalized Ratio |
| IRB | Institutional Review Board |
| LMWH | Low molecular weight heparin |
| MDR | Medical Device Reporting |
| PTCA | Percutaneous Transluminal Coronary Angioplasty |
| SAE | Serious Adverse Event |
| TTA | Time to Ambulation |
| TTH | Time to Hemostasis |
| TTDE | Time to Eligibility for Discharge |
| TTHD | Time to Hospital Discharge |
| UADE | Unanticipated Adverse Device Event |

## 19.2. Definitions

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

ACCESS SITE-RELATED BLEEDING REQUIRING TRANSFUSION
Bleeding originating from the 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 REACHIEVE HEMOSTASIS

Bleeding from the access site, occurring at any time, requiring greater than 30 consecutive minutes of standard compression to re-achieve hemostasis.

ACCESS SITE-RELATED INFECTION REQUIRING INTRAVENOUS ANTIBIOTICS 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-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 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. |

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

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.

CLINICAL EVENTS COMMITTEE (CEC)
An independent committee established to review major complications. Members are not participants in the trial and are independent of Integrated Vascular Systems, Inc.

CO-INVESTIGATOR / SUB-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.

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).

DATA SAFETY MONITORING BOARD
An independent committee established to monitor the overall study status for safety concerns, recommendations for study continuation, discontinuation, or modification.

DEVICE FAILURE / MALFUNCTION
The device does not perform in accordance with the IFU.

DEVICE SUCCESS
Defined as the ability to deploy the delivery system, deliver the collagen, and achieve hemostasis with the Cardiva VASCADE$^{TM}$ 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).

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 investigation-related activities are actually conducted.

INVESTIGATOR
The person responsible for the conduct of the clinical investigation at an investigational site. If an investigation is conducted by a team of individuals at an investigational site, the Investigator is the responsible leader of the team and may be called the Principal Investigator. See also Co-Investigator.

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.

IPSILATERAL LOWER EXTREMITY ARTERIAL EMBOLI
Presence of emboli in the peripheral arterial system of the ipsilateral limb.

LATE ACCESS SITE-RELATED ARTERIAL BLEEDING (i.e., following hospital discharge) Re-bleeding from the puncture site following hospital discharge and up to 30 days post procedure.

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. The total amount of time that any *compression* is held at the arteriotomy site will be recorded for the purposes of this study.

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

NEW ONSET ACCESS SITE-RELATED NEUROPATHY IN THE IPSILATERAL LOWER EXTREMITY NOT REQUIRING SURGICAL REPAIR
New onset access site-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.

PAIN SCALE
The 11-point Box Scale (BS-11) is a pain assessment method using a numerically based scale allowing the subject to indicate the intensity of pain that he/she is experiencing during the use of the investigational device. The scale begins at 0 for "no pain" and has a maximum of 10 for "pain as bad as it could be."

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-RELATED NERVE INJURY (> 30 DAYS)
New onset access site-related nerve injury that persists for > 30 days following device removal.

PROCEDURE SUCCESS
Defined as attainment of final hemostasis using any method 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 is usually identified by angiography or ultrasound..

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

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

SERIOUS ADVERSE EVENT (SAE)
Any untoward medical occurrence that results in death, is life threatening, requires subject hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity.

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.

TRANSIENT LOWER EXTREMITY ISCHEMIA
New (acute) onset of compromised peripheral blood flow, documented by subject symptoms, physical exam and/or, a decreased or absent blood flow on lower extremity angiogram.

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

VASCULAR INJURY REQUIRING 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, thrombin injection, or other means).

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.

## 19.3. Bibliography

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3. Simon A, Bumgarner B, Clark K, et al. Manual versus mechanical compression for femoral artery hemostasis after cardiac catheterization. *Am J Crit Care* 1998;7:308-13.
4. Stuart M. An open market for vascular access closure devices. Start-Up 2004 May:18-26.
5. Kussmaul WG, Buchbinder M, Whitlow PL, et al. Rapid arterial hemostasis and decreased access site complications after cardiac catheterization and angioplasty; Results of a randomized trial of a novel hemostatic device. *J Am Coll Cardiol* 1995:25;1685-92.

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10. Newcombe RG, Interval Estimation for the Difference between Independent Proportions: Comparison of Eleven Methods. Statistics in Medicine 17, 873-890, 1998)

# 20. Attachment 1: Investigator Responsibilities, Records and Reports

## 20.1. Investigator Responsibilities

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

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

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

## 20.2. Investigator Records

CASE REPORT FORMS

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

SCREENING LOG

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

## 20.3. Investigator Reports

FINAL TRIAL REPORT

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

SERIOUS ADVERSE EVENTS (SAEs)

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

DEVICE MALFUNCTIONS

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

### WITHDRAWAL OF APPROVAL

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

# 21. Attachment 2: Sample Informed Consent Form

Insert sample informed consent form (or forms if any addendums)

# 22. Attachment 3: Instructions For Use (IFU)

# 23. Attachment 4: Declaration of Helsinki

**WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI**

**Ethical Principles for Medical Research Involving Human Subjects** Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

## A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

## B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the

subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

## C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

3. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

CARDIVA
MEDICAL, INC.

Date: 7/20/11

To: Document Control

From: Justin Ballotta JB 7/20/11

Subject: Signature Delegation

I, Justin Ballotta, authorize Terry Passarotti to sign all Document Change Notices, Validations, Non-Conforming Material Reports, and all other documents requiring my signature on 7/20/11 – 7/22/11

JB 7/20/11

## Rob Roland

**From:** Justin Ballotta
**Sent:** Wednesday, November 24, 2010 7:32 AM
**To:** Rob Roland
**Subject:** FW: Signature authority for Marlys Chellew

A copy for your records,
Justin

---

**From:** Marlys Chellew [mailto:mchellew@chellewclinical.com]
**Sent:** Wednesday, November 24, 2010 6:58 AM
**To:** Justin Ballotta
**Subject:** Signature authority for Marlys Chellew

Justin,

I'd like to delegate signature authority on my behalf to Diana Espinosa when I am not available to sign documents. This authority is effective as of November 22, 2010 and will continue until further notice.

Thanks,
Marlys Chellew