Clinical Investigation Plan (CIP) and Protocol

"THE AMBULATE TRIAL"

A MULTI-CENTER, RANDOMIZED CONTROLLED TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF THE CARDIVA MID-BORE VENOUS VASCULAR CLOSURE SYSTEM (VVCS) VS. MANUAL COMPRESSION FOR THE MANAGEMENT OF THE FEMORAL VENOTOMY AFTER CATHETER-BASED INTERVENTIONS PERFORMED VIA 6- 12 FR PROCEDURAL SHEATHS WITH SINGLE OR MULTIPLE ACCESS SITES PER LIMB

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

Sponsor:	CARDIVA Medical, Inc. 2900 Lakeside Drive, Suite 160 Santa Clara, CA 95054
Study Responsibility:	CARDIVA Medical, Inc. 2900 Lakeside Drive, Suite 160 Santa Clara, CA 95054
Principal Investigator:	Andrea Natale, MD – Co-Principal Investigator St. David's Medical Center, Austin, TX Steven Compton, MD – Co-Principal Investigator Alaska Heart Institute, Anchorage, AL Mintu Turakhia, MD – Institutional / Operational Principal Investigator Stanford Center for Clinical Research, Palo Alto, CA
Protocol Number:	PTL 0508
Study Centers:	See the study manual for a list of study centers
Version:	Version 03 Draft

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.

Protocol Approval Page

STUDY TITLE:	**"THE AMBULATE TRIAL"** **A MULTI-CENTER, RANDOMIZED CONTROLLED TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF THE CARDIVA MID-BORE VENOUS VASCULAR CLOSURE SYSTEM (VVCS) VS. MANUAL COMPRESSION FOR THE MANAGEMENT OF THE FEMORAL VENOTOMY AFTER CATHETER-BASED INTERVENTIONS PERFORMED VIA 6- 12 FR PROCEDURAL SHEATHS WITH SINGLE OR MULTIPLE ACCESS SITES PER LIMB**
PROTOCOL NUMBER:	PTL 0508
VERSION NUMBER:	03

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

Name/Title	Signature	Date
Justin Ballotta Chief Operating Officer	for JB. (See attached)	12/22/17
Zia Yassinzadeh Chief Technology Officer		12/22/17
Jennifer Lee Director, Quality & Engineering	for JL see attached	12/22/17
Terry Passarotti Director, Regulatory & Clinical Affairs		12/22/17
Marlys Chellew, BSN Independent Clinical Consultant	DocuSigned by: Marlys Chellew 55F5F3BE98F0465...	12/22/2017

Protocol Synopsis

"THE AMBULATE TRIAL"

A MULTI-CENTER, RANDOMIZED CONTROLLED TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF THE CARDIVA MID-BORE VENOUS VASCULAR CLOSURE SYSTEM (VVCS) VS. MANUAL COMPRESSION FOR THE MANAGEMENT OF THE FEMORAL VENOTOMY AFTER CATHETER-BASED INTERVENTIONS PERFORMED VIA 6- 12 FR PROCEDURAL SHEATHS WITH SINGLE OR MULTIPLE ACCESS SITES PER LIMB

Primary Objective	The objective of the trial is to demonstrate the safety and effectiveness of the Cardiva Mid-Bore Venous Vascular Closure System (VVCS) in sealing femoral venous access sites and providing reduced times to ambulation (TTA) compared with manual compression at the completion of catheter-based procedures performed through 6 – 12 Fr introducer sheaths.
Test Device	Cardiva Mid-Bore Venous Vascular Closure System (VVCS) – 6-12 Fr device with 21 Fr Disc (~7 mm)
Indication for Use	The Cardiva Mid-Bore Venous Vascular Closure System (VVCS) is indicated for the percutaneous closure of femoral venous access sites while reducing times to ambulation and discharge eligibility in patients who have undergone catheter-based procedures utilizing 6 – 12 Fr procedural sheaths, with single or multiple access sites per limb, ranging from a single access site in one limb to multiple access sites in both limbs.
Hypothesis	The Cardiva Mid-Bore VVCS provides TTA results that are less than manual compression by a clinically meaningful and statistically significant margin. The rate of major venous access site closure-related complications with the Cardiva Mid-Bore VVCS is non-inferior to the major complication rates of manual compression for sealing femoral venous 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 multiple femoral venous access sites and providing reduced times to ambulation compared with manual compression at the completion of catheter-based procedures performed through 6 - 12 Fr introducer sheaths. Only patients with multiple access sites will be enrolled in order to support the desired indication. Randomization will be stratified to account for patients with varying numbers of access sites in a 1:1 treatment device to control arm ratio to ensure treatment and control arms have the same proportion of access sites/patient, i.e. 3 access sites/patient vs. 4 access sites/patient.
Number of Patients	Approximately 204 prospectively randomized subjects, and up to 60 roll-in subjects
Number of Sites	Up to 20 sites U.S., with a minimum of 8 sites enrolling subjects in the trial.

Duration of Trial	Each enrolled subject will have an office visit at 30 days (± 7 days) post-procedure. Once all subjects have completed this visit, the study will be considered complete.
Ultrasound Sub-Study	At 3-5 select sites, a subset of 25 subjects each from the treatment and control arms will have an ultrasound examination of the bilateral access sites performed at the 30 day (± 7 days) office visit.
Primary Effectiveness Endpoint	Time to ambulation (TTA), defined as elapsed time between removal of the final Mid-Bore VVCS device (treatment arm) or removal of the final sheath (control arm) and when subject stands and walks 20 feet without evidence of venous re-bleeding from the femoral access site **(Per-patient analysis).**

Secondary Effectiveness Endpoints	• Time to discharge eligibility (TTDE), defined as elapsed time between removal of the final Mid-Bore VVCS device (treatment arm) or removal of the final sheath (control arm) and when subject is eligible for discharge based solely on the assessment of the access site, as determined by the medical team. **(Per-patient analysis)**
	• Time to discharge (TTD), defined as elapsed time between removal of the final Mid-Bore VVCS device (treatment arm) or removal of the final sheath (control arm) removal and when subject is discharged from the institution. **(Per-patient analysis)**
	• Procedural Endpoints:
	  ○ Time to Closure Eligibility (TTCE): defined as elapsed time between removal of the last procedural device for the index procedure [1]and removal of the first Mid-Bore VVCS device (treatment arm) or removal of the first sheath (control arm). **(Per-patient analysis).**
	  ○ Time to hemostasis (TTH), defined as elapsed time between removal of the Mid-Bore VVCS device (treatment arm) or removal of the sheath (control arm) and first observed and confirmed venous hemostasis, for each access site. **(Per-access site analysis)**
	  ○ Total Post-Procedure Time (TPPT): defined as elapsed time between removal of the last procedural device for the index procedure and when subject is able to successfully ambulate. **(Per-patient analysis)**
	• Procedure Success, defined as attainment of final hemostasis at all venous access sites and freedom from major venous access site closure-related complications through 30 days **(Per-patient analysis, both arms)**
	• Device Success, defined as the ability to deploy the delivery system, deliver the collagen, and achieve hemostasis with the Mid-Bore VVCS. **(Per-access site analysis, treatment arm only)**

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

[1] See Definitions section for 'last procedural device' definition.

	• Access site-related bleeding requiring transfusion; • Vascular injury requiring surgical repair; • Access site-related infection confirmed by culture and sensitivity, requiring intravenous antibiotics and/or extended hospitalization; • New onset permanent access site-related nerve injury (i.e., persisting for > 30 days); • New onset access site-related nerve injury in the ipsilateral lower extremity requiring surgical repair; • Pulmonary embolism requiring surgical or endovascular intervention and/or resulting in death, to be confirmed by CT pulmonary angiography, lung ventilation/perfusion scan (VQ scan) or autopsy; • Pulmonary embolism NOT requiring surgical or endovascular intervention and/or NOT resulting in death, to be confirmed by CT pulmonary angiography or lung ventilation/perfusion scan (VQ scan).
Secondary Safety Endpoint	On a **per-limb basis**, the rate of combined minor venous access site closure-related complications through 30 days post-procedure, attributed directly to the closure method (i.e., "device-related" with no other likely attributable cause): • Access site-related bleeding requiring greater than 30 minutes of continual manual compression to achieve initial venous hemostasis; • Access site-related hematoma > 6 cm documented by ultrasound; • Late access site-related bleeding (following hospital discharge); • Ipsilateral deep vein thrombosis, confirmed by ultrasound/imaging; • Localized access site infection confirmed by culture and sensitivity, treated with intramuscular or oral antibiotics; • Arteriovenous fistula requiring treatment; • Arteriovenous fistula not requiring treatment; • Pseudoaneurysm requiring thrombin injection, fibrin adhesive injection or ultrasound-guided compression; • Pseudoaneurysm not requiring treatment • Access site-related vessel laceration; • Access site-related wound dehiscence; • Transient access site-related nerve injury.
Pre-Operative Inclusion Criteria	1. 18 to 80 years of age; 2. Capable and willing to give informed consent; 3. Acceptable candidate for an elective, non-emergent catheter-based procedure via the common femoral vein(s) using a 6 to 12 Fr inner diameter introducer

	sheath, with a minimum of 3 and a maximum of 4 femoral venous access sites, and a maximum of 2 access sites/leg; 4. Able and willing to complete a 30 day +/- 7 days follow-up visit; 5. Acceptable candidate for emergent vascular surgery, and/or manual compression of the venous access sites; 6. A total of 50 subjects willing to undergo ultrasound evaluation at the 30 day +/- 7 day visit at select sites. 7. Anticipated prolonged bedrest (5 hours or longer) and / or overnight stay.

Pre-Operative Exclusion Criteria	Subjects will be excluded from participating in this study if they meet any of the following criteria prior to initiation of the index procedure: 1. Advanced refusal of blood transfusion, if it should become necessary; 2. Active systemic infection, or cutaneous infection or inflammation in the vicinity of the groin; 3. Pre-existing immunodeficiency disorder and/or chronic use of high dose systemic steroids; 4. Known history of bleeding diathesis, coagulopathy, hypercoagulability, or current platelet count < 100,000 cells/mm^3; 5. Severe co-existing morbidities, with a life expectancy of less than 12 months; 6. Currently involved in any other investigational clinical trial that may interfere with the outcomes of this study, in the opinion of the Investigator; 7. Femoral arteriotomy in either limb with any of the following conditions: a. access within < 10 days b. any residual hematoma, significant bruising, or known associated vascular complications c. use of a vascular closure device within the previous 30 days; 8. Femoral venotomy in either limb with any of the following conditions: a. access within < 10 days b. any residual hematoma, significant bruising, or known associated vascular complications c use of a vascular closure device 9. Any planned procedure involving femoral arterial or venous access in either limb within the next 30 days or prior to study exit; 10. Any history of deep vein thrombosis, pulmonary embolism or thrombophlebitis; 11. Significant anemia with a hemoglobin level less than 10 g/dL or a hematocrit less than 30%; 12. Renal insufficiency (i.e., serum creatinine of > 2.5 mg/dl); 13. Females who are pregnant, planning to become pregnant within 3 months of the procedure, or who are lactating; 14. Extreme morbid obesity (BMI greater than 45 kg/m2) or underweight (BMI less than 20 kg/m2); 15. Unable to routinely walk at least 20 feet without assistance; 16. Known allergy/adverse reaction to bovine derivatives; 17. Administration of low molecular weight heparin (LMWH) within 8 hours before or after the procedure; 18. Planned procedures or concomitant condition(s) that may extend ambulation attempts beyond 2-3 hours, and/or hospitalization time (e.g., staged procedure, serious co-morbidity), in the opinion of the Investigator.

Intra-Operative Exclusion Criteria	Subjects will be excluded from participating in this study if any of the following exclusion criteria occur during the index procedure: <u>General Intra-op Exclusion Criteria:</u> 1. Any attempt at femoral arterial access during the procedure; 2. Any procedural complications that may extend routine recovery, ambulation and discharge times; 3. If the physician deems that a different method should be used to achieve hemostasis of the venous access sites, or that the subject should not attempt ambulation according to the protocol requirements; 4. ALL venous access sites must comply with the following exclusion criteria immediately prior to randomization: a. Difficult insertion of procedural sheath or needle stick problems at the onset of the procedure (e.g., multiple stick attempts, accidental arterial stick with hematoma, "back wall stick", etc.) in any of the study veins; b. A procedural sheath < 6 Fr or > 12 Fr in inner diameter is present at time of closure; c. A procedural sheath > 12 Fr inner diameter at any time during the procedure. d. Venous access site location is noted to be "high", above the inguinal ligament (cephalad to lower half of the femoral head or the inferior epigastric vein origin from the external iliac vein); e. Intra-procedural bleeding around sheath, or suspected intraluminal thrombus, hematoma, pseudoaneurysm, or AV fistula; f. Length of the tissue tract, the distance between the anterior venous wall and skin, is estimated to be less than 2.5 cm.
Study Administration	
Data Management & Safety Committee Management	Stanford Center for Clinical Research (SCCR) 3172 Porter Drive, Palo Alto, CA 94304
Clinical Research Organization (CRO)	Chellew Clinical Outsourcing, LLC (CCO) 7844 E. Riverdale St., Mesa, AZ 85207
Academic Research Organization (ARO)	Stanford Center for Clinical Research (SCCR) 3172 Porter Drive, Palo Alto, CA 94304
Ultrasound Core Laboratory	Syntactx, LLC 4 World Trade Center 150 Greenwich Street, 44th Floor New York, NY 10007

Table of Contents

1. Introduction

1.1. Background and Rationale

Unmet Clinical Need:

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

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

1) discomfort and pain for the patient;

2) postponement of sheath extraction post-procedure which could lead to more discomfort, increased bleeding risk and discontinuation of anti-coagulation post-procedure;

3) risk of deep venous thrombosis; and

4) risk of failed closure due to inaccurate location of the manual compression site.

AMBULATE, A Clinical Investigation for Venous Closure:

This clinical investigational study is focused on multiple access site venous closure using the Cardiva Mid-Bore VVCS device for closure in these procedures to provide the best potential improvement in TTA over current standard of care and to address the greatest clinical need.

Femoral Arterial vs. Venous Closure:

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

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

Applicability of the VASCADE® Arterial VCS as a platform:

The previously approved VASCADE VCS [P120016][1] is indicated for percutaneous closure of femoral arteries using 5 to 7F procedural sheaths.

The Cardiva Mid-Bore VVCS platform for venous use, based on the proven design of the arterial VASCADE VCS, is particularly promising in venous closure due to the following:

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

VASCADE Arterial VCS RESPECT Study Overview:

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

Endpoints included:

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

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

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

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

VASCADE Arterial VCS Real World Experience for Venous Closure:

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

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

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

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

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

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

1.2. Design Verification Testing

1.2.1. Design verification testing including the following:

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

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

1.3. Pre-clinical Testing

Pre-clinical testing included the following two studies:

- Chronic GLP Animal Study [RPT 0503-01]: safety and efficacy
- Acute Animal Study [RPT 0513-01]: performance

Pre-Clinical Chronic GLP Study Overview [RPT 0503-01]

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

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

- **Abbreviated High-level Results Summary**
  - All sites achieved hemostasis within 2 minutes without any complication
  - Vessel patency confirmed by ultrasound post collagen deployment
  - No gross abnormalities indicative of complications or adverse effects
  - Gross evaluation of end organs did not demonstrate any evidence of distal thromboembolic events
  - Collagen patch was not associated with any type of intraluminal reaction or thrombus
  - No adverse effects or complications identified histologically

- **Conclusion:**
  - Test article met the objectives set forth in study.
  - No gross abnormalities indicative of complications or adverse effects associated with the test procedure to implant site or organ system.
  - Test article sealed veins appropriately using a 12 French introducer sheath and was demonstrated to be safe for its intended use.

Pre-Clinical Acute Study Overview [RPT 0513-01]

The purpose of this acute study was to evaluate device performance for the deployment, de-deployment and device removal in the presence of another indwelling sheath.

- **Objective:**
  - Effectiveness of the proposed VVCS disc (approx. disc diameter 7.1 mm) to provide temporary hemostasis in presence of an adjacent sheath
  - Disc deployment integrity in presence of an adjacent sheath

- **Abbreviated High-level Results Summary:**

- 8 cases were performed
- Average ACT 356 sec. Animals were treated with ASA and Plavix 3 days prior to the study
- Dual access with a 12F sheath and either a 7 or 8F accompanying sheath
- Access separation measured from 2 to 6 mm at vessel level
- All cases showed temporary hemostasis with the disc in presence of a neighboring sheath, as was evident by venograms and lack of any extravasation in surrounding tissue

- **Conclusion:** The study shows that Mid-Bore VVCS disc can be deployed, de-deployed and removed in presence of another indwelling sheath and perform satisfactorily.

1.4. Clinical Studies

RESPECT Trial using VASCADE arterial VCS

VASCADE 6/7F VCS was evaluated in a prospective, multi-center, randomized (2:1) clinical trial (the RESPECT Trial) in 20 sites in the United States and one site in Australia, comparing VASCADE VCS to Manual Compression (MC). The trial involved 420 patients undergoing diagnostic (n = 211) or interventional (n = 209) endovascular procedures, with 275 of those subjects receiving the VACADE device.

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

Table 1 and **Table 2** summarize safety and efficacy data from the RESPECT study.

Since commercial release in 2013, real-world experience with over 124,000 devices sold in the US, the data indicates the ongoing relevance of the clinical trial results (Tables 1, 2):

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

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

Table 1: Access Site-Related Complications at 30 Days by Event

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

*Two-sided Fisher's exact test

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

Table 2: RESPECT Efficacy Endpoint Results

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

1.5. Risks and Benefits

1.5.1. Risks

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

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

1.5.2. Benefits

The potential benefits of the Cardiva Mid-Bore VVCS over manual compression alone to achieve venous hemostasis include reduced time to ambulation, which the trial is intended to evaluate, in combination with a safety profile that is at minimum non-inferior to manual compression.

1.6. Rationale for Ultrasound Sub-study

A sub-study of this pivotal U.S. clinical trial will be performed utilizing independent analysis of non-invasive duplex ultrasound (DUS) imaging in 25 subjects from each pivotal cohort (i.e., right and left femoral venous access sites, constituting 2 exams per subject), who were randomized to and received the assigned treatment. DUS evaluation will be utilized to assess the local vascular impact of the Cardiva Mid-Bore VVCS or manual compression, along with the development of iatrogenic vascular complications. Specific investigational sites will be designated as ultrasound sites. These 3 – 4 sites will include subjects in the ultrasound sub-study imaging until a total of 25 patients have been evaluated in each treatment arm. Ultrasound will be performed at the follow-up office visit. All sub-study sites will be instructed in performance of duplex ultrasonography of the femoral vascular structures, and images will be interpreted by a central core ultrasound laboratory with experience in multicenter vascular device trials.

2. Device Description

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

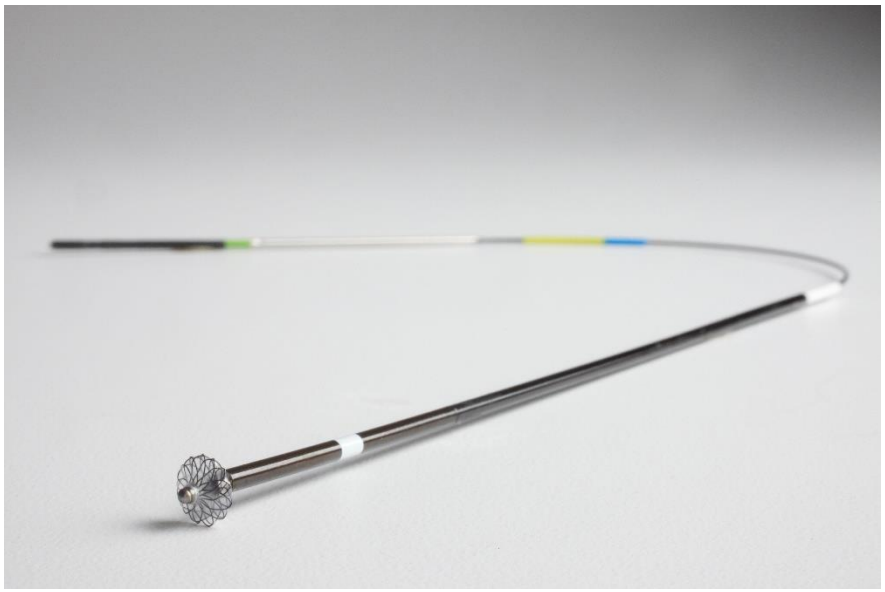
The Cardiva Mid-Bore VVCS is a disposable device based on the previously approved VASCADE 6/7F arterial VCS device. The only significant change with respect to the approved device is an increase in disc diameter from ~19F to ~21F to ensure temporary hemostasis and proper collagen deployment during closure of larger bore holes.

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

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

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

Figure 1: Cardiva Mid-Bore VVCS with Disc Deployed



To use the Cardiva VVCS, the catheter is inserted into the femoral vein through the previously placed introducer sheath. After insertion, the distal tip of the catheter is deployed, opening and expanding a low-profile Nitinol (NiTi) disc within the lumen of the femoral vein. The introducer sheath is then removed from the vessel over the catheter and the low-profile disc is placed against the inner wall, locating the vessel wall and temporarily sealing the venotomy. The position of the device disc against the vessel wall locates the collagen patch in the tissue tract immediately adjacent to the venotomy site (extravascular) and its location is verified using fluoroscopy prior to release. The clip is placed on the device shaft at the surface of the skin to hold the device in place during fluoroscopy.

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

2.1. Device Labeling

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

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

3. Study Objective

The objective of the trial is to demonstrate the safety and effectiveness of the Cardiva Mid-Bore Venous Vascular Closure System (VVCS) in sealing femoral venous access sites and providing reduced times to ambulation (TTA) compared with manual compression at the completion of catheter-based procedures utilizing 6 – 12 Fr inner diameter procedural sheaths, with single or multiple access sites. This study will be considered a success from a statistical perspective if it meets both the Cardiva Mid-Bore VVCS superiority goal for the primary effectiveness analysis and the non-inferiority goal for the primary safety analysis as stated in Section 8.

4. Study Design

4.1. Overview

This is a multi-center, randomized, controlled clinical trial to evaluate the safety and efficacy of the Cardiva Mid-Bore Venous Vascular Closure System (VVCS) compared to manual compression. Subjects will be randomly assigned in a 1:1 scheme to vascular closure with the VVCS or manual compression following percutaneous venous access for catheter-based procedures. Measures of safety and efficacy will be assessed through hospital discharge and 30 (+/- 7) days post-procedure.

4.2. Sample Size

204 subjects will be randomized in this trial in a 1:1 ratio, with randomization stratified by the number of femoral venous access sites (i.e., 3 v. 4). A total of 25 subjects each from the control and treatment arms will be enrolled in an ultrasound sub-study. In addition, up to 60 roll-in subjects may be enrolled.

4.3. Investigational Sites

This trial will be conducted at up to 20 clinical sites in the United States, with a minimum of 8 sites, enrolling subjects. Each site may enroll up to 25% of the pivotal subjects.

5. Study Population

5.1. Selection Criteria

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

5.1.1. Pre-Operative Inclusion Criteria

Pre-Operative Inclusion Criteria	All subjects are required to meet the following inclusion criteria in order to be considered eligible for participation in this trial: 1. 18 to 80 years of age; 2. Capable and willing to give informed consent; 3. Acceptable candidate for an elective, non-emergent catheter-based procedure via the common femoral vein(s) using a 6 to 12 Fr inner diameter introducer sheath, with a minimum of 3 and a maximum of 4 femoral venous access sites, and a maximum of 2 access sites/leg; 4. Able and willing to complete a 30 day +/- 7 days follow-up visit; 5. Acceptable candidate for emergent vascular surgery, and/or manual compression of the venous access sites; 6. A total of 50 subjects willing to undergo ultrasound evaluation at the 30 day +/- 7 day visit at select sites. 7. Anticipated prolonged bedrest (5 hours or longer) and / or overnight stay.

5.1.2. Pre-Operative Exclusion Criteria

Pre-Operative Exclusion Criteria	Subjects will be excluded from participating in this study if they meet any of the following criteria prior to initiation of the index procedure: 1. Advanced refusal of blood transfusion, if it should become necessary; 2. Active systemic infection, or cutaneous infection or inflammation in the vicinity of the groin; 3. Pre-existing immunodeficiency disorder and/or chronic use of high dose systemic steroids; 4. Known history of bleeding diathesis, coagulopathy, hypercoagulability, or current platelet count < 100,000 cells/mm^3; 5. Severe co-existing morbidities, with a life expectancy of less than 12 months; 6. Currently involved in any other investigational clinical trial that may interfere with the outcomes of this study, in the opinion of the Investigator; 7. Femoral arteriotomy in either limb with any of the following conditions: a. access within < 10 days b. any residual hematoma, significant bruising, or known associated vascular complications c. use of a vascular closure device within the previous 30 days; 8. Femoral venotomy in either limb with any of the following conditions: a. access within < 10 days b. any residual hematoma, significant bruising, or known associated vascular complications b. use of a vascular closure device 9. Any planned procedure involving femoral arterial or venous access in either limb within the next 30 days or prior to study exit; 10. Any history of deep vein thrombosis, pulmonary embolism or thrombophlebitis; 11. Significant anemia with a hemoglobin level less than 10 g/dL or a hematocrit less than 30%; 12. Renal insufficiency (i.e., serum creatinine of > 2.5 mg/dl); 13. Females who are pregnant, planning to become pregnant within 3 months of the procedure, or who are lactating; 14. Extreme morbid obesity (BMI greater than 45 kg/m2) or underweight (BMI less than 20 kg/m2); 15. Unable to routinely walk at least 20 feet without assistance; 16. Known allergy/adverse reaction to bovine derivatives; 17. Administration of low molecular weight heparin (LMWH) within 8 hours before or after the procedure; 18. Planned procedures or concomitant condition(s) that may extend ambulation attempts beyond 2-3 hours, and/or hospitalization time (e.g., staged procedure, serious co-morbidity), in the opinion of the Investigator.

5.1.3. Intra-Operative Exclusion Criteria

Intra-Operative Exclusion Criteria	Subjects will be excluded from participating in this study if any of the following exclusion criteria occur during the index procedure: <u>General Intra-op Exclusion Criteria:</u> 5. Any attempt at femoral arterial access during the procedure; 6. Any procedural complications that may extend routine recovery, ambulation and discharge times; 7. If the physician deems that a different method should be used to achieve hemostasis of the venous access sites, or that the subject should not attempt ambulation according to the protocol requirements; 8. ALL venous access sites must comply with the following exclusion criteria immediately prior to randomization: d. Difficult insertion of procedural sheath or needle stick problems at the onset of the procedure (e.g., multiple stick attempts, accidental arterial stick with hematoma, "back wall stick", etc.) in any of the study veins; e. A procedural sheath < 6 Fr or > 12 Fr in inner diameter is present at time of closure; f. A procedural sheath > 12 Fr inner diameter at any time during the procedure. d. Venous access site location is noted to be "high", above the inguinal ligament (cephalad to lower half of the femoral head or the inferior epigastric vein origin from the external iliac vein); e. Intra-procedural bleeding around sheath, or suspected intraluminal thrombus, hematoma, pseudoaneurysm, or AV fistula; f. Length of the tissue tract, the distance between the anterior venous wall and skin, is estimated to be less than 2.5 cm.

5.2. Withdrawal of Subjects

While study withdrawal is discouraged, subjects may withdraw from the study at any time, with or without reason and without prejudice to further treatment. In all cases of withdrawal, the reason(s) for withdrawal (if given) will be recorded upon study termination. In addition, the Investigator may withdraw the subject for any other reason determined by the Investigator to be in the best interest of the subject.

Once randomization is performed, subjects are considered enrolled and must have all peri-procedural data collected regardless of what treatment they receive after randomization, according to the Intent to Treat Principle for analyses of effectiveness.

Subjects who are randomized to VVCS and then never have the device inserted for any reason may be withdrawn after Discharge, since the safety analyses are based on subjects who receive

any part of the assigned treatment. All peri-procedural data must be collected for these subjects for effectiveness analyses.

6. Written Informed Consent

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

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

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

7. Study Procedures and Enrollment

7.1. Duration of Subject Participation

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

7.2. Enrollment

At the completion of the procedure, subjects that meet all the intra-operative eligibility criteria will be randomized 1:1 to use either the Cardiva Mid-Bore VVCS or manual compression for access site hemostasis of all venotomies. Randomization will be stratified by 3 vs. 4 access sites. Once a subject has been randomized, he or she is considered enrolled into the study. See Section 5.2 Withdrawal of Subjects.

7.3. Visit Schedule

The following outlines the required study assessments.

Table 3. Study Event Schedule

	≤ 45 days before Procedure	**At time of Index Procedure**	**Post-Procedure/ Hospital Discharge**	**1-Month (30 days) ± 7 days**
Demographics/ Medical History	X			
Groin assessment		X	X	X
Complaints of pain/nerve injury in lower extremities	X		X	X
Laboratory Tests*:	X			
Pre-op Inclusion / Exclusion Criteria Assessment	X			
Informed Consent	X			
Intra-procedural Exclusion Criteria Assessment		X		
Randomization and Intent to Treat / Enrollment		X		
Study Endpoint Data Collection:**				
TTCE determination		X		
TTH determination		X		
TTA determination			X	
TPPT determination			X	
TTDE determination			X	
TTD determination			X	
Device Success		X		
Procedure Success				X
Anti-platelet / anti-coagulant regimen		X	X	
Pain/anxiety medication regimen			X	
Patient Experience Survey			X	
Adverse Events		X	X	X
Ultrasound Exam (50 subjects)				X

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

**The following study endpoints will require collection of specific clock times, but results will be calculated within the database:

- TTCE: Time to Closure Eligibility (by patient)
- TTH: Time to Hemostasis (by access site)
- TTA: Time to Ambulation (by patient)
- TPPT: Total Post-procedure Time (by patient)
- TTDE: Time to Discharge Eligibility (by patient)

- TTD: Time to Discharge (by patient)

7.4. Study Procedures

7.4.1. Pre-Operative

Prior to the subject's scheduled procedure, obtain a medical history and record the subject's demographic data (age, race, ethnicity, and gender) and baseline information (height, weight, BMI). Review the Pre-operative Inclusion and Exclusion criteria within 45 days prior to the planned procedure date, including collection of the following routine blood tests:

- serum creatinine
- platelet count
- hemoglobin and hematocrit

Review of the subject's medical history and risk factors will be documented. The subject will be asked about any pre-existing lower extremity nerve complaints in both lower limbs (i.e., symptoms, severity). Peri-procedural medications that are taken within 24 hours of the procedure that may affect bleeding (e.g., anti-platelet, anti-coagulant, anti-thrombotic agents, etc.) will be documented.

Document the most recent INR for subjects on warfarin.

7.4.2. Intra-Operative – Data Collection for All Subjects

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

- procedure type: A-Fib, Other
  - If A-Fib, record: paroxysmal, persistent, and chronic / permanent, other
- ablation modality (e.g., RF, Cryo)
- **P0 TIME:** time of first index procedure sheath insertion
- number and location of access site locations (3 or 4)
- techniques used to gain venous access, if any (e.g., ultrasound, micropuncture)
- procedural anti-coagulation administered
- final procedural ACT time and value
- protamine administration, dose and time (if given)
- time of extubation

7.4.3. Intra-Operative – Access Site Requirements

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

- A maximum of 2 femoral venous access sites are allowed per limb.

- All access sites must have procedural sheaths with a minimum of a 6 Fr and a maximum of a 12Fr sheath inner diameter at the end of the case.
- Sheaths larger than 9 Fr must be placed in separate limbs (e.g., cannot place two 10 Fr sheaths in one limb).
- Refer to the Cardiva Mid-Bore VVCS IFU for specific instructions on device use.

7.4.4. Intra-Operative Randomization

At the end of the catheter-based procedure, with the procedural sheaths in place and under fluoroscopic visualization, an injection of contrast will be made to assess sheath placement and the anatomy of all venous access sites to verify the intra-operative eligibility criteria prior to randomization. These images should be saved and printed/stored with the subject's study records for monitoring purposes.

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

Once it has been determined that the subject does not meet any of the general intra-operative exclusion criteria, and that none of the venous access sites meet the specific access site exclusion criteria (i.e., all venous access sites must meet all study criteria for the subject to be eligible), then the subject is eligible for randomization.

- Once randomized, every access site will be closed according to the treatment assignment (i.e., either VVCS or manual compression).
- Study data will be captured for each access site, according to the instructions below.
- ***NOTE: Any subject that is randomized is considered to be enrolled, and all peri-procedural study data must be collected under the Intent to Treat principle regardless of deviations from the assigned treatment. For this reason, it is imperative that randomization is not performed until the case is complete and final eligibility criteria are confirmed.***
- ***If the subject is randomized to Mid-Bore VVCS and it is subsequently discovered that one or more of the access sites is not able to be closed (e.g., complication) apply manual compression to the affected access sites and close all eligible access sites using Mid-Bore VVCS. All study data will still be collected for each access site. See Section 4.2 Withdrawal of Subjects.***

At each investigational site, variable block randomizations will be performed separately by number of venotomy sites via EDC access at the conclusion of the index procedure, while the patient is on the table. Randomization will be stratified by 3 vs. 4 access sites, and there will be a 1:1 randomization ratio for Cardiva Mid-Bore VVCS vs. manual compression for access site closure. Refer to the Manual of Operations for instructions on how to randomize a subject.

7.4.5. Access Site Closure Instructions

The following process will be used to collect procedural data for each of the treatment arms:

Mid-Bore VVCS Treatment Arm Guidelines

If the subject is randomized to receive the Mid-Bore VVCS, the device should be deployed according to procedure in the Instructions for Use (IFU) provided in **Attachment 3**. If protamine is administered, the Investigator may proceed immediately with sheath exchanges and VVCS deployment without re-checking the ACT to obtain a target value.

Document device information:

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

Manual Compression Guidelines:

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

Documenting Access Site Hemostasis in Both Treatment Arms:

While performing the procedure, record the following information[1]:

- **P1 TIME:** time of removal of final index procedure device/catheter
- For each access site, record:
  - Access site location, e.g., right/left leg and relative location with respect to 2nd access site, if applicable e.g. proximal/distal, medial/lateral, etc.
  - Final introducer sheath size (inner diameter and length) at time of closure (i.e. after final sheath exchanges)
  - **TX.1 TIME:** time of removal for Mid-Bore VVCS device (treatment arm) or for removal of sheath (control arm)
  - **TX.2 TIME:** time venous hemostasis is achieved
  - Confirm that venous hemostasis is maintained and confirmed at 5 minutes after recorded hemostasis time (TX.2).
  - Document any light manual compression applied for tissue tract ooze.

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

[1] source worksheets and clock/timers will be provided and required by Sponsor

sites may still be closed with Mid-Bore VVCS, as appropriate.

7.4.6. Post-Operative

After hemostasis is achieved and confirmed at the required intervals, the access site should be monitored every 15 minutes for the first hour for all subjects.

Post-procedure, record the following information:

- **P2 TIME:** Record the date and time the subject was able to ambulate 20 feet without venous re-bleeding from the access sites.
- **P3 TIME:** Record the date and time the subject was eligible for discharge, based solely on the assessment of the access site, as determined by the medical team (i.e., absence of access site bleeding or obvious complications).
- **P4 TIME:** Record the date and time the subject was discharged from the facility.
- Any medication administered for management of pain or anxiety while the subject is on bedrest will be collected.

Ambulation Guidelines by treatment arm:

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

Cardiva Mid-Bore VVCS:

Bed rest for 2 hour minimum to a 2.5 hour maximum, then ambulate if stable. Check groin immediately post ambulation. Re-check groin after 15 minutes to verify status. Any ambulation delay beyond 3 hours final access site hemostasis time that is not related to a medical condition (e.g., pt. is sleeping, no staff available) will be documented, and a Protocol Deviation will be written. NOTE: If one or more of the access sites are not able to be closed with the Mid-Bore VVCS (e.g., complication preventing use of the device, user error), subjects should be maintained on bedrest according to the Investigator's discretion and all study times will be collected. This would not constitute a deviation from the protocol.

Manual Compression:

Follow institutional guidelines for ambulation. Check groin immediately post ambulation. Re-check groin after 15 minutes to verify status. Any delays of > 30 minutes beyond institution's standard practice for ambulation that are not related to a medical condition (e.g., pt. is sleeping, no staff available) will be documented, and a Protocol Deviation will be written.

Time to Discharge Eligibility Guidelines (all subjects):

Approximately 15 (+/- 5) minutes after the subject has successfully completed the ambulation assessment (P2), all access sites should be carefully assessed for the following:

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

If the subject does not exhibit any of these symptoms at any of the access sites, he/she may be considered to be "Eligible for Hospital Discharge" based on this study definition of the access site assessment only. These are basic guidelines for this study-required assessment only, and are not intended to impact actual hospital discharge times for these subjects. Using these guidelines, the Investigator may delegate this TTDE assessment to qualified medical personnel.

Any significant delay in determination of this discharge eligibility (i.e., > 30 minutes after successful ambulation) that is not related to the access site assessment will be documented as a protocol deviation (e.g., no staff available, other condition unrelated to access site).

NOTE: If there is any sign of active bleeding at the access site(s) after ambulation, measures should be taken to re-achieve hemostasis and then the subject re-ambulated when the Investigator determines that it is appropriate to do so. In these cases, TTA and TTDE will be repeated and documented when successful, and the re-bleeding will be documented as an adverse event.

Patient Experience Survey Administration Guidelines [Attachment 4]

All subjects will be given a Patient Experience Survey to complete after successful TTA, at the time of TTDE to characterize their experience while on bedrest post-procedure. The Research designee should give it to the patient, according to the Instructions provide in the Manual of Operations. The completed Survey should be collected at the time of completion. These data will be entered in the eCRF but will not be included in endpoint analyses or hypothesis testing.

Time to Discharge Guidelines (all subjects):

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

Research personnel should attempt to confirm a date for a follow-up visit at 30 (+/-7) days with the subject prior to discharge to ensure compliance. Ultrasound sub-study subjects should have their ultrasound appointments scheduled to ensure compliance.

Documentation of Venous Re-Bleeding at Femoral Access Site:

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

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

7.5. Follow-up at 30 (+/- 7) Days

Subjects should be present for an in-person office visit 30 ± 7 days following their index procedure. The subject should be queried regarding any complications they experienced after hospital discharge and the status of the access site wounds should be assessed. All subjects will be asked about any lower extremity nerve complaints in both lower limbs (i.e., symptoms, severity) that were not existing prior to the index procedure. These data will be captured in the Case Report Forms.

If a subject cannot attend an office visit for any reason, a telephone follow-up should be completed for safety assessment, however this will be documented as a protocol deviation and the subject's follow-up will be considered incomplete. These subjects will not be withdrawn.

At select sites, a subset of 25 subjects from each treatment arm will have an ultrasound exam of the bilateral femoral access sites performed and a digital image recorded for each limb.

7.6. Study Exit

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

8. Assessment of Effectiveness and Safety

8.1. Primary Effectiveness Endpoint

Time to ambulation (TTA): defined as elapsed time between removal of the final Mid-Bore VVCS device (treatment arm) or removal of the final sheath (control arm), and time when subject stands and walks 20 feet without evidence of venous re-bleeding from the femoral access sites **(Per-patient analysis).**

TTA will be reported in hour (hh): minutes (mm).

8.2. Secondary Effectiveness Endpoints

Time to discharge eligibility (TTDE), defined as elapsed time between removal of the final Mid-Bore VVCS device (treatment arm) or removal of the final sheath (control arm), and when subject is eligible for discharge based solely on the assessment of the access site, as determined by the medical team. **(Per-patient analysis).**

TTDE will be reported in hour (hh): minutes (mm).

Time to discharge (TTD), defined as elapsed time between removal of the final Mid-Bore VVCS (treatment arm) or removal of the final sheath (control arm), and when subject is discharged from the institution. **(Per-patient analysis).**

TTD will be reported in hour (hh): minutes (mm).

Procedural Endpoints:

- **Time to Closure Eligibility (TTCE):** defined as elapsed time between removal of the last procedural device/catheter for the index procedure and the removal of the first Mid-Bore

VVCS device (treatment arm) or removal of the first sheath (control arm).
(Per patient analysis).

TTCE will be reported in minutes (hh:mm).

- **Time to hemostasis (TTH**), defined as elapsed time between removal of the Mid-Bore VVCS device (treatment arm) or removal of the sheath (control arm), and first observed and confirmed venous hemostasis, for each access site. **(Per-access site analysis)**

  TTH will be reported in minutes (mm): seconds (ss).

  Total Post-Procedure Time (TPPT): defined as elapsed time between removal of the last procedural device/catheter for the index procedure and when subject is able to successfully ambulate. **(Per-patient analysis)**

  TPPT will be reported in hour (hh): minutes (mm).

Procedure Success, defined as attainment of final hemostasis at all venous access sites and freedom from major venous access site closure-related complications through 30 days
(Per-patient analysis, both arms).

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

See Table 4 for additional time and endpoint details.

Table 4: Study-required Data Collection and Endpoint Calculations

<table>
<tr><th>Time Point</th><th>Reported Units</th><th>Procedure Step</th><th>TTCE</th><th>TTH</th><th>TTA</th><th>TTDE</th><th>TTD</th><th>TPPT</th></tr>
<tr><td>P0</td><td>hh:mm</td><td>Index Procedure: First procedure sheath inserted</td><td></td><td rowspan="3"></td><td rowspan="15"></td><td rowspan="15"></td><td rowspan="15"></td><td></td></tr>
<tr><td>P1</td><td>hh:mm</td><td>Index Procedure: Final Device/Catheter removed from sheath</td><td rowspan="3">T1.1-P1</td><td rowspan="15">P2-P1</td></tr>
<tr><td>-</td><td>-</td><td>Final Sheath Exchange, as applicable</td></tr>
<tr><td>T1.1</td><td rowspan="12">hh:mm:ss</td><td>Access Site 1 - start hemostasis*</td><td rowspan="14"></td><td rowspan="2">T1.2-T1.1</td></tr>
<tr><td>T1.2</td><td>Access Site 1 - confirmed hemostasis</td></tr>
<tr><td>T2.1</td><td>Access Site 2 - start hemostasis*</td><td rowspan="2">T2.2-T2.1</td></tr>
<tr><td>T2.2</td><td>Access Site 2 - confirmed hemostasis</td></tr>
<tr><td>T3.1</td><td>Access Site 3 - start hemostasis*</td><td rowspan="2">T3.2-T3.1</td></tr>
<tr><td>T3.2</td><td>Access Site 3 - confirmed hemostasis</td></tr>
<tr><td>T4.1</td><td>Access Site 4 - as applicable start hemostasis*</td><td rowspan="2">T4.2-T4.1</td><td rowspan="3">P2-TX.1</td><td rowspan="4">P3-TX.1</td><td rowspan="5">P4-TX.1</td></tr>
<tr><td>T4.2</td><td>Access Site 4 - confirmed hemostasis</td></tr>
<tr><td>P2</td><td rowspan="3">hh:mm</td><td>Ambulation</td><td rowspan="3"></td></tr>
<tr><td>P3</td><td>Discharge Eligibility - per medical team</td><td rowspan="2"></td><td></td></tr>
<tr><td>P4</td><td>Discharge</td><td></td></tr>
<tr><td></td><td></td><td>*Where “start hemostasis” is:
Treatment: VVCS removal
Control: Sheath removal</td><td></td><td></td><td colspan="3">Where “X” is final access site for the patient, shown here aligned with access site 4 for simplicity.</td><td></td></tr>
</table>

hh: hours; mm: minutes; ss: seconds

Endpoint Abbreviations:

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

8.3. Primary Safety Endpoint

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

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

8.4. Secondary Safety Endpoint

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

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

- Access site-related wound dehiscence;
- Transient access site-related nerve injury.

9. Statistical Considerations

9.1. Analysis Populations and Data Handling Conventions

9.1.1. Effectiveness

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

Safety analysis will be performed according to the actual treatment received. All subjects who receive any portion of the Cardiva VVCS device treatment will be analyzed as a VVCS patient; subjects who receive manual compression control treatment only as randomized will be analyzed as a manual compression patient.

9.1.3. Missing Data

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

9.2. Statistical Analysis Plan

Results for roll-in patients will be summarized separately and excluded from formal analysis.

9.2.1. Baseline Subject Characteristics

Subject demographics, baseline characteristics and medical history will be summarized descriptively by randomized treatment arm. Mean, standard deviation, median, minimum, and maximum will be reported for continuous variables. Frequencies and proportions will be reported for categorical variables.

9.2.2. Effectiveness

9.2.2.1. Primary Effectiveness (TTA) Analysis

The primary effectiveness endpoint is time to ambulation (TTA) as defined in Section 7.1. Summary statistics for TTA (mean, standard deviation, median, minimum, and maximum) will be reported for all randomized patients (ITT) and further by the randomization stratification factor

(number of access sites per patient: 3 vs. 4) within each treatment arm. The proportions of Cardiva Mid-Bore VVCS converted to manual compression will also be reported.

The main effectiveness analysis will be based on the mean TTA. The hypotheses are as follows.

- H_0: Cardiva Mid-Bore VVCS mean TTA ≥ manual compression mean TTA
- H_A: Cardiva Mid-Bore VVCS mean TTA < manual compression mean TTA

An ANCOVA analysis will be performed adjusting for randomization stratification factor, i.e. 3 vs 4 access sites. A 1-sided $p<0.025$ by t test favoring the Cardiva Mid-Bore VVCS (i.e. shorter TTA) will be regarded as a successful demonstration of the superiority of the Cardiva Mid-Bore VVCS effectiveness over manual compression.

9.2.2.2 Secondary Effectiveness Endpoints Analyses

Secondary effectiveness endpoints include total post procedure time (TPPT), time to discharge eligibility (TTDE), and time to discharge (TTD).

TTH will be compared between the two study arms by the bootstrap method with patient as the re-sampling unit as opposed to access site, as within patient TTH times may be correlated. Otherwise the analysis will be similar to those for the primary safety analysis described in 8.2.3, and the proposed TTH non-inferiority margin will be 5 minutes for VVCS as compared to manual compression.

Lastly, time to closure eligibility (TTCE), procedure success, and proportions of device success (VVCS only, by access site) will be descriptively summarized without hypothesis testing.

9.2.3. Safety

Primary Safety Analysis

The primary safety analysis will be based on the 30-day limb incidence rate of combined major access site closure complications (see 7.3). Both the combined rate and individual complication incidence rates will be reported by treatment received as described in 8.1.2.

The statistical hypotheses are as follows:

- H_0: Cardiva Mid-Bore VVCS rate – manual compression rate ≥ 5%
- H_A: Cardiva Mid-Bore VVCS rate – manual compression rate < 5%

A 2-sided 95% confidence interval will be constructed by the bootstrap re-sampling method, with patient as the sampling unit as opposed to the limb, for the VVCS – manual compression

major complication rate difference. This is to account for an unlikely correlation between two limbs of a patient with respect to major closure complications. One million bootstrap re-sampling simulations will be performed. For each simulation, stratified sampling with replacement (by randomization stratification factor) will be performed separately for the two study arms and the VVCS – manual compression (MC) major complication rate difference will be recorded. With one million simulations, a data distribution will be generated for the VVCS – MC major complication rate difference. With patient as the sampling unit, any data structure (independent or correlated) between the same patient's two limbs is preserved in this data distribution. If the 97.5th percentile of the distribution, i.e. the upper limit of the 2-sided 95% confidence interval for the VVCS – MC difference, is <5%, then the null hypothesis of a ≥5% higher VVCS complication rate will be rejected at a 2-sided 0.05 significance level. In this case the VVCS major complications rate will be considered non-inferior to that of the manual compression.

As an example to illustrate the actual study results required in order to accomplish this goal, assume the two limbs within each patient to be independent (highly likely) and a 2% (4/204) major complication rate is observed for the MC control treatment. The observed VVCS major complication rate must be ≤ 3% (6/204) in order for the 95% confidence upper limit for the difference to be <5%. This confidence interval calculation is based on Newcombe's method derived from Wilson scores. *(Ref: Newcombe RG, Interval Estimation for the Difference between Independent Proportions: Comparison of Eleven Methods, Statistics in Medicine, 17, 8 73-890, 1998)*.

Secondary Safety Analysis

The combined incidence rate and individual complication incidence rates will also be reported by treatment received for access site closure related minor complications. Formal non-inferiority testing will not be conducted for minor complications.

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

9.3. *Sample Size Justification*

Effectiveness

Based on a prior study (RESPECT), mean TTA for manual control is estimated at 7.2 hours. The same mean for Cardiva Mid-Bore VVCS is estimated at 5 hours including an outlier and at 4.3 hours excluding the outlier. With an estimated joint standard deviation of 5.4 hours, the power for reaching a statistically significant difference at 2-sided 0.05 level with a total sample size of 204 (102 per group) is 0.83 including the outlier in the calculation; the same power is 0.97 excluding the outlier.

Safety

For the purpose of sample size/power estimation, we will assume major access site closure complications to be independent between the two limbs of the same subject. Based on clinical experience this is the most likely scenario for these rare events. According to review of the VASCADE arterial VCS RESPECT study[1], the combined major complication rate by limb is estimated to be 2% for both VVCS and manual compression. With these assumptions, simulations were conducted using the R software for a sample size of 204 each for VVCS and manual compression patients. The power for the Newcombe 2-side 95% confidence upper limit to exclude 5% is approximately 0.88.

In order to evaluate the Newcombe method as an approximation to the proposed analysis method, i.e. bootstrap by patient, systematic comparisons were performed between the upper limit of Newcombe and bootstrap confidence intervals. Complication rates of 0% – 3% were selected for comparison, as this range is expected to cover great majority of the actual cases. The results are presented in the following table.

[1] IDE G100246

Table 5: Comparison of Newcombe and Bootstrap 95% CI Upper Limits

Experimental			*Control*				*2-sided 95% CI Upper Limit for p1-p2*			
								*Bootstrap (100k reps)***		
n1	***x1****	***p1****	***n2***	***x2****	***p2****	***p1-p2***	***Newcombe***	***Sim 1***	***Sim 2***	***Sim 3***
204	0	0.000	204	2	0.010	-0.010	0.010	0.000	0.000	NA
204	0	0.000	204	4	0.020	-0.020	0.002	-0.005	0.000	0.000
204	0	0.000	204	6	0.029	-0.029	-0.005	-0.010	-0.005	-0.005
204	2	0.010	204	0	0.000	0.010	0.035	0.025	0.029	NA
204	2	0.010	204	2	0.010	0.000	0.026	0.020	0.025	NA
204	2	0.010	204	4	0.020	-0.010	0.018	0.015	0.015	0.015
204	2	0.010	204	6	0.029	-0.020	0.010	0.005	0.010	0.010
204	4	0.020	204	0	0.000	0.020	0.049	0.039	0.044	0.049
204	4	0.020	204	2	0.010	0.010	0.040	0.034	0.039	0.044
204	4	0.020	204	4	0.020	0.000	0.032	0.025	0.029	0.034
204	4	0.020	204	6	0.029	-0.010	0.024	0.020	0.020	0.025
204	6	0.029	204	0	0.000	0.029	0.063	0.054	0.059	0.064
204	6	0.029	204	2	0.010	0.020	0.054	0.049	0.049	0.054
204	6	0.029	204	4	0.020	0.010	0.045	0.039	0.044	0.049
204	6	0.029	204	6	0.029	0.000	0.037	0.034	0.034	0.039

**x1 and x2 are numbers of major complications, p1 and p2 are proportions of major complications*

***Sim 1: complication data are independent, i.e. all events occur in different patients*

***Sim 2: In one case complications occur in both legs of a patient in the arm with higher complication rate, or in arm 1 (experimental) if rates are the same in both arms*

***Sim 3: In two cases complications occur in both legs of the same patient in the arm with higher complication rate, or in arm 1 (experimental) if rates are the same in both arms. (Scenario only applicable when at least one arm has 4 or more events.)*

The mean difference, p1 – p2, was reproduced in all 42 bootstrap simulations. It can be seen that the Newcombe method is conservative in that its 95% confidence upper limit was uniformly higher than or the same as the corresponding bootstrap upper limit in simulation scenarios Sim 1 and Sim 2, with independent and low correlation complication data between limbs respectively. Out of 15 complication

data scenarios, 2 Newcombe limits were > 0.05. For each of bootstrap Sim 1 and Sim 2, 1 limit was >0.05 but less than the corresponding Newcombe limit. Only in the unlikely scenarios of Sim 3, where 2 patients in the same treatment arm had complications in both legs, did Newcombe and bootstrap upper limits become similar. Therefore we conclude that for power estimation purposes the Newcombe confidence limit is a conservative but satisfactory approximation method; the actual bootstrap power may be slightly higher than the Newcombe estimate.

9.4. Planned Interim Analysis

An interim analysis in support of a CE Mark submission will be conducted to analyze initial subjects randomized to the treatment arm only with respect to efficacy and safety. This interim analysis is not intended to support a decision to continue or to discontinue the trial, or to implement any modifications to trial procedures.

To alleviate potential statistical and operational bias that may be introduced, the execution of the interim analysis shall be a completely confidential process to the study team. All sponsor staff, staff contracted by the sponsor, and investigator staff directly involved in the conduct of the ongoing IDE trial will remain blind to the process and results of the analyses, with the exception of contracted resources involved in the execution of the interim analysis and submission of the results on behalf of the sponsor.

Endpoints to be evaluated using descriptive statistics are as follows:

- Primary efficacy: Time to Ambulation
- Secondary efficacy: Total Post Procedure Time, Time to Hemostasis, Time to Discharge Eligibility, Time to Discharge
- Primary safety: rate of major complications related to the access site
- Secondary safety: rate of minor complications related to the access site

In addition, device success and procedure success will be evaluated, as well as patient experience survey data.

Randomization: This is a single-arm analysis, therefore subjects randomized to control arm will be excluded.

Sample Size: 30-40 sequential subjects randomized to treatment arm from up to 7 centers.

A final clinical report will be prepared at the conclusion of the interim analysis by an agent of the sponsor who is independent from the conduct of the study. The report will be unblinded following the collection of the last patient's procedure data.

10. Data Management – Data Collection and Processing

Standardized eCRFs will be utilized by all participating sites, refer to the Manual of Operations for specifications and instructions. Investigators are responsible for the accurate completion and timely submission of the data collected during the trial. All data from the trial will be entered into eCRFs via a secure, web-based system with password protection. Incoming data will be automatically

reviewed to identify inconsistent or missing data and any adverse events. Any data issues are to be promptly addressed with the Investigator by the CRO. Quality assurance procedures will be established to ensure that complete, accurate and timely data are submitted, that protocol requirements are followed and that complications, adverse events and adverse device effects are correctly reported and investigated, as appropriate. Investigators are to maintain all source documents as required by the protocol, including laboratory results, supporting medical records, and signed Informed Consent forms. The source documents will be used during the regular monitoring visits to verify information from the database against data contained on the completed eCRFs.

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

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

11. Monitoring Procedures

11.1. Monitoring

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

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

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

for all enrolled subjects at the site. It is important that the Investigator and other relevant site personnel are available for consultation with the Monitors during the monitoring visits and that sufficient time is devoted at the site to the monitoring process.

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

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

11.2. Investigational Device Distribution and Accountability

11.2.1. Investigational Device Distribution

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

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

11.2.2. Device Accountability

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

11.2.3. Return of Materials Upon Study Termination

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

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

12. Quality Control and Quality Assurance

12.1. *Site Training*

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

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

12.2. *Investigator and Co-Investigator Training*

An Investigator is defined as the person responsible for the conduct of the clinical investigation at an investigational site. The Investigator is the responsible leader of the team and may be called the Principal Investigator.

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

An Operator is defined as an individual member of the clinical investigation team who is qualified by training and experience (i.e., non-Investigator MD or certified vascular tech), and who is designated to deploy the study device in a study subject under the direction of, and the direct supervision of an Investigator or Co-Investigator.

Prior to enrolling any subjects in the study, Investigators, Co-Investigators and Operators will be provided didactic training with a benchtop model to simulate the closure procedure with the Mid-Bore Venous Vascular Closure System. This training will be provided by a Sponsor-designated proctor. Benchtop training will be followed by study device deployment under proctor in a roll-in subject for up to 4 of the femoral venous access sites. The proctor shall either approve, or require additional training for each individual until all pre-specified training requirements have been met.

Investigators and Co-Investigators will be notified in writing when they have successfully completed the roll-in requirements and are eligible to randomize subjects into the trial, and to deploy the study device without a Sponsor proctor. Operators will be notified in writing when they have successfully completed the roll-in requirements and are eligible to deploy the study device under the direct supervision of an Investigator/Co-Investigator in a consented, qualifying study patient without a Sponsor proctor. An Operator will not have authority to make any decisions about enrollment, but only to deploy the device as directed.

An Investigator and Operator Training & Proctor Log will be utilized to assess and ensure all skills and knowledge levels are satisfactory prior to written approvals by the Sponsor.

These roll-in subjects will be followed in the same fashion as the randomized subjects and evaluated as a separate subject cohort.

12.3. Audits and Inspections

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

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

13. Adverse Events

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
- Results in congenital abnormality

All SAE's will be reported.

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

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

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

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

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

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

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

- Early post-operative pain (within 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:

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

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

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

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

13.3. Device Failures and Malfunctions

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

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

14. Study Committee

14.1. Data Safety Monitoring Committee (DSMC)

An independent combination Clinical Events Committee (CEC) and Data Safety Monitoring Board (DSMB), referred to as the Data Safety Monitoring Committee, or DSMC, shall be responsible for systematic review and adjudication of all reported major and minor access site-closure related endpoint complications. All other events reported to be potentially device- or procedure-related by the Investigator will be reviewed by an independent Safety Manager and/or a member of the DSMC to determine whether it meets criteria for adjudication. In order to enhance objectivity and reduce the potential for bias, the DSMC members shall be independent of the Sponsor as well as the investigational sites/ Investigators.

Members shall consist of at least two (2) independent physicians with experience in catheter-based procedures, and a statistician. A third independent physician may be utilized in cases when disparity occurs between the two primary DSMC reviewers.

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

The DSMC may recommend study termination if safety concerns warrant such action. The DSMC will establish guideline criteria for recommending study termination, to the extent that it is possible for the DSMC to predict adverse events or outcomes, before the proposed study begins.

The Safety Manager will maintain contact with the DSMC members to schedule event reviews 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; the ICH Guidelines for Good Clinical Practices (E6), 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 for written approval. A copy of the written IRB approval of the protocol and Informed Consent form must be received by Cardiva Medical, Inc. prior to recruitment of patients into the study and shipment of investigational product.

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

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

15.3. *Informed Consent Form*

Sample Informed Consent forms are provided in for Roll-In and Randomized subjects in Attachment 2 for the Investigator to prepare for use at his/her site. The Sponsor will review each site's redlines to the ICF and provide written approval prior to site submission of the documents to their respective IRBs. The reviewing IRB must then approve the ICF prior to use. If translations are required for specific populations, the Sponsor will provide certified translations for the site after IRB approval of the site template.

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

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

Written Informed Consent must be recorded appropriately by means of the patient's dated signature on the ICF. The person administering the Informed Consent shall also sign and date the ICF. The patient shall receive a copy of the ICF, and the informed consent process shall be documented in each subject's source record.

15.4. *Amending the Protocol*

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

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

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

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

15.5. *Emergency Actions*

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

15.6. *Protocol Deviations*

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

Investigators shall be required to obtain prior approval from Cardiva Medical clinical study management before initiating deviations from the protocol, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval shall be documented in writing and maintained in clinical study management and Investigator files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, (e.g. subject was not available for scheduled follow-up 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 and non-subject specific deviations, (e.g. unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a physician who has not signed an Investigator agreement or not been trained in the use of the device, etc.), will be reported on the Protocol Deviation case report form. Investigators will also adhere to procedures for reporting study deviations to their IRB in accordance with their specific IRB reporting policies and procedures.

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

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

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

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

15.7. Coverage of Expenses

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

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 and Financial Disclosure Form
- Fully executed Clinical Study Agreement and budget
- A copy of the written IRB approval of the protocol and Informed Consent Forms
- A copy of the IRB-approved Informed Consent Forms
- A copy of the curriculum vitae of the Principal Investigator.

16.2. Source Documentation

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

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

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

16.3. Record Retention & Custody

The Investigator will maintain all essential trial documents and source documentation, in original format, that support the data collected on the study patients in compliance with the ICH/GCP guidelines. Documents must be retained for at least 5 years after the last approval of marketing application or until at least 5 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by

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

16.4. *Criteria for Terminating Study*

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

Possible reasons for study termination include:

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

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

16.6. *Investigator Responsibilities*

- Agree to sign and adhere to the Investigator Agreement
- Be willing to provide required assessments for analysis
- Be willing to perform and be capable of performing treatment procedures as outlined in this protocol and to delegate study responsibilities only to qualified personnel

- Comply with all required elements of this protocol and supply material suitable for quantitative analysis
- Agree to obtain written Informed Consent before any study specific procedures are performed
- Complete all electronic data modules prior to scheduled monitoring visits
- Be willing to change hospital routine if required by protocol, as long as patient safety and well-being is not compromised
- Adhere to all relevant Ultrasound Core Laboratory requirements as applicable.

17. Publication Policy

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

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

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

18. Regulatory Considerations

18.1. Role of Cardiva Medical

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

selection of Investigators (21 CFR 812.43), monitoring (21 CFR 812.46), supplemental applications (21 CFR 812.35 (a) and (b)), maintaining records (21 CFR 812.140 (b)), and submitting reports (21 CFR 812.150 (b)).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

19. Abbreviations and Definitions

19.1. Abbreviations

ACT	Activated clotting time
AE	Adverse Event
AV	Arteriovenous
CFR	Code of Federal Regulations
eCRF	Electronic Case Report Form
CV	Curriculum Vitae
DSMC	Data Safety Monitoring Committee
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
PE	Pulmonary embolism
SAE	Serious Adverse Event
TPPT	Total Post-procedure Time
TTA	Time to Ambulation
TTH	Time to Hemostasis
TTCE	Time to Closure Eligibility
TTDE	Time to Eligibility for Discharge
TTD	Time to Hospital Discharge
UADE	Unanticipated Adverse Device Event

19.2. Definitions

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

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

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

Bleeding originating from the venous access site(s), which has occurred to the degree that transfusion of blood products is necessary to maintain hemodynamic stability.

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

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

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

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

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

Must meet BOTH of the following criteria related to the venous access site(s): 1) positive wound culture requiring treatment with intramuscular or oral antibiotics; and 2) no prolongation of hospital discharge time directly related to complications of access site infection. Does not include administration of prophylactic antibiotic regimens.

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

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

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

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

ACCESS SITE-RELATED VESSEL LACERATION (minor safety endpoint)

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

ACCESS SITE-RELATED WOUND DEHISCENCE (minor safety endpoint)

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

ADVERSE EVENT SEVERITY RATING

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

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

ALLERGIC RESPONSE

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

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

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

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

A connection between the access vein and the adjacent artery that is demonstrated by arteriography or ultrasound, most often characterized by a continuous bruit that is mild to moderate in nature and does not require an intervention in the opinion of the Investigator.

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

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

CO-INVESTIGATOR

Any individual member of the clinical investigation team designated and supervised by the Investigator at an investigational site who performs critical investigation-related procedures and/or makes important investigation-related observations, including enrollment of subjects. See also Investigator and Operator.

CONFIDENTIALITY

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

DATA SAFETY MONITORING COMMITTEE (DSMC)

An independent combination Clinical Events Committee and Data Safety Monitoring Board responsible for systematic review and adjudication of all reported deaths, major and minor vascular complications, and review of all potentially device- or procedure-related adverse events.

DEVICE FAILURE / MALFUNCTION

The device does not perform in accordance with the IFU.

DEVICE SUCCESS

Defined as the ability to deploy the delivery system, deliver the collagen, and achieve hemostasis with the Cardiva Venous Vascular Closure System.

ELECTRONIC CASE REPORT FORM (eCRF)

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

EMBOLISM

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

HEMATOMA

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

HEMOSTASIS - VENOUS

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

INFLAMMATORY RESPONSE

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

INFORMED CONSENT

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

INTERNATIONAL NORMALIZED RATIO (INR)

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

INTIMAL TEAR / DISSECTION

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

INVESTIGATIONAL SITE

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

INVESTIGATOR

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

IPSILATERAL

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

IPSILATERAL DEEP VEIN THROMBOSIS (minor safety endpoint)

Presence of a thrombus in the peripheral venous system of the ipsilateral limb. May be a complication of phlebitis or may result from injury to a vein or from prolonged bed rest. Symptoms include a feeling of heaviness, pain, warmth, or swelling in the affected part.

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

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

LIGHT PRESSURE METHODS

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

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

MANUAL COMPRESSION

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

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

LAST PROCEDURAL DEVICE

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

LOWER EXTREMITY ISCHEMIA

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

OOZING FROM THE ACCESS SITE

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

OPERATOR

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

PERFORATION OF VESSEL WALL

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

PROCEDURE SUCCESS

Defined as attainment of final hemostasis at all venous access sites and freedom from major venous access site closure-related complications through 30 days.

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

A blood vessel abnormality resembling an aneurysm (localized abnormal dilatation of a blood vessel) but consisting of a collection of blood with persistent flow outside an artery, contained by surrounding tissue and due to a leaking hole through all layers of the arterial wall. The leaking hole is due to injury of (e.g., rupture of or trauma to) the arterial wall. The pseudoaneurysm is usually identified by angiography or ultrasound, and may or may not require treatment (e.g., thrombin injection or fibrin adhesive injection).

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

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

PULMONARY EMBOLISM NOT REQUIRING SURGICAL OR ENDOVASCULAR INTERVENTION AND/OR NOT RESULTING IN DEATH (major safety endpoint)

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

PUNCTURE SITE PAIN

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

RE-BLEEDING AT ACCESS SITE

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

RETROPERITONEAL BLEEDING

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

SERIOUS ADVERSE EVENT (SAE)

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

SUB-INVESTIGATOR / CO-INVESTIGATOR

Any individual member of the clinical investigation team designated and supervised by the Investigator at an investigational site who performs critical investigation-related procedures and/or makes important investigation-related observations. See also Investigator.

SUBJECT

An individual who participates in a clinical investigation.

THROMBUS FORMATION

Blood clot formation.

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

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

UNANTICIPATED ADVERSE DEVICE EFFECTS (UADE)

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

VASCULAR INJURY REQUIRING SURGICAL REPAIR (major safety endpoint)

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

VASOVAGAL EPISODE

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

VASOSPASM

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

VESSEL OCCLUSION (ARTERIAL OR VENOUS)

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

VESSEL THROMBUS (ARTERIAL / VENOUS)

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

19.3. Bibliography

1. Dou, E., Winokur, R.S., Sista, A.K. Venous access site closures using the VASCADE vascular closure system. *J. Vasc. Interv. Radiol.* 2016;27:1885–1888.

2. Efron, B, Tibshirani, RJ, *Introduction to the Bootstrap,* Chapman & Hall/CRC Monographs on Statistics & Applied Probability. Boca Raton, FL: CRC Press.

3. Lunneborg, CE, Tousignant JP, Efron's Bootstrap with Application to the Repeated Measures Design. *Multvariate Behavioral Research* 1985;20:161-178.

4. Newcombe RG, Interval Estimation for the Difference between Independent Proportions: Comparison of Eleven Methods. *Statistics in Medicine*. 1985;17:873-890.

5. U. S. Food and Drug Administration/ Center for Devices and Radiological Health / Office of In Vitro Diagnostics and Radiological Health /Center for Biologics Evaluation and Research. (2013). *Assay Migration Studies for In Vitro Diagnostic Devices: Guidance for Industry and FDA Staff.* Washington, DC: Author.

20. Attachment 1: Investigator Responsibilities, Records and Reports

20.1. *Investigator Responsibilities*

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

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

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

20.2. *Investigator Records*

Case REPORT FORMS

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

SCREENING LOG

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

20.3. *Investigator Reports*

FINAL TRIAL REPORT

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

SERIOUS ADVERSE EVENTS (SAEs)

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

DEVICE MALFUNCTIONS

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

WITHDRAWAL OF APPROVAL

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

21. Attachment 2: Sample Informed Consent Forms (Roll-In and Randomized)

Participant Sample Consent Form - ROLL-IN SUBJECTS

Title of Study: "THE AMBULATE TRIAL"

A MULTI-CENTER, RANDOMIZED CONTROLLED TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF THE CARDIVA MID-BORE VENOUS VASCULAR CLOSURE SYSTEM (VVCS) VS. MANUAL COMPRESSION FOR THE MANAGEMENT OF THE FEMORAL VENOTOMY AFTER CATHETER-BASED INTERVENTIONS PERFORMED VIA 6- 12 FR PROCEDURAL SHEATHS WITH SINGLE OR MULTIPLE ACCESS SITES PER LIMB

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

Principal Investigator:

Institution:

Your Consent

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

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

Purpose & Background of the Study

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

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

The new device ("study device") has some minor changes to it that make it more suitable for use in closing holes in veins, and now it must be tested in a new clinical study to show that it has similar results to the VASCADE device.

This study will enroll about 204 patients and up to 60 Roll-In patients at up to 20 hospitals in the United States. At each hospital, each of the study doctors will enroll at least one "roll-in" patient prior to enrolling patients in the randomized study (where there is a 50:50 chance of receiving the study device or manual compression to close the holes). For each roll-in patient such as you (if you agree to take part in the study), the use of the study device will be done under the direct supervision of a representative of Cardiva Medical. In addition, the doctors may also have a trained assistant perform a roll-in case. This "assistant" is a medical professional who is qualified by training and experience, and who assists the study doctor with deploying one or all of the devices you will receive during your procedure, under direct supervision of the study doctor.

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

Your participation in this study will last 30 days (± 7 days). The expected total time for all patients to complete the study is about 9 months.

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

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

Pre-Procedure Before the procedure you will have a medical interview to make sure you qualify for the study (are eligible to take part in the study) and you will have your blood drawn (approximately 1-2 teaspoons) for laboratory testing (creatinine, platelet count, hemoglobin, hematocrit, and INR if on warfarin). These are normal blood tests that are drawn before a procedure like yours.

Procedure During the procedure your doctor will insert 3 or 4 small plastic tubes to gain access to the large veins in both of your legs (femoral veins). He/she will then insert small tubes of various sizes into each of these access sites so that the medical equipment needed to perform your heart procedure can be inserted into your body for use. Since you will receive blood thinning medications as part of your regular procedure, your doctor will monitor your blood to determine how long it takes you to stop bleeding.

When your doctor is finished with the procedure and your doctor feels it is okay for you to take part in the study, your doctor and/or the assistant will insert a small device (study device) in the tube into each one of the vein holes in your leg. The device will implant a collagen patch to close or seal-off the holes in your veins. Light pressure may be held for a couple of minutes after the device is implanted.

Post-Procedure After the procedure, the puncture site (place where the hole was made for the heart catheters) will be checked often to make sure it is not bleeding.

After you get up to walk, but before you are discharged from the hospital you will be given a short "Patient Experience Survey" to complete. It will ask you

how you feel about the time you were on bedrest after your procedure. This is for the study only and will not be part of your medical records.

30 days You will need to come in thirty (± 7) days after the procedure to be checked by the doctor. He/she will check the place where the holes were in your legs to make sure they have healed properly.

These are normal steps used in this type of heart procedure.

Possible Risks

The safety of this device has been tested and proven in several previous research studies of over 350 human patients without serious problems or deaths. The collagen patch is similar to other collagen-based closure devices used in surgery to close small holes. In a large FDA approval study called RESPECT, a total of 417 subjects were enrolled. Two-thirds (275 patients) received the VASCADE device, and one-third (142) received manual compression to close a single artery hole (femoral artery). Safety results were similar in both groups.

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

- allergic response (to the material in the device or collagen)
- arterio-venous fistula (abnormal connection between artery and vein) (0.4%)
- bleeding/oozing from the puncture site (2.9%); bleeding requiring transfusion (0%)
- bruising at the puncture site (<0.05%)
- death
- deep vein thrombosis (thrombus formation in a vein in the leg) (1%)
- device failure / malfunction (4%)
- edema (swelling in the tissues)
- embolization (thrombus, air, calcific debris, device floating downstream)
- hematoma (bleeding under the skin) (2%)
- infection at the access site
- inflammatory response (inflammation)
- intimal tear / dissection (tear of the leg vein or artery wall)
- laceration of the vessel wall
- lower extremity ischemia (lack of oxygen to the leg)
- peripheral nerve injury (nerve damage to the leg) (<0.05%)
- perforation of the vessel wall (puncture of the vessel wall)

- pseudoaneurysm (abnormal collection of blood with persistent flow outside an artery due to a leaking hole in the artery due to injury) (1.8%)
- pulmonary embolism (blockage of an artery in the lungs)
- puncture site pain (1%)
- retroperitoneal bleeding (bleeding in the area behind the abdomen) (<0.05%)
- vasospasm (spasm of the artery)
- vasovagal response (slowed heart rate with possible fainting)
- vascular injury requiring repair (vessel damage requiring repair)
- vessel occlusion (blockage of the artery or vein)
- vessel thrombus (blood clot in the artery or vein)
- wound dehiscence (separation of wound edges)

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

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

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

Possible Benefits

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

Financial Responsibility

The study sponsor will pay the costs of tests, exams, and procedures that are performed only because you are in this study (are not part of your regular treatment). The study devices used in this study will be provided free of charge by Cardiva Medical, Inc. You or your insurance company will be responsible for all costs of your usual ongoing medical care. This includes the cost of your procedure (except the study device), hospital care and services, and any follow-up that would be performed as part of your medical care outside of this study. If your insurance company requires any co-payment or deductible, you will be responsible for making that payment. You will not be paid for your participation in this clinical trial, and there is no financial reward or compensation in any form *[sites may add a modest stipend of $75 for return travel to the site for the follow-up visit].*

Compensation for Injury

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

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

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

Privacy, Confidentiality & Disclosure of Information

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

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

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

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

New Information Arising During the Project

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

Termination of the Study

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

Right of Refusal and Alternative Treatments

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

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

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

- It would be dangerous for you to stay in the study
- You have not followed the instructions of your study doctor and/or study staff
- You become pregnant
- You need treatment not allowed in the study
- The Sponsor decides to end the study
- Other unexpected circumstances

Inquiries

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

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

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

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

Study Participant's Bill of Rights

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

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

Consent

Your signature below indicates that:

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

_____ _____/_____/_____

Signature of Participant Date

_____

Printed Name of Participant

_____ _____/_____/_____

Signature, Person Conducting Informed Consent Discussion Date

_____

Printed Name, Person Conducting Informed Consent Discussion

Participant Sample Consent Form – RANDOMIZED SUBJECTS

Title of Study: "THE AMBULATE TRIAL"

A MULTI-CENTER, RANDOMIZED CONTROLLED TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF THE CARDIVA MID-BORE VENOUS VASCULAR CLOSURE SYSTEM (VVCS) VS. MANUAL COMPRESSION FOR THE MANAGEMENT OF THE FEMORAL VENOTOMY AFTER CATHETER-BASED INTERVENTIONS PERFORMED VIA 6- 12 FR PROCEDURAL SHEATHS WITH SINGLE OR MULTIPLE ACCESS SITES PER LIMB

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

Principal Investigator:

Institution:

Your Consent

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

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

Purpose & Background of the Study

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

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

The new device ("study device") has some minor changes to it that make it more suitable for use in closing holes in veins, and now it must be tested in a new clinical study to show that it has similar results to the VASCADE device.

If you choose to take part in the study, you will be randomly (like the flipping of a coin) assigned to one of two groups: a "study group" in which the collagen patch (Cardiva VVCS study device) is used, or a "control group" in which it is not. The collagen patch is considered investigational for use in veins (not approved for sale). In the "control group", you will not have the device, but will have firm pressure placed on the leg vein holes for the amount of time it takes for the vein to clot and stop bleeding. This is known as "manual compression" and is a usual way of closing the venous holes for this procedure.

A "randomized study" means that you will have a 1:1 chance (equal chance) of being placed in either group, with an equal number of patients receiving the collagen patch as those who will receive manual compression. To determine which group you will be in, an electronic data system will randomly assign you to either treatment group. Your study doctor will not be able to choose which group you are assigned to. If you are assigned to the collagen patch ("study") group and any problems arise that make it difficult or unsafe to use the device, your study doctor will decide whether to go ahead and use the device or to proceed with manual compression to close the holes in your veins. Your study doctor may have an assistant who is trained to use the device help with deploying one or all of the study devices. Your study doctor will directly supervise and make all decisions about the procedure, even when an assistant is used.

This study will enroll about 204 patients and 60 roll-in patients (training cases) at up to 20 hospitals in the United States. Your participation in this study will last 30 days (± 7 days). The expected total time for all patients to complete the study is about 9 months.

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

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

Pre-Procedure Before the procedure you will have a medical interview to make sure you qualify for the study (are eligible to take part in the study) and you will have your blood drawn (approximately 1-2 teaspoons) for laboratory testing (creatinine, platelet count, hemoglobin, hematocrit, INR if on warfarin). These are normal blood tests that are drawn before a procedure like yours.

Procedure During the procedure your doctor will insert 3 or 4 small plastic tubes to gain access to the large veins in both of your legs (femoral veins). He/she will then insert small tubes of various sizes into each of these access sites so that the medical equipment needed to perform your heart procedure can be inserted into your body for use. Since you will receive blood thinning medications as part of your regular procedure, your doctor will monitor your blood to determine how long it takes you to stop bleeding.

When your doctor is finished with the procedure and your doctor feels it is okay for you to take part in the study, he/she will log in to a study web site to find out which treatment (group) you will be assigned to, to close the holes in the veins.

- If assigned to the "study group", your study doctor and possibly a trained assistant will insert a small device (study device) in the tube into each one of the vein holes in your leg. The device will implant a

collagen patch to close or seal-off the holes in your veins. Light pressure may be held for a couple of minutes after the device is implanted.

- If assigned to the "control" group, your study doctor and/or an assistant will apply pressure over each one of the vein holes in your legs until the blood clots and there is no evidence of bleeding. This is the usual procedure for closing these veins.

Post-Procedure After the procedure, the puncture site (place where the hole was made for the heart catheters) will be checked often to make sure it is not bleeding.

After you get up to walk, but before you are discharged from the hospital you will be given a short "Patient Experience Survey" to complete. It will ask you how you feel about the time you were on bedrest after your procedure. This is for the study only and will not be part of your medical records.

30 days You will need to come in thirty (± 7) days after the procedure to be checked by the doctor. He/she will check the place where the holes were in your legs to make sure they have healed properly.

Ultrasound Study ***[selected sites to add this section]***

About 50 patients will be included in a small sub-study to receive an ultrasound procedure. The ultrasound will be taken to look for any problems where the tubes were in both of your legs, and will be done in both groups of patients for comparison. It does not use x-rays and is done by placing a wand on the skin. It usually takes about an hour to perform the test. It rarely causes any pain or discomfort. This test will be done at the time of your 30 day visit if you agree to be a part of this sub-study.

These are normal steps used in this type of heart procedure. The only difference is that you have a 50:50 chance that your doctor will be using a device to close the venous holes to stop the bleeding instead of holding longer pressure on the holes to stop the bleeding.

Possible Risks

The safety of this device has been tested and proven in several previous research studies of over 350 human patients without serious problems or deaths. The collagen patch is similar to other collagen-based closure devices used in surgery to close small holes. In a large FDA approval study called RESPECT, a total of 417 subjects were enrolled. Two-thirds (275 patients) received the VASCADE device, and one-third (142) received manual compression to close a single artery hole (femoral artery). Safety results were similar in both groups.

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

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

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

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

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

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

Possible Benefits

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

Financial Responsibility

The study sponsor will pay the costs of tests, exams, and procedures that are performed only because you are in this study (are not part of your regular treatment). The study devices used in this study will be provided free of charge by Cardiva Medical, Inc. You or your insurance company will be responsible for all costs of your usual ongoing medical care. This includes the cost of your procedure (except the study device), hospital care and services, and any follow-up that would be performed as part of your medical care outside of this study. If your insurance company requires any co-payment or deductible, you will be responsible for making that payment. You will not be paid for your participation in this clinical trial, and there is no financial reward or compensation in any form *[sites may add a modest stipend of $75 for return travel to the site for the follow-up visit].*

Compensation for Injury

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

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

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

Privacy, Confidentiality & Disclosure of Information

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

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

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

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

New Information Arising During the Project

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

Termination of the Study

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

Right of Refusal and Alternative Treatments

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

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

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

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

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

Inquiries

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

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

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

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

Study Participant's Bill of Rights

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

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

Consent

Your signature below indicates that:

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

_____	_____/_____/_____
Signature of Participant	Date
_____	
Printed Name of Participant	
_____	_____/_____/_____
Signature, Person Conducting Informed Consent Discussion	Date
_____	
Printed Name, Person Conducting Informed Consent Discussion	

[Ultrasound sub-study sites only, indicate whether the patient has consented to participate in the Ultrasound sub-study and have patient initial at the time of consent.]

□ **_____** ***(patient initials)*** "**Ultrasound subject**" - Your doctor has agreed to have his/her patients undergo an ultrasound exam of the access sites in both legs at the 30 day office visit. There will be up to 50 subjects participating at up to 5 of the hospitals until all 50 have been enrolled. **Initial this line if you consent to be a part of this sub-study and to have the ultrasound performed at your 30 day visit**.]

22. Attachment 3: Instructions For Use (IFU)

CARDIVA MEDICAL, INC.

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

INSTRUCTIONS FOR USE

IFU 3972 Rev - 03

For Investigational Use Only

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

DESCRIPTION

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

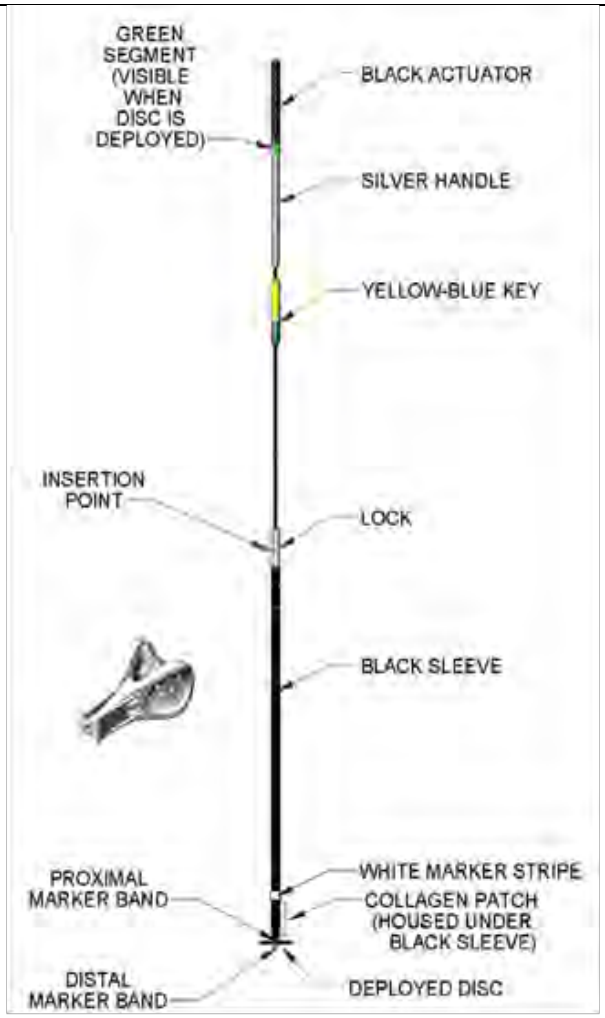


Fig. 1 – MID-BORE Venous Vascular Closure System (VVCS)

INDICATIONS FOR USE

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

CONTRAINDICATIONS

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

WARNINGS

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

PRECAUTIONS

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

SPECIAL PATIENT POPULATIONS

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

- Less than 18 years of age;
- Pregnant and/or lactating women;
- Pre-existing immunodeficiency disorder and/or chronic use of systemic steroids;
- Known significant coagulopathy/bleeding disorder such as thrombocytopenia (platelet count <100,000/mm^3), thrombasthenia, hemophilia, von Willebrand’s disease or anemia (Hemoglobin <10g/dL, Hematocrit <30%);
- Previous vascular grafts or surgery at the target vessel access site;
- Symptomatic ipsilateral lower extremity ischemia;
- Femoral venous lumen less than 6 mm;
- Length of the tissue tract, the distance between the anterior venous wall and skin, is estimated to be less than 2.5cm;
- INR ≥1.8 if patient received warfarin;
- Fibrinogen level < 150 mg/dl if patient received fibrinolytic agent;
- Extreme morbid obesity (BMI > 45 kg/m2) or underweight (BMI < 20 kg/m^2);

Adverse Events

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

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

DEVICE PREPARATION AND PROCEDURE

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

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

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

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

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

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

Device	Model	Sheath Size (French)	Sheath Length	Disc Size	Collagen Patch Length	Device Working Length	Maximum OD (with collapsed Disc)
Cardiva MID-BORE VVCS	800-612C	6F – 12F	up to 12 cm	7.0	15 mm	15 cm	2.1 mm

2. Inspect the package for damage (breaks, tears, open seals, water damage, etc.) and verify that expiration date has not passed.

3. Using standard sterile technique, remove the tray containing the MID-BORE VVCS Catheter and Clip from the foil pouch. Carefully remove MID-BORE VVCS Catheter and Clip from the tray. Examine the device by first verifying that the Black Sleeve is locked in position and the Collagen Patch is not exposed. Also verify that the Yellow-Blue Key **(Figure 2)** is not engaged in the Lock (the Lock is located at the proximal aspect of the Black Sleeve), and the Yellow-Blue Key is located at the proximal end of the Catheter Shaft. Inspect the Catheter further by examining the deployed MID-BORE VVCS Disc. To deploy the Disc, hold the Silver Handle firmly and pull back on the Black Actuator until it locks in place. When the Disc is locked in the deployed position, the Green Segment

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

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

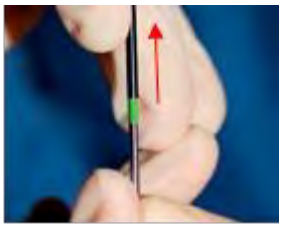


Fig. 3 – Pull back on Black Actuator Tip to deploy the Disc

Fig. 4 – Deployed & Collapsed Disc

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

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

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

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

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

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

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

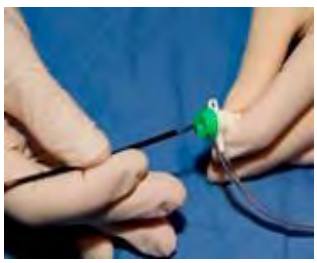


Fig. 6 – Insert device into hub of introducer sheath

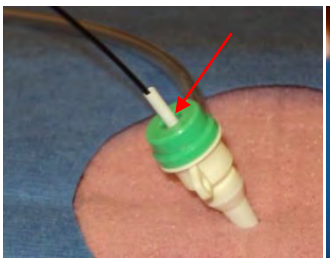


Fig. 7 – Insert device half way of the Lock

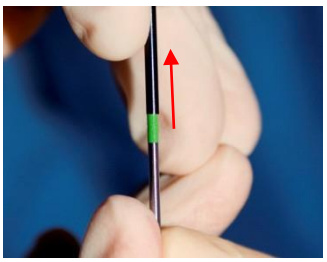


Fig. 8 – Pull back on Black Actuator Tip to deploy the MID-BORE VVCS Disc

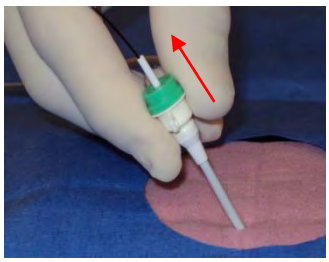


Fig. 9 – Grasp hub of sheath and remove over catheter

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

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

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

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

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

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

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

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

12. Once temporary hemostasis is achieved, apply the Clip to the Black Sleeve at skin level as shown in **Figure 10.** Utilize fluoroscopy to verify that the deployed Disc is positioned against the intimal surface of the venotomy by noting the position of the more proximal radiopaque marker. The marker should be at the venotomy site. The Collagen Patch is immediately proximal to this Marker Band. The Distal Marker Band locates the distal end of the Disc.

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

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

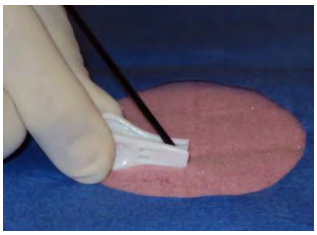


Fig. 10 – Apply Clip to Black Sleeve at skin level

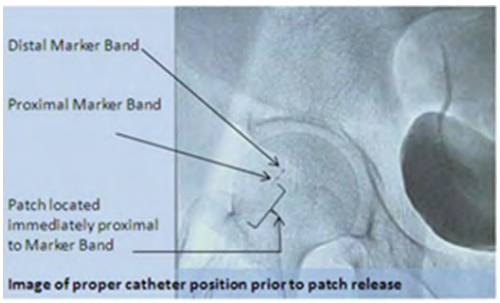


Fig. 11 – Fluoroscopic image demonstrating proper position of Disc

EXTRA-VASCULAR COLLAGEN PATCH DEPLOYMENT AND DEVICE REMOVAL

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

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

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

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

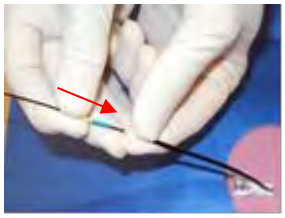


Fig. 12 – Unlock the Black Sleeve by sliding Yellow-Blue Key into the Lock

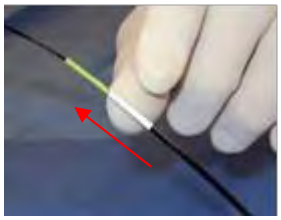


Fig. 13 – Retract the Black Sleeve by grasping the Lock and applying gentle upward tension toward the Silver Handle

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

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

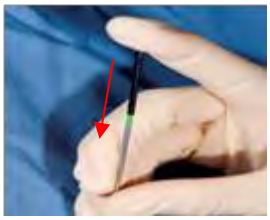


Fig. 16 – Collapse the Disc by pressing on the Black Actuator Tip

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

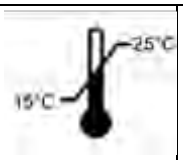
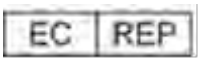
15. Observe for complete hemostasis. Manual compression can be used to decrease or stop any tract ooze until full hemostasis is achieved.

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

16. Apply sterile dressing to site per institution protocol. Maintain bed rest and periodically check site until patient is ready to ambulate.

17. Complete information on Patient Implant Card and provide to the patient.

GRAPHICAL SYMBOLS ON THE MID-BORE VVCS PACKAGING

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

CARDIVA MEDICAL, INC.

Design *for* what's humanly possible

Cardiva Medical, Inc.
2900 Lakeside Drive, Suite # 160
Santa Clara, CA 95054
USA
Tel: +1 408-470-7170
US Toll Free Tel: 1-866-602-6099
US Toll Free Fax: 1-866-602-1795

www.cardivamedical.com

EC REP

Authorized Representative:

MedPass International Ltd.
Bretforton, Evensham, Worcestershire.,
WR11 7JJ,United Kingdom
Tel/Fax: +44 (0) 14 52 619 222
medpass.ar@medpass.org

LIMITED WARRANTY

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

23. Attachment 4: Patient Experience Survey

SUBJECT ID: [ ][ ] - [ ][ ][ ]
SITE # SUBJECT #

SUBJECT INITIALS: [ ][ ][ ]
F M L

Patient Experience Survey

Instructions to the Research Staff:

- For <u>all subjects</u> during Discharge Eligibility Evaluation, please provide the following survey pages one at a time to the subject under evaluation.
- The Survey consists of 3 levels that should be read and answered in order.
- On completion of each survey page, review for completeness and clarity, then provide the subject the next survey page, as applicable.
- On completion of all applicable survey pages, enter the data in the eCRF and file source documents.

Instructions to the Patient: Please read the questions and respond by <u>circling only one number</u> from 0-10 on the scale below each question.

Examples:

1. How do you feel about the length of time you spent lying on your back after the procedure? 0 1 2 3 **(4)** 5 6 7 8 9 10 Very Dissatisfied Very Satisfied	2. How do you feel about the length of time you spent lying on your back after the procedure? 0 1 2 3 **(4 5)** 6 7 8 9 10 Very Dissatisfied Very Satisfied
Correct	Incorrect

Prior to Administering the Survey to the patient, determine which Survey forms will be needed:

- Survey Level 1: All Patients (Page 2)
- Survey Level 2:
  - Manual Compression (Page 3)
  - Mid-Bore VVCS Treatment Arm *(circle one)* (Page 4)
- Survey Level 3: Previous Cardiac Ablation Procedure? Yes / No *(circle one)*
  - If Yes, Page 5

	/
Printed name of person administering survey	Title
	/
Signature	Date

SUBJECT ID: [ ][ ] - [ ][ ][ ]
SITE # SUBJECT #

SUBJECT INITIALS: [ ][ ][ ]
F M L

All Patients:
Level 1 – Patient Experience during Bedrest

Instructions: Please read the questions and respond by circling only one number from 0-10 on the scale below each question.

1. How do you feel about the length of time you spent lying on your back after the procedure?

0 1 2 3 4 5 6 7 8 9 10

Very Dissatisfied Very Satisfied

---

2. Please rate the discomfort you felt while lying on your back after the procedure.

0 1 2 3 4 5 6 7 8 9 10

Very Dissatisfied Very Satisfied

---

3. Please rate the pain you felt while lying on your back after the procedure.

0 1 2 3 4 5 6 7 8 9 10

Very Dissatisfied Very Satisfied

Signature Date

SUBJECT ID: [ ][ ] - [ ][ ][ ]
SITE # SUBJECT #

SUBJECT INITIALS: [ ][ ][ ]
F M L

Manual Compression Arm:

Level 2 – Patient Experience: Bedrest Preferences

Patient Instructions: Please read the questions and respond by circling only one number from 0-10 on the scale below each question.

1. How would have you felt about the length of time you spent lying on your back after the procedure if it were 2-3 hours shorter?

0 1 2 3 4 5 6 7 8 9 10

Very Dissatisfied Very Satisfied

---

2. Please rate the discomfort you would have felt lying on your back after the procedure if it were 2-3 hours shorter.

0 1 2 3 4 5 6 7 8 9 10

Very Dissatisfied Very Satisfied

---

3. Please rate the pain you would have felt lying on your back after the procedure if it were 2-3 hours shorter.

0 1 2 3 4 5 6 7 8 9 10

Very Dissatisfied Very Satisfied

Signature Date

SUBJECT ID: [ ][ ] - [ ][ ][ ]
SITE # SUBJECT #

SUBJECT INITIALS: [ ][ ][ ]
F M L

Treatment Device (Mid-Bore VVCS) Treatment Arm

Level 2 – Patient Experience: Bedrest Preferences

Patient Instructions: Please read the questions and respond by circling only one number from 0-10 on the scale below each question.

1. How would have you felt about the length of time you spent lying on your back after the procedure if it were 2-3 hours longer?

0 1 2 3 4 5 6 7 8 9 10

Very Dissatisfied Very Satisfied

---

2. Please rate the discomfort you would have felt lying on your back after the procedure if it were 2-3 hours longer.

0 1 2 3 4 5 6 7 8 9 10

Very Dissatisfied Very Satisfied

---

3. Please rate the pain you would have felt lying on your back after the procedure if it were 2-3 hours longer.

0 1 2 3 4 5 6 7 8 9 10

Very Dissatisfied Very Satisfied

Signature Date

SUBJECT ID: [ ][ ] - [ ][ ][ ]
SITE # SUBJECT #

SUBJECT INITIALS: [ ][ ][ ]
F M L

Patients with a Previous Cardiac Ablation Procedure

Level 3: Comparison to Bedrest Experience from the Previous Procedure

1. How do you feel about the length of time you spent lying on your back compared to your previous procedure?

0 1 2 3 4 5 6 7 8 9 10

Very Dissatisfied Very Satisfied

---

2. Please rate the discomfort you felt while lying on your back compared to your previous procedure.

0 1 2 3 4 5 6 7 8 9 10

Very Dissatisfied Very Satisfied

---

3. Please rate the pain you felt while lying on your back compared to your previous procedure.

0 1 2 3 4 5 6 7 8 9 10

Very Dissatisfied Very Satisfied

Signature Date