ReliaSeal / P22-8301

Version: 3.0 / 31Jan2023

Clinical Study Protocol

A MULTICENTER, PROSPECTIVE, RANDOMIZED, CONTROLLED, OPEN LABEL TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF MYNX CONTROL™ VENOUS VASCULAR CLOSURE DEVICE 6F-12F VS. MANUAL COMPRESSION IN PATIENTS WHO HAVE UNDERGONE ENDOVASCULAR PROCEDURES UTILIZING UP TO 12F PROCEDURAL SHEATHS

ReliaSeal

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Model/Specification:	MX61260
Sponsor's Name/Address:	Cordis US Corp. 14201 NW 60th Ave Miami Lakes, FL 33014
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Approval Signatures

I AM THE PRIMARY AUTHOR OF THIS STUDY PROTOCOL AND CONFIRM TO THE BEST OF MY KNOWLEDGE IT IS COMPLETE AND ACCURATE.

Name	Role	Signature	Date
Jenny Jimenez	Clinical Project Manager	Jenny Jimenez	*Electronically signed by: Jenny Jimenez* *Reason: Reviewed* *Date: Feb 3, 2023 09:54 EST*

I HAVE REVIEWED THE STUDY PROTOCOL AND CONFIRM TO THE BEST OF MY KNOWLEDGE IT IS COMPLETE AND ACCURATE.

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A MULTICENTER, PROSPECTIVE, RANDOMIZED, CONTROLLED, OPEN LABEL TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF MYNX CONTROL™ VENOUS VASCULAR CLOSURE DEVICE 6F-12F VS. MANUAL COMPRESSION IN PATIENTS WHO HAVE UNDERGONE ENDOVASCULAR PROCEDURES UTILIZING UP TO 12F PROCEDURAL SHEATHS

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Investigator Protocol Signature Page

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study in accordance with the design and specific provisions outlined herein.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the investigational product and the conduct of the study.

I will use the informed consent form approved by Sponsor and the IRB and will fulfill all responsibilities for submitting pertinent information to the IRB responsible for this study.

I also agree to report all information or data in accordance with the protocol and I agree to report any serious adverse events (SAE), and unanticipated adverse device effect (UADE) as defined in the protocol.

I further agree that Sponsor and/or designee have access to any original source documents from which case report form (CRF) information may have been generated.

I also agree to have control over all clinical supplies (including investigational product) provided by Sponsor and/or designees and collect and handle all clinical specimens in accordance with the protocol.

The below signed confirm herewith to have read and understood this study protocol and/or amendment and appendices; furthermore, to accomplish this study in accordance with the protocol, ICH/GCP guidelines, applicable international standards and all applicable country, local and federal regulations; and to accept respective revisions conducted by authorized personnel of Sponsor and by regulatory authorities.

_____ Principal Investigator (print)	
_____ Principal Investigator (signature)	_____ Date
_____ Institution Name/Location	

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A MULTICENTER, PROSPECTIVE, RANDOMIZED, CONTROLLED, OPEN LABEL TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF MYNX CONTROL™ VENOUS VASCULAR CLOSURE DEVICE 6F-12F VS. MANUAL COMPRESSION IN PATIENTS WHO HAVE UNDERGONE ENDOVASCULAR PROCEDURES UTILIZING UP TO 12F PROCEDURAL SHEATHS

ReliaSeal
Protocol Number: P22-8301
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Protocol Synopsis

Primary Objective	To demonstrate safety and efficacy of the MYNX CONTROL™ Venous Vascular Closure Device 6F-12F vs. manual compression in sealing femoral venous access sites in patients who have undergone endovascular procedures utilizing up to 12F, with single or multiple access sites in one or both limbs.
Device Name	MYNX CONTROL™ Venous Vascular Closure Device 6F-12F
Device Model Number	MX61260CL
Device Category	Class III medical device
Indication for Use	Current indication: MYNX CONTROL™ Vascular Closure Device is indicated for use to seal femoral arterial access sites while reducing times to hemostasis and ambulation in patients who have undergone diagnostic or interventional endovascular procedures utilizing a 5F, 6F, or 7F procedural sheath. Proposed expanded indication sought: The MYNX CONTROL™ Venous VCD 6F-12F is indicated for use to seal femoral venous access sites while reducing times to hemostasis and ambulation in patients who have undergone diagnostic or interventional endovascular procedures utilizing 6F to 12F procedural sheaths, with single or multiple access sites in one or both limbs.
Hypothesis	Time to ambulation will be significantly less for patients treated with the MYNX CONTROL ™ Venous Vascular Closure Device than those using manual compression. Time to hemostasis will be at least 5 minutes less for patients treated with the MYNX CONTROL ™ Venous Vascular Closure Device than those using manual compression. Rate of combined major venous access site closure-related complications through 30 days post procedure for patients treated with the MYNX CONTROL ™ Venous Vascular Closure Device will be non-inferior to the rate for patients using manual compression.
Study Design	A multicenter, prospective, randomized, controlled, open label clinical trial designed to evaluate safety and efficacy of use of MYNX CONTROL™ Venous Vascular Closure Device 6F-12F vs. manual compression to seal femoral access sites in patients who have undergone endovascular procedures utilizing up to 12F procedural sheaths in one or both limbs.
Number of Patients	204 patients (2:1 randomized - 136 VCD:68 manual compression)
Reference/Control Treatment	Manual Compression

Study Purpose	To demonstrate safety and efficacy of the MYNX CONTROL™ Venous Vascular Closure Device 6F-12F vs. manual compression in sealing femoral venous access sites in patients who have undergone endovascular procedures utilizing one or more procedural sheaths up to 12F with single or multiple access sites in one or both limbs.
Study Centers	Approximately 15 study sites will participate in United States, with a minimum of 5 sites enrolling in the trial.
Duplex Ultrasound sub study	At select sites, a subset of 72 subjects (48 from the device group and 24 from the control group) will have an ultrasound examination of the access sites performed during the index procedure, at the time of discharge and at the 30 day (± 7 days) office visit (only for those subjects that have documented evidence of complications at the discharge ultrasound).
Eligibility Criteria	Inclusion Criteria: ALL patients must meet the following criteria prior to enrollment: 1.) Age ≥18 2.) Able and willing to provide informed consent and to complete a follow-up visit at 30 ± 7 days 3.) Planned catheter-based procedures via the common femoral vein(s) using up 6F to 12F introducer sheaths which meet indications for elective, nonemergent interventions of disease state, without contraindications for emergent vascular surgery or manual compression of the venous access sites Exclusion Criteria: Patients will be excluded if ANY of the following exclusion criteria apply: 1.) Any use of systemic steroids (IV or oral) within 30 days of procedure 2.) History of deep vein thrombosis, pulmonary embolism, or thrombophlebitis within 6 months of procedure 3.) Presence of thrombocytopenia (platelet count < 100,000 cells/mm3) or anemia (hemoglobin < 10 g/dL, hematocrit < 30%) 4.) History of bleeding disorders such as hemophilia or von Willebrand's disease 5.) Currently involved in any other investigational clinical trial 6.) Documented history of uncontrolled hypertension (i.e., systolic blood pressure > 180 mm Hg), or critical illness requiring intravenous vasopressors for blood pressure stabilization 7.) Femoral arteriotomy or venotomy in either limb within 10 days pre procedure 8.) Use of VCD in either limb within 30 days of procedure 9.) Any planned procedure involving femoral arterial or venous access in either limb within 30 days of procedure or prior to study exit 10.) Renal insufficiency (i.e., serum creatinine > 2.5 mg/dL) 11.) Patients who are pregnant, planning to become pregnant during the study period, or lactating 12.) Body-mass index (BMI) > 45 kg/m2 or <20 kg/m2 13.) Unable to routinely walk at least 20 feet without assistance

	14.) Known allergy/adverse reaction to polyethylene glycol or contrast medium 15.) Planned procedures (including staged) or concomitant conditions/comorbidities that per investigator's judgment may extend ambulation attempts beyond 2-3 hours, and/or require extended hospitalization or re-hospitalization 16.) Previous vascular surgery or repair in the vicinity of the target access site within the previous 90 days of the procedure 17.) Active systemic infection, or cutaneous infection or inflammation in the vicinity of the target access site 18.) Current COVID-19 infection (with or without symptoms), positive test for COVID- 19 within 14 days, or recent exposure to a person with COVID-19 infection 19.) Patients who refuse blood transfusion if it were to be needed 20.) Patients with expected life of less than 30 days Patients who meet ANY of the following criteria during the index procedure will be excluded: 1.) Any attempt at femoral arterial access or inadvertent arterial puncture with hematoma during the procedure 2.) Any procedural complications that may interfere with routine recovery, ambulation, or discharge eligibility times 3.) Physician deems that a different hemostasis approach for venous access sites is necessary 4.) Physician deems that the subject should not attempt protocol-required ambulation (reference ambulation protocol per section 14.2) 5.) Venous access site location is noted to be above the inguinal ligament (cephalad to lower half of the femoral head or the inferior epigastric vein origin from the external iliac vein) 6.) Intra-procedural bleeding around sheath, or suspected intraluminal thrombus, hematoma, pseudoaneurysm, or AV fistula 7.) 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.) 8.) A < 6F or > 12F procedural sheath is present at any time during the procedure or at closure
Primary Endpoint(s)	Primary Effectiveness Endpoint • Time to Ambulation (TTA): Defined as time (in hours) between removal of the MYNX CONTROL™ Venous Vascular Closure Device 6F-12F device (device group) or of the final sheath (control group) and when subject stands and walks 20 feet without evidence of rebleeding from any femoral venous access site. • Time to Hemostasis (TTH): Defined as time (in minutes) between removal of each MYNX CONTROL™ Venous Vascular Closure Device 6F-12F device (device group) or of each sheath (control group) and first observed and confirmed venous hemostasis (per access site analysis)

	Primary Safety Endpoint: Rate of CEC adjudicated combined **major** venous access site closure- related complications through 30 days post procedure, attributed directly to VCD or manual compression without other likely cause. • Access site-related bleeding requiring transfusion, surgical intervention, or rehospitalization • Vascular injury requiring surgical repair • Access site-related infection confirmed by culture and sensitivity, requiring intravenous antibiotics and/or extended hospitalization • New onset, permanent (i.e., persisting at 30-day follow-up) access site-related nerve injury • New onset access site-related nerve injury 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 Endpoint(s)	Secondary Safety Endpoint: Rate of CEC adjudicated combined **minor** venous access site closure related complications within 30 days post-procedure, attributed directly to VCD or manual compression without other likely cause. • Pseudoaneurysm – Treated with thrombin injection, fibrin adhesive injection, or ultrasound guided compression and documented by ultrasound • Pseudoaneurysm – Not requiring treatment • AV Fistula requiring treatment, documented by ultrasound • AV Fistula not requiring treatment, documented by ultrasound • Access site related hematoma > 6 cm documented by ultrasound • Access site-related bleeding requiring > 30 min to achieve hemostasis • Late access site-related bleeding (following hospital discharge eligibility) • Transient loss of ipsilateral lower extremity pulse • Ipsilateral deep vein thrombosis documented by ultrasound • Transient access site-related nerve injury • Access site-related vessel laceration • Access site wound dehiscence • Local access site infection confirmed by culture and sensitivity, treated with intramuscular or oral antibiotics – minor • Local access site inflammatory reaction – Minor • Allergic reaction • Ecchymosis

	Secondary Effectiveness Endpoints: • Time to Discharge Eligibility- defined as elapsed time (in hours) between removal of the final MYNX CONTROL™ Venous VCD (device group) or removal of the final sheath (control group) and when subject is eligible for discharge from the institution based on the assessment of the attending physician. • Procedural Success: attainment of final hemostasis at all venous access sites without major venous access site closure-related complications through 30 days • Device Success (for device group): ability to successfully deploy the MYNX CONTROL™ Venous VCD delivery system, deliver the polyethylene glycol hydrogel sealant, and achieve hemostasis (device group only)
Additional Endpoints	Pain score at time of discharge eligibility.
Sample Size	Total enrollment of 204 patients (2:1 randomized – 136 VCD: 68 manual compressions)
Duration of Subject Participation	ALL patients will be followed through 30 days post procedure. Once all enrolled patients have completed follow-up, the study will be considered complete.
Statistics/Testing Methods	Data analysis will follow the intention-to-treat principle and will be conducted at the per access site or per patient level as indicated below, with a non-inferiority analysis for primary safety endpoint and superiority analyses for primary and powered secondary effectiveness endpoint.

Table 1. Time and Event Schedule (Please refer to Section 14 for details)

	Screening (-30 to day 0)	At time of Index Procedure (day 0)	Post-Procedure/	Pre-discharge	1-Month (30 ± 7 days)
Informed consent (within 60 days of index procedure)	X				
Pre-op Inclusion / Exclusion Criteria Assessment	X				
Demographics	X				
Physical exam/Medical History	X				X
Laboratory Tests (PLT, WBC, HGB, HCT, creatinine, PT or INR)	X[1]				X
Intra-procedural Exclusion Criteria Assessment		X*			
Randomization		X			
Study Endpoint Data Collection:					
TTH determination		X			
TTA determination			X		
TTDE determination			X		
Device Success		X			
Procedure Success					X
Concomitant Medications (e.g., anti-platelet, anti-coagulant, anti-thrombotic agents, etc.)	X	X	X		X
Post Op Pain assessment			X		
Adverse Events		X	X		X
Ultrasound Exam (DUS sub-study only)				X **	X ***

[1] Laboratory tests should be done within -7 to 0 days of index procedure
* Intra-op inclusion/exclusion criteria will be evaluated once operator is able to visualize and assess sheath placement and the anatomy of all venous access sites
** Ultrasound is required for subjects in the DUS sub-study only
*** Ultrasound may be required at 30 days if complication is observed on discharge DUS for subjects in DUS sub-study

1 Study Management Team

Table 2: Study Management Team

Sponsor	Cordis US Corp
Medical Monitor	Nusrath Sultana, MD
National Principal Investigator	Javier Sanchez, MD
Monitoring	NAMSA
Data Management	Medrio
Safety Management	NAMSA
Statistics	NAMSA
Medical Writing	NAMSA
Duplex Ultrasound Core Lab	NAMSA

2 Introduction

Techniques for closure of an arteriotomy or venotomy site have evolved from direct suture-based surgical closure to the use of VCDs. VCDs were developed in the 1990s with the aim of achieving hemostasis efficiently in a way that is satisfactory to the patient with limited complications.[9, 10] Ideally, VCDs should safely attain complete hemostasis, close the access site regardless of the size, and this should be achievable even with the use of anticoagulants.[9]

The target patient population indicated for VCDs are patients undergoing diagnostic and/or interventional procedures involving access to the coronary or peripheral vascular system and patients with contraindications to undergo surgery due to operative risk and comorbidities. Following percutaneous vascular access, VCDs are used to achieve hemostasis after interventional or diagnostic endovascular procedures. VCDs, such as the MYNX VCD Product Family and EXOSEAL VCD Product Family provide a method of achieving hemostasis at the femoral access sites in patients who have undergone endovascular procedures utilizing a 5F, 6F, or 7F procedural sheath. These procedures are generally performed by physicians from a broad range of medical specialties to include interventional radiology, vascular surgery, and cardiology, as well as smaller subspecialists trained in the application of endovascular techniques. For this study, we have expanded the indication of the MYNX CONTROL VCD to include up to 12F procedural sheath for femoral venous access. Procedures treated using this larger bore sheath include, but are not limited to, cardiac ablations, structural heart procedures, and cardiac interventions.

The traditional and most used alternative to VCDs is manual compression (MC). MC is considered the standard of care and is relied upon either primarily or when VCDs fail. MC is labor-intensive and results in considerable discomfort for the patient. Meta-analyses comparing MC to VCDs showed that with MC there was an increase in time-to-hemostasis (TTH), time-to-ambulation (TTA). [15, 16] An increased risk of hematoma formation was associated with MC. [15] The rate of complications was comparable between VCDs and MC (12% for VCDs and 13% for MC), however, major complications were lower in the VCD group.[16] VCDs were associated with a low risk of infection and thrombosis (0.6% for infection; 0.3% for thrombosis).[16]

The MYNX CONTROL™ Venous Vascular Closure Device (VCD) is indicated for use to seal femoral arterial access sites while reducing times to hemostasis and ambulation in patients who have undergone diagnostic or interventional endovascular procedures utilizing a 5F, 6F or 7F procedural sheath.

2.1 Product characteristics

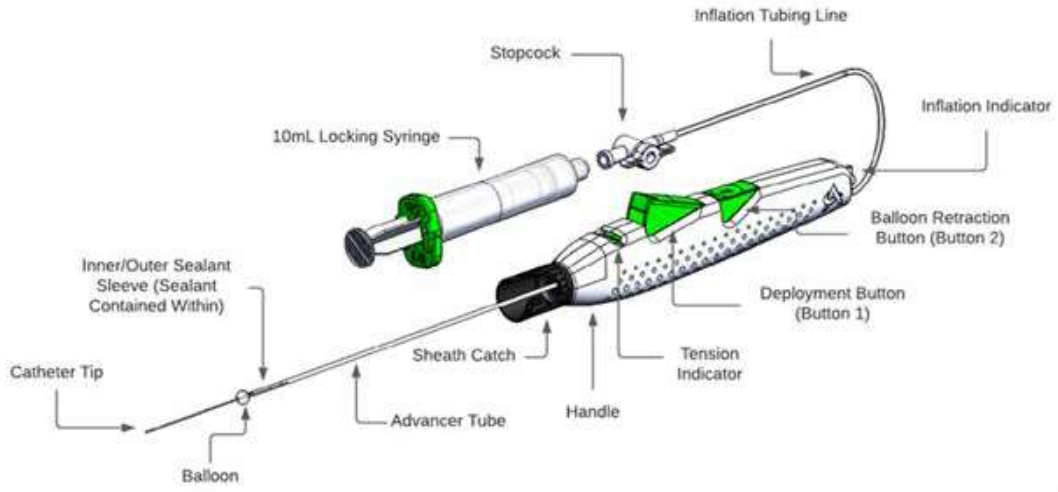
The MYNX CONTROL™ Venous Vascular Closure Device (VCD) is designed to achieve femoral vein hemostasis via delivery of the GRIP TECHNOLOGY™ sealant, an extravascular, water-soluble synthetic hydrogel, using a balloon catheter in conjunction with a standard procedural sheath. The GRIP TECHNOLOGY™ sealant is made of a polyethylene glycol (PEG) material which expands upon contact with blood and subcutaneous fluids. Refer to Figure 1 (below).

2.2 Structural composition, operation principle and mechanism of action

The MYNX VCD product family are designed to achieve hemostasis of femoral access sites following diagnostic or interventional endovascular procedures. Hemostasis is accomplished via delivery of an extravascular polyethylene glycol (PEG) sealant using a balloon catheter (delivery system) in conjunction with a standard procedural sheath. Upon contact with blood and subcutaneous fluids, the sealant expands and adheres to the arteriotomy or venotomy to achieve hemostasis. The sealant is resorbed by the body within 30 days.

The design of the MYNX CONTROL™ Venous VCD is based on the design of the current MYNX CONTROL™ VCD (arterial). The only difference in design is the Sheath Catch. The Sheath Catch facilitates the withdrawal of the 6F/7F Catheter Sheath Introducer (CSI) from the tissue tract during the withdrawal of the MYNX CONTROL™ VCD (current). This is achieved by a distal hook which latches onto the sideport on the CSI. The proposed sheath catch design on the MYNX CONTROL™ Venous VCD will be based on the current design but will allow larger CSIs (up to 12F) to fit into the Sheath Catch. Like the current Sheath Catch design, connection to the CSI will be achieved with a distal hook and be universally compatible with the leading CSI brands on the market.

Figure 1: MYNX CONTROL™ Venous Vascular Closure Device 6F-12F



3 Study Objectives

To demonstrate safety and efficacy of the MYNX CONTROL™ Venous Vascular Closure Device 6F-12F vs. manual compression in sealing femoral venous access sites in patients who have undergone endovascular procedures utilizing one or more procedural sheaths up to 12F.

4 Indication

Proposed Indications for Use:

The MYNX CONTROL™ Venous VCD 6F-12F is indicated for use to seal femoral venous access sites while reducing times to hemostasis and ambulation in patients who have undergone diagnostic or interventional endovascular procedures utilizing 6F to 12F procedural sheaths, with single or multiple access sites in one or both limbs.

5 Contraindications

There are no known contraindications for the MYNX CONTROL™ Venous Vascular Closure Device 6F-12F.

6 Precautions

The MYNX CONTROL™ Venous VCD should only be used by a trained licensed physician or healthcare professional. The MYNX CONTROL™ Venous VCD should not be used in patients with a known allergy to PEG. The MYNX CONTROL™ Venous VCD should not be used with sheaths longer than 12 cm effective length or incompatible sheaths listed in **Table 3.** Exposure to temperatures above 25°C (77°F) may damage the components.

Table 3

MANUFACTURER	DESCRIPTION
Cook	Check-Flo® Performer® Introducer

7 Warnings

Do not use if components or packaging appear to be damaged or defective or if any portion of the packaging has been previously opened. DO NOT REUSE OR RESTERILIZE. The MYNX CONTROL™ Venous VCD 6F-12F is for single use only. The catheter is loaded with a single Hydrogel sealant. Reuse of the device would result in no delivery of Hydrogel sealant. Reuse of this product, including after reprocessing and/or re-sterilization, may cause a loss of structural integrity which could lead to a failure of the device to perform as intended and may lead to a loss of critical labeling/use information all of which present a potential risk to patient safety. Do not use the MYNX CONTROL™ Venous VCD 6F-12F if the puncture site is located above the inguinal ligament based upon bony landmarks, since such a puncture site may result in a hematoma/bleed. Perform a femoral venogram (as applicable) to verify the location of the puncture site. Do not use the MYNX CONTROL™ Venous VCD 6F-12F if the puncture is through the posterior wall as such punctures may result in a retroperitoneal hematoma/bleed.

8 Benefits/Risks

8.1 Benefits

There are several resource and time saving benefits associated with the use of VCDs. Time-to-hemostasis (TTH), time-to-ambulation (TTA) and time-to-discharge eligibility(TTDE) have all been reported to be reduced with the use of VCDs.[70] Meta-analyses of RCTs showed that that TTH was significantly shorter with VCDs compared to MC.[12, 15, 16, 71, 72] TTH was reduced by approximately 11-17 minutes using VCDs compared to MC.[15, 71] TTA has also been shown to be significantly reduced by using VCDs compared to MC.[15, 16, 71] In a meta-analysis of RCTs, TTA was reduced by 4.5 hours using VCDs compared to MC.[71] One study showed that clip-based VCDs were associated with a shorter TTH and TTA compared to suture based-devices.[72] TTD was also shown to be shorter when VCDs were used compared to MC. However, it was noted that TTD has generally reduced since 2005 due to the emphasis on same day discharge.[71] The use of VCDs also has a cost-benefit, due to the reduction in labor incurred by MC, the decreased length of hospital stay and utilization of hospital resources.[70] Cost-effectiveness analysis shows that diagnostic or interventional procedures where VCDs were used were less expensive.[61] Other benefits of VCDs include improved patient satisfaction and comfort levels, due to the reduced TTA and earlier TTD.[61]

As per clinical study data available for CORDIS VCDs, the devices provide an acceptable risk/benefit profile. Based on the clinical study data accumulated to evaluate the safety and effectiveness of these devices, the results for clinical studies show excellent rates of technical success and reduced time to hemostasis, ambulation, and discharge for the CORDIS VCDs. This indicates that with the use of these devices, patients have the potential to experience significant clinical improvements.

The potential benefits of the MYNX CONTROL™ Venous VCD for 6-12F over manual compression alone to achieve venous hemostasis have not yet been proven and outcomes will be evaluated because of this trial.

8.2 Risks

The most serious recognized risks associated with femoral vessel closure procedures occur rarely and include, but are not limited to, the following:

- Vascular injury requiring repair
- New onset, permanent (i.e., persisting at 30-day follow-up) access site-related nerve injury
- Bleeding or hematoma at any venous access site requiring transfusion, surgical intervention, or re-hospitalization
- New ipsilateral lower extremity ischemia requiring invasive/non-invasive intervention
- Generalized access site related infection requiring intravenous antibiotics and/or extended hospitalization
- Retroperitoneal bleed

- Vessel Occlusion
- Pulmonary embolism
- Death

Other less serious potential risks (can be managed clinically or pharmaceutically) are included, but are not limited to, the following:

- Pseudoaneurysm – Treated with thrombin injection
- Pseudoaneurysm – Not requiring treatment
- AV Fistula
- Hematoma > 6 cm
- Access site-related bleeding requiring > 30 min to achieve hemostasis
- Late access site-related bleeding (following hospital discharge)
- Ipsilateral lower extremity arterial emboli
- Transient loss of ipsilateral lower extremity pulse
- Ipsilateral deep vein thrombosis
- Transient access site-related nerve injury
- Access site-related vessel laceration
- Local access site infection – Minor
- Local access site inflammatory reaction – Minor
- Allergic reaction
- Ecchymosis

9 Study Design

9.1 Overview

This study is a multicenter, prospective, randomized, controlled, open label clinical study to enroll 204 patients with an additional group of patients to be part of the initial roll-in phase. The 204 patients will be randomized to either a device arm or a manual compression arm using a 2:1 randomization scheme (136 MYNX CONTROL™ patients and 68 manual compression patients). Two (2) roll-in patients per physician will be allowed. All patients who sign the informed consent and randomized to either treatment group will be followed through 30 days post procedure. There will be up to 15 participating study sites, with a minimum of five (5) sites, all located in the United States. Details of the randomization and roll-in process can be found in section 16.1. Each study site will be limited to enrolling a maximum of 45 subjects.

9.2 Duplex 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 48 device subjects and 24 MC subjects pre-discharge and potentially again at the 30-day follow-up if an observation of a complication occurred on the pre-discharge ultrasound. Specific investigational sites will be designated as ultrasound sites. These sites will include subjects in the ultrasound subset imaging until a total of 72 patients have been evaluated in both groups. Informed consent will be obtained from all

subjects participating in this sub-study. All sub-study sites will be instructed to perform duplex ultrasonography of the femoral vascular structures. Images will be uploaded and interpreted by an independent core lab. NAMSA is the core lab for this sub study.

NAMSA
4 World Trade Center
150 Greenwich Street, 49th FL
New York, NY 10007

10 Study Population/Selection Criteria

The following outline the specific inclusion and exclusion criteria for the study. Before the study randomization, a patient must meet all the inclusion and no exclusion criteria.

Prior to any study-specific activities, all patients must sign and date the most current IRB-approved Informed Consent Form (ICF).

10.1 Inclusion Criteria

Patients must meet ALL the following inclusion criteria to be enrolled in the study:

1. Age ≥18
2. Able and willing to provide informed consent and to complete a follow-up visit at 30 days
3. Planned catheter-based procedures via the common femoral vein(s) using up 6F to 12F introducer sheaths which meet indications for elective, nonemergent interventions of disease state, without contraindications for emergent vascular surgery or manual compression of the venous access sites

10.2 Exclusion Criteria

Patients will be excluded if they meet ANY of the following exclusion criteria:

10.2.1 Pre-procedural Exclusion Criteria

Patients who meet any of the following criteria before the index procedure will be excluded:

1. Any use of systemic steroids (IV or oral) within 30 days of procedure
2. History of deep vein thrombosis, pulmonary embolism, or thrombophlebitis within 6 months of procedure
3. Presence of thrombocytopenia (platelet count < 100,000 cells/mm3) or anemia (hemoglobin < 10 g/dL, hematocrit < 30%)
4. History of bleeding disorders such hemophilia or von Willebrand's disease
5. Currently involved in any other investigational clinical trial
6. Documented history of uncontrolled hypertension (i.e., systolic blood pressure > 180 mm Hg), or critical illness requiring intravenous vasopressors for blood pressure stabilization
7. Femoral arteriotomy or venotomy in either limb within 10 days pre procedure

8. Use of VCD in either limb within 30 days of procedure
9. Any planned procedure involving femoral arterial or venous access in either limb within 30 days or prior to study exit
10. Renal insufficiency (i.e., serum creatinine > 2.5 mg/dL)
11. Patients who are pregnant, planning to become pregnant during the study period, or lactating
12. Body-mass index (BMI) > 45 kg/m2 or <20 kg/m2
13. Unable to routinely walk at least 20 feet without assistance
14. Known allergy/adverse reaction to polyethylene glycol or contrast medium
15. Planned procedures (including staged) or concomitant conditions/comorbidities that per investigator's judgment may extend ambulation attempts beyond 2-3 hours, and/or require extended hospitalization or re-hospitalization
16. Previous vascular surgery or repair in the vicinity of the target access site within the previous 90 days of the procedure
17. Active systemic infection, or cutaneous infection or inflammation in the vicinity of the target access site
18. Current COVID-19 infection (with or without symptoms), positive test for COVID- 19 within 14 days, or recent exposure to a person with COVID-19 infection
19. Patients who refuse blood transfusion if it were to be needed
20. Patients with expected life of less than 30 days

10.2.2 Intra-Procedural Exclusion Criteria

Patients who meet any of the following criteria during the index procedure will be excluded:

1. Any attempt at femoral arterial access or inadvertent arterial puncture with hematoma during the procedure
2. Any procedural complications that may interfere with routine recovery, ambulation, or discharge eligibility times
3. Physician deems that a different hemostasis approach for venous access sites is necessary
4. Physician deems that the subject should not attempt protocol required ambulation (reference ambulation protocol per section 14.2)
5. Venous access site location is noted to be above the inguinal ligament (cephalad to lower half of the femoral head or the inferior epigastric vein origin from the external iliac vein)
6. Intra-procedural bleeding around sheath, or suspected intraluminal thrombus, hematoma, pseudoaneurysm, or AV fistula
7. 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.)
8. A < 6F or > 12F procedural sheath is present at any time during the procedure or at closure

11 Study Endpoints

11.1 Primary Endpoints

11.1.1 Primary Safety Endpoint

Rate of CEC adjudicated combined **major** venous access site closure-related complications through 30 days post procedure, attributed directly to VCD or manual compression without other likely cause.

- Access site-related bleeding requiring transfusion, surgical intervention, or rehospitalization
- Vascular injury requiring surgical repair
- Access site-related infection confirmed by culture and sensitivity, requiring intravenous antibiotics and/or extended hospitalization
- New onset, permanent (i.e., persisting at 30-day follow-up) access site-related nerve injury
- New onset access site-related nerve injury 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)

11.1.2 Primary Effectiveness Endpoint

Time to Ambulation (TTA): Defined as elapsed time (in hours) between removal of the MYNX CONTROL™ Venous Vascular Closure Device 6F-12F device (device group) or of the final sheath (control group) and when subject stands and walks 20 feet without evidence of rebleeding from any femoral venous access site.

Time to Hemostasis (TTH): Defined as elapsed time (in minutes) between removal of each MYNX CONTROL™ Venous Vascular Closure Device 6F-12F device (device group) or of each sheath (control group) and first observed and confirmed venous hemostasis (per access site analysis).

11.2 Secondary Endpoints

11.2.1 Secondary Safety Endpoint

Rate of CEC adjudicated combined **minor** venous access site closure related complications within 30 days post-procedure, attributed directly to VCD or manual compression without other likely cause. Types of minor complications include:

- Pseudoaneurysm – Treated with thrombin injection, fibrin adhesive injection, or ultrasound guided compression and documented by ultrasound
- Pseudoaneurysm – Not requiring treatment
- Arteriovenous fistula requiring treatment, documented by ultrasound
- Arteriovenous fistula not requiring treatment, documented by ultrasound
- Access site-related Hematoma > 6 cm documented by ultrasound
- Access site-related bleeding requiring > 30 min to achieve hemostasis
- Late access site-related bleeding (following hospital discharge eligibility)
- Transient loss of ipsilateral lower extremity pulse
- Ipsilateral deep vein thrombosis documented by ultrasound
- Transient access site-related nerve injury
- Access site-related vessel laceration
- Access site wound dehiscence
- Localized access site infection confirmed by culture and sensitivity, treated with intramuscular or oral antibiotics– Minor,
- Local access site inflammatory reaction – Minor
- Allergic reaction
- Ecchymosis

11.2.2 Secondary Effectiveness Endpoints include the following:

Time to Discharge Eligibility: defined as elapsed time (in hours) between removal of the final MYNX CONTROL™ Venous Vascular Closure Device 6F-12F device (device group) or removal of the final sheath (control group) and when subject is eligible for discharge from the institution based on the assessment of the attending physician.

Procedural Success: attainment of final hemostasis at all venous access sites without major venous access site closure-related complications through 30 days.

Device Success (for device group): ability to successfully deploy the MYNX CONTROL™ Venous VCD delivery system, deliver the polyethylene glycol hydrogel sealant, and achieve hemostasis (device group only).

11.3 Other/Additional Endpoints

- Venous access site related pain at time of discharge eligibility measured by pain scores

12 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 which are not standard-of-care. The study team shall follow all steps below when obtaining Informed Consent:

1. Provide each prospective subject/legal representative with a full explanation of the study (including all potential benefits and risks) and the informed consent form (ICF).

    a. The informed consent form (ICF) should enable the subject or legal representative to understand:
        - the nature, objectives, benefits, implications, risks, and inconveniences of the clinical investigation
        - the subject's rights and guarantees regarding his/her protection, his/her right to refuse to participate in and the right to withdraw from the clinical investigation at any time without any resulting detriment and without having to provide any justification
        - the conditions under which the clinical investigation is to be conducted, including the expected duration of the subject's participation in the clinical investigation; and the possible treatment alternatives, including the follow-up measures if the participation of the subject in the clinical investigation is discontinued.

    b. The ICF shall:
        - Be comprehensive, concise, clear, relevant, and understandable to the subject or legal representative
        - Be provided in a prior interview with a member of the clinical investigation team who is appropriately qualified under national law and delegated to this responsibility; gives special attention to the information needs of specific patient populations and individual patients as well as to the methods used to provide the information; verifies the subject has understood the information
        - Include information about an applicable damage compensation system; and
        - Include the unique, study identification number and information about the availability of clinical study results to the subject, to the extent possible, via a clinical study report and summary presented in terms understandable to the intended user, irrespective of the outcome of the clinical study.

2. Allow the prospective subject/legal representative to read the most current IRB approved informed consent form (ICF) and address any/all their questions.

3. Obtain written consent (signature and date on the ICF) from the prospective subject/legal representative after the Investigator and/or designee is assured they understand all implications of participating in the study.

A copy of the ICF signed by the subject/legal representative and the Investigator and/or designee obtaining consent will be provided to the subject. In addition to the most current, IRB-approved ICF, the subject/legal representative must provide a signed HIPAA authorization and any other locally required documents, as applicable.

The Investigator and/or designee must clearly document the process for obtaining informed consent, including the date/time of obtaining consent, in the subject's medical record. It is the Investigator's responsibility to ensure that the informed consent process is performed in accordance with ICH-GCP applicable international standards and all applicable local and federal regulations.

Documented informed consent must be obtained within 60 days prior to the index procedure.

Exceptions to obtaining documented informed consent prior to the initiation of study-specific procedures would be in cases where necessary to eliminate an immediate apparent hazard and protect the life or physical well-being of a study subject.

13 Screening and Enrollment

13.1 Screening Period

13.1.1 Screening Assessments

In addition to obtaining written consent, the following assessments must be performed, and the subject verified to meet all pre-procedural inclusion criteria and none of the exclusion criteria prior to the procedure.

1) **Demographic Data**: Including but not limited to age, sex, weight, height, and race.
2) **Medical/Surgical History**: (30 days prior to the procedure) Review and documentation of subject's medical history, allergy assessment and risk factors.
3) **Physical Examination**: Assessment per sites Standard of Care and to include collection of concomitant med and Laboratory Evaluations as below, height, weight, and BMI
4) **Concomitant Medications:** 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
5) **Laboratory Evaluations:** (within one week prior to index procedure):
   - blood routine examination (PLT, WBC, HCT, HGB, and creatinine),
   - coagulation function (prothrombin time (PT) or INR),
   - pregnancy testing for women with fertility.

13.1.2 Screen Failures and Pre-screen Failures

Any consented patient who is confirmed to not qualify for study participation according to the eligibility criteria will be considered a screen failure and will neither be treated with the

investigational device nor be followed per protocol. Signed informed consent forms and all applicable documentation including source records indicating rationale for screen failure classification and screening logs will be reviewed during monitoring visits for all screen failure patients.

Pre-screen failures are defined as patients who are confirmed to not qualify for study participation according to the eligibility criteria after review of their medical records (i.e. prior to providing informed consent). Such patients will neither be treated with the study devices nor followed per protocol.

13.2 Enrollment

The subject will be enrolled into the study at the end of the index procedure and once all procedural sheaths are in place under imaging guidance. It is at this time that the anatomy of all venous access sites is evaluated, and intra-procedural eligibility criteria can be verified. 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, then the subject is eligible for randomization.

14 Treatment Plan

14.1 Index Procedure

The Instructions for Use (IFU) provides detailed information on the product, safety, storage, design, deliverability, and sizing specifications. All information within the IFU should be referenced prior to each procedure and implantation of the study device.

If a subject is randomized to receive manual compression, it should be performed according to the institution's standard of care 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.

If a subject is on Warfarin, any pre-procedure standard of care requirements should be followed.

The following will be collected at the time of the procedure:

- **A0:** Time of first index procedure sheath insertion
- **A1 Time:** time of removal of final index procedure device
- **Sheath sizes used during procedure**
- For each access site, the following should be recorded:
  - Access site location (left/right leg and location with respect to 2nd access site, if applicable)
  - **HX.1 Time:** time of removal of MYNX CONTROL™ Venous device (device group) or removal of sheath (control group)

- **HX.2 Time:** time venous hemostasis is achieved.
- Confirm venous hemostasis is maintained at 5 min after recorded hemostasis time (HX.2)
- Use of adjunctive compression (e.g., light manual compression, sandbags, or mechanical compression devices)

14.2 Post-Procedure Care/Discharge

Following the index procedure, the site will notify the Sponsor of the subject enrollment status within the study database

The following will be documented after the procedure:

1. **A2 Time:** Date and time the subject was able to ambulate 20 feet without venous re-bleeding from the access site(s).
2. **A3 Time:** Date and time the subject is eligible for discharge based on the assessment of the attending physician or delegate.
3. **A4 Time:** Date and time the subject was discharged.
4. Concomitant Medications: 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
5. Adverse event monitoring, including labs as per standard of care to assess any adverse event
6. Time to Ambulation- Defined as time (in hours) between removal of the final VCD (device group) or of the final sheath (control group) and when subject stands and walks 20 feet without evidence of rebleeding from any femoral venous access site.

NOTE: Since TTA is a primary effectiveness endpoint, the following ambulation guidelines apply to both groups.

- For the device group, ambulation must be attempted within 2-2.5 hours from time of final VCD removal. The groin should be checked every 15 minutes to verify status. Any ambulation delay beyond 2.5 hours will be considered a protocol deviation unless it is medically justified and documented.
- For the control group, institutional guidelines should be followed for ambulation. The groin should be checked every 15 minutes to verify status. Reasons for any ambulation delays beyond the institution's standard of practice should be documented.

7. Time to Discharge Eligibility- defined as elapsed time between removal of the final MYNX CONTROL™ Venous VCD (device group) or removal

of the final sheath (control arm) and when subject is eligible for discharge from the institution based on the assessment of the attending physician or delegate. (Per-patient analysis)

8. Pain scale assessment
9. Duplex Ultrasound (pre-discharge) for those patients enrolled in DUS sub-study

NOTE 1: 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.

NOTE 2: TTDE is not intended to impact the actual discharge time of the subjects from the hospital. Any delay of this discharge eligibility determination (i.e. >30 minutes following successful ambulation) unrelated to access site(s) assessment will be documented as a protocol deviation.

14.3 Recommended Medication Regimen

Discharge medication should be administered per institutions standard of care and at the discretion of the Investigator. Details of this regimen must be recorded in the appropriate Case Report Form.

14.4 Follow-up Visits/Assessments

All subjects will be required to complete a 30±7-day follow-up. The follow-up will include the following assessments:

1) **Concomitant Medications:** 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
2) **Laboratory Evaluations:**
   - blood routine examination (PLT, WBC, HCT, HGB and creatinine),
   - coagulation function (prothrombin time (PT) or INR)
3) **Adverse event monitoring**
4) **Duplex Ultrasound:** for those subjects included in the DUS sub-study where a documented access site complication has been observed on the Discharge Ultrasound. Subjects should have their ultrasound appointments scheduled to ensure compliance.

NOTE: Every effort should be made to complete the required 30-day follow-up assessments on-site. If the subject is unable to complete an on-site 30-day follow-up, visit may be conducted by phone. If visit is conducted via phone, concomitant medications and safety information should be collected from subject or from subject's friend/family, if possible. Regardless, if visit is on-site or via phone, every

attempt should be made to acquire all study assessments (including lab evaluations).

For DUS subset study – this must be obtained on-site. If visit is out of window to obtain DUS, document this as protocol deviation.

A Protocol Deviation will need to be completed for all study subjects who do not complete all 30-day follow-up visit assessments. If the missed visit is COVID-related, it will be categorized as such in the protocol deviation.

14.5 Lost to Follow-up

For all active subjects, the site must first make three (3) contact attempts to reach the subject. If unsuccessful, the Investigator must then send a certified letter to the subject. All contact attempts must be adequately documented in the subject's source documents. When possible, the subject's primary care physician should also be asked for assistance with contacting the subject.

The subject will be considered lost to-follow-up only under the following circumstances:

- The site learns that all methods of contacting the subject are no longer viable (e.g., telephone number not in service, no forwarding address provided, no current/correct contact information available from the subject's primary care physician).
- Failure to reach/hear from the subject for the final protocol-required follow-up visit after all required contact attempts have been made.

14.6 Unscheduled Visits

Unscheduled follow-up visits may be required to evaluate a subject from time to time to ensure the safety of study subjects. All complications and adverse events will be evaluated by the Investigator and reported according to Sponsor and IRB regulations.

If an unscheduled follow-up visit is required, the site study team will assess if the subject has undergone any interventional treatment or experienced any adverse events since the last protocol specified visit and will record such information on the appropriate CRF pages. All relevant information required to assess the event should be maintained in the subject's medical records and all relevant documentation required for event adjudication should be provided as requested by the Sponsor.

The following assessments may need to be completed at an unscheduled visit:

- Concomitant medications
- Physical examination
- Duplex Ultrasound (for subjects in the DUS sub-study with complications at discharge DUS)
- Adverse event monitoring
- Laboratory evaluations (see follow-up visit assessments in section 14.4)

14.7 Subject Early Discontinuation

Every subject should be encouraged to remain in the study until they have completed the final, protocol-required follow-up visit at 30 days +/- 7 days post-discharge. If subject participation is prematurely discontinued, the reason for such must be documented in the subject's source documents and the CRF. Possible reasons for a subject's early exit from the study may include, but are not limited to, the following:

- Withdrawal of consent – Subject decides to withdraw from the study. This decision must be "independent" (i.e., made by the subject) and documented in the subject's source records and the CRF. The reason for withdrawal of consent should also be inquired from the subject and documented if provided.
- Physician discretion – The Investigator may choose to withdraw a subject from the study for reasons which include, but are not limited to, safety concerns.
- Death
- Lost to follow-up – all methods of contacting the subject are no longer viable or the subject is unable to be reached to complete the 30-day follow-up visit.

Subjects who discontinue from the study early will not be replaced. Subjects who withdraw voluntarily or are withdrawn from the study per Investigator discretion cannot re-enter the study. The investigator(s)/institution(s) should arrange for any continued safety monitoring, treatment and/or follow-up of subjects who withdraw/are withdrawn from the study or determined as lost to follow-up as per standard-of-care/best clinical judgement. The Investigator can use existing data and may ask for the subject's permission to collect follow-up data about status and/or condition, including information related to the device performance, effectiveness, or safety. If permission is granted, the relevant data will be included in the clinical study report.

14.8 Subject Study Completion

The clinical study will be considered complete when the last enrolled subject has completed the 30-day follow-up visit or protocol-required assessment. The sponsor will provide end-of-study notification to all participating sites for submission to their IRBs.

15 Adverse Event Reporting

Any person who identifies an event or information that could impact subjects', users', or other persons' safety has an obligation to inform the Investigator and the sponsor of their concerns.

15.1 Adverse Event

An Adverse Event (AE) is any untoward medical occurrence in a subject, whether anticipated or unanticipated. All AEs are reported from the subject's start time of enrollment until their exit from the study (i.e., point of study completion or premature discontinuation). AEs will be recorded and followed until resolution or stabilization of the event or until the subject has exited the study.

Anyone should be encouraged to report AEs immediately upon awareness and may volunteer information at any time. At each evaluation, the Investigator will assess if an adverse event has occurred and will obtain all information required to complete the appropriate AE CRF(s). If an event occurs at an outside institution, the Investigator should obtain all or as much of the required AE information as possible.

For each AE, the Investigator should report at a minimum, the term/description, start/end dates, severity, serious/non-serious classification, treatment, and outcome of the AE and determine its causality/association to the investigational product or procedures involved in the clinical study.

All sites will be trained on severity and causality of AEs and completing the AE Case Report Form

15.2 Serious Adverse Events

A Serious Adverse Event (SAE) is a type of AE and defined as any untoward medical occurrence that:

a) Led to a death
b) Led to a serious deterioration in the health of the subject that
   - Results in a life-threatening illness or injury
   - Results in a permanent or significant impairment of a body structure or a body function
   - Requires hospitalization or prolongation of existing hospitalization
   - Results in an important medical event which jeopardizes the subject and may require medical or surgical intervention to prevent permanent impairment to a body structure or one of the above outcomes
c) Led to fetal distress, fetal death or a congenital abnormality or birth defect

The Investigator must report all SAEs to the Sponsor and/or designee by any applicable method within 24 hours or one working day of first awareness of the event by the study team at the institution and provide any additional information as required by the Sponsor/designee. The Electronic Data Capture (EDC) system should be the principal system used in reporting these events, if possible. In the case of death, all available information, e.g., autopsy or other post-mortem findings, including causality/association to the investigational product, should be provided. The medical monitor of this study will decide if more follow-up information is needed in case the event is not resolved at the time of subject exit from the study.

The Investigator shall notify their IRB of SAEs which occurred at their site in accordance with their institutional requirements.

SAEs will be recorded and followed until resolution or stabilization of the event or until the subject has exited the study.

In the case of death, all available information, e.g., autopsy or other post-mortem findings, including causality/association to the investigational product, should be provided.

15.3 Unanticipated Adverse Device Effects

An unanticipated adverse device effect (UADE) is defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with an investigational product, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with an investigational product that relates to the rights, safety, or welfare of patients.

Potential UADEs occurring during the study must be reported by the Investigator to the Sponsor [through the EDC system or by other available means within 24 hours or one working day of first awareness of the event by the study team at the institution.

- If the Sponsor confirms the reported event qualifies as a UADE and presents as an unreasonable risk(s) to study subjects, they will terminate the entire study, or parts of the study presenting that risk, within 5 working days of that determination and within 15 working days of first receipt of UADE notification as well as notify the applicable regulatory authorities.
- If the Sponsor confirms the reported event qualifies as a UADE, sponsor will notify the applicable regulatory authority(ies), all participating Investigators and reviewing IRBs/ECs within 10 working days of first receipt of UADE notification. Investigators are responsible for reviewing information received about UADEs.

UADEs will be recorded and followed until resolution or stabilization of the event or until the subject has exited the study.

15.4 Sponsor Progress Reports

The Sponsor will submit progress reports with safety updates to the FDA, all participating Investigators, and all participating IRBs on at least an annual basis, as per federal regulations. These updates will be individualized for each institution and will include a summary of the study status, enrollment figures, any safety concerns, any outcomes, or recommendations from the Data Safety Monitoring Board (DSMB) as well as a listing of all adverse events reported.

16 Statistics/Data Analyses

16.1 Randomization

This is a randomized, controlled, open label study. Before the first subject is enrolled in the study, a randomization schedule will be generated by the study statistician and uploaded into an electronic database that can be accessed via computer. The schedule will be generated using a

permuted block approach. Randomization will be performed at the conclusion of the index procedure, while the patient is on the table and the operator is able to visualize all access sites to verify eligibility. Since one of the primary endpoints of this study is time to ambulation, randomization will be done at the patient level to avoid the possibility of a patient receiving both MYNX CONTROL™ Venous VCD and manual compression. Randomization will be stratified by study center with a 2:1 randomization ratio for MYNX CONTROL™ Venous VCD vs. manual compression for access site closure. Roll-in patients will not be randomized. All roll-in patients will receive the MYNX CONTROL™ Venous VCD.

Any physician delegated as "Operator" on the Delegation of Authority log needs to have two (2) roll-in patients prior to randomizing any subject.

16.2 Device Failures and Malfunctions

A device malfunction is considered a failure of a device to meet any of its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the IFU/Clinical Protocol.

If a product malfunction occurs, the site must notify within 24 hours or one working day the Sponsor and/or enter details of the complication and its management in the respective CRF. If applicable, the malfunctioned product and any other materials used during the index procedure should be returned according to the Sponsor's instructions.

If a product malfunction occurs, detailed information on the product, circumstances of the malfunction as well as any complications and their management will be collected and reported.

Any patients randomized to the device arm who do not receive the MYNX CONTROL™ Venous VCD due to device malfunction would be treated with (converted to) manual compression, or much less likely – surgery – to close the access site. All device failure patients should be followed to 30 days and have a visual assessment of the access site(s) at that time. Such visual assessments are particularly important since patients experiencing device failures are more likely to have access site-related complications, and a complete and accurate evaluation of these patients is important to help ensure a rigorous IDE study.

16.3 Analysis Population

Analyses for the safety and efficacy endpoints will be performed using the intent-to-treat (ITT) population. The ITT population will consist of all patients randomized in the study and will be analyzed in the group to which they were randomized regardless of the treatment actually received.

Supportive analyses for the safety and efficacy endpoints will be performed on the as-treated (AT) population and the per-protocol (PP) population. The AT population will consist of all randomized subjects, but they will be analyzed according to what device/treatment they actually received. The

PP population is a subset of the ITT population consisting of subjects that do not have any major protocol deviation that might affect the measurement of the primary endpoints.

16.4 Statistical Hypotheses for Endpoints

Primary Effectiveness Endpoint- Primary efficacy will be measured using co-primary endpoints consisting of Time to Ambulation (TTA) and Time to Hemostasis (TTH) as defined below:

- **Time to Ambulation (TTA)**-Defined as elapsed time (in hours) between removal of the final VCD (device group) or of the final sheath (control group) and when subject stands and walks 20 feet without evidence of rebleeding from any femoral venous access site.

  The null and alternative hypotheses of the primary effectiveness comparison for TTA are given below

$$Ho: \mu_{Mynx\ Control} \geq \mu_{manual\ compression}$$

$$Ha: \mu_{Mynx\ Control} < \mu_{manual\ compression}$$

Where μ_x is the average time to ambulation for the specified group

- Time to **Hemostasis (TTH)-** Defined as elapsed time (in minutes) between removal of each VCD (device group) or of each sheath (control group) and first observed and confirmed venous hemostasis (per access site analysis)

The null and alternative hypotheses of the primary effectiveness comparison for TTH are given below:

$$Ho: \mu_{manual\ compression} - \mu_{Mynx\ Control} \leq 5$$

$$Ha: \mu_{manual\ compression} - \mu_{MynxControl} > 5$$

Where $\mu_{xx}$is the mean time to hemostasis for the indicated group and 5 minutes is the superiority margin.

16.5 Primary Safety Endpoint

The primary safety endpoint is defined as the rate of combined major venous access site closure- related complications through 30 days post procedure, attributed directly to VCD or manual compression without other likely cause.

- Access site-related bleeding requiring transfusion, surgical intervention, or rehospitalization
- Vascular injury requiring surgical repair
- Access site-related infection confirmed by culture and sensitivity, requiring intravenous antibiotics and/or extended hospitalization

- New onset, permanent (i.e., persisting at 30-day follow-up) access site-related nerve injury
- New onset access site-related nerve injury 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)

The null and alternative hypotheses of the primary safety comparison are given below:

$$Ho: P_{Mynx\ Control} \geq P_{manual\ compression}$$

$$Ha: P_{Mynx\ Control} < P_{manual\ compression}$$

where P_X is the proportion limbs experiencing a major venous access site closure- related complications through 30 days post procedure and δ is the non-inferiority window.

16.6 Secondary Safety Endpoint

Rate of CEC adjudicated combined minor venous access site closure related complications within 30 days post- procedure, attributed directly to VCD or manual compression without other likely cause.

- Pseudoaneurysm – Treated with thrombin injection, fibrin adhesive injection, or ultrasound guided compression and documented by ultrasound
- Pseudoaneurysm – Not requiring treatment
- AV Fistula requiring treatment, documented by ultrasound
- Arteriovenous fistula not requiring treatment, documented by ultrasound
- Access site related Hematoma > 6 cm documented by ultrasound
- Access site-related bleeding requiring > 30 min to achieve hemostasis
- Late access site-related bleeding (following hospital discharge eligibility)
- Transient loss of ipsilateral lower extremity pulse
- Ipsilateral deep vein thrombosis documented by ultrasound
- Transient access site-related nerve injury
- Access site-related vessel laceration
- Access site wound dehiscence
- Local access site infection confirmed by culture and sensitivity, treated with intramuscular or oral antibiotics – Minor
- Local access site inflammatory reaction – Minor
- Allergic reaction
- Ecchymosis

16.7 Secondary Effectiveness Endpoints

- Time to Discharge Eligibility- defined as elapsed time (in hours) between removal of the final MYNX CONTROL™ Venous VCD (device group) or removal of the final sheath (control group) and when the subject is eligible for discharge from the institution based on the assessment of the attending physician.
- Procedural Success: attainment of final hemostasis at all venous access sites without major venous access site closure-related complications through 30 days.
- Device Success: ability to successfully deploy the MYNX CONTROL™ Venous VCD delivery system, deliver the polyethylene glycol hydrogel sealant, and achieve hemostasis (device group only).

16.8 Sample Size Determination

In determining sample size for this study, it is necessary to take both TTA and TTH into account since the study is using both as co-primary endpoints. The total sample size for the study is determined to be 204 patients and is based on the following assumptions:

TTA Assumptions

Power	90%
Alpha	1-sided 0.025
Allocation	2:1 VCD:MC
VCD mean	3 hours[78]
MC mean	6 hours
Standard Deviation	6 hours
Attrition correction	5%

Power	SD	MC SS	VCD SS	Total SS
90	6	68	136	204

TTH Sample size justification: For the endpoint of time to hemostasis, a generalized linear mixed model will be used to compare the MYNX CONTROL™ Venous VCD device with manual compression (control). Initial estimates of the average time to hemostasis were taken from historical MYNX family devices and compared to manual compression. Previous MYNX family studies only studied one access site per subject within the femoral artery. The observed average time to hemostasis as well as the standard deviations of those measurements helped inform the design of this trial where the standard deviation would be used as an estimate of subject-to-subject variation. For the current study, it is assumed that each subject will have up to 4 access

sites in the femoral vein. These access sites will be closed with either the MYNX CONTROL™ Venous VCD device or manual compression. Only one method of closure will be used per subject. Time to hemostasis will be measured for each access site separately.

It is assumed that hemostasis times are log-normally distributed. Using previous study data, estimates of μ and σ of the lognormal distribution were obtained and used in the calculation of sample size for this endpoint.

A generalized linear mixed model is used with the subject as a random effect. To adjust for the correlation in hemostasis time between the access sites within subject, it is assumed that the correlation structure is compound symmetric. The Type I error rate was set to a one-sided 0.025 (or equivalently, a two-sided 0.05 level) for the purposes of sample size calculation. A sample size of 150 patients (100 MYNX CONTROL™ Venous VCD and 50 manual compression) will provide approximately 95% power to detect a difference in hemostasis times of seven (7) minutes between MYNX CONTROL™ Venous VCD and manual compression. Note that these calculations were made in the log transformed space to assess power. Also, the variation between access sites within patients was estimated as approximately half of the variation observed between patients.

The specific model used is:

$$y_{ijk} = \mu + \tau_i + S_{j(i)} + e_{k(ij)}$$

where τ_i is the treatment effect and S_{ij} is the random effect of subject within treatment. e_{ijk} is the unexplained variation in the model. Further, it is assumed that:

$$y_{ijk} \sim N(\mu_{ij}, \sigma^2)$$

$$S_{j(i)} \sim N(0, \sigma_S^2)$$

and

$$e_{k(ij)} \sim N(0, \sigma_e^2)$$

TTH Assumptions

Power	~95%
Alpha	1-sided 0.025
Allocation	2:1 VCD:MC
VCD mean	6
MC mean	13
Standard Deviation	Determined in the log transformed space
Attrition correction	5%

Total Sample Size	150 patients

Sample Size for Primary Safety Endpoint: The primary safety endpoint of major venous access site closure-related complications through 30 days post-procedure, attributed directly to VCD or manual compression without other likely causes will be analyzed using a non-inferiority approach based on a generalized estimating equation (GEE) approach for logistic regression, using a working compound-symmetric covariance structure. This method would account for potential within subject correlation. We will perform the test at the one-sided 0.025 alpha level. For the purposes of sample size calculation, both groups are assumed to have a 1.5% major complication rate. The non-inferiority window has been established at 5 percentage points.

Within-subject correlation can affect the power of the study depending on the degree of correlation. However, the degree of correlation within-subject due to potentially multiple limbs is unknown and there is no robust and relevant data on which to base any associated assumption. Since this is unknown, sample size is conservatively calculated assuming only one limb per subject, or in other words, the number of subjects in the study assuming independence between subjects. Calculations for a two-sample test of binomial proportions for a Z test under a normal approximation show a sample size of 204 subjects should provide approximately 80% power for this endpoint. To the extent that some subjects will contribute multiple limbs to the actual analysis, the power would be higher than that from calculations based only on the number of independent subjects. Though missing data for the primary safety endpoint is unlikely, the additional data contributed by multiple limbs will help offset any power loss due to missing data.

Sample Size for Secondary Endpoint: Initial estimates for the secondary endpoint of time to discharge eligibility were obtained from the VASCADE MVP Venous Vascular Closure System (Cardiva Medical Inc.) Summary of Safety and Effectiveness Data. The average time to discharge eligibility for VASCADE was 3.1 ± 1.3 hours and for manual compression it was 6.5 ± 1.9 hours. For sample size calculation, the Type 1 error rate was set to 0.025. A sample size of 23 total subjects provides more than 95% power to demonstrate that the average time to discharge eligibility is significantly less for the MYNX CONTROL™ Venous group relative to manual compression.

The sample size for adequate power on the primary safety endpoint was the largest and will be used as the sample size for this trial.

16.9 Statistical Analysis Methods

Except where otherwise specified, the following general principles apply to the planned statistical analyses. All descriptive statistical analyses will be performed using SAS version 9.4 or higher, unless otherwise noted (SAS Institute Inc., Cary, NC) or other widely accepted statistical or graphical software as required. Derived variables will be independently verified by an independent programmer / statistician. The program review will also include whether analyses conform to specifications of the Statistical Analysis Plan.

For categorical variables, the numerator, denominator, rate (%) and exact 95% CI will be calculated. For continuous variables, the median, mean, standard deviation, interquartile range, number of observations, minimum and maximum values, and 95% CI, as appropriate, will be presented.

For each parameter, the baseline value will be defined as the last non-missing value collected at the time closest to but before treatment with the investigational device.

All statistical tests will be performed at the two-sided 0.05 significance level, unless otherwise noted. Listings of patient data will be created for all study parameters.

16.9.1 Primary Analysis

Efficacy

The primary efficacy endpoints will be analyzed separately.

The average time to ambulation in each treatment group will be compared using a standard T-test.

The average time to hemostasis will be compared to the treatment groups using a generalized linear mixed model where subject is considered a random effect with multiple access sites. The times to hemostasis in the manual compression group will be reduced by 5 minutes to account for the hypothesis that the time to hemostasis for the MYNX CONTROL™ Venous VCD is at least 5 minutes less than manual compression. The analysis will consist of testing the coefficient on the fixed effect for treatment group. If that coefficient is found to be significantly different from zero, then the direction will be evaluated to assure that the hemostasis time is reduced on average when using MYNX CONTROL ™ Venous VCD.

Safety

The safety analysis will be completed on a per-limb basis.

This endpoint will be analyzed using a GEE approach for a logistic regression model with a compound symmetric working covariance structure where occurrence of an AE is the binary response variable and treatment group is the only explanatory variable. Least square means for each treatment group and the risk difference between groups will be calculated along with the two-sided 95% confidence interval. The one-sided 97.5% confidence bound (equivalent to the appropriate bound from the two-sided 95% interval) will be compared to the non-inferiority window. If the upper bound is less than the non-inferiority window, then the two treatment groups will be considered non-inferior relative to the proportion of limbs experiencing a major venous access site closure-related complication.

As a supplementary analysis, a generalized linear mixed model will be used where subject will be entered into the model as a random effect and a compound symmetric correlation structure applied to those subjects contributing two limbs.

Trial Success

This trial will be considered a success if both primary efficacy endpoints and the primary safety endpoint are achieved.

16.9.2 Secondary Safety Analysis

The secondary safety analysis of combined minor venous access site closure related complications within 30 days post-procedure, attributed directly to VCD or manual compression without other likely cause will be summarized on a per-limb basis. The proportion of limbs experiencing a minor closure related complication will be calculated for each treatment group along with 95% confidence intervals. The difference between the proportions will then be estimated along with a 95% confidence interval.

16.9.3 Secondary Efficacy Analyses

Time to Discharge Eligibility, defined as the elapsed time between removal of the final MYNX CONTROL™ Venous VCD (device group) or removal of the final sheath (control group), and when the subject is eligible for discharge from the institution (in hours) will be summarized on a per-patient basis.

Time to discharge eligibility is a powered secondary endpoint. The average time to discharge eligibility will be compared between the device and control groups at the 0.025 level of significance. The specific hypotheses being tested are:

$$Ho: \mu_{Mynx\ Control} \geq \mu_{manual\ compression}$$

$$Ha: \mu_{Mynx\ Control} < \mu_{manual\ compression}$$

where μ_x is the average time to discharge eligibility for the specified group. A p-value for this one-sided test less than 0.025 will indicate that the time to discharge eligibility for the subjects using the MYNX CONTROL™ Venous Vascular Closure Device (VCD) was significantly less than for those where manual compression was used. The standard two group T-test will be used to make this comparison.

The difference between treatment groups in average time to discharge will also be estimated with 95% confidence intervals calculated using the T-distribution.

The following secondary endpoints are considered ad hoc analyses and are not powered.

Procedural Success defined as the attainment of final hemostasis at all venous access sites without major venous access site closure-related complications through 30 days will be summarized on a per access site basis and on a per-limb basis. Procedural success will be estimated for each treatment group separately with 95% confidence intervals followed by an

estimate of the difference in procedural success between the treatment groups and a 95% confidence interval on the difference.

Device Success defined as the ability to deploy the VCD delivery system, deliver the polyethylene glycol hydrogel sealant, and achieve hemostasis will be summarized on a per access site basis for the device group only. The proportion of device successes will be estimated along with a 95% confidence interval.

16.9.4 Additional analysis

The type of major complication will also be compared on a per-limb basis. Frequency distributions for the type of complication will be constructed for each treatment group and the frequency distributions will be examined informally. This analysis is for information purposes only.

16.9.5 Analysis of Roll-in Subjects

The roll-in subjects will be summarized descriptively. No formal analysis will be done. Roll-in subjects will not be part of the main analysis population. Details can be found in the statistical analysis plan.

16.9.6 Study site poolability

Study site poolability for the primary endpoint of time to ambulation will be analyzed using a two-way analysis of variance (ANOVA) model. The first factor in this model will be treatment group and the second factor will be study site. The treatment group by study site interaction will also be added to the model. If the interaction term is not significant at the 0.15 level, then the study sites will be pooled for the analysis of this endpoint.

Study site poolability for the primary endpoint of time to hemostasis will be analyzed using the general linear mixed model outlined in section 16.8. To that model fixed effects for study site and treatment group by study site interaction will be added. If the interaction term is not significant at the 0.15 level, then the study sites will be pooled for the analysis of this endpoint.

Study site poolability for the safety endpoint will be analyzed on a per limb basis. A GEE logistic regression model with main effects of treatment group and study site along with an interaction term between those main effects will be fit to the data. If the interaction term is not significant at the 0.15 level, then the study sites will be pooled for the analysis of this endpoint.

16.9.7 Interim Analysis

An interim analysis in support of a CE Mark submission will be conducted to analyze initial subjects randomized to the device group 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 and Time to Hemostasis.
- Secondary efficacy: Time to Discharge Eligibility, Procedure success, and Device Success.
- Primary safety: rate of major complications related to the access site.
- Secondary safety: rate of minor complications related to the access site.

This is a single-arm analysis, therefore subjects randomized to control arm will be excluded from the interim analysis. A sample size of 68 sequential subjects randomized to treatment arm will be collected for the interim analysis. 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.

16.10 Sub-Group Analysis

A sub-group analysis will be completed for the primary safety and primary efficacy endpoints. This analysis is not powered and is strictly for information purposes. The sub-groups for this analysis are those subjects that contributed only 1 limb and those subjects that contributed 2 limbs. The same analysis outlined above for the primary safety and efficacy endpoints will be completed within each sub-group separately. Additional analyses to demonstrate the homogeneity of the treatment effect and homogeneity of the major complication rates are detailed in the SAP.

Major and minor complications will also be analyzed based on the number of access sites and sheath size, major and minor complications will be stratified by number of access sites per leg (1, 2, 3, or 4 sites), total number of access sites per patient (1, 2, 3, or 4 sites), and sheath size (small size vs. large size). Details are provided in the SAP.

A sub-group analysis will also be performed utilizing independent analysis of non-invasive duplex ultrasound (DUS) imaging in 72 subjects from both arms (48 device and 24 control) at the time of the procedure, pre-discharge and potentially again at the 30-day follow-up (only for those subjects that have documented evidence of access site complications at the discharge ultrasound). Specific investigational sites will be designated as ultrasound sites. These sites will include subjects in the ultrasound subset imaging until a total of 72 patients have been evaluated in both treatment arms. Ultrasound will be performed at the follow-up office visit only if a complication was detected at discharge. All sub-study sites will be instructed in performance of duplex ultrasonography of the femoral vascular structures. Images will be interpreted by:

NAMSA
4 World Trade Center

150 Greenwich Street, 49th FL
New York, NY 10007

At the time of the procedure, and at discharge, the proportion of subjects exhibiting a complication on DUS imaging will be calculated along with 95% confidence intervals constructed using the Clopper-Pearson method. For those subjects that required a DUS at the 30 day follow-up, the proportion of subjects still exhibiting a complication will be calculated along with a 95% confidence interval constructed using the Clopper-Pearson method.

16.11 Missing Data

While all reasonable efforts will be made to obtain the data required to evaluate this endpoint, it is expected that some patients may not be able to provide data due to several reasons (loss to follow-up, study withdrawal, death). For all primary and secondary analyses, no imputation of missing data is planned. Patients who have ascertainment of status at a later out-of-window date (for example, patients who are known to be free of events past discharge eligibility but missed the discharge visit) are not considered missing as their status is known and their data will be used as noted previously. The primary endpoint rate will be calculated as the number of patients who had an event prior to the milestone visit divided by the number of evaluable patients who had sufficient follow up (e.g., at least discharge visit) plus any patients who had an event prior to the milestone visit. In other words, the denominator will be adjusted for missing follow up data.

A sensitivity analysis will be done to assess the impact of missing data on the conclusion of the primary analyses. Details of the analysis are provided in the SAP.

16.12 Reporting

A final clinical summary will be developed for this study upon completion of all subject follow-up visits/database lock for the last required follow-up visit in the study.

This will be provided to the applicable regulatory authorities as well as all participating Investigators and Institutional Review Boards. Interim reports will also be developed and provided only as required.

17 Quality Control and Quality Assurance

17.1 Regulatory and Ethical Compliance

The Sponsor maintains a quality management system with written Standard Operating Procedures (SOP) to ensure that clinical studies are conducted, and data are generated, documented, and reported in compliance with the study protocol and the requirements of ICH E6 Good Clinical Practice, and the requirements of all applicable regulatory authorities. The staff at Cordis is trained regularly to ensure adherence to these SOPs.

17.2 Data Quality Assurance

Study procedures to ensure the quality of all data collected and analyzed within this study include, but are not limited to, the following:

- Qualified Investigators, study sites and monitors will be selected.
- The investigational device was provided to Investigators/sites after being tested and released according to appropriate standards.
- Training will be provided to and documented for all Investigators and study personnel, which includes, but is not limited to, a review of the protocol, investigational product, CRFs, EDC system, GCP guidelines and study expectations. Training of Investigators will occur at the site initiation visit (prior to the start of any study-related activities), at any Investigator meetings and as necessary (e.g., when there are changes to the study team)
- Training will be provided to all study monitors on the study protocol, background/therapeutic area and GCP-conforming monitoring activities. Monitors will receive project-specific monitoring conventions and all forms needed to document the monitoring activity (e.g., forms for monitoring reports, investigational product accountability).
- The Sponsor and/or designee will conduct source document verification, as specified in the sponsor's monitoring plan by comparing original source documentation against the CRFs. Any discrepancies identified will be resolved with the Investigator, or designee, as appropriate.
- Appropriate edit checks incorporated within the EDC system and regular/periodic reviews of the data by Data Management will verify the completeness and accuracy of the data. Like the study monitor, Data Management will post queries to data points in need of further clarification and/or correction from sites (like the study monitor) and will keep the Sponsor informed of the status of queries and completeness of the study database.

17.3 Clinical Data

The case report form (CRF) for each subject is a record of their eligibility to enter the study, medical history, pre-procedure/baseline assessments, concomitant medications, all investigational product used during the index procedure, all procedural complications, and adverse events as well as data from discharge, all follow-up, and any unscheduled visits. It is the obligation of each Investigator (or designee) to ensure that all source documents (e.g., medical files, clinic charts, diagnostic films, nursing files), are available to support all data points collected within the CRF for every screened and/or enrolled subject. All information obtained during and between all protocol-required procedures needs to be clearly documented within the subject's source documentation and CRF.

Qualified site staff trained to the protocol, CRFs and EDC system will perform primary data collection and data entry into the CRFs in a timely manner following subject enrollment and/the completion of study-required assessments/follow-up visits. Data will be collected from patients' hospital charts, imaging films, and/or other medical records, which the Investigator is responsible to ensure are adequate to support all CRF entries. Corrections to CRFs will be performed by the

Investigator or other authorized study site personnel. A record of study site personnel authorized to perform CRF data entry and/or corrections will be maintained by the site and provided to the Sponsor.

The Investigator must sign and date the specified section(s) within the CRF to confirm that s/he has reviewed the data and that the data are complete and accurate.

17.4 Monitoring

The Sponsor (and/or designee) will oversee the conduct and progress of the study at each investigational site. In addition to regular communications with the site, the Sponsor (and/or designee) will conduct interim monitoring visits (IMV) at periodic intervals to verify the following:

- The rights and well-being of the patients are protected
- The study is conducted according to International Council for Harmonization (ICH) and Good Clinical Practices (GCP) (ICH E6), the Declaration of Helsinki (1964) and all national, state, and local laws of the pertinent regulatory authorities
- The study is conducted in compliance with all requirements identified within the approved protocol/ amendment(s)
- The data reported in the CRFs/EDC system are accurate, complete, and verifiable from source documentation.

The study monitor will complete verification of the above primarily from review and assessment of regulatory documents, signed informed consent forms, accountability records and storage of investigational product and CRF/EDC system entries against all source documents. The monitor will also post and address queries within the EDC system and discuss the conduct of the study with the Investigator and study team. CRFs would need to be completed in a timely manner, within five (5) working days or one (1) week, to ensure availability for IMVs. Complete details regarding the monitoring procedures followed for the study are described in the study monitoring plan.

The Investigator must agree to provide study monitors with direct access to the office/clinic/facilities, medical records/source data/source documents for all enrolled patients, regulatory documents, and any/all other applicable study-related documents to enable the proper completion of IMVs.

Interim monitoring visits (IMVs) will be conducted throughout the course of this study according to the Sponsor's Monitoring Plan. Monitoring visit frequency at sites will be based on factors including, but not limited to, the rate and volume of enrollment, timing of completing follow-up visits and overall compliance.

17.5 Protocol Modifications

17.5.1 Protocol Amendments

Changes to the research covered by this protocol must be implemented through a formal protocol amendment. Change(s) to only logistical or administrative aspects of the study will be reflected in the study protocol if/when it is next amended to address any changes to the research. Protocol amendments may be initiated by the Sponsor or at the request of the Investigator. In either case, however, all protocol amendments must be approved by the Sponsor, signed, and dated by the Investigator and approved by the IRB prior to implementation.

17.5.2 Protocol Deviations/Noncompliance

A protocol deviation is defined as a divergence from a specific element of the study protocol (e.g., missed assessment, visit out of window, violation of inclusion/exclusion criteria). Sites must comply with all requirements of the study protocol to control the number of protocol deviations to the extent possible. This does not include circumstances where necessary to eliminate an immediate hazard to study subjects (see section below) or that involve only logistical or administrative aspects of the study.

Protocol deviations for inability to perform office visits, exams or procedures due to COVID-19 pandemic should be completed and a notation of "COVID-19" in the CRF for each deviation.

The study monitor will verify the conduct of the study follows the currently approved protocol at each site and will identify any deviations from the protocol. The study monitor will also determine if there are any other issues of noncompliance (e.g., with IRB requirements, regulations from applicable regulatory authorities). If any protocol deviations or other areas of noncompliance are noted, the Investigator, site staff and/or study monitor will ensure corrective actions are implemented and evaluate the effectiveness of those corrective actions. Recurrence of noncompliance may require development of a formal corrective action plan that includes a suspension in enrollment and/or other actions. All protocol deviations and other issues of noncompliance at a site will be monitored closely by the Sponsor and/or designee(s) and will be reported to the applicable regulatory authorities and/or the IRB, as required.

17.5.3 Emergency Deviations

Emergency deviations are allowed only in cases where the change is necessary to eliminate an immediate apparent hazard and protect the life or physical well-being of a study subject. Such cases must be reported to the Sponsor/Medical Monitor and the IRB in writing within five (5) working days of the occurrence and will still be entered as protocol deviations in the CRF.

17.6 Audits

The Sponsor and/or designee and the FDA may contact the participating institution to inform the Investigator of an upcoming audit and/or inspection, which may be routine or "for cause". In the

event the Investigator receives notification from FDA of an audit/inspection for this study, the Investigator should immediately notify the Sponsor. The Investigator must agree to provide direct access to the office/clinic/facilities, medical records/source documents for all enrolled patients, regulatory documents, and any/all other applicable study-related documents to all representatives of the Sponsor and/or designee and all regulatory authorities to enable proper completion of the audit/inspection.

17.7 Subject Confidentiality

Subject confidentiality will be maintained throughout the clinical study. A unique subject identification number will be assigned to every consented study subject, which will identify all data reported for that subject and ensure the data can be traced back to their source records. Subject identification will be created using a five-digit numeric value beginning with site number (XX) followed by subject numbers (YYY) such as 01-001.

Data relating to the study may be made available to all representatives of the Sponsor and/or designee and third parties (e.g., in the case of an audit performed by regulatory authorities) provided the data are treated confidentially and that the patient's privacy is guaranteed.

17.8 Institutional Review Board (IRB)

Prior to study initiation, the protocol, informed consent form and all other applicable study-related documents, including any written materials to be provided to patients, and any advertisement for patient recruitment (if applicable), must be submitted for review by a certified IRB. The IRB must be registered with the U.S. Department of Health and Human Services (HHS). Written approval or favorable opinion of these documents must be obtained and submitted to the Sponsor prior to screening and enrolling any patients and initiating any study-related activities.

The Investigator will prepare the draft informed consent form (ICF) and provide to the Sponsor and/or designee for approval prior to submission to the IRB. If the Sponsor requires any changes, a revised draft of the ICF incorporating these changes must be approved by the Sponsor prior to IRB submission. If the IRB requires additional changes, these must be reviewed and approved by the Sponsor prior to resubmission to the IRB. Copies of the final, IRB-approved ICF and all other IRB-approved study documents must be submitted to Sponsor or designee.

The Investigator or authorized designee will promptly report all changes in research activity and all unanticipated events/issues involving risks to human patients to the IRB. All Sponsor-approved amendments to the study protocol, ICF, etc. must be approved by the IRB prior to implementation. All other changes to research activities must be approved by the Sponsor and IRB prior to implementing, except when necessary to eliminate an immediate apparent hazard to the patient.

At least annually, or more frequently if required by IRB policy, the Investigator or authorized designee must submit a study progress report to their IRB to obtain continuing review approval for the study prior to the expiration of the most recent approval. Additionally, the Investigator must provide notification to their IRB, within three (3) months following the completion, termination, or

discontinuation of the study at the specific site and provide the acknowledgement letter from the IRB to the Sponsor.

For U.S. sites, IRBs must retain all study-related records for at least three (3) years following completion of the study, per the requirements of applicable regulatory authorities, or longer if required by local laws.

18 Record Keeping/Publication Policy

All required subject data must be recorded on CRFs provided by the Sponsor and/or designee for verification against subject source documents by the study monitor(s). A printout of the CRFs cannot be used as source documentation.

18.1 Record Retention

All study records (e.g., correspondence, regulatory documents, CRFs and all source documents (informed consent forms, laboratory reports, progress notes, medical histories, physical and diagnostic findings, diagnoses, procedure/assessment dates and investigational product disposition records etc.) that support the CRFs) must be retained in the files of the responsible Investigator for a minimum of two (2) years from the latter of these two (2) dates, as communicated by the Sponsor, unless a longer retention period is required by the IRB or applicable local laws:

- the date on which the entire investigation is terminated or completed, or
- the date the records are no longer required to support a premarket approval (PMA) application

If the Investigator plans to archive or relocate/transfer the study records, (s)he must notify the Sponsor, in writing, of the transfer location, duration, and the procedure for accessing the study documentation. The Sponsor must approve of the planned archival or relocation/transfer, in writing, prior to its occurrence. All study records must be accessible upon request by the applicable regulatory authorities, the Sponsor and/or designee until destruction is possible.

If the Investigator retires, relocates, or for other reasons, withdraws from assuming primary responsibility for keeping the study records, written notice (transfer of obligation) must be submitted to the Sponsor and IRB indicating the name and address of the new custodian accepting primary responsibility.

For U.S. sites, IRBs must retain all study-related records for at least three (3) years following completion of the study, per the requirements of applicable regulatory authorities, or longer if required by local laws.

18.2 Use of Information and Publications

This study will be registered in Clinicaltrials.gov, a publicly accessible database, through which the results of this study will also be reported. All information concerning the Sponsor (Cordis), MYNX CONTROL™ Venous Vascular Closure Device, patent application, manufacturing

processes, and scientific data supplied by the Sponsor to the Investigator and not previously published, is considered confidential and remains the sole property of the Sponsor. The Investigator understands the information developed in the clinical study will be used by the Sponsor in connection with a PMA application and thus may be disclosed as required to other Investigators or government regulatory authorities.

At the conclusion of the study, a manuscript may be prepared for publication of results across multiple study centers in a reputable scientific journal. The publication of the principal results from any single study center is not allowed until the preparation and publication of the multi-center results. Exceptions to this rule require prior approval of the Sponsor. The analysis of pre-specified and non-pre-specified endpoints will be performed by (the Sponsor/designated entity for data management/statistics). Secondary analyses as well as other proposed investigations will require the approval of the Sponsor. For purposes of timely abstract presentation and publication, secondary publications will be delegated to the appropriate principal authors.

19 Investigational Product Accountability

19.1 Study Investigational Product Accountability

The investigational product must be kept in a secure location with restricted access to authorized members of the study team and stored according to the conditions outlined in the Instructions for Use (IFU)/ Investigator Brochure (IB). The investigational product is intended solely for use by the Investigator or Sub-Investigator(s) and can only be used in clinical study patients. Investigational product-related study documentation to be maintained includes, but is not limited to, the following:

- Packing slips provided with each investigational product shipment (signed and dated)
- An up-to-date, complete, and accurate investigational product accountability log showing receipt, usage or implant and return or final disposition of all investigational product shipped to the site
- All other device accountability records including source documents and/or package labels of investigational product used in implanted patients, shipping labels, delivery confirmations, etc.
- Copies of investigational product malfunction and return forms (for sterile and opened/malfunctioned product)

All product on site labeled with “CAUTION Investigational device: Limited by Federal (or United States) law to investigational use.”, regardless of whether used or opened and/or unused, will be inventoried and accounted for throughout the study. The Investigator and/or authorized designee will maintain adequate records of the receipt, use, and disposition of the investigational product as required by protocol and applicable country, local and federal regulations

Product on site will be inventoried and accounted for in the CRFs. At a minimum, the lot number, size (length and diameter) and use by date (UBD) of all products will be captured. All AEs, investigational product malfunctions and other product issues must also be recorded in the CRFs.

19.2 Instructions for Return of Investigational Product

The Sponsor will provide instructions and ensure training to all sites on the re-package and return of investigational product, the appropriate form(s) that must be completed and the address(es) to which the product must be returned based on whether it is opened/unopened and unused, expired, damaged, mislabeled, a product complaint or malfunction has occurred, or study enrollment has been completed.

20 Committees

20.1 Clinical Events Committee

The Clinical Events Committee (CEC) is responsible for the review and final adjudication of adverse events using source documents provided by sites to categorize clinical events and clinical endpoints in the study. The CEC will establish study-related guidelines for the requisite source data and the algorithm followed to classify a clinical event (according to the study definition). The Sponsor will review the definitions prior to the start of the adjudication process.

The CEC will consist of qualified physicians with the appropriate expertise for the type of investigational product or condition under study. The CEC is an independent body, functioning separately from the Sponsor, the investigational sites or anyone otherwise involved in the conduct of the study or the clinical care of study patients. Members will not have any scientific, financial, or other conflict of interest related to the Sponsor or the study Investigators. As appropriate, members of the CEC will be blinded to the primary results of the trial.

The CEC will be responsible for providing adjudication results and minutes of their meetings to the Sponsor for internal review.

The structure and function of the CEC will be documented in the CEC Charter.

20.2 Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) is a body of professionals (primarily comprised of physicians, a biostatistician, and/or a medical ethicist) which reviews overall study data at intervals pre-determined before the start of the study and/or based on subject enrollment accrual and/or event accrual to assess progress and identify any safety concerns or other issues. The DSMB is independent of the Sponsor, the investigational sites or anyone otherwise involved in the conduct of the study. Members will not have any scientific, financial, or other conflict of interest related to the Sponsor or the study Investigators.

All serious adverse events, device-related complications/malfunctions and events related to the primary safety endpoint will be included in safety reports provided to the DSMB.

The DSMB will be responsible for providing to the Sponsor, minutes of their meetings and any recommendations regarding early termination, suspension, or modifications to the study, if the safety and well-being of the patients is in jeopardy.

The structure and function of the DSMB will be documented in the DSMB Charter.

21 Early Termination or Suspension

The Sponsor, DSMB, IRBs, regulatory authorities or the Investigator may choose to temporarily suspend or prematurely terminate the study if the safety and well-being of the patients is in jeopardy.

The Sponsor reserves the right to temporarily suspend or prematurely terminate this study either at a single site, multiple sites or across all sites at any time for reasons including, but not limited to:

- Safety or ethical issues – e.g., if in the opinion of the responsible investigator, the incidence and/or severity of adverse events in the study indicates a potential health hazard caused by treatment with the investigational product
- Inaccurate or incomplete reporting of data
- Non-compliance
- Unsatisfactory enrollment with respect to quality or quantity
- Technical reasons (e.g., change in personnel)

If the Sponsor prematurely terminates or suspends the study, they will promptly notify the applicable Investigator(s)/institution(s) and the regulatory authority(ies) of the termination or suspension and the reason(s) for such, in accordance with applicable regulatory requirement(s). The applicable IRB(s)/EC(s) should also be informed and provided with the reason(s) for termination or suspension by the Sponsor or by the Investigator(s)/institution(s), in accordance with applicable regulatory requirement(s). Additionally, in the case of premature termination, the Sponsor will provide direction on the return of all unused investigational product and other study materials. In the case of a temporary suspension at a single site, multiple sites, or across all sites, the Sponsor will ensure all the necessary activities are performed before resuming the study, if approved to continue (e.g., benefit-risk reviewed and remain acceptable or revised).

If the Investigator terminates or suspends the study without prior agreement with the Sponsor, he/she will promptly provide all details to the institution, the Sponsor, and the IRB.

If the IRB terminates or suspends the study, the Investigator will promptly inform the Sponsor with written explanation.

In any case, the investigator(s)/institution(s) must arrange for any continued safety monitoring, treatment and/or follow-up of patients, unless it has been determined by the Investigator that the continued follow-up may jeopardize the rights, safety, and/or welfare of the subject.

Subject enrollment may be paused or terminated early if the Sponsor or DSMB determines that the potential benefits of the investigational product/procedure are unlikely to outweigh the risks. For example, if the probability of achieving the target primary endpoint falls below a certain threshold, the trial will be stopped or paused for re-evaluation.

Appendix A. Definitions

Allergic reaction: The hypersensitive response of the immune system of an allergic individual to a substance.

Asymptomatic: Without symptoms. For example, an asymptomatic infection is an infection with no symptoms.

Blood clot: Blood that has been converted from a liquid to a solid state. Also called a thrombus.

Complication: In medicine, an additional problem that arises following a procedure, treatment or illness and is secondary to it.

Device related complication - complication attributed to the device (e.g., graft migration, graft infection, etc.).

Procedure-related complications - complication not attributed to device but arises following the procedure (e.g., cardiac issue, renal insufficiency, etc.).

Death: All-cause mortality.

Device deficiency: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Includes malfunctions, use errors, and inadequate labelling.

Device malfunction: The failure of a device to meet any of its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the IFU/IB.

Dilation: The process of enlargement, stretching, or expansion. The word "dilatation" means the same thing. Both come from the Latin "dilatare" meaning "to enlarge or expand."

Inflammation: A basic way in which the body reacts to infection, irritation or other injury, the key feature being redness, warmth, swelling and pain. Inflammation is now recognized as a type of nonspecific immune response.

Occlusion: A complete absence of flow within a blood vessel.

Peripheral: Situated away from the center, as opposed to centrally located.

Rupture: A break or tear in any organ or soft tissue

Scan: The data or image obtained from the examination of organs or regions of the body by gathering information with a sensing device.

Stroke: Any acute, new, persistent, documented neurological deficit ending in death or lasting greater than 24 hours and classified by a physician as a stroke.

Thrombosis – Formation of thrombus within a blood vessel leading to significant limitation of blood flow, requiring secondary intervention to restore blood flow (e.g., thrombolysis, thrombectomy, PTA)

Ultrasound: High-frequency sound waves used to bounce off tissues using special devices. The echoes are then converted into a picture called a sonogram.

Appendix B. Acronyms and Abbreviation

Acronym / Abbreviation	Term
ACT	Activated clotting time
AE	Adverse event
AP	Anterior/Posterior
ARF w/ Dialysis	Acute Renal Failure with Dialysis
ARF w/o Dialysis	Acute Renal Failure without Dialysis
atm	Atmospheric pressure
AV	Arterial Venous
BID	Twice Daily
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood urea nitrogen
CAD	Coronary Artery Disease
CAD	Carotid Artery Disease
CBC	Complete blood count
cc	cubic centimeter
CEC	Clinical Events Committee
CFA	Common Femoral Artery
CFR	Code of Federal Regulations
CHF	Coronary Heart Failure
CI	Confidence Interval
CK	Creatine kinase
CK-MB	Creatine kinase myocardial-band isoenzyme
cm	Centimeter
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine Phosphokinase
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computerized Axial Tomography Scan
CVA	Cerebrovascular accident
DIC	Disseminated Intravascular Coagulation
dl	deciliter
DM	Data Management
DSMB	Data and Safety Monitoring Board
DUS	Duplex Ultrasound
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
Fr	French (sizing unit for devices)
GCP	Good Clinical Practice
GGE	Generalized Estimating Equation
GI	Gastrointestinal
gm	Gram
HCT	Hematocrit
HGB	Hemoglobin
HHS	Health and Human Services (Department of)
HIPAA	Health Insurance Portability and Accountability Act

Acronym / Abbreviation	Term
HR	Heart Rate
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
ICU	Intensive Care Unit
IDE	Investigational Device Exemption
IFU	Instructions for Use
IMA	Inferior Mesenteric Artery
in	Inch
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
IVRS	Interactive Voice Response System
IVUS	Intravascular ultrasound
LPO	Left Posterior Oblique
L/l	Liter
m/Mon	Month
MC	Manual Compression
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MI	Myocardial infarction
mm	Millimeter
mmHg	Millimeters of mercury (unit of pressure)
MHLW	Ministry of Health, Labor and Welfare
NSTEMI	Non-ST segment Elevation Myocardial Infarction
NYHA	New York Heart Association
OR	Operation Room
PE	Physical Examination
PLT	Platelet
PMA	Premarket Approval
PMS	Post Marketing Surveillance study
PRN	As Required
RPO	Right Posterior Oblique
PRO	Patient-Reported Outcomes
PT	Prothrombin Time
PTA	Percutaneous transluminal angioplasty
PTT	Partial Thromboplastin Time
PVD	Peripheral Vascular Disease
QD	Once Daily
RBC	Red blood cell
RCT	Randomized Controlled Trial
RVD	Reference vessel diameter
SAE	Serious adverse event
SD	Standard deviation
SMA	Superior Mesenteric Artery
SVS	Society for Vascular Surgery
TAA	Thoracic Aortic Aneurysm
TIA	Transient Ischemic Attack
TLR	Target lesion(s) revascularization

Acronym / Abbreviation	Term
TTA	Time to Ambulation
TTDE	Time to Discharge Eligibility
TTH	Time to Hemostasis
UADE	Unanticipated Adverse Device Effect
UBD	Use by date
ULN	Upper Limit of Normal
US/USA	United States/United States of America
USFDA	United States Food and Drug Administration
VCD	Vascular Closure Device
VO	Volume obstruction
WBC	White blood cell
WHO	World Health Organization
WNL	Within Normal Limit

Appendix C. References

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