RELIASEAL
STATISTICAL ANALYSIS PLAN

Title:	**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**
Short Title:	**ReliaSeal**
Protocol Number:	**P22-8301**
Product:	**MYNX Control™ Venous Vascular Closure Device 6F-12F**
Model:	**MX61260**
Sponsor:	**Cordis US Corp.** **14201 NW 60th Avenue** **Miami Lakes, FL 33014, USA**
Version:	**4.0**
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STATISTICAL ANALYSIS PLAN SIGNATURE APPROVAL PAGE

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LIST OF ABBREVIATIONS

ABBREVIATIONS	TERM
AAA	Abdominal Aortic Aneurysms
AE	Adverse Event
AHA	American Heart Association
AP	Anterior/Posterior
ASA	Aspirin
AV	Arterial Venus
BMI	Body Mass Index
BP	Blood Pressure
CEC	Clinical Events Committee
CRF	Case Report Form
CT	Cat Scan (Computerized Axial Tomography Scan)
CVA	Cerebral Vascular Accident
DUS	Duplex Ultrasound
DM	Data Management
DSMB	Data and Safety Monitoring Board
EKG/ECG	Electrocardiogram
FDA	Food and Drug Administration
FEV	Forced Expiratory Volume in one second
Fr	French (sizing unit for devices)
GCP	Good Clinical Practice
GEE	Generalized Estimating Equation
GLP	Good Laboratory Practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IFU	Instructions for Use
ITT	Intent to Treat
KUB	Kidney, ureter, and Bladder X-Ray
MAE	Major Adverse Event
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
N/A	Not Applicable
NIDDM	Non-Insulin-Dependent Diabetes Mellitus
NIHSS	National Institute Health Stroke Scales
OS	Open Surgical
PD	Protocol Deviation
PMA	Pre-Marketing Approval
QCA	Quantitative Carotid Angiography
QSR	Quality System Regulations
RVD	Reference Vessel Diameter
SAE	Serious Adverse Event
SG	Stent Graft
UADE	Unanticipated Adverse Device Effect
ULN	Upper Limit of Normal
UNL	Upper Normal Levels
US/USA	United States/ United States of America

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1 INTRODUCTION

This document outlines the detailed statistical analysis methods to provide the appropriate clinical information on "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."

Note: The MYNX Grip VCD is indicated for use to seal femoral arterial and femoral venous 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 STUDY OBJECTIVE

The primary objective of this study is 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.

3 STUDY DESIGN

This study is a multicenter, prospective, randomized, controlled, open label clinical study to enroll 204 subjects with an additional group of subjects to be part of the initial roll-in phase. The number of roll-in patients will be determined based on physician training and usability. All subjects who sign the informed consent and are randomized to either treatment arm will be followed through 30 days post procedure. There will be approximately 15 participating study sites all located in the United States.

Of the 204 subjects targeted for enrollment, 72 (48 MYNX CONTROL™, 24 Manual Compression) will be enrolled in the duplex ultrasound (DUS) sub-study (see section 8.7). In the event that the full 72 subjects are not consented for the DUS sub-study by the time the targeted 204 subjects are enrolled, enrollment will continue beyond the targeted 204 subject until 72 subject have consented to participate in the DUS study.

4 ENDPOINTS

4.1 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)

4.2 Effectiveness Endpoints

The co-primary efficacy endpoints Time to Ambulation (TTA) and Time to Hemostasis (TTH) as defined below:

- **Time to Ambulation (TTA)**-Defined as time (in hours) between removal of the final VCD (treatment arm) or of the final sheath (control arm) 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 VCD (treatment arm) or of each sheath (control arm) and first observed and confirmed venous hemostasis per access site.

5 SAMPLE SIZE

All sample sizes were calculated assuming a 2:1 ratio of MYNX CONTROL™ VCD to manual compression.

Time to Ambulation:

Time to ambulation is a co-primary endpoint for effectiveness. The Type 1 error for this calculation was set at 0.025 for a one-sided test. Assuming that the treatment group ambulates in 3.0 hours on average and the control group ambulates in 6.0 hours and both groups have a standard deviation of 6.0 hours, then an effective sample size of 192 subjects provides 90% power to detect this difference in time to ambulation between the two groups of subjects. Adjusting for a missing data rate of 5%, total enrollment is 204 subjects.

Time to Hemostasis:

Time to hemostasis is a co-primary endpoint for effectiveness. The Type 1 error for this calculation was set at 0.025 for a one-sided test. 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 sample size calculation, it is assumed that each subject has 3 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 where time to hemostasis averaged 6 minutes for the MYNX CONTROL™ Venous VCD device and 13 minutes for manual compression, 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. 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

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

To adjust for the correlation in hemostasis time between the access sites within subject it is assumed that the correlation structure is compound symmetric. A sample size of 150 subjects (100 MYNX CONTROL™ VCD and 50 manual compression) will provide approximately 95% power to detect a difference in hemostasis times of 7 minutes between MYNX CONTROL™ 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 subject was estimated at approximately half of the variation observed between subjects.

Major Complication Rate:

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 is the primary safety endpoint. The one-sided Type I error was set to 0.025 for the purpose of sample size calculation. The safety endpoint will be analyzed using a non-inferiority approach on a per limb basis. 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 not robust and relevant data on which to base any associated assumption. Since this is unknown, conservatively sample size is 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 numbers 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.

Time to Discharge Eligibility (secondary endpoint):

Initial estimates for 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 MVP Venous Vascular Closure System (Cardiva Medical Inc.) 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 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.

Study Sample Size:
The sample size for adequate power on the primary safety endpoint was the largest and will be used as the overall sample size for this trial.
The study also incorporates a DUS sub study with enrollment target of 72 randomized subjects.This substudy is not powered and does not impact the primary statistical design and the main analytical cohort of the first 204 subjects that are randomized .

6 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 subjects randomized in the study and will 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.

Subjects randomized to the MYNX CONTROL™ Venous VCD that do not receive the device due to device malfunction and are subsequently treated with manual compression, will remain part of the ITT analysis population. These subjects will also be part of the AT analysis population and analyzed in the manual compression group. They will not be part of the PP analysis population.

7 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 subject 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 subject level to avoid the possibility of a subject 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 subjects will receive the MYNX CONTROL™ Venous VCD.

8 STATISTICAL METHODS OF ANALYSIS

8.1 General Considerations

All statistical programming will be performed using SAS® version 9.4 or above, or other widely accepted statistical or graphical software.

Summary tables will be based only on all available data. 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 specified.

The analyses described in this section assume that 204 subjects have been enrolled and 30-day follow-up complete, and that 72 of those subjects have been consented to the DUS sub-study. If the sub-study has not completed enrollment by the time 204 subjects are enrolled in the main study, the analyses described below, with the exception of the DUS sub-study, will be completed on the full 204 subjects and study results will be declared as planned .This will be considered the primary analysis.

Enrollment will continue until 72 subjects are consented to the DUS sub-study. Once follow-up in the sub-study is complete, all analyses will be re-run on the full complement of subjects enrolled and that analysis will be considered as a supplemental dataset..This plan ensures the statistical methodology for the primary analysis remains unaltered.

8.2 Subject Disposition

Subject accountability will be summarized in tabular form.

8.3 Subject Demographics and Baseline Variables

All baseline variables will be summarized using descriptive statistics. Continuous variable will be summarized using the mean, standard deviation, N, and range. Categorical variable will be summarized as frequencies and proportions. Baseline variables for the two subject groups will be summarized separately

8.4 Analyses of Safety Endpoints

8.4.1 Primary Safety Endpoint Analysis

The primary safety endpoint analysis will be performed on a per limb basis. The null and alternative hypotheses of the primary safety comparison are given below:

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

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

where P_X is the proportion of limbs experiencing a major venous access site closure-related complications through 30 days post-procedure and δ is the non-inferiority window. For this analysis, δ is set at 5 percentage points.

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 will be calculated along with a 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 those subjects contributing two limbs.

8.4.2 Secondary Safety Endpoint 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.

8.4.3 Additional Safety 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.

8.5 Analyses of Effectiveness Endpoints

8.5.1 Primary Effectiveness Endpoint Analysis

There are two co-primary effectiveness endpoints: Time to hemostasis, and time to ambulation.

The average time to ambulation in each treatment group will be compared using a standard T-test. The test will be done on a per subject basis. The null and alternative hypotheses are:

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

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

where μ_x is the average time to ambulation for the specified group. A p-value for this one-sided test less than 0.025 will indicate that the time to ambulation for the subjects using the MYNX CONTROL™ Venous VCD was significantly less than for those where manual compression was used.

The average time to hemostasis will be analyzed on an access site level. 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 μ_x is the mean time to hemostasis for the indicated group and 5 minutes is superiority margin.

The average time to hemostasis will be analyzed using a generalized linear mixed model where subject is considered a random effect with multiple access sites and treatment group is a fixed effect. 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 device 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. This test is by default a two-sided test, so a p-value of 0.05 or less with the direction of the difference showing shorter times for MYNX

CONTROL™ Venous VCD will correspond to a one-sided test at the 0.025 level results in achieving this endpoint.

If the distribution assumptions (normality, lognormality) for the primary effectiveness endpoints do not hold based on Shapiro-Wilk test at the 0.05 alpha level, a non-parametric Wilcoxon rank sum test will be used to compare the treatment groups.

8.5.2 Secondary Effectiveness Endpoint Analysis

Time to Discharge Eligibility- defined as elapsed time between removal of the final Mid-Bore VVCS device (treatment arm) or removal of the final sheath (control arm) and when the subject is eligible for discharge from the institution based on the assessment of the attending physician. The average time to discharge eligibility will be compared between the treatment 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 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 average times will also be calculated along with a 95% confidence interval based on the T-distribution.

The remaining secondary endpoint comparisons between MYNX CONTROL™Venous VCD and manual compression are considered ad hoc analyses.

If the distribution assumption of normality the secondary effectiveness endpoint does not hold based on Shapiro-Wilk test at the 0.05 alpha level, a non-parametric Wilcoxon rank sum test will be used to compare the treatment groups.

Procedural Success: attainment of final hemostasis at all venous access sites without major venous access site closure-related complications through 30 days. The proportion of subjects achieving procedural success will be calculated for each treatment group. Those proportions will be compared using both the Pearson Chi-square statistic and Fisher's Exact Test.

Device Success: ability to deploy the VCD delivery system, deliver the polyethylene glycol hydrogel sealant, and achieve hemostasis. This endpoint will be summarized for

the MYNX CONTROL™ Venous VCD arm only. The proportion of devices that achieve success will be estimated along with a 95% confidence interval calculated using the Clopper-Pearson (exact binomial) method.

8.6 Adverse Events

Adverse events (AE), Serious Adverse Events (SAE), Major Adverse Events (MAE), and Unanticipated Adverse Device Effects (UADE) will be tabulated (or listed) separately for each treatment group. The table or listing will contain the term or description, start and end dates, severity, outcome, and causality or association to the investigational product or procedures involved in the clinical study. These summary tables will present descriptive statistics and no formal testing will be done.

8.7 Sub-Group Analysis

A sub-group analysis will be completed for the primary safety and primary efficacy endpoints as outlined in Section 8.5. This analysis is not powered and is strictly for information purposes. The sub-groups are:

- Race
- Sex (females vs. males)
- Total Number of access sites
- Number of access sites per limb
- Sheath size
- Number of limbs (1 vs. 2)

Of the identified sub-groups, the following groups: the total number of access sites, Number of access sites per limb, sheath size and the number of limbs subgroup will be analyzed for both the major and minor complications noted within the study between both treatment groups.

For time to ambulation and time to hemostasis, homogeneity of the treatment will be tested using a linear model. Treatment group will be one factor while sub-group will be the second factor in the model and an interaction term between treatment group and sub-group will be added to the model. The interaction term will be tested at the 0.15 level of significance. If the p-value is greater than 0.15 then the treatment effect will be considered homogeneous. For the safety endpoint, homogeneity of the major venous access site closure-related complication rate through 30 days post-procedure will be modeled using a logistic regression model. As for the effectiveness endpoint, a treatment group by sub-group interaction will be added to this model and tested at the 0.15 level of significance. If the p-value is greater than 0.15 then the major complication rates will be considered homogeneous.

A sub-group analysis will also be performed utilizing independent analysis of non-invasive duplex ultrasound (DUS) imaging in 48 subjects from the MYNX CONTROL™ group and 24 subjects from the manual compression group at the time of the procedure, pre-discharge and potentially again at the 30-day follow-up. 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 (48 MYNX

CONTROL™, 24 Manual Compression). 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 the following central core laboratory:

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.

8.8 Analysis of Roll-in Subjects

Roll-in subjects will be summarized using descriptive statistics. No formal hypothesis testing will be done on this group.

Time to ambulation will summarized using the mean, median, standard deviation, sample size, minimum, and maximum. A 95% confidence interval for the average time to hemostasis will be calculated using the T-distribution.

Time to hemostasis will first be summarized across access sites within each subject by calculating the mean time to hemostasis by averaging the individual site-specific times. Time to hemostasis will then be summarized across subjects by calculating the mean, median, standard deviation, sample size, minimum, and maximum. A 95% confidence interval for the average time to hemostasis will be calculated using the T-distribution.

The proportion of roll-in subjects experiencing a major access related complication will be calculated along with a 95% confidence interval constructed using the Clopper-Pearson method.

8.9 Protocol Deviations

Protocol deviations will be listed by category. Descriptive statistics will be used to summarize the number of times a deviation happened over the course of the trial.

9 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 5. 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 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.

10 INTERIM ANALYSIS

An interim analysis in support of a CE Mark submission will be conducted to analyze initial subjects randomized to the treatment arm only with respect to efficacy and safety. This interim analysis is not intended to support a decision to continue or to discontinue the trial, or to implement any modifications to trial procedures. To alleviate potential statistical and operational bias that may be introduced, the execution of the interim analysis shall be a completely confidential process to the study team. All sponsor staff, staff contracted by the sponsor, and investigator staff directly involved in the conduct of the ongoing IDE trial will remain blind to the process and results of the analyses, with the exception of contracted resources involved in the execution of the interim analysis and submission of the results on behalf of the sponsor. Endpoints to be evaluated using descriptive statistics are as follows:

- Primary efficacy: Time to Ambulation 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.

11 HANDLING OF MISSING DATA

While all reasonable efforts will be made to obtain the data required to evaluate this endpoint, it is expected that some subjects 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. Subjects who have ascertainment of status at a later out-of-window date (for example, subjects who are known to be free of events past discharge 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 subjects who had an event prior to the milestone visit divided by the number of evaluable subjects who had sufficient follow up (e.g., at least discharge visit) plus any subjects who had an event prior to the milestone visit.

A sensitivity analysis will be conducted for the endpoints of time to hemostasis, time to ambulation, and time to discharge eligibility using a simple pattern mixture model approach. For each treatment group, the overall mean is a weighted average of the observed data and the unobserved data. Assumptions on the unobserved data need to be used in order to assess the sensitivity of the study conclusions. For the control group, the mean of the unobserved data will be set equal to that of the observed data essentially assuming the missing data are missing at random. For the MYNX CONTROL™ Venous VCD group, the mean of the unobserved data will be incrementally increased by a pre-specified Δ until the overall interpretation of the endpoint changes. For time to hemostasis, the mean of the unobserved data will be increased in increments of 1 minute. For time to ambulation and time to discharge eligibility, Δ will be increased in increments of 0.5 hour. Once Δ has increased to the point that the endpoint conclusions change, then the feasibility of that increase will be assessed from a clinical standpoint.

The same type of sensitivity analysis will be done for the safety endpoint where the unobserved data in both groups starts out the same as the observed data. The sensitivity analysis for safety will be performed using the logit of the observed proportion of limbs with a major complication. The logit in the MYNX CONTROL™ Venous VCD group will then be incrementally increased until non-inferiority between the two groups cannot be established. This change in logit will then be interpreted from a clinical standpoint.