

Essential Medical, Inc.

Pivotal Clinical Study to Evaluate the Safety and Effectiveness of
MANTA Vascular Closure Device

Statistical Analysis Plan

Protocol No. PSD-109 Revision F

Version 1.5

Date:

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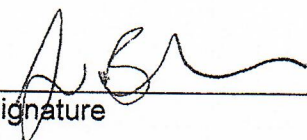
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SIGNATURE PAGE

I confirm that this Statistical Analysis Plan accurately describes the planned statistical analyses to the best of my knowledge and was finalized before database lock.

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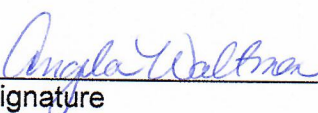

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TABLE OF CONTENTS

SIGNATURE PAGE	2
1 GENERAL AND TECHNICAL ASPECTS.....	7
2 Clinical Trial Design and Objectives	7
2.1 Clinical Trial Design	7
2.2 Clinical Trial Treatments	8
2.2.1 Treatment Groups	8
2.2.2 Blinding.....	8
2.3 Clinical Trial Objectives.....	8
2.4 Primary Study Hypotheses.....	8
2.4.1 Primary Safety Hypothesis.....	8
2.4.2 Primary Effectiveness Hypothesis.....	9
2.5 Safety Assessments.....	10
2.5.1 Primary Safety Variable.....	10
2.5.2 Secondary Safety Variables.....	10
2.6 Effectiveness Assessments.....	11
2.6.1 Primary Effectiveness Variable.....	12
2.6.2 Secondary Effectiveness Variables.....	12
2.7 Additional Endpoints	12
2.8 Other Variables	12
2.8.1 Subject Characteristics	12
2.8.2 Procedural and Discharge Data	13
2.8.3 Exploratory Analyses	14
3 Determination of Sample Size.....	14
4 Analysis Populations.....	14
4.1 Primary Analysis Cohort	15
4.2 Per Protocol Set.....	15
4.3 Safety Evaluation Set	15
4.4 Roll-In Cohort.....	15
5 Data conventions and definitions	16
5.1 Handling of Missing Data	16
5.2 Poolability Analysis and Stratification.....	16
5.3 Covariates.....	16
5.4 Subgroup Analyses	17
5.5 Standard Calculations.....	17
5.5.1 Age	17
5.5.2 BMI	17
5.5.3 Clinical Trial Duration.....	17
6 Statistical Analysis Methods	17
6.1 Summarizing and Tabulating Collected Data.....	17
6.1.1 Subject Disposition and Withdrawals	18

6.1.2	Protocol Deviations.....	18
6.1.3	Demographics and Other Baseline Characteristics.....	19
6.1.4	Concomitant Medications	19
6.2	Analysis of Effectiveness Data	19
6.2.1	Primary Effectiveness Endpoint.....	19
6.2.2	Secondary Effectiveness Endpoints	19
6.2.3	Procedural and Discharge Data	20
6.3	Analysis of Safety Data	21
6.3.1	Adverse Events.....	22
6.3.2	Primary Safety Endpoint:.....	22
6.3.3	Secondary Safety Endpoint:	22
7	Adjudication of Clinical Endpoints.....	23
8	Changes in the Planned Analyses.....	24
9	Appendix A: Table of Contents for Tables, Listings, and Figures.....	25
10	Appendix B: Effective Puncture Size Algorithm	30

TABLE LIST OF ABBREVIATIONS

Abbreviation/ Acronym	Definition
ABI	Ankle/brachial index
ACT	Activated clotting time
ADE	Adverse device effect
AE	Adverse event
BARC	Bleeding Academic Research Consortium
BAV	Balloon aortic valvuloplasty
BMI	Body mass index
CA	Competent authority
CAC	Clinical acceptance criterion/criteria
CE	Conformité Européene (European Conformity)
CEC	Clinical events committee
CFR	(U.S.) Code of Federal Regulations
CRF	Case report form
CRO	Contract research organization
CTA	Computed tomography angiography
DMP	Data management plan
DSMC	Data and safety monitoring committee
EC	Ethics committee
eCRF	Electronic case report form
EU	European Union
EVAR	Endovascular aneurysm repair
F	French (1F = 0.33 mm); used for defining catheter size
FDA	U.S. Food & Drug Administration
FIH	First in human
HCT	Hematocrit
ID	Inner diameter
INR	International normalized ratio
IRB	Institutional review board
ISO	International Organization for Standardization
NYHA	New York Heart Association
OD	Outer diameter
PAC	Primary Analysis Cohort
PG	Performance goal
PMA	Pre-market approval
PPS	Per Protocol Set
SAE	Serious adverse event
SADE	Serious adverse device effect
SAP	Statistical Analysis Plan
SES	Safety Evaluation Set

SFAR	Sheath to femoral artery ratio
SOPs	Standard operating procedures
STS	Society of Thoracic Surgeons
TAVR/TAVI	Transcatheter aortic valve replacement / transcatheter aortic valve implantation
TTA	Time to ambulation
TTH	Time to hemostasis
UADE	Unanticipated adverse device effect
USADE	Unanticipated serious adverse device effect
VARC	Valve Academic Research Consortium
VCD	Vascular closure device

1 GENERAL AND TECHNICAL ASPECTS

The objective of this statistical analysis plan is to specify the planned analysis and reporting for the clinical trial protocol PSD-109, sponsored by Essential Medical, Inc. It is intended to describe the statistical methodology and data conventions to be used in the statistical programming and the creation of tables, figures, and listings.

This statistical analysis plan is based on the clinical trial protocol, PSD-109 (Rev. F), dated June 2, 2017. The format and content of the Statistical Analysis Plan (SAP) are structured to provide sufficient detail to meet the requirements specified by the International Conference on Harmonization (ICH) E9: Guidance on Statistical Principles in Clinical Trials. Note that ISO 14155:2011 does not include specified requirements for a SAP.

All programs will be written using SAS (Statistical Analysis System) version 9.4 or higher. SAS programs will be written for all tables, figures and listings. All outputs will be transferred into .rtf-files. These files will be generated separately for the tables and figures of Section 14 and the listings of Section 16.2 of the appendix of the clinical study report.

2 CLINICAL TRIAL DESIGN AND OBJECTIVES

2.1 Clinical Trial Design

This is a multi-center, prospective, single-arm clinical investigation designed to evaluate the safety and effectiveness of the MANTA vascular closure device in achieving hemostasis in femoral arterial access sites in subjects undergoing percutaneous transcatheter interventional procedures using a large-bore procedure sheath. This investigation is being conducted for purposes of supporting a PMA approval in the United States, as well as other global regulatory approvals.

A minimum of five and up to 25 clinical sites in the United States, European Union, and/or Canada will participate in the trial. Approximately 263 subjects will be treated with either the 18F MANTA device or the 14F MANTA device to yield 250 subjects available for analysis at the 30-day primary safety endpoint, accounting for a 5% loss to follow-up rate. This group is termed the Primary Analysis Cohort. In addition to these 263 subjects, up to two subjects will be enrolled per treating Investigator (the Roll-In Cohort) to allow Investigators to learn how to use the MANTA device; these subjects will be summarized separately from the Primary Analysis Cohort.

Up to 90 days prior to the scheduled index procedure, the medical records of potential study subjects are screened for selected study inclusion/exclusion criteria to determine whether the subject is a potential candidate for the study. If a candidate, the subject will then be approached prior to the index procedure and the study will be explained. If a subject agrees to the study, he/she will provide written informed consent after which time, the subject will be screened to the study baseline inclusion/exclusion criteria. If all criteria are met, during and immediately following the index procedure, the subject will be assessed for the intra-procedure exclusions to confirm continued eligibility before undergoing treatment with the MANTA device. Subjects are considered enrolled in the clinical investigation after they have provided written informed consent and have been determined to meet all eligibility criteria, including the intra-procedure exclusion criteria.

Subjects can then undergo the procedure, during which the Investigator will select the correct size of MANTA closure device, depending on the size of the femoral sheath or interventional device used for the procedure. After the procedure, subjects will be assessed for Time to Hemostasis

(the primary effectiveness endpoint) and other post-procedure evaluations. Subjects will be discharged from the hospital when deemed ready by the Investigator and will return for follow-up visits at 30 ± 7 days and at 60 ± 14 days post procedure to assess for any major or minor complications or adverse events. Subjects will undergo a clinical exam, a target femoral access site external visual assessment, a duplex ultrasound exam (no 60-day ultrasound if no findings at 30 days), and be assessed for medication use and ABI at these follow-up visits.

2.2 Clinical Trial Treatments

2.2.1 Treatment Groups

There is only one treatment group in this trial; all subjects will be treated with the MANTA vascular closure device. A minimum of 50% of subjects will be treated with the 18F MANTA device and the remainder will be treated with the 14F MANTA device. The Sponsor will monitor the study with respect to the number of subjects receiving each device to encourage recruitment of a balance of cases. There is no randomization in this investigation.

The primary analysis of the study will be performed on the Primary Analysis Cohort. The Roll-In Cohort will be analyzed separately from the Primary Analysis Cohort; the Roll-In Cohort data will not be analyzed or compared to the Performance Goals or Clinical Acceptance Criterion.

2.2.2 Blinding

Due to the physical and clinical nature of the MANTA device, neither the Investigator nor the subject will be blinded.

2.3 Clinical Trial Objectives

The objectives of this study are to evaluate the safety and effectiveness of MANTA in achieving hemostasis in femoral arterial access sites in patients undergoing percutaneous transcatheter interventional procedures using a large-bore procedure sheath.

2.4 Primary Study Hypotheses

2.4.1 Primary Safety Hypothesis

The primary safety hypothesis is that the rate of Major Complications in the Primary Analysis Cohort (the proportion of subjects with one or more Major Complications as defined in Section 2.5.1 below) within 30 days of the procedure is less than the Performance Goal of 19.9%. This Performance Goal was derived from data in the published literature on the use of single or multiple Proglide/Prostar devices in large-bore procedures and from the clinical judgment of expert advisors.

Null hypothesis: The rate of Major Complications within 30 days of the procedure is not less than the Performance Goal of 19.9%.

$H_0: \pi \geq 0.199$

Alternative hypothesis: The rate of Major Complications within 30 days of the procedure is less than the Performance Goal of 19.9%.

$$H_A: \pi < 0.199,$$

where π is the population Major Complication rate. The rate of Major Complications in subjects treated with the MANTA device within 30 days will be presented along with the exact one-sided upper 97.5% confidence bound. If this upper confidence bound is less than 19.9%, the study will have met its primary safety objective.

If more than 13 of the subjects in the Primary Analysis Cohort (5% of the 250 assumed to achieve statistical power) are lost to follow-up or die due to a reason other than a Major Complication, the Major Complication rate will also be estimated from a Kaplan-Meier rate statistical curve. Subjects lost to follow-up will be censored at the date of their last contact. Subjects who die due to a reason other than a Major Complication will be censored at their date of death. An asymptotic one-sided upper 97.5% confidence bound will be placed on the estimated major complication rate at 30 days using the estimated survival curve and the standard error formula given by Peto, Peto, and Armitage¹ in Statistical Note 6. If this upper confidence bound is less than 19.9%, the study will have met its primary safety objective.

In addition, the proportion of subjects with each individual Major Complication will be presented along with their two-sided exact 95% confidence intervals.

2.4.2 Primary Effectiveness Hypothesis

The primary effectiveness hypothesis is that population mean Time to Hemostasis in the Primary Analysis Cohort is less than the Performance Goal of 10 minutes. This Performance Goal was derived from data in the published literature on the use of single or multiple Proglide/Prostar devices in large-bore procedures and from the clinical judgment of expert advisors.

Null hypothesis: The mean Time to Hemostasis in the study is not less than the Performance Goal of 10 minutes.

$$H_0: \mu \geq 10$$

Alternative hypothesis: The mean Time to Hemostasis in the study is less than the Performance Goal of 10 minutes.

$$H_A: \mu < 10$$

where μ is the population mean Time to Hemostasis. The mean Time to Hemostasis will be presented along with the exact one-sided upper 97.5% confidence bound. If this upper confidence bound is less than 10 minutes, the study will have met its primary effectiveness objective.

¹ Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. analysis and examples. *British Journal of Cancer*. 1997;35(1):1-39.

2.5 Safety Assessments

The primary and secondary safety analyses will be performed on the Safety population, defined as all enrolled study subjects in the Primary Analysis Cohort in whom an attempt to use the device is made (use of the puncture locating dilator prior to assessment of intra-procedure exclusions is not considered an attempted use of the device). Roll-in subjects will be summarized separately and will not be analyzed against the safety Performance Goal or Clinical Acceptance Criterion.

All adverse events will be MedDRA coded and will be presented by Preferred Term and System Organ Class. The Clinical Events Committee (CEC) will review and adjudicate certain adverse events, as defined in the protocol, and determine whether an event is a Major Complication, Minor Complication, or VARC-2 Major Vascular Complication for the primary and secondary safety endpoints.

2.5.1 Primary Safety Variable

The primary safety endpoint is the percentage of subjects with one or more Major Complications listed below within 30 days of the procedure. Major Complications include the following events:

Major Complications:

- i. Vascular injury attributable to the MANTA device requiring surgical repair or stent-graft;
- ii. Access site-related bleeding that is attributable to failure of or sub-optimal performance of the MANTA device and that results in transfusion;
- iii. New onset ipsilateral lower extremity ischemia that originates with the common femoral artery, is attributable to the MANTA device, causes a threat to the viability of the limb, and requires surgical repair or additional percutaneous intervention;
- iv. Access site-related nerve injury attributable to the MANTA device that is permanent (lasting >30 days) or requires surgical repair; and
- v. Access site-related infection requiring intravenous antibiotics and/or extended hospitalization.

2.5.2 Secondary Safety Variables

The secondary safety endpoints include:

1. The percentage of subjects with one or more Minor Complications within 30 days of the procedure;
2. The percentage of subjects with one or more VARC-2 Major Vascular Complications within 30 days of the procedure.

Minor Complications will be qualitatively, but not statistically, assessed against a Clinical Acceptance Criterion of 20% as derived from data in the published literature on the use of single or multiple Proglide/Prostar devices in large-bore procedures and from the clinical judgment of expert advisors. This CAC will not be statistically tested. VARC-2 Major Vascular Complications will not be statistically tested against a PG or qualitatively assessed against a CAC.

Minor Complications:

- i. Non-treated pseudoaneurysm attributable to the MANTA device and documented by ultrasound;
- ii. Non-treated or treated arteriovenous (AV) fistula attributable to the MANTA device and documented by ultrasound;
- iii. Pseudoaneurysm treated with ultrasound-guided compression, ultrasound-guided thrombin injection or ultrasound-guided fibrin adhesive injection;
- iv. Access site hematoma that is attributable to failure of or sub-optimal performance of the MANTA device, is ≥ 10 cm and is confirmed by ultrasound;
- v. Late (following hospital discharge) access site-related bleeding;
- vi. Ipsilateral lower extremity arterial emboli attributable to the MANTA device;
- vii. Ipsilateral vein thrombosis attributable to the MANTA device;
- viii. Transient access site-related nerve injury;
- ix. Access site wound dehiscence; and
- x. Localized access site infection treated with intramuscular or oral antibiotics.

Major Vascular Complications: Adapted² from the VARC-2 Clinical Guidelines³:

- i. Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) leading to death, life threatening or major bleeding, visceral ischemia, or neurological impairment OR
- ii. Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR
- iii. The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia or neurological impairment OR
- iv. Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR
- v. Surgery for access site-related nerve injury OR
- vi. Permanent access site-related nerve injury.

In addition to the pre-determined categories of Major Complications, Minor Complications, and VARC-2 Major Vascular Complications, all adverse events recorded throughout the entire 60-day duration of the study will be categorized and summarized descriptively by type, severity, and relationship to device/procedure. Serious Adverse Events (SAEs) and Unanticipated Adverse Device Effects (UADEs) will also be summarized. Adverse events will not be statistically tested against a PG or qualitatively assessed against a CAC.

2.6 Effectiveness Assessments

The primary and secondary effectiveness analyses will be performed on both the Primary Analysis Cohort population and the Per Protocol population. Roll-in subjects will be summarized separately

² The Major Vascular Complications definition from the VARC-2 guidelines was adapted as follows: The first bullet of the definition ("Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudoaneurysm OR") was deleted from the definition used in this protocol, as these adverse events are entirely unrelated to the femoral access site.

³ Kappetein AP, Head SJ, G  n  reux P et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: The Valve Academic Research Consortium-2 consensus document. J Thorac Cardiovasc Surg 2013;145:6-23.

from the Primary Analysis Cohort and will not be tested against the effectiveness Performance Goal.

2.6.1 Primary Effectiveness Variable

The primary effectiveness endpoint is the mean Time to Hemostasis, defined as the elapsed time between MANTA deployment (withdrawal of sheath from artery) and first observed and confirmed arterial hemostasis (no or minimal subcutaneous oozing and the absence of expanding or developing hematoma).

2.6.2 Secondary Effectiveness Variables

The secondary endpoints include:

1. Proportion of subjects with Technical Success
2. Proportion of subjects with Ambulation Success
3. Proportion of subjects with Treatment Success
4. Mean Time to Ambulation
5. Mean Procedure Time

These secondary endpoints are defined in Section 6.2.2.

2.7 Additional Endpoints

Not applicable.

2.8 Other Variables

2.8.1 Subject Characteristics

The following subject characteristics will be collected and analysis will be performed on both the Primary Analysis Cohort population and the Per Protocol population. Roll-in subjects will be summarized separately from the Primary Analysis Cohort. All analysis populations will also be summarized by endovascular procedure type.

- Subject disposition
- Protocol deviations and other reasons for exclusion from analysis sets
- Demographic variables will include:
 - Age
 - Age Category (<65, 65-79, and 80+ years)
 - Gender
 - Race
 - Ethnicity
 - Height
 - Weight
 - BMI

- Other baseline characteristic variables will include:
 - Prior surgical history events of interest
 - Baseline laboratory results of interest
 - Anti-coagulant and anti-platelet concomitant medications at baseline and during procedure

The following data will be provided as by-subject listings:

- Discontinued subjects
- Protocol deviations
- Subjects excluded from the per protocol set
- Demographics, including STS cardiac surgery risk score (TAVI subjects only)
- Medical and surgical history
- Concomitant medications
- Procedural and discharge data
- Device deficiencies
- Effectiveness data
- Adverse events
- Baseline laboratory results
- Clinical examination results
- Pregnancy test results
- Ipsilateral Ankle-brachial Index results
- Ultrasound results

2.8.2 Procedural and Discharge Data

The following data will be collected during the procedure and discharge and analysis will be performed on both the Safety Evaluation Set and the Per Protocol population. A separate analysis will also be performed for the Roll-in subjects.

1. Endovascular procedure type
2. Procedure sheath brand
3. Procedure sheath size (F)
4. Index device manufacturer/brand
5. Index device size (mm)
6. Effective puncture size (F)
7. MANTA size (14F or 18F)
8. Target artery (left or right)
9. Target artery diameter (mm)
10. Sheath to femoral artery ratio (SFAR)
11. Pre-deployment ACT (sec)
12. Use of adjunctive methods to obtain hemostasis
13. Use of adjunctive methods for treating oozing
14. Any thrombus observed on the MANTA components (Y/N)
15. Post-deployment angiogram results

16. Time to discharge post-MANTA deployment
17. Time to discharge post-ambulation
18. Mean ABI scores at baseline, pre-procedure, post-procedure, discharge, follow-up
19. Ultrasound findings post-procedure and at follow-up
20. Device deficiencies

Other procedure data will be reported in by-subject listings. Definitions for these data points are provided in Section 6.2.3.

2.8.3 Exploratory Analyses

Additional exploratory analyses will be performed as needed.

3 DETERMINATION OF SAMPLE SIZE

The sample size for this study was based on the primary effectiveness and safety endpoints of Time to Hemostasis and major complication rate. The population Time to Hemostasis is assumed to be 6 minutes, with a standard deviation of 11 minutes. Based on these assumptions and a normal distribution, 62 subjects will provide 80% power to reject the primary effectiveness hypothesis at a one-sided significance of 0.025.

The population Major Complication rate is assumed to be 13%. Based on this assumption, 250 subjects will provide 80% power to reject the primary safety hypothesis at a one-sided significance of 0.025. Therefore, the necessary sample size is driven by the primary safety endpoint and is 250 subjects.

Assuming a lost to follow-up rate of approximately 5%, the study will treat a total of 263 subjects to ensure an adequate sample size of 250 subjects meeting the 30-day primary safety endpoint.

4 ANALYSIS POPULATIONS

The Primary Analysis Cohort will include all enrolled study subjects in whom an attempt to use the device is made, excluding the first two roll-in subjects treated per each Investigator. Subjects who sign the consent form but are deemed ineligible for the study prior to any attempt to use the MANTA device will not be included in the Primary Analysis Cohort or the Roll-In Cohort. Use of the MANTA puncture locating dilator at the beginning of the large-bore intervention procedure is not considered an attempt to use the MANTA device. Placement of the MANTA sheath following confirmation of intra-procedure exclusions is the start of attempted device use, and the time this sheath is removed will define the starting time of efficacy assessments.

The Primary Analysis Cohort, the Per Protocol Set, and the Safety Evaluation Set as described below will be comprised of the subjects in the Primary Analysis Cohort. Subjects in the Roll-In Cohort will be summarized separately from subjects in the Primary Analysis Cohort.

The following populations will be defined for the statistical analysis of this clinical trial:

4.1 Primary Analysis Cohort

The Primary Analysis Cohort (PAC) will consist of all non-roll-in subjects in whom an attempt to use the device was made (i.e., subjects who sign the consent form but are deemed ineligible for the study prior to any attempt to use the MANTA device will not be included in the efficacy analyses). Subjects who are excluded due to intra-procedural exclusions will be excluded from the efficacy analyses as long as the MANTA sheath has not been introduced; use of the MANTA puncture locator at the beginning of the procedure is not considered "attempted use" of the MANTA device.

4.2 Per Protocol Set

The Per Protocol Set (PPS) is the subset of subjects in the PAC for whom all assessments planned in the protocol were performed with no major protocol deviations. Major protocol deviations will include:

1. Informed Consent procedure violations
2. Inclusion/Exclusion violations
3. Missing/out-of-window by >12 month baseline CTA
4. Missing Time to Hemostasis
5. Missing 30-day visit

Subjects found to have major protocol deviations will be excluded from the PPS. The Per Protocol analysis of the primary and secondary effectiveness endpoints and primary safety endpoints will be used for supportive analysis.

4.3 Safety Evaluation Set

The Safety Evaluation Set (SES) will consist of all non-roll-in subjects in whom an attempt to use the MANTA device was made. (i.e., subjects who sign the consent form but are deemed ineligible for the study prior to any attempt to use the MANTA device will not be included in the safety analyses). Subjects who are excluded due to intra-procedural exclusions will be excluded from the safety analyses as long as the MANTA sheath has not been introduced; use of the MANTA puncture locator at the beginning of the procedure is not considered "attempted use" of the MANTA device. The Safety population will be used for the analysis of safety endpoints as well as procedural and discharge data.

4.4 Roll-In Cohort

Up to two roll-in subjects per operator using either MANTA device will be enrolled to allow investigators to learn how to use the MANTA device. Data from the Roll-In Cohort will be summarized separately from the Primary Analysis Cohort for safety and effectiveness and will not be tested statistically against the Performance Goals.

5 DATA CONVENTIONS AND DEFINITIONS

5.1 Handling of Missing Data

Missing data will not be imputed for safety endpoints. However, if more than 13 subjects in the Primary Analysis Cohort either die for a reason other than a Major Complication or are lost to follow up within 30 days of treatment, then the rate of Major Complications will also be estimated by the Kaplan-Meier method, to allow for subjects who are censored before a Major Complication can be observed. See Section 2.4.1 for further details.

For effectiveness endpoints, it is highly unlikely that there will be missing data for Time to Hemostasis, Technical Success, Ambulation Success, Time to Ambulation, Treatment Success or Procedure Time. However, if any of these data are missing (i.e., in the event that Time to Hemostasis cannot be evaluated because a surgical repair must be performed), the worst value observed for any subject at the same study site within each analysis cohort, will be imputed for the missing value. Missing data for a subject in the Primary Analysis Cohort will be imputed with the worst value observed for any Primary Analysis Cohort subject at the same study site, and missing data for a subject in the Roll-In Cohort will be imputed with the worst value observed for any roll-in subject at the same study site.

No other imputations will be carried out for missing data.

5.2 Poolability Analysis and Stratification

Analyses of the primary effectiveness and primary safety endpoints will be performed to assess the comparability of study sites. Sites with fewer than 5 subjects each will be pooled into a composite site.

Time to Hemostasis in the Primary Analysis Cohort population will be analyzed by a one-way analysis of variance that includes the effect of the study site. If the study site means differ ($p < 0.15$) then additional analyses will be performed to explore the cause of the difference, in particular if the differences are caused by differences in some baseline factor.

Major Complications in the Safety population will be analyzed by Pearson's chi square to assess if the Major Complication rates differ among study sites. If the study site rates differ ($p < 0.15$) then additional analyses will be performed to explore the cause of the difference, in particular if the differences are caused by differences in some baseline factor.

Stratified analyses will not be performed.

5.3 Covariates

As a supportive analysis, a covariate analysis will be conducted to assess the impact of various factors on the primary effectiveness endpoint. The following covariates will be examined:

- Gender
- Race
- Ethnicity
- Age Category

- Procedure type (e.g., TAVI, EVAR)
- MANTA device size
- Index device type (Manufacturer/Brand)
- Effective puncture size
- Sheath to femoral artery ratio (SFAR)

For each categorical covariate, Time to Hemostasis in the Primary Analysis Cohort population will be analyzed by a one-way analysis of variance that includes the effect of the covariate. If the subgroup means differ ($p < 0.05$) then additional analyses will be performed to explore the cause of the difference, in particular if the differences are caused by another demographic factor. Major Complications in the Safety population will be summarized by levels of the covariate only.

For continuous covariates (SFAR), Time to Hemostasis in the Primary Analysis Cohort population will be analyzed by univariate regression. If the regression is significant ($p < 0.05$) then additional analyses will be performed to explore the cause. Association of SFAR with Major Complications, Minor Complications and VARC-2 Major Vascular Complications will be examined through odds ratio analysis (see 6.3.3).

5.4 Subgroup Analyses

There are no subgroup analyses planned for this clinical trial.

5.5 Standard Calculations

5.5.1 Age

Age will be calculated as the number of completed years between the subject's birth date and the date of informed consent.

5.5.2 BMI

Body Mass Index will be calculated as the subject's weight in kilograms divided by height in meters squared (kg/m^2).

5.5.3 Clinical Trial Duration

Clinical trial duration will be calculated as the total number of days each subject is in the clinical trial.

$$\text{Duration} = (\text{Date of subject completion, death or withdrawal} - \text{Date of Procedure}) + 1$$

6 STATISTICAL ANALYSIS METHODS

6.1 Summarizing and Tabulating Collected Data

All data from this clinical trial will be provided in data listings by site, subject, and time point, as applicable.

Continuous and categorical variables will be summarized by descriptive statistics. Standard descriptive statistics for continuous variables will be the number of observations, mean, median, standard deviation, minimum and maximum. Standard descriptive statistics for categorical variables will be counts and percentages; percentages will be computed relative to the size of the reference population. 95% confidence intervals will also be provided where appropriate.

6.1.1 Subject Disposition and Withdrawals

There will be a detailed accounting of all subjects who sign an informed consent to participate in this trial. The number of subjects within each of the following groups will be summarized in total and by site: signed informed consent, intra-procedure screen failures, discontinued, and completing the study according to the protocol.

Reasons for discontinuations will be summarized by site using the following categories:

- Subject is lost to follow up
- Adverse event
- Explantation of the device
- Subject voluntarily withdraws
- Subject is withdrawn by the Investigator or Sponsor
- Sponsor or Investigator terminated study
- Death
- Other

In addition, there will be a listing of all discontinued subjects, which will include site, reason for discontinuation, and duration of study participation before discontinuation.

6.1.2 Protocol Deviations

The deviations occurring during the clinical trial will be determined to be major or minor by the Sponsor and data management group prior to database lock and will be summarized descriptively. A by-subject listing of all deviations will also be prepared. Categories of protocol deviations include:

- Informed Consent Procedure
- Inclusion/Exclusion
- Concomitant Medication/Therapy
- Laboratory Assessments/Procedures
- Study Procedures
- SAE Reporting/UADE Reporting
- Visit Schedule/Interval
- Other

6.1.3 Demographics and Other Baseline Characteristics

Demographics (age, gender, race, and ethnicity) and baseline characteristics (height in cm, weight in kg, BMI) will be summarized by descriptive statistics.

Prior surgical history events of interest (CABG, PCI, Pacemaker/ICD, Neurovascular Intervention, and Peripheral Intervention) and baseline laboratory tests of interest (creatinine, hematocrit, hemoglobin, INR, platelets, and urea nitrogen) will also be summarized by descriptive statistics.

All clinical examination results, medical history, and baseline laboratory tests (reported in SI units) will be provided as by-subject listings.

6.1.4 Concomitant Medications

Anti-coagulant and anti-platelet concomitant medications at baseline and during procedure will be summarized by generic drug name.

All concomitant medications will also be provided as by-subject listings.

6.2 Analysis of Effectiveness Data

6.2.1 Primary Effectiveness Endpoint

Time to Hemostasis is defined to be the elapsed time between MANTA deployment (withdrawal of sheath from artery) and first observed and confirmed arterial hemostasis (no or minimal subcutaneous oozing and the absence of expanding or developing hematoma). The mean Time to Hemostasis (in minutes) will be presented along with the one-sided upper 97.5% confidence bound. If this upper confidence bound is less than 10 minutes, the study will have met its primary effectiveness objective.

6.2.2 Secondary Effectiveness Endpoints

The secondary endpoints are defined below. Summary statistics will be reported for each endpoint, but there will be no formal statistical test performed. Continuous variables will be summarized using descriptive summary statistics such as mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized as counts and percentages.

Technical Success: A subject will be considered a Technical Success if percutaneous vascular closure is obtained with the MANTA device without the use of unplanned endovascular or surgical intervention.

Ambulation Success: A subject will be considered an Ambulation Success if he/she is able to ambulate for at least 20 feet/6 meters without re-bleeding.

Treatment Success: A subject will be considered a Treatment Success if he/she has Time to Hemostasis ≤ 10 minutes and has no Major Complications (as defined above in 2.5.1).

Time to Ambulation: The elapsed time (in hours) between MANTA deployment (withdrawal of sheath from artery) and when ambulation is achieved (subject standing and walking at least 20 feet/6 meters without re-bleeding).

Procedure Time: The elapsed time (in minutes) from initial skin break (first needle insertion) to time when the post-deployment angiogram is completed.

6.2.3 Procedural and Discharge Data

The secondary endpoints are defined below. Summary statistics will be reported for each endpoint, but there will be no formal statistical test performed. Continuous variables will be summarized using descriptive summary statistics such as mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized as counts and percentages. Procedure sheath size, index device, index device size, MANTA size, target artery, target artery diameter, pre-deployment ACT, pre-deployment blood pressure, use of adjunctive methods for hemostasis or oozing, thrombus, and post-deployment angiogram results will also be summarized by endovascular procedure.

Effective puncture size (EPS) (mm): Derived from the combination of procedure sheath brand/size and index device/size, based on an algorithm developed by the sponsor. The algorithm is attached in Appendix B.

Endovascular procedure type: As completed on the eCRF, either TAVI, EVAR, Impella, or Other.

Procedure sheath brand: Derived from the sheath size/brand from the eCRF.

Procedure sheath size (F): As completed on the eCRF.

Index device manufacturer/brand: Derived from the Large Bore Device Used: Brand and Manufacturer from the eCRF.

Index device size (mm): As completed on the eCRF as Large Bore Device Used: Size (units).

MANTA size: As completed on the eCRF, either 18F or 14F.

Target artery: As completed on the eCRF, either Left Common Femoral Artery or Right Common Femoral Artery.

Target artery diameter (mm): As completed on the eCRF as recorded from baseline CTA.

Sheath to femoral artery ratio (SFAR): Calculation is as follows: $(EPS / 3.0)\text{mm} / (\text{target artery diameter})\text{mm}$

Pre-deployment ACT (sec): As completed on the eCRF.

Pre-deployment systolic and diastolic blood pressure (mmHg): As completed on the eCRF.

Use of adjunctive methods to obtain arterial hemostasis: Instances of need for adjunctive methods to achieve arterial hemostasis summarized by method, either manual compression, contralateral balloon, mechanical device, stent-graft, surgical repair, or other.

Use of adjunctive methods for treating oozing: Instances of subcutaneous oozing summarized by treatment, either light manual pressure, light mechanical pressure, sand bag, pressure dressing, or other.

Any thrombus observed on the MANTA components: As completed on the eCRF as whether thrombus was observed after removal, yes or no, and which component(s) were affected.

Post-deployment angiogram results: As completed on the eCRF, either target artery patent at MANTA deployment site, stenosis <50% at MANTA deployment site, stenosis ≥50% at MANTA deployment site, or other.

Time to discharge post-MANTA deployment: The elapsed time (in hours) from MANTA deployment (withdrawal of sheath from artery) and when subject is discharged.

Time to discharge post-ambulation: The elapsed time (in hours) from MANTA deployment (withdrawal of sheath from artery) and when ambulation is achieved (subject standing and walking at least 20 feet/6 meters without re-bleeding).

Mean ABI scores: Collected and summarized at baseline, post-procedure, discharge, and follow-up.

Ultrasound evaluations as evaluated by the VasCore Core Lab: Collected and summarized at post-procedure and follow-up, defined as:

- CFA PSV summary statistics, counts of CFA stenosis categories (patent, 50-99%, Occluded, Unknown, N/A), SFA PSV summary statistics
- Counts of arterial venous fistula, intimal artery defect, or mass present (if mass reported, type and size)
- Counts of patent CFV, CFV acute thrombus, patent proximal femoral vein, proximal femoral vein acute thrombus present (yes, no, unknown, N/A)

If a subject underwent more than one ultrasound for a scheduled visit, the latest result will be used for analysis.

Device deficiencies: Instances of device deficiency will be summarized by type of deficiency experienced as detailed on the Device Deficiency eCRF and by MANTA device size.

6.3 Analysis of Safety Data

The Safety Evaluation Set will be used for all safety analyses. All safety parameters will be presented descriptively and as data listings. Continuous variables will be summarized using descriptive summary statistics such as mean, median, standard deviation, minimum and maximum. Categorical variables will be summarized as counts and percentages. Unless otherwise specified, at each level of subject summarization, a subject will be counted only once. If there is more than one occurrence of an event, the event of the worse severity or the worst-case relationship category will be summarized.

6.3.1 Adverse Events

Adverse events will be coded using MedDRA dictionary (Version 20.0) and will be classified by system organ class (SOC) and preferred term (PT). Adverse events meeting certain criteria as defined in Section 9.7 of the protocol and Section 7 below will be adjudicated by the Clinical Events Committee and be designated a Major Complication, Minor Complication, or VARC-2 Major Vascular Complication for the primary and secondary safety endpoints as applicable.

6.3.2 Primary Safety Endpoint:

The Major Complication rate is defined to be the proportion of subjects in the safety evaluation set with one or more Major Complications. The Major Complication rate will be presented along with the one-sided upper 97.5% confidence bound. If this confidence bound is less than 19.9%, the study will have met its primary safety objective.

If a significant number of subjects (>5%) are lost to follow-up or die due to a reason other than a major complication, the Major Complication rate will also be estimated as a Kaplan-Meier rate. Subjects lost to follow-up will be censored at the date of their last contact. Subjects who die due to a reason other than a Major Complication will be censored at their date of death. An exact one-sided upper 97.5% confidence bound will be placed on the estimated major complication rate at 30 days using the formula given by Peto, Peto, and Armitage⁴. If this upper confidence bound is less than 19.9%, the study will have met its primary safety objective.

Additionally, the proportion of subjects with each individual Major Complication will be presented along with their two-sided exact 95% confidence intervals.

6.3.3 Secondary Safety Endpoint:

The proportion of subjects with Minor and Major VARC-2 complications will be presented. Minor complications will be qualitatively evaluated against the CAC of 20%. Summary statistics will be reported, but no formal statistical test will be performed.

Additional Safety analyses will report the incidence of adverse events:

- Overall (i.e., regardless of severity or relationship to procedure or device)
- By severity grade as determined by the Investigator (mild, moderate, or severe):
 - **Mild:** awareness of a sign or symptom that does not interfere with the subject's usual activity or is transient, resolved without treatment and with no sequelae.
 - **Moderate:** interferes with the subject's usual activity and/or requires symptomatic treatment.
 - **Severe:** symptom(s) causing severe discomfort and significant impact on the subject's usual activity and requires treatment.
- By relationship to the device and by relationship to the procedure as determined by the Investigator:
 - **Not Related:** An AE which cannot be attributed to the study device or initial study procedure.

⁴ Peto R. Pike MC, Armitage P, et al. *op cit.*

- **Unknown Relationship:** The relationship of the AE to the device or procedure cannot be determined.
- **Possible:** The clinical event occurs within a reasonable time sequence to study procedure/study device and there is some evidence to “possibly” suggest a causal relationship. However, the influence of other factors such as underlying disease, concomitant medications, or concurrent treatment may have contributed to the event.
- **Probable:** The temporal sequence between the device use or procedures and the event is such that the relationship is likely or subject’s condition or concomitant therapy could have caused the AE.
- **Definite:** The clinical event occurs in a plausible time relationship to study procedure/study device and cannot be explained by any concurrent disease or other devices, drugs or chemicals.

Adverse events with relatedness categorized as possible, probable, or definite will be considered “device-related” or “procedure-related” as appropriate.

Overall frequency and the frequency of Major Complications, Minor Complications, and VARC-2 Major Vascular Complications will also be summarized by endovascular procedure type, MANTA device size, and effective puncture size. Procedural causality will be summarized by endovascular procedure type, and device causality will be summarized by MANTA device size.

Additionally, the rate of interventions required to treat Major Complications, Minor Complications, and VARC-2 Major Vascular Complications will be summarized. Overall Major Complication, Minor Complication, and VARC-2 Major Vascular Complication rates will also be summarized by age category, sex, race, and ethnicity categories. Odds ratio estimates (and their CIs) obtained from logistic regression will be used to measure the strength of the association between SFAR and having one of the above complication events.

7 ADJUDICATION OF CLINICAL ENDPOINTS

The Clinical Events Committee (CEC) will review individual adverse events that meet the following criteria:

- Adverse events that are categorized by the investigator on the eCRF as “associated with the target artery and/or the ipsilateral leg (not the contralateral side)”; OR
- Adverse events in the other two categories (“associated with the contralateral access site” or “systemic adverse events”) that are categorized by the investigator as possibly, probably or definitely device-related.

In addition, the medical monitor will review programmed listings for all AEs that are not captured by the criteria above to identify any additional AEs that appear to meet the endpoint definitions and should be reviewed and adjudicated by the CEC. All adverse events reported will be adjudicated as to whether they were device or procedure related by the CEC. Device relationship may be changed after adjudication. The CEC will determine if each reviewed adverse event meets the definition of a Major Complication or a Minor Complication or neither definition. In addition, the CEC will adjudicate each AE as to whether it is a VARC-2 Major Vascular Complication.

Analysis of the primary and secondary safety endpoints will be based on CEC-adjudicated data. The decisions of the CEC will overrule those of the Investigator for endpoint analyses.

8 CHANGES IN THE PLANNED ANALYSES

Not applicable.