Essential Medical

Prospective Multicenter MANTA™ Vascular Closure Device
Ultrasound Guided Closure Study (MANTA ULTRA Closure)
Protocol No. ST-3370

Statistical Analysis Plan

ST-3387, Version B

February 02, 2022

Prepared by

Manya Harsch, Technomics Research LLC

Table of Contents

1 Purpose

This Statistical Analysis Plan (SAP) is intended to provide additional details for planned summaries of the data in support of generating a final report for the clinical study, "Prospective Multicenter MANTA™ Vascular Closure Device Ultrasound Guided Closure Study," protocol ID ST-3370, Version A.

All analyses will be performed using validated statistical software such as SAS version 9.4 or other well-known statistical packages.

Note that a separate tables/figures/listings (TFL) template will be prepared separately in support of this SAP to help clarify expected summaries for the Sponsor.

2 Background

The MANTA ULTRA trial is a prospective single arm trial designed to evaluate the safety of ultrasound (U/S) guided deployment of MANTA Vascular Closure Device (VCD). The MANTA device has been previously approved for use in the U.S., and this trial is focused on the addition of using ultrasound to establish the safety of U/S guided closure with MANTA VCD.

All subjects enrolled are expected to undergo Transcatheter aortic valve replacement (TAVR) procedures and a report will be prepared for submission to FDA for approval once the first 75 consecutively enrolled subjects, with a maximum of 15 subjects per site, have reached 30 days.

A total of 150 subjects, with a maximum of 30 subjects per site, undergoing elective TAVR procedures utilizing a femoral arterial access site with a MANTA VCD closure device will be evaluated. Additionally, up to 2 roll-in subjects per operator will be enrolled to allow investigators to learn how to use MANTA VCD ultrasound guided closure technique

The data collection schedule is provided in Table 1 below.

2.1 Table 1. Data collection schedule

Assessment	Screen-ing Visit	TAVR Proce-dure	Closure Procedure			Post-proce-dure	Dis-charge	Follow-up (FUP)	
			Pre	During	Post			30 Day (±7 Days)	12 Month (±30 Days)
Subject Eligibility / Informed Consent / Applicable PHI Authorization form*	X								
Medical History	X								
Medications[1]	X	X	X	X	X	X	X	X	X
Laboratory Tests	X[2]								
Pregnancy Test	X[9]								
CT Angiographic Scan	X[3]								
Ultrasound[4] (access and assessment)		X		X					
ACT / SBP			X[5]						
Adjunctive Devices				X	X				
Target Femoral angiography					X[6]				
Target Femoral access site assessment					X	X	X	X	X[7]
Time to Hemostasis					X[8]				
Delayed Ambulation/Discharge						X	X		
Adverse Events			X	X	X	X	X	X	X[7]
Subsequent Secondary Intervention					X	X	X	X	X

*Or other form required by applicable U.S. or Canadian laws governing the use and disclosure of individually identifiable protected health information (PHI)

1. The following medications will be recorded on the eCRF for each subject: cardiovascular medications (e.g., anti-hypertensives, anti-arrhythmic, etc.), anti-coagulants, anti-thrombotic and anti-platelets. Any changes to these medications should be documented throughout the course of the 12 month follow up.
2. Considered standard of care and are to be done according to the site's standard of care practice for pre-procedure labs for the TAVR procedure (hemoglobin, creatinine, and platelet count, International Normalized Ratio (INR))
3. Screening Visit CT Scan to assess both limbs for presence/absence/severity of calcium, atherosclerotic disease, tortuosity, and acceptable flow rates
4. Ultrasound for access SOC; Ultrasound data collection during closure
5. Prior to all closure methods, record ACT and systolic BP (per MANTA VCD warnings SBP<180mmHg; recommend ACT<250 seconds prior to closure)
6. Post-closure, perform target (ipsilateral) femoral angiography from contralateral access site to ensure patency into the ipsilateral common femoral artery
7. At 12m follow-up, target femoral access site assessment will be questions completed via phone; adverse events will only pertain to target access site
8. 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).
9. Female subjects of child bearing potential only. Test to be conducted within 7 days of TAVR procedure or according to standard of care for TAVR procedures requiring contrast and angiography. Urine pregnancy test is acceptable.
10. Any additional surgical or percutaneous interventions post the index large bore procedure that occurred on the MANTA (ipsilateral) leg, such as percutaneous coronary intervention (PCI), through the 12 month phone follow-up

3 Clinical Events Committee

An independent Clinical Events Committee (CEC) will be established for this study. The CEC will consist of three interventional cardiologist physicians. CEC members will be physicians chosen based on their clinical expertise and have no association with this study for which they will adjudicate events. Prior to the start of subject enrollment, the CEC will approve a charter containing criteria for event evaluation.

The CEC will be responsible for adjudicating the following events and determining their device and procedure relatedness:

- All 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)";
- All Adverse Events marked on the eCRF that are categorized by the investigator as having a possible, probable or causal relationship with the MANTA device.

The CEC will classify each AE as to whether it is a Large Bore Access-site Related VARC-2 Major Vascular complication (LBAR Major) or Large Bore Access-site Related VARC-2 Minor Vascular complication (LBAR Minor) complication or neither. Analysis of the primary and secondary safety endpoints will be based on CEC adjudicated data.

In some cases, grouping of inter-related adverse events into a primary adverse event may be appropriate due to all events being symptoms of the same incident. The CEC will select the primary event among the inter-related site reported events.

4 Data & Safety Monitoring Committee

A Data & Safety Monitoring Committee (DSMC) will be established for this study. The DSMC will be independent from the Sponsor and the study investigators. It will consist of at least three (3) members: two interventional cardiologist physicians that will also act on the CEC and an independent statistician; the two physicians must have extensive experience with large-bore cardiovascular interventions, preferably experience using the MANTA VCD. The DSMC will be established and operate according to a charter defined prior to the initiation of the trial. The DSMC will review cumulative adverse event data and will recommend study termination if safety concerns warrant such action. If the DSMC believes it is possible to predict adverse events, guideline criteria for recommending study termination will be established before enrollment in the study begins. The DSMC will meet by phone or face-to-face, at least two times during the study in order to assure close and timely monitoring of adverse events and outcomes.

5 Sample Size Requirements

The performance goal and the postulated event rate in the prospective study population are based upon clinical judgement supported by outcomes from comparable published studies in Table 2 below; in particular rows pertaining to studies of similar size to the proposed 75 patients are shown in bold. Results for all studies shown used VARC-2 definitions.

Table 2. Safety Performance of MANTA from published literature

		VARC-2 Major Complication			
Reference	**N MANTA VCD subjects**	**Essential Medical Sponsored**	**Independent MANTA VCD Studies**	**Overall**	**95% Confidence Interval***
Van Mieghem 2017 (CE Mark)[1]	**50**	**2.0%**		**2.0%**	**0.0%, 10.6%**
Wood 2019 (IDE Study)[2]	263	4.2%		4.2%	2.1%, 7.4%
Van Mieghem 2020 (MARVEL)[3]	500	4.0%		4.0%	2.5%, 6.1%
Biancari 2018[4]	**107**		**9.3%**	**9.3%**	**4.6%, 16.5%**
DePalma 2018[5]	**89**		**1.1%**	**1.1%**	**0.0%, 6.1%**
Gheorghe 2019[6]	169		0.6%	0.6%	0.0%, 3.3%
Hoffman 2018[7]	**75**		**10.7%**	**10.7%**	**4.7%, 19.9%**
Moccetti 2019[8]	**100**		**7.0%**	**7.0%**	**2.8%, 13.9%**
Moriyama 2019[9]	**111**		**7.0%**	**7.0%**	**3.2%, 13.7%**
Van Wiechen 2021[10]	**102**		**1.9%**	**1.9%**	**0.2%, 6.9%**
Moccetti 2021[11]	**100**		**1.0%**	**1.0%**	**0.2%, 5.4%**
Weighted Average	**1666**	**3.9%**	**4.4%**	**4.2%**	**2.0, 8.4%**

* CI's were estimated from reported VARC-2 performance using exact binomial methods

Based on these results, the population LBAR Major complication rate is hypothesized to be 4.2%, the weighted average of the above rates. Examining the confidence intervals above, the upper confidence limits for comparably-sized studies range from 5.4% to 19.9%, corresponding to point estimates of 1.0% to 10.7%. A performance goal of 14.2%, which is based on clinical judgement regarding device performance, falls well within this range, indicating that it is constructed in a fashion consistent with prior findings in the literature.

Additionally, though Sponsor does not intend to demonstrate better safety outcomes than with use of the current approved procedure, determining deployment depth of MANTA using the depth locator, the value of 14.2% is more stringent than the performance goal of 19.9% which was accepted for the MANTA VCD PMA study.

Using these inputs, a one-sided alpha of 0.025 and at least 80% power, 69 subjects will provide adequate power to reject the primary safety hypothesis. To ensure an adequate sample size of subjects meeting the 30-day primary safety endpoint, and to account for patient attrition, data from the first 75 consecutive subjects (with a maximum of 15 subjects at any one site to cap enrollment at 20% of subjects enrolled per site) in the Primary Analysis Cohort (PAC) will be analyzed and submitted as to support a PMA supplement for revised labeling to include the U/S-guided method.

Additional subjects will be enrolled as part of the PAC to provide supplementary data in support of future publications for a total of 150 enrolled subjects (with a maximum of 30 subjects at any one site to cap enrollment at 20% of subjects enrolled per site) in the overall study.

Additionally, roll-in subjects (up to 2 per operator per site) using the MANTA VCD will be enrolled to allow investigators to learn how to use the U/S guided therapy with the MANTA VCD. This group will be analyzed separately and not count towards the PAC.

The rate of LBAR Major Complications within 30 days of the procedure will be presented along with the exact one-sided upper 97.5% confidence bound. If this upper confidence bound is less than 14.2%, the study will have met its primary objective.

6 Statistical Analyses and Study Objectives

6.1 Cohort Definitions

Primary Analysis Cohort (PAC): Subjects in the PAC that have had an attempt to use the MANTA VCD with use of U/S to guide placement. The first 75 consecutively enrolled subjects of this cohort will be submitted as a PMA supplement. A total of 150 subjects will make up the total PAC.

Roll-in Cohort: Additionally, up to 2 roll-in subjects per operator using the MANTA VCD will be enrolled to allow investigators to learn how to use the U/S guided therapy with the MANTA VCD. Roll-in subjects will not count towards the 150 subjects making up the PAC.

6.2 Timing of Reports

In additional to the required IDE annual progress reports, there will be two reports prepared: the primary analysis report once 75 subjects have completed their 30 day follow-up (see details below), and a Final Report.

The primary analysis report will be prepared once the first 75 consecutively enrolled subjects in the PAC have either completed their 30 day visit or withdrawn from the trial. The primary safety endpoint will include subjects from the 75 subjects only unless more than 15 subjects have been enrolled at a single site. If this unlikely situation occurs, then the first 15 enrolled subjects from that site will be included to achieve no more than 20% of patients coming from a single site. All remaining endpoints will summarize what data are available at that time as endpoints are intended to be descriptive in nature and involve no hypothesis testing.

A final report will be prepared once the trial is complete, where all subjects have completed their 12 month visit or withdrawn from the study and sites are closed. All available subject data will be included at this time. A 95% confidence interval for the main safety endpoint will still be prepared but the basis for approval is intended to use the primary analysis report.

6.3 Primary Safety Endpoint: LBAR Major complications

Endpoint: Large Bore Access-site Related VARC-2 Major Vascular (LBAR Major) Complication within 30 days (adapted from VARC-2 Definitions)[10]

- 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
- Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR

- The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia or neurological impairment OR
- Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR
- Surgery for access site-related nerve injury OR
- Permanent access site-related nerve injury

AEs will be reviewed by the CEC to determine if they meet one or more of these criteria and this adjudication for endpoint classification will be used in analysis.

Hypothesis:

The primary safety hypothesis is that the LBAR Major complication rate (proportion of subjects with one or more) is less than the Performance Goal of 14.2%, as follows:

$H_O: \pi \geq 0.142$

vs.

$H_A: \pi < 0.142$,

where π is the population LBAR Major Complication rate within 30 days.

The primary safety hypothesis is that the rate of LBAR Major complications within 30 days of the procedure is less than the performance goal of 14.2%.

Stated in words, the hypothesis is:

Null hypothesis: The rate of LBAR Major complications within 30 days of the procedure not less than the performance goal of 14.2%

Alternate hypothesis: The rate of LBAR Major complications within 30 days of the procedure is less than the performance goal of 14.2%

Subjects to include:

The first 75 chronologically enrolled subjects in the Analysis Cohort where an attempt to use the MANTA device is made (enrolled subjects without an attempt will not be included).

Statistical Analysis:

The proportion of subjects with a LBAR Major Complication at 30 days post procedure will be summarized as number, percent and exact 95% 2-sided confidence interval for the calculated proportion. The probability of experience at least one LBAR Major complication in 30 days post procedure will be tested versus the performance goal using an exact binomial test comparing to a one-sided alpha of 0.025.

6.4 Secondary Endpoints

6.4.1 Secondary Endpoint 1: Time to Hemostasis (Effectiveness)

Endpoint:

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). Time to Hemostasis should be inclusive of any time that manual or mechanical pressure is applied specifically to stop arterial bleeding. Do not include time spent when light digital or mechanical pressure is done to treat oozing, or if short manual compression is done as a preventative measure as part of standard of care. Exact times will be collected on electronic Case Report Forms (eCRFs).

Subjects to include: All subjects in Analysis Cohort with a procedure attempt will be included in this analysis.

Statistical analysis: The time to hemostasis will be summarized using descriptive statistics including mean, standard deviation, median, interquartile range, minimum and maximum, and mean time will be calculated.

6.4.2 Secondary Endpoint 2: Technical Success (Effectiveness)

Endpoint: 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 as collected on eCRFs.

Subjects to include: All subjects in Analysis Cohort with a procedure attempt will be included in this analysis.

Statistical analysis: The number of subjects and percentage of patients will be calculated for the percentage of subjects with technical success.

6.4.3 Secondary Endpoint 3: Ambulation Success (Effectiveness)

Endpoint: 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 as collected on eCRFs.

Subjects to include: All subjects in Analysis Cohort with a procedure attempt will be included in this analysis.

Statistical analysis: The number of subjects and percentage of patients will be calculated for the percentage of subjects that are able to ambulate.

6.4.4 Secondary Endpoint 4: Time to Ambulation (Effectiveness)

Endpoint: The elapsed time between MANTA deployment (withdrawal of MANTA sheath from artery) and when ambulation is achieved (subject standing and walking at least 20 feet/6 meters without re-bleeding) as collected on eCRFs.

Subjects to include: All subjects in Analysis Cohort with a procedure attempt will be included in this analysis.

Statistical analysis: The time to ambulation will be summarized using descriptive statistics including mean, standard deviation, median, interquartile range, minimum and maximum, and mean time will be calculated.

6.4.5 Secondary Endpoint 5: Treatment Success (Effectiveness)

Endpoint: A subject will be considered a Treatment Success if he/she has Time to Hemostasis ≤10 minutes and has no LBAR Major Complications within 30 days.

Subjects to include: All subjects in Analysis Cohort with a procedure attempt will be included in this analysis.

Statistical analysis: The number of subjects and percentage of patients will be calculated for the percentage of subjects with treatment success.

6.4.6 Secondary Endpoint 6: Procedure Time (Effectiveness)

Endpoint: Defined as elapsed time from initial skin break (first needle insertion) to time when the post-deployment angiogram is completed as collected on eCRFs.

Subjects to include: All subjects in Analysis Cohort with a procedure attempt will be included in this analysis.

Statistical analysis: The procedure time will be summarized using descriptive statistics including mean, standard deviation, median, interquartile range, minimum and maximum will be calculated.

6.5 Secondary Endpoint 7: LBAR Minor Complications (Safety)

Endpoint: Large Bore Access-site Related VARC-2 Minor Vascular (LBAR Minor) Complication within 30 days (adapted from VARC-2 Definitions):

- Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysms, hematomas, percutaneous closure device failure) not leading to death, life-threatening or major bleeding, visceral ischemia, or neurological impairment OR
- Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR
- Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR
- Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft) OR
- Percutaneous closure device failure - Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning).

AEs will be reviewed by the CEC and they will adjudicate whether an AE meets one or more of these events and this adjudication for endpoint classification will be used in analysis.

Subjects to include: All subjects in Analysis Cohort with a procedure attempt will be included in this analysis.

Statistical analysis: The number of subjects and percentage of patients will be calculated for the percentage of subjects with one or more LBAR Minor complication within 30 days.

6.6 Additional Analyses

Descriptive statistics will be used to report on the additional analyses. Comparisons may be made between subjects with and without LBAR Major or Minor Complications.

- Long-term LBAR Major and Minor complications
- Quantify Procedural and Post-procedural Characteristics such as:
    - Readmission rates within 30 days
    - Delayed ambulation for subjects with LBAR Major or LBAR Minor Complications
    - Delayed discharge for subjects with LBAR Major or LBAR Minor Complications
    - Use of adjunctive devices required at large bore access site (Angioseal, ProGlide, Prostar XL, balloon, stent, covered stent, or surgical repair)
- Subsequent Secondary Intervention(s) (For example, any additional surgical or percutaneous interventions post the index large bore procedure that occurred on the MANTA (ipsilateral) leg, such as percutaneous coronary intervention (PCI), through the 12 month follow-up phone call.)

6.7 Adverse Events and Device Deficiencies

Adverse events (AEs) and device deficiencies will be collected throughout this trial. AEs will be classified using the MedDRA coding system and will be summarized by System Organ Class and Preferred Term.

Adverse events that are determined to be related to the device or procedure ("associated with the target artery and/or the ipsilateral leg (not the contralateral side") will be sent to the CEC for adjudication. The exact process will be finalized in the CEC charter. The CEC will adjudicate procedure and device relatedness of these events and whether events met an LBAR Major or Minor Complication. These adjudications will overrule investigator classifications for summarizing data.

For relatedness, classifications of Causal/Definite, Probably, Possible and Unknown (if any) will be considered related.

AEs will be summarized by count and proportion of subjects experiencing one or more events by seriousness, severity, device and procedure relatedness, and time period (day 0 (procedure)-discharge, discharge-30 days, 0-30 days, 31-60, 61-180 days, and 181-study exit).

Any UADEs, ADEs or SADEs will be summarized as well.

Device deficiencies collected on a separate eCRF form will also be summarized and indicate if any deficiencies resulted in any adverse events.

7 Poolability of Data

Analyses of the primary safety endpoint will be performed to assess the comparability of study sites. Sites with fewer than 5 subjects each will be included in summaries by site but excluded from poolability analysis.

LBAR Major Complications will be analyzed by Fisher's Exact test 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.

8 Data Conventions and Missing Data

Every effort will be undertaken to limit premature discontinuations and ascertain completeness of data collection throughout the course of the study. It is unlikely that there would be missing data for the LBAR Major complication endpoint as a 30 day follow-up visit is typically standard of care for TAVR patients; therefore all subjects with an attempted procedure are expected to be followed for at least 30 days. The 12 month follow up assessment will be conducted via phone; sites will ensure that subject contact details are on file correctly when concluding the 30 day visit.

No imputations will be made for missing endpoint data. All available data will be summarized for any summary provided the subject has a procedure attempt.

If an onset date for an AE is incomplete, every effort will be made by the clinical team to identify and collect a valid date from the site, but in case any are incomplete, then the following rules will be used:

- If the day of the month is missing, the first of the month will be used unless it precedes the procedure date. Then the procedure date will be used.
- If the month is missing the date of the procedure will be used.
- No year is expected to be missing as the follow-up is quite short, but the date of procedure will be used if missing the year.

9 Appendices:

9.1 Appendix 1: Definitions of Relatedness of Adverse Events

Each reported AE will be assessed by the Investigator for its primary suspected relationship to the U/S guided MANTA VCD deployment/device or to the interventional procedure.

- Study AEs related to the interventional procedure (e.g., TAVR procedure) or closure of a non-target access site are considered Procedure-Related AEs.
- Study AEs related to the MANTA VCD and/or the U/S deployment method (in total, the closure procedure) are considered Device-Related AEs.
- Study AEs that are related to neither the interventional procedure nor use of the MANTA VCD are considered NOT related to the device or procedure.

The causal relationship of an AE to the device or procedure will be classified as follows:

Not related: relationship of the event to the device or procedure can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has no temporal relationship with the use of the investigational device or the procedures;

- the event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the event;
- the event involves a body-site or an organ not expected to be affected by the device or procedure
- the event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- harms to the subject are not clearly due to use error;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the adverse event.

Possible: relationship of the event with use of the investigational device or the procedure is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probable: relationship of the event with use of the investigational device or the procedure seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.

Causal relationship: the event is associated with the investigational device or procedure beyond a reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that:
  - the investigational device or procedure is applied to
  - The investigational device or procedure have an effect on;
- the event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible);
- other possible causes (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use.

In order to establish the relatedness, not all criteria listed above might be met at the same time depending on the type of device/procedures and the serious event.

9.2 Appendix 2: Definitions from the Protocol

Adjunctive Compression: Compression methods (including sandbags, compression bandages, and light manual pressure) for controlling cutaneous or subcutaneous oozing.

Adverse Device Effect (ADE): Adverse event (see definition below) resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Adverse Event (AE): Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. Note: This definition includes events related to the investigational medical device. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational devices.

Ambulation Success: A subject will be considered an Ambulation Success if a previously ambulatory patient (until day of TAVR) is able to ambulate for at least 20 feet/6 meters without re-bleeding.

Bleeding: Definitions used in conjunction with definitions of LBAR Major complications and LBAR Minor complications below. As defined in the VARC-2 Clinical Guidelines:

Life-threatening or disabling bleeding:

- Fatal bleeding (BARC type 5) OR
- Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) OR
- Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) OR
- Overt source of bleeding with drop in hemoglobin ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units* (BARC type 3b)

Major bleeding (BARC type 3a):

- Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND
- Does not meet criteria of life-threatening or disabling bleeding

Minor bleeding (BARC type 2 or 3a, depending on the severity):

- Any bleeding worthy of clinical mention (e.g., access site hematoma) that does not qualify as life-threatening, disabling, or major

Cachexia: Defined as very thin, or body mass index <20 kg/m^2.

Device Deficiency: Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance; includes device malfunctions, use errors and inadequate labeling.

Ecchymosis: An area of subcutaneous discoloration caused by the extravasation of blood into the subcutaneous tissue not associated with a definable, palpable subcutaneous mass.

Hematoma: An expanding or non-expanding subcutaneous mass of blood greater than 2 cm in its longest axis, confirmed by U/S.

Hemostasis (Time to): 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). Time to Hemostasis should be inclusive of any time that manual or mechanical pressure is applied specifically to stop arterial bleeding. Do not include time spent when light digital or mechanical pressure is done to treat oozing, or if short manual compression is done as a preventative measure as part of standard of care.

Large Bore Access-sire Related Major Vascular (LBAR Major) Complications: Adapted from the VARC-2 Clinical Guidelines[1]:

- 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
- Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR
- The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia or neurological impairment OR
- Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR
- Surgery for access site-related nerve injury OR
- Permanent access site-related nerve injury

Large Bore Access-site Related VARC-2 Minor Vascular Complication (LBAR Minor): Adapted from VARC-2 Clinical Guidelines:

- Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysms, hematomas, percutaneous closure device failure) not leading to death, life-threatening or major bleeding, visceral ischemia, or neurological impairment OR
- Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR
- Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR
- Vascular repair or the need for vascular repair (via surgery, U/S-guided compression, transcatheter embolization, or stent-graft) OR

[1] 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

- Percutaneous closure device failure - Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)

Morbid Obesity: Defined by the position of the access needle whereby less than one third of the access needle is above the skin line indicating the subject is morbidly obese, or body mass index >40 (weight in kg divided by square of height in meters).

Nerve Injury: Any ipsilateral transient or permanent sensory or motor neurologic deficit of the femoral nerve, or anterior or lateral cutaneous femoral nerve, or evidence of sacral plexus injury from documented retroperitoneal bleeding, as determined by a neurologist.

Oozing: Bleeding of a cutaneous or subcutaneous origin that can be controlled with the application of light compression methods (sandbags, compression bandages, or light manual pressure) and which do not apply sufficient compression to control arterial bleeding. Light manual compression may be substituted by light compression from a mechanical device.

Operators: Medical personnel trained and qualified to the clinical use of the medical device (MANTA VCD)

Pre-existing Hematoma: An expanding or non-expanding subcutaneous mass of blood present prior to the start of the access site closure.

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

Serious Adverse Device Effect (SADE): An Adverse Device Effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.

Serious Adverse Event (SAE): An SAE is an Adverse Event that:

- Led to death,
- Led to serious deterioration in the health of the subject, that either resulted in
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function, or
    - in-patient or prolonged hospitalization, or
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by this protocol, without serious deterioration in health, is not considered a serious adverse event.

Severe Peripheral Vascular Disease: Any of the following:

- Severe claudication when ambulating <100 feet
- Weak or absent pulses in the affected limb
- ABI <0.5 at rest
- Known stenosis >50% in the iliac or femoral artery on the affected side
- Prior vascular bypass surgery involving the affected femoral artery

Stable Access Site Status: Defined as ability to walk at least 20 feet/6 meters, freedom from orthostatic hypotension [defined as stable blood pressure and heart rate after ambulating], ability to void and a stable access site without bleeding or expansion of a prior hematoma.

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

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

Time to Hemostasis: 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). Time to Hemostasis should be inclusive of any time that manual or mechanical pressure is applied specifically to stop arterial bleeding. Do not include time spent when light digital or mechanical pressure is done to treat oozing, or if short manual compression is done as a preventative measure as part of standard of care.

Treatment Success: A subject will be considered a Treatment Success if he/she has Time to Hemostasis ≤10 minutes and has **no** LBAR Major complications within 30 days.

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, 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 a device that relates to the rights, safety, or welfare of subjects.

Unanticipated Serious Adverse Device Effect (USADE): A Serious Adverse Device Effect, which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. Note: An anticipated serious adverse device effect is a serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

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Author:

Manya Harsch
_____ Date: 02/03/2022

Manya Harsch, Principal Statistician
Technomics Research

Revision History		
Rev.	**Description**	**CO#**
A	Initial Release	CO55686
B	Section 3: Added the CEC will consist of three interventional cardiologist physicians. Added a new section, Section 4 to add DSMC duties which was required by FDA. Section 5: Updated year of van Weichen publication. Section 6.4: Removed language regarding calculating 95% confidence intervals (CI) for secondary endpoints per FDA feedback “Because of the close relationship between confidence interval and hypothesis testing in statistical inference, please note it is not appropriate to report confidence interval of the secondary endpoints in the labeling without prespecified hypotheses along with strategies for addressing the issue of multiplicity.”	CO57488

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3090DA3A-AD2B-4CD4-B1DF-43B2272A7EB7

TRANSACTION DETAILS	DOCUMENT DETAILS
Reference Number 3090DA3A-AD2B-4CD4-B1DF-43B2272A7EB7	**Document Name** St3387 Rb Sap For Manta Ultra Closure Study Clean - Sent
Transaction Type Signature Request	**Filename** st3387_rb_sap_for_manta_ultra_closure_study_clean_-_sent.pdf
Sent At 02/03/2022 15:27 EST	**Pages** 19 pages
Executed At 02/03/2022 15:29 EST	**Content Type** application/pdf
Identity Method email	**File Size** 314 KB
Distribution Method email	**Original Checksum** 779afdafbfabd0d25288ef611a08b3220d9e3e5f324aa868cea002dd04cf1552
Signed Checksum 580111f73c9b55879b3bbbc398e2d4b3902133643f47e6da5d4e42ce04f4049f	
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