Official Title: SAP for Post-Market Clinical Registry to Evaluate the Safety and Performance of MANTA Vascular Closure Device Under Real World Conditions in the European Union (MARVEL)

NCT Number: NCT03330002

Document Date: January 15, 2020

Statistical Analysis Plan

for

MARVEL - "MAnta Registry for Vascular Large-borE Closure"

Protocol No. PSD-212 Rev C.

(Post-Market Clinical Registry to Evaluate the Safety and Performance of MANTA Vascular Closure Device Under Real World Conditions in the European Union)

Version A

January 15, 2020

Prepared by

Manya Harsch, Technomics Research LLC

LCD-015 DDB 29Jan2020

Table of Contents

1 Purpose

This Statistical Analysis Plan (SAP) is intended to provided additional details for planned summaries of the data in support of generating a final report for the clinical study, "Post-Market Clinical Registry to Evaluate the Safety and Performance of MANTA Vascular Closure Device Under Real World Conditions in European Union (MARVEL)", protocol ID PSD-212 Rev C.

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

Note that a tables/figures/listings (TFL) template was prepared in support of this SAP to help clarify expected summaries.

2 Background

The MARVEL trial is an observational post-market study intended to gather real world outcome data on the use of the CE marked MANTA Vascular Closure Device following percutaneous cardiac or peripheral procedures using large bore (10-18F ID) interventional devices. This study also fulfills EU regulatory requirements for post-market clinical follow-up.

The 14F MANTA Vascular Closure Device is indicated for closure of femoral arterial access sites following the use of 10-14F devices or sheaths (maximum OD/profile of 18F), and the 18F MANTA Vascular Closure Device is indicated for closure of femoral arterial access sites following the use of 15-18F devices or sheaths (maximum OD/profile of 25F). Procedures include transfemoral TAVI, EVAR and TEVAR; however, all participants must meet indications for use and contra-indications as described in the Instructions for Use and sites must adhere to registry requirements.

Up to 500 patients will be implanted at up to 20 sites with MANTA VCD which will consist of 2 cohorts.

- Cohort 1 restricted to TAVI procedures (T Group) - T Group will require a CT scan at baseline and a femoral angiogram post-MANTA deployment.
- Cohort 2 includes all other on-label CE-marked medical devices in accordance with MANTA device IFU excluding TAVI procedures (NT Group) - such as mechanical circulatory support (MCS), EVAR and TEVAR procedures. NT Group does not require CT scan at baseline or angiography post-MANTA deployment.

The original protocol specified that subjects would be followed-up at 30-days post-procedure. Mid-study, the protocol was updated to extend follow-up by adding a 12M visit for a subset of 100-120 subjects.

The data collection schedule is provided in Table 1 below.

Table 1. Data collection schedule

Assessment/ Interval	Screening	Index Procedure	MANTA Procedure			Post procedure	Hospital Discharge	Follow-up	
			pre-MANTA closure	MANTA closure	post-MANTA closure			30D (±7 days)	12M[5] (± 30 Days)
Subject Eligibility/ Informed Consent	X								
Medical History	X								
Medication	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]	X[1]
CT Angiographic Scan	X[2]*								
ACT/Systolic Blood Pressure				X[3]					
Femoral Angiography		X			X[4]*				
Target Femoral Access Site Visual Assessment					X	X	X	X	X
Time to Hemostasis					X				
Time to Ambulation							X		
Adverse Events		X	X	X	X	X	X	X	X

1. Medications (only Aspirin, Clopidogrel, Vitamin K Antagonists and, NOAC"s: [eloxaban, rivaroxaban, dabigatran, apixaban] will be collected)

2. Screening Visit CT Scan to assess both limbs for presence/absence of calcium, atherosclerotic disease, tortuosity, and acceptable flow rates.

3. Prior to MANTA closure, record ACT and systolic BP (per contraindications BP<180; recommend ACT below 250 seconds prior to closure)

4. Post-MANTA closure, perform target (ipsilateral) common femoral angiography from contralateral access site to ensure patency into the ipsilateral common femoral artery
   * #2 CT Angiographic Scan and #4 Post MANTA femoral angiogram are required in cohort 1

5. A subset of study enrollment, 100-120 subjects at up to 7 sites, will complete the 12M follow-up visit.

LCD-015 DOB 29Jan2020

3 Clinical Events Committee

An independent Clinical Events Committee (CEC) will be established for this study. The CEC will include members qualified to review adverse event data for this study. During the CEC review, a designated CEC member is responsible for reviewing the documentation for events that occurred in their country. If complex events emerge, the designated CEC member can ask the CEC Chair to convene a conference call to discuss the specific event(s). The CEC will be established and operate according to a charter defined prior to the initiation of the trial. The CEC will review individual adverse events that meet the following criteria:

- AEs that are considered by the investigator to be definitely, probably or possibly device related will be adjudicated by CEC parallel to enrollment. Additionally, outcomes not associated with the MANTA device may also be adjudicated by CEC.

The primary responsibilities of the CEC over the course of the study are to review and refine serious adverse event definitions, and to review and adjudicate serious adverse events.

The CEC will determine if each reviewed adverse event meets the definition of a VARC-2 Major femoral vascular complication or a VARC-2 Minor femoral vascular complication[1] or neither definition. For each AE reviewed, the CEC may also adjudicate its device-relatedness. Any analysis of the primary and secondary safety endpoints will be based on CEC-adjudicated data.

Specifically, the CEC will review:

- Any adverse events that are possibly, probably or definitely related to the MANTA device. The CEC members will adjudicate whether each event is a VARC-2 Major or Minor Femoral Vascular Complications within 30 days following procedure or whether it is no-event (does not meet either definition). determine the percentage of subjects with one or more VARC-2 Major or Minor Femoral Vascular Complications within 30 days following procedure.

The following events below will not be submitted for adjudication as these events do not meet the definitions of VARC-2 Major/Minor vascular complications or definitions in the MARVEL Protocol PSD-212.

- Hematoma: less than 2 cm in size or no size is recorded for the hematoma and it requires no treatment or requires only prolonged/adjunctive compression.
    - Rationale: Per MARVEL Protocol PSD-212, a hematoma is defined as an expanding or non-expanding subcutaneous mass of blood greater than 2 cm in its longest axis, confirmed by ultrasound, and VARC-2 excludes percutaneous closure device failure requiring only manual compression from minor vascular complications.
- Minor Bleeding: requiring no treatment or requiring only prolonged/adjunctive compression.
    - Rationale: Per VACR-2 criteria, minor bleeding requiring adjunctive compression is not categorized as a VARC-2 major/minor vascular complication and percutaneous closure device failure requiring only manual compression is excluded from minor vascular complications.

The CEC member will provide the following assignments for each AE:

- If AE resulted in death, classify death:

  - Cardiac
  - Non-cardiovascular
  - Vascular
- If AE resulted in bleeding complications: (yes/no)
  - If yes, define event type below:
    - BARC 0
    - BARC 1
    - BARC 2
    - BARC 3a
    - BARC 3b
    - BARC 3c
    - BARC 4
    - BARC 5a
    - BARC 5b
- VARC-2 Major Complication (yes/no)
  - Type of classification (from drop down list)
- VARC-2 Minor Complication (yes/no)
  - Type of classification (from drop down list)
- Device relatedness
  - Not related
  - Unknown
  - Possible
  - Probably
  - Definite
- Procedure relatedness
  - Not related
  - Unknown
  - Possible
  - Probably
  - Definite

The CEC adjudications will be documented in a controlled limited access Excel spreadsheet.

4 Sample Size Requirements

Up to 500 subjects are considered a meaningful sample size to assess real-world use of the MANTA device. There is no statistical basis for the sample size. Up to 20 sites will be included in the trial.

5 Statistical Analyses and Study Objectives

Statistical analyses will consist of descriptive statistics mean, standard deviation, median, minimum/maximum and 95% confidence intervals for continuous data and counts, proportions and 95%

LOD-05 DOB 29Jan2020

confidence intervals for categorical data. Data will be qualitatively compared to VARC-2 endpoints in the literature.

All subjects with an attempted procedure where femoral artery access was initiated and MANTA device was attempted will be included in the performance and safety measures. The performance and safety endpoints will be summarized for the overall population, by cohort (TAVR vs not TAVR), and by MANTA device size (14 or 18 Fr) at a minimum. The 12M safety endpoint will also be summarized for the 12M cohort.

At the time this SAP was drafted, enrollment has closed, but follow-ups are still being completed. One subject had both sides (left and right femoral arteries) used for procedures of all enrolled subjects so summaries may be either patient based (number of participants) or device based (number of participants + 1).

The protocol specified that results will be compared to values observed in the literature. This comparison can be made by comparing the 95% confidence intervals to rates from literature. If the rate is within the 95% confidence interval, the prespecified intention is to report that a difference between the prior literature reported rate and the MARVEL study's observed rate has not been demonstrated. At a minimum, the results will be compared to the observed rates from the 2 pre-market trials, the EU Pre-Market Clinical Study (Netherlands and Italy, N=50) and the U.S. Pivotal trial (N=263 primary analysis cohort).

Table 2. Rates from pre-market trials for MANTA device

Trial	Time to Hemostasis (min) Mean ± SD, Median, Range, upper 97.5% confidence bound	Major Complication Rate (%) percent, 97.5% upper confidence bound	Major VARC-2 Complication Rate (%) percent	Minor Complication Rate (%) percent
EU Pre-market study (N=50)	2.38 ± 6.63 0.4 Range: 0, 37 97.5% UCB = N/A	3/50 (6%)	1/50 (2%)	0/50 (0%)
FDA PMA results (N=263)	1.09 ± 2.63 0.4 97.5% UCB = 1.41	5.3% 97.5% UCB = 8.8%	4.2%	2.7%

Additional VARC-2 complication rates have been pulled from the literature and are summarized in Table 3 below.

Table 3. Rates of major and minor VARC-2 complication rates from Literature Review Update PSD-281, Rev A, 07 Feb 2019, prepared by Essential Medical, a wholly owned subsidiary of Teleflex.

Article	VCD	N	Major VARC2 (%)	Minor VARC2 (%)	Weighted Major VARC2 (%)	Weighted Minor VARC2 (%)
Biancari	MANTA	107	9.3	3.7	6.1	4.8
Moriyama	MANTA	111	7	6		
De Palma	MANTA	89	1.1	4.6		
Mach	Perclose (assorted)	466	6	14.4	6	14.4
Moriyama	Proglide	111	8	13	5.1	6.7
Honda	Proglide x1 + echo	63	1.6	19.1		
Sorropago	Proglide x1 + glue	250	0	1.6		
	Proglide x1 or x2	58	17.2	15.5		
Biancari	Proglide x2	115	12.2	2.6		
Mas-Peiro	Proglide x2	100	2	4		
Veulemens	Prostar	389	1.2	12.3	2.5	15.0
Kochman	Prostar	203	6.9	18.2		
Lareyre	Prostar	340	1.8	25.5		
De Palma	Prostar	257	1.9	2.7		
Overall (weighted)		**2659**	**4.2**	**11.5**		

5.1 Performance Endpoint: Time to Hemostasis

Objective: To quantify the real-world time to hemostasis using the MANTA devices.

Endpoint: 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). Exact time collected and reported on Artery Assessment and Procedure electronic Case Report Forms (eCRFs).

Hemostasis success is defined as hemostasis at the puncture site within 10 minutes of removing the MANTA sheath without need for manual or mechanical compression and without later rebleeding (trivial or subcutaneous oozing will not be considered bleeding; light finger pressure to control subcutaneous oozing will not be considered manual compression). Classification of success reported on Artery Assessment and Procedure eCRFs.

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

Statistical analysis (both patient and device based): The time to hemostasis will be summarized using descriptive statistics including mean, standard deviation, median, interquartile range, minimum and maximum, and 95% confidence intervals will be calculated (device-based summary and patient-based using the longest time). Additionally, the proportion of subjects with hemostasis success will be summarized along with a 95% confidence interval (patient-based summary).

5.2 Safety Endpoint 1: VARC-2 Major Complications

Objective: To quantify the real-world VARC-2 major femoral vascular complication incidence using the MANTA device.

Endpoint: The percentage of patients with one or more VARC-2 Major femoral vascular complications as adapted from VARC-2 definitions within 30 days following procedure. The classification of "major" will be determined by the CEC and will be recorded in the CEC spreadsheet.

VARC-2 Major femoral vascular complication definition:

- Femoral 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; OR,
- downstream distal embolization (lower extremities) requiring surgery or resulting in amputation; OR,
- the use of unplanned endovascular or surgical intervention associated with death, major femoral bleeding; 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 femoral access site-related nerve injury; OR,
- permanent femoral access site-related nerve injury.

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

Statistical analysis (patient based): The number of subjects, percentage of patients and 95% confidence intervals for the percentage of subjects will be calculated at a minimum for subjects experiencing any type of major complication as previously defined. Additional summaries may include splitting into adverse event type as collected via the case report forms.

5.3 Safety Endpoint 2: VARC-2 Minor Complication

Objective: To quantify the real-world VARC-2 minor femoral vascular complication incidence using the MANTA device.

Endpoint: The percentage of patients with one or more VARC-2 Minor femoral vascular complications (and no major VARC-2 complications) as adapted from VARC-2 definitions within 30 days following procedure.

Minor femoral vascular complication definition:

- Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneuysms, hematomas, percutaneous closure device failure) not leading to death, life-threatening or major bleeding; OR,
- downstream distal embolization (lower extremities) treated with embolectomy and/or thrombectomy and not resulting in amputation; 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).

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

Statistical analysis (patient based): The number of subjects, percentage of patients and 95% confidence intervals for the percentage of subjects will be calculated at a minimum for subjects experiencing any type of minor complication as previously defined. Additional summaries may include splitting into adverse event type as collected via the case report forms.

5.4 Safety Endpoint 3: Long-term Device Related SAEs

Objective: To quantify real-world long-term safety using the MANTA device.

Endpoint: The percentage of patients with one or more events on ipsilateral leg with MANTA device as described in the main safety endpoints beyond 30 days for each event:

- VARC-2 major complication
- VARC-2 minor complication (with no major VARC-2 complication)

Subjects to include: All subjects that have enrolled in the longer-term follow-up with a procedure attempt will be included in this analysis.

Statistical analysis (patient based): The number of subjects, percentage of patients and 95% confidence intervals for the percentage of subjects will be calculated at a minimum for subjects experiencing a major VARC2 complication and again for minor VARC2 complication.

5.5 Additional Summaries

Additional summaries will be prepared similar to the effectiveness and safety endpoints using descriptive statistics. These summaries will be prepared for the overall population, by cohort (TAVR vs not TAVR), and by MANTA device size (14 or 18 Fr) at a minimum. Some summaries will be repeated for the 12M subset as appropriate.

At a minimum the following items will be included:

1. Baseline demographics and characteristics
    - Age
    - Gender
    - BMI
    - STS score (TAVR group only)
    - Medical history (prior history of PCI, CABG, Hypertension, LVEF < 20%, kidney dysfunction (GFR < 60 umol/L), pacemaker, peripheral artery disease, stroke/CVA)
    - Medications at baseline

i. ASCAL
ii. Oral anticoagulants
iii. New oral anticoagulants
iv. Clopidogrel
v. Heparin
vi. Other anticoagulants

2. Procedure characteristics
   - Target artery characteristics
     i. Diameter
     ii. Calcification
     iii. Side (left/right/both)
     iv. Presence of scar tissue in groin on treated side
   - Procedure type
   - Hemostasis time (descriptive statistics and success (<10 min) – primary performance endpoints
   - MANTA procedure time
   - MANTA device sizes
     i. Instances of size mismatch (where the device size exceeds the artery size)
     ii. Sheath-to-femoral-artery ratio
   - Device deficiencies
   - Procedure success (proportion of subjects with no VARC-2 major complications within 30 days)

3. 30 Day Follow-up / Exit
   - Average follow-up (exit date – procedure date) in days
   - Medication at each time point (during procedure, post procedure, 30 day follow-up/exit)
   - Summarize type of follow-up (in person/at office or via phone call)
   - Reason for study exit (as reported via eCRFs).
4. 12 Month Follow-up (for subset of 100-120 subjects)
   - Average follow-up (exit day of 12 month – procedure date) in days
   - Provide baseline demographics for subjects that had 12M follow-up comparing to overall population.
   - Target Femoral Access Site Visual Assessment
   - Adverse Events occurring on MANTA side only from day 38 to 12M visit
   - Medication at each time point (12month follow-up/exit)
     Reason for study exit (as reported via eCRFs)
5. Analysis of primary and secondary safety endpoints and hemostasis by on and off-label device use. On label means meeting indications per IFU.

5.6 Adverse Events

Adverse events were collected for both MANTA related AEs and non-MANTA related AEs. All events that occur during or after the procedure will be summarized (events prior to treatment will not be included) as identified via "Phase of study in which AE developed" on first page of AE eCRF.

The CEC will adjudicate procedure and device relatedness. Classifications of Definite, Probably, Possible and Unknown will be considered related. Note that a template of the tables figures listings (TFL) template was developed for how to present these data.

1. MANTA related AEs will be summarized summarizing the count and % of patients experiencing one or more events.
    a. An overview (overall, VARC-2 Major femoral vascular complication, VARC-2 Minor femoral vascular complication, device related serious AE, device related AE, and any unanticipated serious adverse device effect (USADE)).
    b. Summary of MANTA related:
        i. VARC 2 Major femoral vascular complication and definition element
            1. Overall
            2. CEC procedure related
            3. CEC device related
        ii. VARC 2 Minor femoral vascular complication and definition element
            1. Overall
            2. CEC procedure related
            3. CEC device related
        iii. VARC 2 Major femoral complication and definition element by timing
            1. Overall
            2. CEC procedure related
            3. CEC device related
        iv. VARC 2 Minor femoral complication and definition element by timing
            1. Overall
            2. CEC procedure related
            3. CEC device related
        v. AES by MedDRA coding System Organ Class (SOC) and Preferred Term (PT)
            1. Overall AE
            2. Investigator determined if CEC not available related AE
            3. CEC procedure related AE
        vi. SAES by MedDRA coding System Organ Class (SOC) and Preferred Term (PT)
            1. Overall SAE
            2. Investigator determined if CEC not available related SAE
            3. CEC procedure related SAE
    c. Listings will be generated
        i. MANTA related (investigator determined):
            1. patient ID, onset (days post proc), event, MedDRA SOC/PT, description of treatments/interventions, status (outcome), severity, seriousness, and MANTA relatedness (unknown, possible, probably or definite), and CEC VARC2 determination and proc/device relatedness.

ii. Not MANTA related (reduced list due to reduced data collection):
    1. Patient ID, onset, MedDRA SOC/PT, status, and seriousness.

2. Long-term MANTA AEs (Day 31-12M) will be summarized by seriousness for subjects that participated in the extended follow-up for the whole cohort, the 30 day cohort and the 12M cohort.
3. Death summaries: any subjects that died will summarized by cause of death as adjudicated by CEC. Additionally, all AEs for those subjects will be listed.

6 Data Conventions and Missing Data

No imputations will be made for missing 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 of missing the date of the procedure will be used.
- No year is expected to be missing as the follow-up is quite short.

7 Appendix 1: Definitions from the protocol

Adjunctive Compression: Compression methods (including sand bags, 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 medical device. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to devices.

Cachexia: Defined as very thin, or body mass index <20 kg/m2.

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 ultrasound.

Hemostasis Success: Hemostasis at the puncture site within 10 minutes of removing the MANTA sheath without need for manual or mechanical compression and without later rebleeding (trivial or subcutaneous oozing will not be considered bleeding; light finger pressure to control subcutaneous oozing will not be considered manual compression).

Major and Minor Access Site Related Complications (as described below): within 30 days of procedure. Adapted from the VARC-2 Clinical Guidelines [3]

Major femoral vascular complications: Composite endpoint that includes any of the following adverse events:

- Femoral 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, lifethreatening or major bleeding; OR,
- Downstream distal embolization (lower extremities) requiring surgery or resulting in amputation; OR,
- The use of unplanned endovascular or surgical intervention associated with death, major femoral bleeding; 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 femoral access site-related nerve injury; OR,

- Permanent femoral access site-related nerve injury (lasting>30 days).

Minor femoral vascular complications: Composite endpoint that includes any of the following adverse events:

- Femoral access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneuysms, hematomas, percutaneous closure device failure) not leading to death, life-threatening or major bleeding; OR,
- Downstream distal embolization (lower extremities) treated with embolectomy and/or thrombectomy and not resulting in amputation; 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, ultrasoundguided compression, transcatheter embolization, or stent-graft); OR,
- Percutaneous closure device failure*; OR,
- Any other adverse event that is definitely or probably device-related or access-site related.

*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 (sand bags, 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.

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

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:

- Lead to death
- Lead to life threatening or major bleeding - requiring transfusion of two or more whole blood/RBC
- Lead to a permanent injury or permanent impairment to a body structure or a body function
- In patient or prolonged hospitalization
- Medical or surgical intervention to prevent life-threatening illness
- Lead to visceral ischemia

Note: For this study, 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 <30 meters
- Weak or absent pulses in the affected limb
- Known stenosis >50% in the iliac or femoral artery on the affected side
- Prior vascular bypass surgery involving the affected femoral artery

Significant Calcium: Visible calcium on fluoroscopy or CTA. Document calcium on MFACS scale (MFACS is not exclusionary), Manta Femoral Artery Calcification Score (MFACS)

- 0 - No calcification
- 1 - Minor calcification
- 2 – Moderate anterior and posterior wall calcification
- 3 – Significant posterior wall calcification
- 4 – Significant anterior wall calcification
- 5 – Circumferential wall calcification

Stable Access Site Status: Defined as ability to walk at least 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.

Time to Ambulation: The elapsed time between post-MANTA deployment (time suture cut away from body) and when ambulation is achieved (patient standing and walking at least 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).

Total MANTA Procedure Time: The elapsed time between pre-MANTA deployment (exchange of procedure sheath with MANTA sheath) to post-MANTA deployment (time suture cut away from body).

Procedure Success: A patient will be considered a Procedure Success if he/she has no Major Complications (as defined above) within 30 days post procedure.

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.

8 References

1.) Kappetein AP, Head SJ, Généreux 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.

Author:

Manya Harsch Date: 01-16-2020

Manya Harsch, Principal Statistician
Technomics Research

Documentation Routing Coordinator:

Darra Bigelow Date: 01-16-2020

Darra Bigelow, Clinical Manager

Approvals:

Nancy Frame Date: 01-16-2020

Nancy Frame, Senior Regulatory Product Specialist

Christopher Buller Date: 01-17-2020

Dr. Chris Buller, Medical Director, CMA

Revision History		
Rev.	**Description**	**Date**
A	MARVEL Statistical Analysis Plan (SAP)	15Jan2020

LCD-015
DPB 29Jan2020