



## CLINICAL STUDY PROTOCOL

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

**Protocol Number:** PSD-109

**Investigational Device:** MANTA 14F and 18F Vascular Closure Devices

**Study Type:** Multicenter prospective single-arm clinical investigation

**Date:** June 2, 2017

**Version:** F

**Sponsor:** Essential Medical, Inc.  
227 East King Street  
Suite 227  
Malvern, PA 19355  
USA

**Sponsor Contact:** Angela Waltman  
Senior Clinical Project Manager  
Telephone: +1 610-202-0436  
Email: [angela@essmedclosure.com](mailto:angela@essmedclosure.com)

**European Authorized Representative\*:** MedPass International Ltd.  
Windsor House  
Bretforton  
Evesham  
Worcestershire  
WR11 7JJ, United Kingdom

\*for potential EU sites

This protocol has been prepared in compliance with U.S. 21 CFR Part 812 and current International Standard EN-ISO 14155:2011, Clinical Investigations of medical devices for human subjects – Good Clinical Practices; Annex A (normative) Clinical Investigation Plan (CIP).

## Protocol Signature Page

The Investigator agrees to conduct the clinical study which is the subject of this protocol in accordance with the Clinical Study Agreement, this protocol, all applicable laws and regulations, and the conditions of approval imposed by the reviewing Institutional Review Board or Ethics Committee.

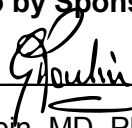
### Agreed to by Investigator:

\_\_\_\_\_  
Principal Investigator

\_\_\_\_\_  
Date

\_\_\_\_\_  
Principal Investigator (print)

### Agreed to by Sponsor:

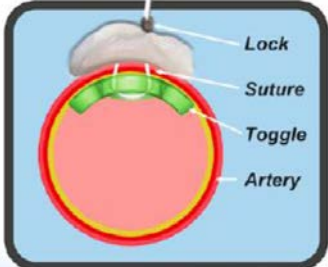

  
\_\_\_\_\_  
Gary Roubin, MD, PhD  
Chief Medical Officer

**7/5/2017**  
\_\_\_\_\_

Date

Sponsor – Essential Medical, Inc.

## Protocol Synopsis

Protocol Element	Details
Title	Pivotal Clinical Study to Establish the Safety and Effectiveness of MANTA Vascular Closure Device
Protocol ID	PSD-109
Investigational device	MANTA 14F and 18F Vascular Closure Devices
Overall Study Design	Multicenter prospective single-arm clinical investigation
Background	<p>MANTA is an active collagen-based vascular closure device (VCD), designed for safe and effective femoral access site closure in patients undergoing procedures requiring large-bore sheaths (10-18F ID).</p> <p>Current available VCD (i.e., single or multiple suture-based devices [Proglide or Prostar]) are not specifically designed for closing large arteriotomy; therefore ease of use and effectiveness are limitations. The features of the MANTA device are simple and operator friendly deployment, improved reliability of anchor-suture-collagen lock and seal, tension control for safety, performance, and patient comfort.</p> <p>The present study is intended to support a PMA approval for the MANTA device in the U.S. First in Human experience was obtained in 16 subjects, and an EU pre-market study was conducted in 50 subjects, both with favorable clinical outcomes.</p>
Indications for Use	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).
Device Description	The MANTA device, developed by Essential Medical, Inc., is a VCD intended for use in catheterization laboratories following percutaneous cardiac or peripheral procedures that use the retrograde common femoral artery access route for large bore (10-18F ID) interventional devices. The function of MANTA is to percutaneously close the puncture in the artery wall (arteriotomy) through which the catheters were inserted for the procedure. The closure device consists of a hemostatic plug (collagen) in the tissue tract on the outside of the artery, which is held in place by suture linked to a small molded polymer toggle positioned inside the artery. A tiny stainless steel lock is used to secure the components in a sandwich through and on either side of the arteriotomy.
Device Illustration	<div style="display: flex; justify-content: space-around;"> <div style="text-align: center;"> <p>MANTA Plug</p>  </div> <div style="text-align: center;"> <p>MANTA Handle</p>  </div> </div>

Protocol Element	Details
Purpose of the Study	To demonstrate the safety and effectiveness of MANTA in achieving hemostasis in femoral arterial access sites in subjects undergoing percutaneous transcatheter interventional procedures using a large-bore procedure sheath for purposes of obtaining a PMA approval in the U.S. The study will evaluate times to hemostasis and ambulation, technical success, ambulation success, treatment success, procedure time, and the rate of access-site-related complications; the primary endpoints will be compared to Performance Goals (PG) derived from published literature and the clinical judgment of expert advisors.
Number of Subjects	<p>Analysis Cohort: Minimum of 250 subjects undergoing large-bore intervention, with a minimum of 50% treated with the 18F MANTA device and the remainder treated with the 14F MANTA device; a total of 263 subjects will be treated to account for up to a 5% loss to follow-up.</p> <p>Roll-In Cohort: Additionally, up to 2 roll-in subjects per operator using either MANTA device will be enrolled to allow investigators to learn how to use the MANTA device</p>
Number & Location of Investigational Sites	A minimum of 5 and up to 25 sites in the U.S., EU and/or Canada
Duration of the Investigation	<p>Enrollment: approximately 8 months</p> <p>Subject Follow-up: 60 days</p> <p>Total duration: Approximately 10 months</p>
Investigational Device	14F and 18F MANTA Vascular Closure Devices
Comparator	Performance Goals (PG) and a Clinical Acceptance Criterion (CAC) 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.
Primary Endpoints	<p><b>Safety:</b> Major Complications, within 30 days of procedure</p> <p><b>Effectiveness:</b> 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).</p>
Secondary Endpoints	<p><b>Safety:</b></p> <ul style="list-style-type: none"> <li>• Minor Complications, within 30 days of procedure</li> <li>• VARC-2 Major Vascular Complications, adapted from the VARC-2 criteria, within 30 days of procedure</li> </ul> <p><b>Effectiveness:</b></p> <p><u>Technical Success:</u> 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.</p> <p><u>Ambulation Success:</u> 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.</p> <p><u>Time to Ambulation:</u> The elapsed time 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).</p>

Protocol Element	Details
	<p><u>Treatment Success:</u> A subject will be considered a Treatment Success if he/she has Time to Hemostasis <math>\leq 10</math> minutes and has no Major Complications (as defined above).</p> <p><u>Procedure Time:</u> Defined as elapsed time from initial skin break (first needle insertion) to time when the post-deployment angiogram is completed.</p>
Inclusion Criteria	<ol style="list-style-type: none"> <li>1. Candidate for elective or planned (i.e., not emergent or urgent) percutaneous transcatheter interventional procedure via a 10-18F size retrograde common femoral artery approach (i.e., transcatheter aortic valve implantation [TAVI], endovascular aneurysm repair [EVAR], Impella® use)</li> <li>2. Vessel size would allow for access for the MANTA device as determined by baseline CTA: minimum vessel diameter 5mm for the 14F MANTA and 6mm for the 18F MANTA</li> <li>3. Eligible for sheath removal in the catheterization lab</li> <li>4. Age <math>\geq 21</math> years</li> <li>5. Understand and sign the study specific written informed consent form</li> <li>6. Able and willing to fulfill the follow-up requirements</li> <li>7. In the investigator's opinion, patient is suitable for the MANTA vascular closure device, conventional hemostasis techniques and participation in an investigational trial</li> </ol>
Exclusion Criteria	<p><b>Baseline Exclusions:</b></p> <ol style="list-style-type: none"> <li>1. Known to be pregnant or lactating</li> <li>2. Immunocompromised or with pre-existing autoimmune disease</li> <li>3. Systemic infection or a local infection at or near the access site</li> <li>4. Significant anemia (hemoglobin <math>&lt; 10</math> g/dL, hematocrit <math>&lt; 30\%</math>)</li> <li>5. Morbidly obese or cachectic (BMI <math>&gt; 40</math> kg/m<sup>2</sup> or <math>&lt; 20</math> kg/m<sup>2</sup>)</li> <li>6. Known bleeding disorder including thrombocytopenia (platelet count <math>&lt; 100,000</math> cells/UL), thrombasthenia, hemophilia, or von Willebrand disease</li> <li>7. Allergy to bovine materials or any other device material, including collagen and/or collagen products, polyglycolic or polylactic acid, stainless steel or nickel</li> <li>8. Femoral artery puncture in target groin within the prior 14 days, recent femoral artery puncture in target groin that has not healed appropriately, and/or prior vascular closure device placement in target common femoral artery that the investigator determines may interfere with the MANTA device</li> <li>9. Common femoral artery with calcium, as determined by baseline CTA, precluding safe access in the opinion of the investigator or severe peripheral vascular disease as evidenced by severe claudication when ambulating <math>&lt; 100</math> feet, weak or absent pulses in the affected limb, or ABI <math>&lt; 0.5</math> at rest.</li> <li>10. Previous iliofemoral intervention in region of access site, including but not limited to prior atherectomy, stenting, surgical or grafting procedures in the access area</li> <li>11. Patients who have undergone use of an intra-aortic balloon pump through the arterial access site within 30 days prior to the baseline evaluation</li> <li>12. Undergoing therapeutic thrombolysis</li> <li>13. Patients in whom oral anticoagulation therapy cannot be stopped for the peri-procedural period or patients with INR <math>&gt; 1.8</math> at the time of the procedure.</li> </ol>

Protocol Element	Details
	<p>14. Patient unable to be adequately anti-coagulated for the procedure</p> <p>15. Patients who are not mobile and are confined to a wheelchair or bed</p> <p>16. ST-elevation MI within 30 days prior to procedure or acute coronary syndrome (i.e., unstable angina or myocardial infarction) <math>\leq</math>48 hours before the catheterization procedure</p> <p>17. NYHA class IV heart failure</p> <p>18. Left ventricular ejection fraction <math>&lt;</math>20%</p> <p>19. Unilateral or bilateral lower extremity amputation</p> <p>20. Renal insufficiency (serum creatinine <math>&gt;</math>2.5 mg/dl) or on dialysis therapy</p> <p>21. Existing nerve damage in the ipsilateral leg</p> <p>22. Further planned endovascular procedure within the next 30 days</p> <p>23. Patients who have already participated in the IDE study</p> <p>24. Currently participating in another clinical trial of an unapproved investigational device or drug that has not concluded the follow-up period</p> <p>25. Patient cannot adhere to or complete the investigational protocol for any reason including but not limited to geographical residence, psychiatric condition or life threatening disease</p> <p>26. Common femoral artery <math>&lt;</math>5mm in diameter for the 14F MANTA or <math>&lt;</math>6 mm in diameter for the 18F MANTA, common femoral artery stenosis resulting in a vessel diameter <math>&lt;</math>5mm in diameter for the 14F MANTA or <math>&lt;</math>6 mm in diameter for the 18F MANTA, or <math>&gt;</math>50% diameter femoral or iliac artery stenosis</p> <p><b>Intra-Procedure Exclusions</b></p> <p>27. Puncture site in the profunda femoris artery, superficial femoral artery, or at the bifurcation of these arteries</p> <p>28. Common femoral artery suspected to have experienced a back wall puncture or underwent <math>&gt;</math> one (1) <u>arterial</u> puncture during the catheterization procedure</p> <p>29. Difficult dilation from initial femoral artery access (e.g., damaging or kinking dilators) while step dilating up to the large-bore device.</p> <p>30. Presence of ipsilateral femoral venous sheath</p> <p>31. Puncture site located above the most inferior border of the epigastric artery (IEA) and/or above the inguinal ligament based upon bony landmarks</p> <p>32. Marked tortuosity of femoral or iliac artery</p> <p>33. Patient did not receive any antiplatelet or anticoagulant medications before or during the endovascular interventional procedure</p> <p>34. ACT <math>&gt;</math>250 seconds prior to removal of the sheath or interventional device</p> <p>35. Systolic blood pressure <math>&gt;</math>180 mm Hg or diastolic blood pressure <math>&gt;</math>110 mm Hg, unless systolic or diastolic pressure can be lowered by pharmacological agents prior to closure</p> <p>36. Antegrade puncture during the index procedure</p> <p>37. Interventional sheath or device in place <math>&gt;</math>6 hours</p> <p>38. Possible bacterial contamination of the procedure sheath or surrounding tissues during the procedure</p> <p>39. Intra-procedural complication(s) at the femoral access site pre-sheath removal including: 1. Bleeding or swelling around the large bore sheath that may indicate hematoma formation and/or pseudoaneurysm formation; and 2. Peri-procedural angiographic evidence of thrombus formation or significant injury in the aorta or iliac</p>

Protocol Element	Details
	vessels associated with procedural large bore sheath placement and/or sub-optimal anticoagulation 40. Systolic blood pressure <90 mm Hg just prior to planned vascular closure 41. Procedure sheath or interventional device >25F outer diameter required during the procedure
Follow-Up	Clinical follow-up at 30 and 60 days post-procedure

## Schedule of Assessments

Assessment/ Interval	Screening	Index Proce- dure	Pre- MANTA Closure Procedure	MANTA Closure Procedure	Post- MANTA Closure Procedure	Hospital Discharge	30D & 60D Follow-Up <sup>4</sup>
Subject Eligibility/Informed Consent	X						
Clinical Exam	X						X
Medical History	X						
Medication Use	X					X	X
Laboratory Tests	X <sup>7</sup>						
Pregnancy Test	X <sup>1</sup>						
CT Angiographic Scan	X <sup>8</sup>						
ABI (Ankle Brachial Index)	X				X	X	X
Duplex U/S						X <sup>6</sup>	X <sup>5</sup>
Femoral Angiography		X <sup>2</sup>			X <sup>3</sup>		
Activated Clotting Time (ACT)			X				
Target Femoral Access Site External Visual Assessment			X		X	X	X
Time to Hemostasis					X		
Time to Ambulation						X	
Adverse Events		X	X	X	X	X	X

1. Female subjects of child bearing potential only. Test to be conducted within 7 days of planned Index procedure or according to standard of care for percutaneous interventional procedures requiring contrast and angiography. Urine pregnancy test is acceptable.
2. After gaining femoral artery access and prior to large-bore sheath placement, perform target (ipsilateral) common femoral angiography to rule out intra-procedure exclusion criteria.
3. Within approximately 10 minutes post-MANTA deployment, perform target (ipsilateral) common femoral angiography from contralateral access site to evaluate patency into the ipsilateral common femoral artery.
4. 30 day follow-up window is  $\pm 7$  days; 60 day follow-up window is  $\pm 14$  days.
5. Duplex ultrasound should be performed at 60-day visit if there are abnormal ultrasound findings at 30-day visit.
6. Ultrasound must be performed no later than 48 hours post-MANTA deployment, if discharge is delayed. In addition, any suspected hematoma, pseudoaneurysm or AV fistula at the MANTA site should be confirmed with ultrasound.
7. Within 7 days of planned index procedure or according to standard of care for percutaneous interventional procedures requiring contrast and angiography.
8. Within 180 days prior to subject informed consent.



## Abbreviations/Acronyms

<b>Abbreviation/ Acronym</b>	<b>Definition</b>
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
PG	Performance goal
PMA	Pre-market approval
SAE	Serious adverse event
SADE	Serious adverse device effect
SOPs	Standard operating procedures
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

## Revision History

Version	Date	Summary of Changes/ Affected Sections
A	May 23, 2016	Initial Release
B	July 19, 2016	Revised to address FDA comments during IDE review and approval conditions
C	August 31, 2016	Revised to address additional FDA comments in conditional approval letter, HPA recommendations to improve clarity of protocol, adjust ultrasound schedule to eliminate unnecessary studies, address potential investigator input
D	September 30, 2016	Revised to address interactive comment during IDE supplement review
E	December 15, 2016	Revised to address FDA comments in conditional approval letter regarding safety endpoint definitions and to update PG/CAC; added Medicare generalizability text to Section 15; added VARC-2 Major Vascular Complications as secondary safety endpoint; minor revisions to exclusion criteria to correct errors and oversights; revision to screening/baseline section to clarify timing of consent vs. standard of care tests; increase baseline window for CTA to 180 days from 90 days; clarify purpose of ultrasound data and core lab.
F	June 2, 2017	Increase number of investigational sites from 20 to 25. Add statements regarding ultrasound confirmation of hematoma, pseudoaneurysm and AVF to schedule of assessments and section 7.7.

## Table of Contents

Protocol Signature Page .....	2
Protocol Synopsis.....	3
Schedule of Assessments.....	8
Abbreviations/Acronyms .....	9
Revision History.....	11
Table of Contents .....	12
1 Introduction.....	16
1.1. Large Bore Vascular Interventions.....	16
1.2. MANTA Large Bore Vascular Closure Device .....	16
1.3. Pre-Clinical Investigation Results.....	17
1.4. Previous Clinical Experience .....	17
1.5. Study Rationale.....	23
1.6. Device Description.....	23
1.6.1 Study Materials .....	23
1.6.2 Indications for Use .....	23
1.7. Manufacturer/Sponsor.....	23
1.8. Regulatory Classification .....	23
1.9. Site Selection and Investigator Training.....	24
2 Justification of the Design of the Study.....	25
3 Risks and Benefits of the Investigational Device and Study .....	26
3.1. Anticipated Clinical Benefits.....	26
3.2. Anticipated Adverse Device Effects.....	26
3.3. Risk Mitigation .....	26
3.4. Risk to Benefit Rationale .....	26
4 Protocol Definitions .....	27
5 Study Objectives.....	31
6 Study Design.....	32
6.1. General.....	32
6.2. Minimization of Bias.....	32
6.3. Randomization .....	32

6.4.	Subject Replacement .....	32
6.5.	Study Population .....	32
6.5.1	Number of Subjects .....	32
6.5.2	Inclusion Criteria .....	33
6.5.3	Exclusion Criteria .....	33
6.5.4	Subject Withdrawal or Discontinuation .....	35
6.5.5	Enrollment .....	35
6.5.6	Duration of the Study .....	35
7	Study Procedures .....	36
7.1.	Screening – Phase I .....	36
7.2.	Informed Consent .....	36
7.3.	Screening – Phase II .....	36
7.4.	Screening – Phase III .....	37
7.5.	Assignment of Subject Number .....	37
7.6.	Procedure .....	38
7.7.	Post-Procedure Evaluations .....	39
7.8.	Subject Follow-up .....	40
7.9.	Ultrasound and Core Lab .....	40
8	Statistical Methods .....	41
8.1.	Study Hypotheses .....	41
8.1.1	Effectiveness .....	41
8.1.2	Safety .....	41
8.2.	Sample Size Considerations .....	42
8.3.	Data Analysis .....	42
8.3.1	Endpoints .....	42
8.3.2	Interim Analysis .....	43
8.3.3	Final Analysis .....	43
8.3.4	Subgroup Analysis .....	43
8.3.5	Poolability Analysis .....	44
8.3.6	Missing Data .....	44
8.4.	Minimum and Maximum Subject Recruitment for Analysis .....	44
9	Adverse Events .....	45
9.1.	Definitions .....	45

9.2.	Potential Adverse Events and Adverse Device Effects .....	45
9.3.	Relationship of Adverse Event to Device/Procedure .....	46
9.4.	Severity of Adverse Events .....	46
9.5.	Reporting of Adverse Events .....	46
9.5.1	SAE and AE Reporting to Sponsor.....	46
9.5.2	SAE Reporting to IRB and FDA – US .....	47
9.5.3	SAE Reporting to EC and CA – EU.....	47
9.5.4	SAE Reporting to IRB and CA – Canada .....	47
9.6.	Device Deficiencies .....	48
9.7.	Clinical Events Committee (CEC) .....	48
9.8.	Data & Safety Monitoring Committee (DSMC).....	48
10	Medication .....	50
11	Vulnerable Population .....	51
12	Data Management.....	52
12.1.	Case Report Forms .....	52
12.2.	Data Management .....	52
12.3.	Data Retention .....	52
12.4.	Other Aspects of Clinical Quality Assurance .....	52
13	Clinical Monitoring.....	54
13.1	Clinical Research Organization .....	54
13.2	Monitoring .....	54
13.3	Initial Procedures .....	55
13.4	Review of Study Documents .....	55
13.5	Device Accountability .....	55
14	Protocol Deviations and Amendments.....	57
14.1.	Protocol Adherence and Deviations.....	57
14.2.	Corrective and Preventive Actions .....	57
14.3.	Investigator Disqualification Criteria.....	57
15	Statements of Compliance.....	58
16	Publication Policy .....	59
16.1.	Publication by Essential Medical, Inc. ....	59
16.2.	Publication by Investigational Sites.....	59
17	References .....	60

Appendix 1. Instructions for Use..... 61  
Appendix 2. Performance Goal Rationale..... 62

# 1 Introduction

## 1.1. *Large Bore Vascular Interventions*

The advent of percutaneous cardiac and peripheral procedures performed through large bore arteriotomies, such as transcatheter aortic valve implantation (TAVI), endovascular aneurysm repair (EVAR), and balloon aortic valvuloplasty (BAV), demonstrates a need for a safe and effective vascular closure device (VCD) to replace the current standard of care of surgical cut-down/repair or use of multiple small bore suture-mediated closure devices that were not designed for large bore punctures.

The Proglide suture-mediated VCD (Abbott Vascular) is approved in the EU and US for large bore arteriotomy closure (up to 21F), and the Prostar XL (also Abbott Vascular) is approved in the EU for closure up to 24F.[1,2] There are extensive publications on the use of both devices for large bore closure.[3] Other VCDs approved for smaller size sheaths (6-10F), primarily Angio-Seal (St. Jude Medical), have been used off-label for the purpose of closing large bore arteriotomies; limited results of this off-label use have been published.[4] Literature review demonstrates that VCDs are useful to vascular surgeons and interventional cardiologists and radiologists in large bore closure, reducing time to hemostasis at the arteriotomy site, procedure time and access site complications compared to the surgical cut-down approach.[3,5]

However, the available VCDs were not originally designed for large bore arteriotomy closure and are time-consuming and clumsy to use. There is a clinical need for a purpose-designed large-bore VCD that is safe and rapidly closes the arteriotomy with effective hemostasis and that is easy and quick to use. This is the intended purpose of the MANTA VCD, subject of this study.

## 1.2. *MANTA Large Bore Vascular Closure Device*

Both the 14F and 18F MANTA Vascular Closure Devices (VCD) utilize an implant, composed of an intra-arterial resorbable polymer toggle, non-resorbable suture and an extra-arterial hemostatic collagen pad, to “sandwich” the arteriotomy closed (Figure 1). No alternative devices designed specifically for large bore closure are commercially approved in the U.S. The MANTA VCD has been specifically designed to address the unmet need of large bore arteriotomy closure.



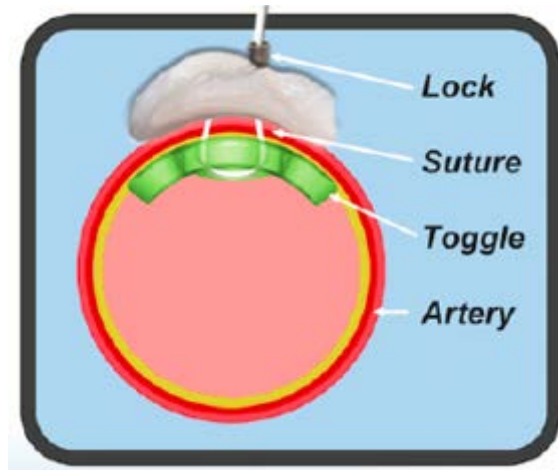


Figure 1: Illustration of the MANTA Vascular Closure Device

### 1.3. *Pre-Clinical Investigation Results*

Extensive preclinical testing, including bench, animal and biocompatibility testing, has been completed on the MANTA devices. This testing has demonstrated that the MANTA device is safe and performs as intended by the manufacturer. The bench testing demonstrated that the MANTA device meets its design inputs. Biocompatibility testing demonstrated that the materials used in the MANTA device are biocompatible. The extensive animal testing demonstrated that the MANTA devices, both 14F and 18F, perform as intended in the exposed aorta of an animal model and that the devices, particularly the intra-arterial toggle, encapsulate and resorb as expected without adverse tissue reactions.

### 1.4. *Previous Clinical Experience*

Three clinical studies have been conducted on the MANTA devices, two First-in-Human (FIH) studies and a single-arm pre-market study in the EU.

#### **First in Human (FIH) Trials (November 2014-July 2015, Asuncion, Paraguay):**

##### 18F FIH Study

This was a prospective, non-randomized, single-site, non-blinded feasibility study to evaluate the initial safety and preliminary efficacy of the Essential Medical 18F MANTA Vascular Closure System. Six (6) subjects undergoing BAV were enrolled, and 5 subjects were treated with the 18F MANTA device; the MANTA device was not used in one case due to lost vascular access during the initial procedure sheath placement.

Time to hemostasis (TTH) averaged 84 seconds for the 5 subjects treated with MANTA. There were no device-related adverse events. See Figure 2 for an example post-procedure Doppler ultrasound and image of the access site. One subject died due to a heart attack during hemodialysis; this was reported at the one month follow up and was unrelated to the procedure or to the investigational device. A second subject death occurred during aortic valve surgery prior to 90 day follow up; this death was also unrelated to the device. There were no other complications or adverse events at follow up, which included routine radiography of the deployment area and Doppler ultrasound to evaluate flow for all subjects.

### 14F FIH Study

This was a prospective, non-randomized, single-site, non-blinded feasibility study to evaluate the initial safety and preliminary efficacy of the Essential Medical 14F MANTA Vascular Closure System. In total, 11 subjects undergoing BAV were enrolled and treated with the 14F MANTA device. The device was successfully deployed in 5 of the first 6 cases, and hemostasis was achieved within 1-7 minutes. In 3 of these 5 cases, additional light manual pressure for 5-20 minutes was required to control oozing. In all 5 cases, 24-hour follow-up ultrasound revealed no abnormalities and good flow.

In one of the 6 cases, prolonged time to hemostasis, a hematoma and pseudoaneurysm occurred. This was believed to be due to difficulty placing the initial sheath. It was also determined that a large hematoma had formed intra-procedurally from the difficult femoral puncture and therefore resulted in a MANTA deployment with a challenging puncture locating step. This subsequently resulted in suboptimal MANTA deployment and longer time to hemostasis. Manual pressure of 26 minutes was required to obtain hemostasis following 20mg of protamine to reverse the heparin and bring down the activated clotting time (ACT). On 24-hour follow-up ultrasound, a pseudoaneurysm was seen at the puncture site. A Femo-Stop was applied for 3 hours, which resolved the pseudoaneurysm. The subject was discharged without further sequelae.

In the second series of cases, the MANTA device was successfully deployed in 5 of 5 BAV cases, and hemostasis was achieved within 0-2 minutes in each of the 5 cases. Manual compression was not needed in any of the cases. In 4 of 5 cases, 24-hour follow-up ultrasound revealed no abnormalities and good flow.

In one of the 5 cases, the initial sheath placement for the procedure was performed with difficulty; the investigator believes this may have been due to fibroid tissue in the right femoral vein. During the post-procedure ultrasound, it was noted that a pseudoaneurysm had developed and low blood flow through the target vessel was observed. A review of the periprocedural angiogram after the case showed an arterial dissection of the target vessel prior to introduction of the MANTA device. Following the case review, the investigators concluded that the femoral artery had been severely damaged during dilation prior to the index procedure. They further concluded that the damage to the vessel was unrelated to the MANTA device and that the MANTA device was instrumental in closing the puncture given the severely damaged vessel.

Immediate post procedure subject implanted with MANTA during FIH study

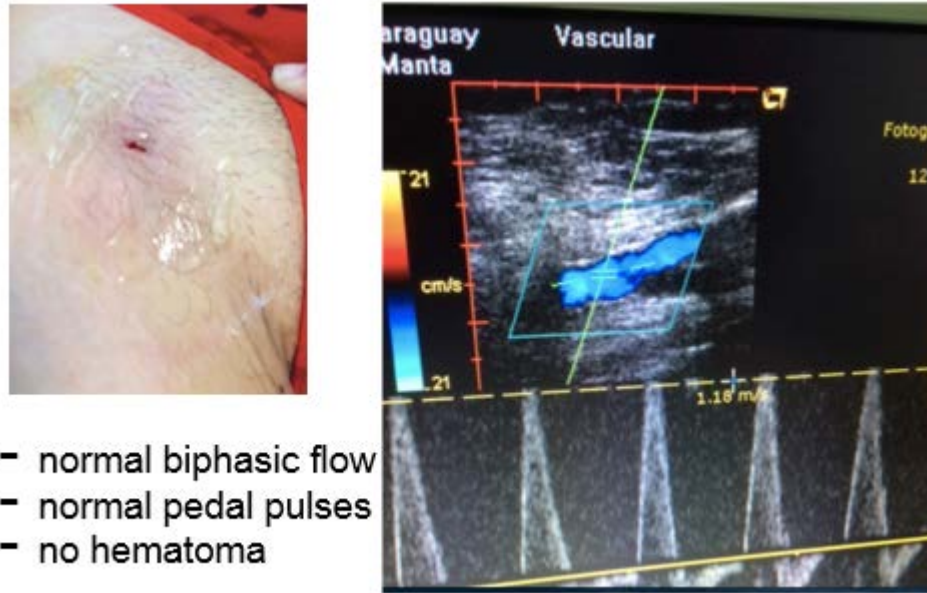


Figure 2: FIH Puncture Site and Duplex Ultrasound Photos

**EU Pre-Market Clinical Study (July 2015 – March 2016, The Netherlands & Italy):**

This was a prospective, non-randomized, multi-site, non-blinded study to evaluate the safety and performance of the 14F and 18F MANTA Vascular Closure Devices at 3 sites, one in Italy and two in the Netherlands. The study was conducted to generate data to support a CE mark in the EU. Fifty (50) subjects were enrolled and treated with the MANTA device. The synopsis of the final clinical study report is excerpted here in abbreviated form:

**Study objectives**

In this prospective, multi-center, open-label, single-arm clinical investigation '*Clinical Study to Evaluate the Safety and Performance of MANTA Vascular Closure Device*' the safety and performance of the MANTA VCD in subjects who had undergone interventional procedures using a 10F to 18F procedural sheath were evaluated. Specifically, the primary safety endpoint was assessed by evaluation of access site related Major Complications in comparison to published literature on hemostasis techniques for closing large bore punctures (primarily, surgical closure and suture-mediated percutaneous closure [i.e., single or multiple Proglide/Prostar devices]). The primary performance endpoint was assessed by Hemostasis Success. Secondary objectives were to evaluate the Minor Complications, Time to Hemostasis, Time to Ambulation, and Treatment Success.

## Results

The study population consisted of subjects who were candidates for non-emergent transcatheter interventional procedures via a 10-18F femoral sheath (e.g., TAVR, BAV, EVAR). Treated subjects were followed for 60 days post-procedure.

In total, 50 subjects were treated at 3 centers in Europe. The first subject was enrolled on 22 July 2015 and the last subject was enrolled on 27 January 2016. The first subject out was on 7 October 2015 and the last subject out was on 22 March 2016. Sixteen (16) subjects were treated with the 14F MANTA device (32%) and 34 were treated with the 18F MANTA device (68%). Of the enrolled subjects, 23 subjects were male (46%) and 27 were female (54%). Mean age was  $79.5 \pm 8.3$  years, mean weight was  $75.4 \pm 15.6$  kg, mean height was  $164.1 \pm 10.0$  cm, and mean Body Mass Index was  $27.8 \pm 4.4$  kg/m<sup>2</sup>.

### *Primary Safety Endpoint*

The primary safety endpoint was to evaluate the percentage of patients with one or more Major Complications reported from the procedure until the first study visit ( $30 \pm 7$  days following procedure). Three (3) Major Complications were reported in 3 subjects (6%). A non-inferiority test comparing these results with results from the SEVAR (surgical closure) arm as obtained in the PEVAR trial [5], demonstrated strong evidence that rate of Major complications was non-inferior to the published SEVAR results ( $p < 0.05$ ).

### *Primary Performance Endpoint*

The primary performance endpoint was to evaluate the percentage of patients with Hemostasis Success. Hemostasis Success was achieved in 47 subjects (94.0%). For the 3 subjects that did not reach Hemostasis Success, hemostasis was obtained in 37, 27 and 13 minutes and manual pressure was required for 6-11 minutes.

### *Secondary Safety Endpoint*

The secondary safety endpoint was to evaluate the percentage of patients with one or more Minor Complications reported from the procedure until the first study visit ( $30 \pm 7$  days following procedure). Five (5) Minor Complications were reported in 5 subjects (10%).

### *Secondary Performance Endpoints*

The secondary performance endpoint Time to Hemostasis was to evaluate the elapsed time between MANTA deployment and the first observed and confirmed arterial hemostasis. Mean Time to Hemostasis was 2 minutes and 23 seconds (Standard deviation: 6 minutes and 38 seconds; Median: 24 seconds; Minimum: 2 seconds; Maximum: 37 minutes and 10 seconds). For 37 subjects (74%), Time to Hemostasis was reported as  $\leq 1$  minute; for 10 subjects (20%), 1 to 10 minutes were required until hemostasis was achieved; and for 3 subjects (6%), more than 10 minutes and manual pressure were required until hemostasis achievement

The secondary performance endpoint Time to Ambulation was to evaluate the elapsed time between MANTA deployment and when ambulation is achieved. Mean Time to Ambulation was 44 hours and 10 minutes (Standard deviation: 25 hours and 7 minutes; Median: 43 hours and 34

minutes; Minimum: 3 hours and 42 minutes; Maximum: 142 hours and 1 minute). For 5 subjects (10%), Time to Ambulation was reported as less than 24 hours; for 28 subjects (56%) Time to Ambulation was between 24 and 72 hours; and for 6 subjects (12%) more than 72 hours were required until ambulation. Hemostasis was maintained during ambulation for all subjects with available data (n=41).

The secondary performance endpoint Treatment Success was to evaluate the number of subjects that had Hemostasis Success and no Major Complications reported. Treatment Success was achieved in 47 subjects (94%). Absence of Hemostasis Success, as well as presence of one or more Major Complications, occurred in the same 3 subjects.

### *Safety Assessment*

All adverse events (AEs) that were reported were assessed for type, severity, and device or procedure relatedness. In total, 101 AEs were reported during the course of the study, involving 45 subjects (90%). Forty-six (46, 45.5%) of these events were classified as 'not related' to the device. Of the 101 reported AEs, 25 were classified as 'serious'. Twenty-two (22, 88.0%) of these serious events were classified as 'not related' to the device. None of the AEs nor any of the SAEs were unanticipated.

The most common reported AE concerned a hematoma at the access site, which was reported 29 times (in 58% of the subjects) (10 times (20%) hematoma > 6 cm; 19 times (38%) hematoma ≤ 6 cm). One (1) of these hematomas was classified as 'moderate' severity, all others were classified as 'mild'.

Femoral artery stenosis was reported in 17 cases (34%). Although all events were reported as possible (2 cases, 4%) or definite (15 cases, 30%) related to the device, all events were classified as 'mild' severity and none of these femoral artery stenoses required intervention.

Twenty-five (25) AEs were classified as 'serious', involving 20 subjects (40%), of which 3 were probably or definitely device related (2 excessive access site bleedings; 1 pseudoaneurysm). All 3 events were classified as Major Complications.

During the course of the study, 4 subjects died. One (1) subject suffered from renal insufficiency and infection (cause unknown); another subject suffered from a cerebrovascular accident; 1 subject suffered from intestinal perforation; and the fourth subject suffered from a systemic infection. None of these events was considered related to the device nor to the procedure.

There were no unanticipated serious adverse device effects reported for any of the subjects.

## **Discussion**

### *Safety*

The 3 Major Complications reported were the only safety events that were classified as potentially or definitely device-related SAEs. For 2 of these events the Sponsor concluded that these events were a result of minor manufacturing deficiencies. Necessary corrective action has been taken to improve the manufacturing process and limit the associated safety risk.

In total, 10 AEs described an access site related hematoma > 6 cm. The investigator who treated these subjects, confirmed that this concerned an ecchymosis in 5 cases (50%), which is sometimes difficult to distinguish from a hematoma. This information was accompanied by ultrasound data in 3 cases, where the hematoma at the artery was assessed as 0.96, 2.28 and 0.82 cm<sup>2</sup>. The 5 remaining cases concerned true hematomas based on visual assessment and available ultrasound data and those were classified as Minor Complications. No other Minor Complications were reported during the course of the study.

The AE termed 'stenosis at the access site' has only been reported at site 01. The observed difference in frequency proportion may be due to an interest bias. The involvement of an independent interpreter, e.g. by use of a qualified core lab, would limit the interpretation bias in future studies.

A large number of unrelated AEs can be anticipated with a study population as included in this study, with a mean age of 79.5 years (Standard deviation: 8.3 years; Median 80.7 years; Minimum 42.6 years; Maximum 90.4 years) and who are undergoing a significant intervention. Additionally, physical exam at baseline revealed that 46 subjects (92%) were suffering from one or more comorbid conditions prior to MANTA treatment.

#### *Performance*

Hemostasis Success was obtained in 94% of the subjects. The mean Time to Hemostasis reported in this study was 2 minutes and 23 seconds. The minimum reported Time to Hemostasis was 2 seconds and 74% of the subjects had a time to hemostasis reported that was less than 1 minute. These results indicate excellent performance of the device, given that the MANTA device is used for vascular closure of very large punctures. Outer diameters of the index procedure sheaths which the 18F MANTA device closed were as large as 24.5F (8.17 mm).

The subjects for whom no Hemostasis Success was obtained (n=3, 6%) were the same subjects for whom a Major Complication was reported, as well as for whom a Time to Hemostasis of more than 10 minutes was reported.

#### **Conclusion**

Results from this study demonstrate the excellent performance of the MANTA closure device in achieving hemostasis in 94% of the treated subjects, with 74% achieving hemostasis within 1 minute in patients that underwent percutaneous transcatheter interventional procedures using a 10-18F procedure sheath. Three (3) Major Complications were reported (two (2) of which were associated with minor manufacturing issues that have been corrected), accounting for 6% of the treated population, demonstrating strong evidence that the proportion of MANTA subjects with Major complications were non-inferior to those of the SEVAR trial (p<0.05).

In conclusion, the results of this study demonstrate that the MANTA vascular closure device is safe and performs as intended by the Sponsor.

## **1.5. Study Rationale**

The rationale for this study is to evaluate the safety and effectiveness of the MANTA VCD to close the femoral arteriotomy following percutaneous cardiovascular procedures utilizing large bore sheaths, such as TAVI and EVAR, for purposes of supporting a U.S. PMA approval and other regulatory submissions.

## **1.6. Device Description**

### **1.6.1 Study Materials**

The 18F MANTA VCD consists of the closure implant, an 18F insertion sheath, an 18F introducer, and an 8F puncture locating dilator. Similarly, the 14F MANTA VCD consists of the closure implant, a 14F insertion sheath, a 14F introducer and an 8F puncture locating dilator. The MANTA implants are composed of a delivery handle containing an absorbable collagen pad, a stainless steel locking component, and an absorbable polymer toggle that are connected by a non-absorbable suture. Hemostasis is achieved primarily by the mechanical means of the toggle-arteriotomy-collagen sandwich, which is supplemented by the coagulation-inducing properties of the collagen. The extra-vascular stainless steel lock secures and marks the location of the absorbable unit. The MANTA VCD components are not made from latex rubber. The device is sterile and intended for single use only.

Refer to the Investigator Brochure for details of the device, its materials and construction, bench and animal testing. Refer to Appendix 1 for the Instructions for Use.

### **1.6.2 Indications for Use**

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).

## **1.7. Manufacturer/Sponsor**

The Legal Manufacturer of the MANTA vascular closure device and the Sponsor of this study is:  
Essential Medical, Inc.  
227 East King Street  
Malvern, PA 19355, U.S.A.

## **1.8. Regulatory Classification**

In the U.S., the MANTA vascular closure device is a class 3 device, subject to Pre-Market Approval (PMA).

In the EU, the MANTA vascular closure device is classified as a Class III device per rules 8 and 17 of Annex IX of the Medical Devices Directive 93/42/EEC.

### **1.9. Site Selection and Investigator Training**

The primary consideration in operator and site selection for the MANTA US trial is adequate experience with large-bore interventions, vascular closure devices and conducting clinical trials, commitment to safety, and consistency in adherence to the clinical protocol. Prior to performing the MANTA procedures, training materials will be reviewed with each Investigator and clinical coordinator. The study protocol, appropriate subject selection and enrollment will also be reviewed. All Investigators will be certified as successfully trained on the device use with cases that were proctored by a previously trained Investigator or by a company representative. Each site will be permitted to enroll up to 2 roll-in cases per operator that will not be analyzed with the Analysis Cohort and during which the investigators will receive hands-on training in the use of the MANTA device (subjects designated as roll-in cases that are subsequent screen failures will not be counted towards the roll-in limit). All roll-in training cases must meet eligibility criteria for the trial.



## 2 Justification of the Design of the Study

Closure of large bore (10-25F) arteriotomies after interventional procedures is problematic. Once the procedure has been completed, the physician must close and obtain hemostasis at the puncture, which is in a high-pressure artery and may be as large as 8mm in diameter. Currently, this is accomplished by manual compression at the lower end of this size range (typically <12F) or surgical access/repair or use of suture-mediated VCDs at the higher end of sheath sizes (above 12F). Consequently, the vascular complication rates for procedures utilizing large bore sheaths, such as TAVI and EVAR, have been reported at up to 20%.[2]

Manual compression involves the application of firm pressure to the access site by a physician, nurse or technician or using a mechanical device, such as the Femo-Stop, until bleeding stops. With the surgical approach, the femoral artery is typically exposed at the initiation of the procedure to introduce the large-bore sheaths; at the end of the procedure, the artery is sutured closed. In either case, the patient must then remain in a supine position for many hours until the access site is stable and the patient can ambulate. This process is especially time consuming if the patient has received anti-coagulant or anti-platelet drugs.

VCDs originally approved for smaller bore arteriotomies (10F and smaller), primarily the suture-mediated devices, are now commonly used to close these larger punctures. Using a “preclose” technique that involves placing the sutures prior to sheath placement, this was initially an off-label practice, but the Abbott Vascular suture-mediated VCDs (Proglide and Prostar XL) are now labeled for large bore closure in the EU (both devices) and US (Proglide only). However, neither was specifically designed for the closure of large-bore punctures. As such, the use of these VCDs for large punctures is complex, requiring placement of the sutures at the beginning of the interventional procedure, time-consuming and not user friendly.

The MANTA vascular closure device is innovative in that it is specifically designed to close large bore (10-18F ID) punctures following percutaneous transcatheter cardiac and peripheral interventions. The MANTA design utilizes the foundation of the existing smaller bore Angio-Seal and X-Seal “tethered collagen plug” design of closure devices (i.e., the resorbable anchor and collagen plug) and builds on that foundation with innovations to specifically address the larger bore requirements. This includes holding the anchor within a separate release tube until it is safe to deploy the anchor close to the artery wall puncture; this prevents the anchor from deploying too far within the artery, catching across the artery and potentially deploying collagen into the vessel. A lever on the deployment handle actively deploys the anchor at the appropriate time and position.

This clinical investigation is designed to investigate safety and effectiveness of the MANTA Vascular Closure Device in patients who are scheduled to undergo a transcatheter interventional procedure with a large-bore femoral access site for purposes of supporting a PMA approval in the U.S., as well as other global regulatory approvals.

### **3 Risks and Benefits of the Investigational Device and Study**

#### **3.1. Anticipated Clinical Benefits**

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). The MANTA device is expected to provide consistent, immediate hemostasis and to be deployed in less than sixty (60) seconds. The current method(s) of large bore puncture closure involve the use of either multiple suture-based small bore closure devices, or a surgical cut-down to manually suture the artery closed. The use of multiple small bore closure devices is cumbersome and can be unreliable in completely closing a large bore puncture. Similarly, a surgical cut-down, while effective, extends the length of the procedure and carries with it all the inherent risks of surgery. The published literature indicates that use of vascular closure devices, while cumbersome, reduces complication rates compared to surgical repair.[2] The potential benefit of the MANTA device is that the device is custom-designed to close large-bore punctures; if the device is successful at closing these arteriotomies without additional complications compared to the suture-mediated closure devices, the method would be easy to use, simple and reduce complications compared to surgical repair.

#### **3.2. Anticipated Adverse Device Effects**

Use of the MANTA device carries risk from procedural error, inherent use hazards, and device failure. A complete list of anticipated adverse device effects can be found in Section 9.2 - Potential Adverse Events and Adverse Device Effects.

Risks from the clinical study itself are negligible. The only non-standard test required by the study protocol is duplex ultrasound of the femoral artery prior to discharge and at follow-up. Ultrasound is a non-invasive standard diagnostic test that carries almost no risk, apart from the possibility of minimal patient discomfort from the pressure of the transducer. All of the other study procedures are standard of care for interventional peripheral and cardiac procedures.

#### **3.3. Risk Mitigation**

In accordance with ISO 14971:2012, Essential Medical, Inc. has taken measures to ensure the device is designed, manufactured and tested appropriately to mitigate and control these risks through systematic risk analysis, in-process controls and final inspection, labeling, instructions for use, and post-market surveillance. As a result, the residual risk is as low as possible.

#### **3.4. Risk to Benefit Rationale**

The potential benefits of the MANTA device are expected to outweigh the aforementioned mitigated risks and exceed or meet the performance of current treatment methods, and the study itself carries almost no additional risk. Therefore, the clinical study is justified by the risk/benefit ratio.

## 4 Protocol Definitions

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 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 he/she is able to ambulate for at least 20 feet/6 meters without re-bleeding.

Bleeding: Definitions used in conjunction with definitions of Major Vascular Complications and Minor Vascular Complications below. As defined in the VARC-2 Clinical Guidelines [6]:

*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  $\geq 5$  g/dL or whole blood or packed red blood cells (RBCs) transfusion  $\geq 4$  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<sup>2</sup>.

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.

Echymosis: 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: Cessation of common femoral artery bleeding as determined by visual inspection. Cutaneous or subcutaneous oozing that is readily treated by light compression methods (sand bags and light manual pressure) which do not apply sufficient compression of the femoral artery to control arterial bleeding is considered to meet the definition of hemostasis.

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.

Major Vascular Complications: Adapted<sup>1</sup> from the VARC-2 Clinical Guidelines [6]:

- 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

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;

---

<sup>1</sup> 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.

- iv. Access site hematoma that is attributable to failure of or sub-optimal performance of the MANTA device, is  $\geq 10$  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.

**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.

**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

Significant Calcium: Visible calcium on fluoroscopy or CTA.

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 device without the use of unplanned endovascular or surgical intervention.

Time to Ambulation: The elapsed time 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).

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).

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

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.

## 5 Study 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 for purposes of obtaining a PMA approval in the U.S. and supporting other global regulatory submissions. The study will evaluate Time to Hemostasis, Ambulation Success, Time to Ambulation, Technical Success, Treatment Success, Procedure Time, and the percentage of access-site-related complications in comparison to Performance Goals and a Clinical Acceptance Criterion as derived from published literature on other hemostasis techniques for closing these large bore punctures (suture-mediated percutaneous closure [i.e., single or multiple Proglide/Prostar devices]) and based on the clinical judgment of expert advisors. Refer to Appendix 2 for a copy of the Performance Goal rationale (excluding the referenced literature reviews).

The specific study endpoints are:

Primary Safety Endpoint: The percentage of subjects with one or more Major Complications, as defined in Section 4, within 30 days following the procedure.

Primary Effectiveness Endpoint: Mean Time to Hemostasis, as defined in Section 4

Secondary Safety Endpoints: The percentage of subjects with one or more Minor Complications, as defined in Section 4, within 30 days following the procedure; and the percentage of subjects with one or more VARC-2 Major Vascular Complications, as defined in Section 4, within 30 days following the procedure

Secondary Effectiveness Endpoints: Mean Time to Ambulation, mean Procedure Time and percentage of subjects with Technical Success, with Ambulation Success and with Treatment Success, as defined in Section 4.

## **6 Study Design**

### **6.1. General**

A prospective, multi-center, single-arm clinical investigation to evaluate the safety and effectiveness of MANTA in achieving hemostasis in femoral arterial access sites in patients undergoing percutaneous transcatheter interventional procedures using large-bore sheaths or devices. The study will evaluate Time to Hemostasis, Technical Success, Treatment Success, Ambulation Success, Time to Ambulation, Procedure Time, and the rate of access-site-related Major and Minor Complications in comparison to Performance Goals and a Clinical Acceptance Criterion derived from published literature on other hemostasis techniques for closing these large bore punctures (suture-mediated percutaneous closure [i.e. multiple Proglide/Prostar devices]) (see Appendix 2) and based on the clinical judgment of expert advisors. The study will be conducted at a minimum of 5 and up to 25 investigational sites in the U.S., EU and/or Canada.

### **6.2. Minimization of Bias**

Potential for bias during this investigation has been minimized by design of a well-controlled study, expected conduct under the terms of an approved study protocol, use of specific inclusion and exclusion criteria, careful definitions for study procedures and outcomes, use of standardized complication definitions based on published guidelines, use of a CEC/DSMC, and prospectively defined methods of data analysis.

### **6.3. Randomization**

There is no randomization in this investigation.

### **6.4. Subject Replacement**

See Section 6.5.1 below. A total of 263 subjects will be treated to account for up to a 5% loss to follow-up and to ensure a final Analysis Cohort of 250 subjects with 30 days of follow-up (that is, who meet the primary safety endpoint).

### **6.5. Study Population**

#### **6.5.1 Number of Subjects**

The Analysis Cohort will include a minimum of 250 treated subjects, with a minimum of 50% receiving 18F MANTA and the remainder receiving 14F MANTA. The Sponsor will monitor the study with respect to the number of subjects receiving each device to encourage recruitment of a balance of cases. 263 subjects are planned to be treated to account for up to a 5% loss to follow-up prior to the 30-day primary safety endpoint. More than 263 subjects may be consented, as there will certainly be baseline and intra-procedural screen failures.

Additionally, up to 2 roll-in subjects per operator using either MANTA device will be enrolled to allow investigators to learn how to use the MANTA device (the Roll-In Cohort); roll-in data will be analyzed separately from the Analysis Cohort and will not be tested statistically versus the Performance Goals.



### 6.5.2 Inclusion Criteria

Patients who meet all of the following inclusion criteria will be eligible for the study:

1. Candidate for elective or planned (i.e., not emergent or urgent) percutaneous transcatheter interventional procedure via a 10-18F size retrograde common femoral artery approach (i.e., transcatheter aortic valve implantation [TAVI], endovascular aneurysm repair [EVAR], Impella® use)
2. Vessel size would allow for access for the MANTA as determined by baseline CTA: minimum vessel diameter 5mm for the 14F MANTA and 6mm for the 18F MANTA
3. Eligible for sheath removal in the catheterization lab
4. Age  $\geq 21$  years
5. Understand and sign the study specific written informed consent form
6. Able and willing to fulfill the follow-up requirements
7. In the investigator's opinion, patient is suitable for the MANTA vascular closure device, conventional hemostasis techniques and participation in an investigational trial

### 6.5.3 Exclusion Criteria

Patients with any one of following exclusion criteria will NOT be eligible for the study:

#### **Baseline Exclusions:**

1. Known to be pregnant or lactating
2. Immunocompromised or with pre-existing autoimmune disease
3. Systemic infection or a local infection at or near the access site
4. Significant anemia (hemoglobin  $< 10$  g/dL, hematocrit  $< 30\%$ )
5. Morbidly obese or cachectic (BMI  $> 40$  kg/m<sup>2</sup> or  $< 20$  kg/m<sup>2</sup>)
6. Known bleeding disorder including thrombocytopenia (platelet count  $< 100,000$  cells/UL), thrombasthenia, hemophilia, or von Willebrand disease
7. Allergy to bovine materials or any other device material, including collagen and/or collagen products, polyglycolic or polylactic acid, stainless steel or nickel
8. Femoral artery puncture in target groin within the prior 14 days, recent femoral artery puncture in target groin that has not healed appropriately, and/or prior vascular closure device placement in target common femoral artery that the investigator determines may interfere with the MANTA device
9. Common femoral artery with calcium, as determined by baseline CTA, precluding safe access in the opinion of the investigator or severe peripheral vascular disease as evidenced by severe claudication when ambulating  $< 100$  feet, weak or absent pulses in the affected limb, or ABI  $< 0.5$  at rest
10. Previous iliofemoral intervention in region of access site, including but not limited to prior atherectomy, stenting, surgical or grafting procedures in the access area
11. Patients who have undergone use of an intra-aortic balloon pump through the arterial access site within 30 days prior to the baseline evaluation
12. Undergoing therapeutic thrombolysis
13. Patients in whom continuous oral anticoagulation therapy cannot be stopped for the peri-procedural period or patients with INR  $> 1.8$  at the time of the procedure
14. Patient unable to be adequately anti-coagulated for the procedure
15. Patients who are not mobile and are confined to a wheelchair or bed

16. ST-elevation MI within 30 days prior to procedure or acute coronary syndrome (i.e., unstable angina or myocardial infarction)  $\leq$ 48 hours before the catheterization procedure
17. NYHA class IV heart failure
18. Left ventricular ejection fraction  $<$ 20%
19. Unilateral or bilateral lower extremity amputation
20. Renal insufficiency (serum creatinine  $>$ 2.5 mg/dl) or on dialysis therapy
21. Existing nerve damage in the ipsilateral leg
22. Further planned endovascular procedure within the next 30 days
23. Patients who have already participated in the IDE study
24. Currently participating in another clinical trial of an unapproved investigational device or drug that has not concluded the follow-up period
25. Patient cannot adhere to or complete the investigational protocol for any reason including but not limited to geographical residence, psychiatric condition or life threatening disease
26. Common femoral artery  $<$ 5mm in diameter for the 14F MANTA or  $<$ 6 mm in diameter for the 18F MANTA, common femoral artery stenosis resulting in a vessel diameter  $<$ 5mm in diameter for the 14F MANTA or  $<$ 6 mm in diameter for the 18F MANTA, or  $>$ 50% diameter femoral or iliac artery stenosis

**Intra-Procedure Exclusions:**

27. Puncture site in the profunda femoris artery, superficial femoral artery, or at the bifurcation of these arteries
28. Common femoral artery suspected to have experienced a back wall puncture or underwent  $>$  one (1) arterial puncture during the catheterization procedure
29. Difficult dilation from initial femoral artery access (e.g., damaging or kinking dilators) while step dilating up to the large-bore device
30. Presence of ipsilateral femoral venous sheath
31. Puncture site located above the most inferior border of the epigastric artery (IEA) and/or above the inguinal ligament based upon bony landmarks
32. Marked tortuosity of femoral or iliac artery
33. Patient did not receive any antiplatelet or anticoagulant medications before or during the endovascular interventional procedure
34. ACT  $>$ 250 seconds prior to removal of the sheath or interventional device
35. Systolic blood pressure  $>$ 180 mmHg or diastolic blood pressure  $>$ 110 mm Hg, unless systolic or diastolic pressure can be lowered by pharmacological agents prior to closure
36. Antegrade puncture during the index procedure
37. Interventional sheath or device in place  $>$ 6 hours
38. Possible bacterial contamination of the procedure sheath or surrounding tissues during the procedure
39. Intra-procedural complication(s) at the femoral access site pre-sheath removal including: 1. Bleeding or swelling around the large bore sheath that may indicate hematoma formation and/or pseudoaneurysm formation; and 2. Peri-procedural angiographic evidence of thrombus formation or significant injury in the aorta or iliac vessels associated with procedural large bore sheath placement and/or sub-optimal anticoagulation
40. Systolic blood pressure  $<$ 90 mm Hg just prior to planned vascular closure
41. Procedure sheath or interventional device  $>$ 25F outer diameter required during the procedure

#### **6.5.4 Subject Withdrawal or Discontinuation**

An individual subject may be prematurely stopped from study participation at the subject's, investigator's or sponsor's request for the following reasons:

- Adverse event
- Subject is lost-to-follow-up
- Explantation of the device
- Subject voluntarily withdraws
- Subject is withdrawn by the investigator or sponsor
- Death
- Other

Reasons for withdrawal and discontinuation of any subject from the investigation must be recorded on the eCRF. If withdrawal is due to problems of safety or lack of performance, the subject shall be followed up, if possible.

#### **6.5.5 Enrollment**

A subject is considered enrolled in the clinical investigation after he/she has provided written informed consent and has been determined to meet all eligibility criteria, including the intra-procedure exclusion criteria. Patients who fail one or more of the eligibility criteria are screen failures and are not enrolled in the study. The reason for screen failure will be recorded. Subjects who withdraw consent or are exited by the investigator prior to implantation of the MANTA Vascular Closure Device are exited from the study without data acquisition, other than the reason for exit.

#### **6.5.6 Duration of the Study**

The enrollment period is expected to take approximately 8 months. The follow-up period is 60 days post-procedure. Total duration of the study is approximately 10 months.

## 7 Study Procedures

### 7.1. Pre-Screening

Up to 90 days prior to the index procedure visit, the Investigator or his/her designee (e.g., study coordinator) will review the patient's medical record to screen for selected study inclusion and exclusion criteria to determine if the patient is a potential candidate for the study.

### 7.2. Informed Consent

All subjects must provide written informed consent in accordance with the reviewing Institutional Review Board (IRB) or Ethics Committee (EC). The principal investigator at each site is responsible for obtaining informed consent, even if delegated to another study team member, and must retain a copy of the executed consent form for each subject consented.

After being screened as described in Section 7.1 above, the patient will be approached prior to the interventional procedure by a member of the site's clinical team to present the study and, if the patient is willing, to obtain written informed consent. The background of the proposed study and the potential benefits and risks of the procedures and study will be explained to the patient. If the patient agrees, he/she will be required to sign the IRB-approved consent form before continuing with the study screening process. Failure to obtain written informed consent excludes the patient from the study. A notation that the subject consented to participate in the study, including the date and time of consent, must be made in the patient's medical record.

### 7.3. Screening and Baseline Visit Data Collection

Informed consent will be obtained from the subject prior to conducting any study-related activities. Data available in the patient's medical record for standard of care exams and tests may be utilized to fulfill screening and baseline requirements and do not need to be repeated if performed within 30 days prior to the informed consent. Computed Tomography scan with angiography (CTA) may be performed within 180 days prior to informed consent. The laboratory tests listed below are considered standard of care and are to be done within seven (7) days prior to percutaneous interventions or according to the site's standard of care. If seven (7) days is not standard of care, the laboratory tests must be drawn within the timeframe specified by the investigational site's standard practice for pre-procedure labs prior to the interventional procedure.

#### **Computed Tomography Angiography (CTA) Scan**

All subjects must have a high-quality baseline CTA of the aorta, iliac and common femoral vessels. The baseline CTA will be utilized to measure the femoral vessel size at the planned access site. Disease and calcium deposits will also be assessed for size and locations and how they may affect the use of the MANTA closure device with regard to subject exclusion.

#### **Demographics, Medical History, Clinical Exam**

- Demographic data including gender, height, weight, BMI and date of birth
- Medical history and relevant clinical examination, including blood pressure and ipsilateral Ankle/Brachial Index
- STS Adult Cardiac Surgery Risk Score (TAVI cases only)
- List of relevant prescription medications as described in Section 10

### **Laboratory Tests**

- Complete blood count, including hemoglobin, hematocrit, MCV, BUN, creatinine, prothrombin time, partial thromboplastin time, and platelet count
- International normalized ratio (INR) if subject is on warfarin

### **Pregnancy Test**

- Women of child-bearing potential must receive a pregnancy test within **7** days of the index procedure or according to the site's standard of care for interventional procedures involving contrast and angiography; a urine test is acceptable.

If the subject meets any of the exclusions associated with Baseline Tests, he/she will be a screen failure.

## **7.4. Screening and Interventional Procedure Data**

The following tests and other selected assessments will be performed during the index interventional procedure prior to attempted MANTA deployment to confirm that the patient does not meet any of the intra-procedure exclusions (see Section 6.5.3):

### **Angiogram**

All subjects will have an intra-procedural angiographic evaluation of the target (ipsilateral) femoral artery prior to large-bore sheath placement, preferably just after gaining needle access. Confirm that the access site is in the common femoral artery and is centered in the anterior vessel wall. Femoral angiography is a worldwide "Standard of Care" diagnostic test performed during percutaneous transcatheter procedures, such as TAVI.

### **Activated Clotting Time (ACT)**

ACT will be measured and recorded at the end of the interventional procedure just prior to (within 10 minutes of) MANTA deployment.

If the subject meets any of the intra-procedure exclusions, he/she will be a screen failure.

## **7.5. Assignment of Subject Number**

If the subject meets all of the screening requirements described above, he/she will be enrolled in the study and assigned a unique identification number. Subject numbers will be assigned in sequential order via the study EDC system. The subject number will consist of five digits. The first two digits will designate the study site. The last three digits will designate the subject by number in sequential order (i.e., subject number 11-001 will be the first subject at site 11; 11-002 will be the second subject at site 11, etc.). Roll-in subjects will be identified as such through a database entry. The Investigator will maintain a log that links the subject number to his/her identity; this information will not be made available to the Sponsor and will be kept in a safe location.

## **7.6. Procedure**

At the start of the interventional procedure, it is recommended that the operator should access the target (ipsilateral) femoral vessel using angiographic or ultrasound control to ensure precise anterior wall entry placement preferably using micropuncture approach.

### MANTA Vascular Closure System Selection and Use

Select the correct size of MANTA closure device, depending on the size of the femoral sheath or interventional device used for the procedure. 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).

If the subject has two femoral access sites that are 10-18F, only one may be closed with the MANTA device. The other site must be closed according to the site's standard of care. All safety and effectiveness assessments will be made only with respect to the target access site in which the MANTA is attempted/deployed.

Prior to use, refer to the Instructions for Use for a complete description of the indications, contraindications, cautions, precautions, and warnings.

### Arterial Sheath Removal

MANTA treatment requires that the arterial sheath be removed in the catheterization lab as soon as possible after completion of the intervention. Prior to the start of the MANTA procedure, use local anesthetic as needed to re-anesthetize the area around the access site. Perform a careful visual examination of the access site to determine if any intra-procedural exclusions have been met; if so, the patient should be excluded. Time of deployment and adjunctive method(s) used to achieve hemostasis will be documented on the eCRF.

### MANTA Treatment Procedure and Guidelines

The following guidelines are provided for management of the access site during and following the MANTA deployment procedure. It is recommended that Investigators closely adhere to these guidelines; however, specific ambulation and anticoagulation regimes should follow standard hospital procedures and clinician practices.

- (1) After sheath/device removal, perform MANTA deployment procedure in accordance with the instructions for use. Record time of deployment.
- (2) Note any thrombus formation on any of the MANTA components.
- (3) Record time of hemostasis on the MANTA Procedure Form. Refer to section below titled "Monitoring Time to Hemostasis".
- (4) If oozing occurs or hemostasis is not achieved after MANTA deployment, refer to section below titled "Treatment of Oozing/Continued Bleeding".
- (5) Within approximately 10 minutes of MANTA deployment, perform target (ipsilateral) common femoral angiography from the contralateral access site, to evaluate patency into the ipsilateral common femoral artery.
- (6) Assess circulatory status per hospital's standard protocol, including ipsilateral ankle/brachial index.
- (7) The subject's head may be elevated 45° during the bed rest phase as oozing subsides.
- (8) Pressure dressings may be applied.

- (9) The subject's access site should be evaluated every 15 minutes ( $\pm 5$  minutes) for the first hour following access site hemostasis, then according to the site's standard of care. Access site checks will be recorded on the eCRF.

#### Monitoring Time to Hemostasis

Time to Hemostasis is measured from the time the MANTA sheath is withdrawn from the artery until first observed and confirmed arterial hemostasis. As Time to Hemostasis is a primary endpoint for this study, it is critical to measure it accurately. If manual or mechanical compression is required, every attempt should be made to check for hemostasis as frequently as logistically and medically possible to obtain accurate Time to Hemostasis. It is important to declare hemostasis within 1 minute after it is achieved. Time to Hemostasis should be inclusive of any time that manual or mechanical pressure is applied (excluding light digital or mechanical pressure to treat oozing).

The following is a suggested, but not required, method for managing arterial bleeding: If hemostasis is not immediate upon deployment, apply manual pressure and check the access site for hemostasis at approximately one minute increments following sheath withdrawal through 10 minutes, and then at approximately two-minute intervals through 20 minutes, until hemostasis. If hemostasis is not achieved by 20 minutes, the access site should be managed per medical judgement inclusive of use of a contralateral balloon or mechanical compression device. A checking interval of 5 minutes is recommended in these cases if deemed medically appropriate.

#### Treatment of Oozing/Continued Bleeding

- Oozing that is controllable with compression bandages, sand bags or light manual pressure is subcutaneous in origin. Light manual compression may be substituted with light compression applied by a mechanical compression device.
- Bleeding which is not controlled by light manual compression should be controlled by compression of the femoral artery via mechanical or manual compression.
- If necessary, balloon occlusion from the contralateral access site may be performed; such balloon occlusion will not be considered an unplanned intervention.
- Failing these steps, rescue measures may include placement of a stent-graft at the access site or surgical intervention.

### **7.7. Post-Procedure Evaluations**

1. It is recommended that 6 hours after removal of the access sheath, if the femoral access site is suitable for ambulation and if medically indicated, the subject should be asked to stand at bedside.
  - a. If the subject successfully stands with no or minimal oozing, the subject should be asked to walk 20 feet/6 meters. If the subject ambulates successfully, record the ambulation time on the eCRF.
  - b. If the subject is unable to walk 20 feet/6 meters or it is not medically advisable or logistically feasible to attempt ambulation, the subject should remain in bed. Attempt to ambulate the subject when medically indicated. When the subject ambulates successfully, record the ambulation time on the eCRF.
  - c. Lack of an ambulation attempt at 6 hours or ambulation at an earlier or later timepoint will not be considered a protocol deviation.
  - d. Following successful ambulation, the subject should be returned to bed. Perform access site checks per hospital standard of care following successful ambulation.

2. A duplex ultrasound will be performed prior to discharge (but no later than 48 hours post-MANTA deployment) to evaluate femoral blood flow. In addition, any suspected hematoma, pseudoaneurysm or AV fistula at the MANTA site should be confirmed with ultrasound.
3. Ipsilateral ankle/brachial index will be assessed prior to discharge.
4. When the subject is ready for discharge (at a minimum, defined as ability to walk 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), record the date and time of discharge on the eCRF.

### **7.8. Subject Follow-up**

All subjects will undergo a follow-up examination at 30±7 days and at 60±14 days post procedure to assess for any major or minor complications or adverse events. All subjects will be assessed for ipsilateral ankle/brachial index at both follow-up visits. All subjects will undergo a femoral duplex ultrasound exam at the 30-day follow-up. If abnormalities are detected at the 30 day ultrasound based on investigational site review, the test should be repeated at the 60 day assessment.

### **7.9. Ultrasound and Core Lab**

Each site is responsible for performing ultrasound examinations according to the ultrasound Core Laboratory imaging protocol. All ultrasound images will be transferred to and evaluated by a Core Lab. All ultrasound data will be produced by the Core Lab according to standard criteria established by the Core Lab. If necessary for comparison purposes, baseline CTA images will also be provided to the Core Lab for assessment; these will be requested from the investigational sites as needed.

It is the responsibility of each site to perform the local interpretation of the ultrasound examination for clinical assessment. The Core Lab will not be responsible to notify the site of any abnormal findings that are identified in the study. The responsibility of the Core Lab is to complete the data collection forms and submit these to the Sponsor. Data obtained from the core lab readings will be used for study purposes only and not for clinical treatment of the subject. Essential Medical will use only the measurements provided by the Core Lab for analysis. If the Core Lab determines that the data are unreadable, the site will be responsible for having the subject return for another assessment.



## 8 Statistical Methods

### 8.1. Study Hypotheses

#### 8.1.1 Effectiveness

The primary and secondary effectiveness analyses will be performed on both the Primary Analysis dataset (all Analysis Cohort subjects with an attempt to treat and having an assessment of the primary effectiveness parameter) and the Per-Protocol dataset (subjects from the Intent-to-Treat dataset with no major protocol violations). Results based on the Primary Analysis and the Per-Protocol datasets will be presented in the clinical report. Differences between the results will be examined. All primary and secondary effectiveness parameters will be analyzed. Roll-in subjects will be analyzed separately from the Analysis Cohort.

The primary effectiveness hypothesis is that mean Time to Hemostasis is less than the Performance Goal of 10 minutes, as follows:

$H_0: \mu \geq 10$   
vs.  
 $H_A: \mu < 10,$

where  $\mu$  is the population mean Time to Hemostasis.

The secondary endpoints are as follows:

1. Technical Success
2. Ambulation Success
3. Time to Ambulation
4. Treatment Success
5. Procedure Time

Technical Success, Ambulation Success, Time to Ambulation, Treatment Success and Procedure Time will be analyzed and reported but there will be no formal statistical test on these endpoints.

#### 8.1.2 Safety

The primary and secondary safety analyses will be performed on all enrolled study subjects in the Analysis Cohort in whom an attempt to use the device is 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 analysis). In addition all adverse events recorded during the study will be summarized, and severity and relatedness to the device and/or procedure will be reported. Roll-in subjects will be analyzed separately from the Analysis Cohort. The primary safety endpoint is Major Complications, as defined in Section 4.

The primary safety hypothesis is that the Major Complication rate (proportion of subjects with one or more Major Complications) is less than the Performance Goal of 19.9%, as follows:

$H_0: \pi \geq 0.199$   
vs.  
 $H_A: \pi < 0.199,$

where  $\pi$  is the population Major Complication rate.

The secondary safety endpoint is Minor Complications. Minor Complications will be qualitatively assessed against a Clinical Acceptance Criterion of 20%. This CAC will not be statistically tested.

VARC-2 Major Vascular Complications will be reported as another second safety endpoint but will not be statistically tested against a PG or qualitatively assessed against a CAC.

## **8.2. Sample Size Considerations**

The population Time to Hemostasis is assumed to be 6 minutes, with a standard deviation of 11 minutes. Based on these assumptions, 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.

To ensure an adequate sample size of subjects meeting the 30-day primary safety endpoint in case of losses to follow-up (estimated to be 5%), the study will treat a total of 263 subjects.

## **8.3. Data Analysis**

### **8.3.1 Endpoints**

The following Effectiveness Endpoints will be evaluated for the MANTA device, definitions are provided in Section 4 above:

1. Time to Hemostasis (Primary)
2. Technical Success (Secondary)
3. Ambulation Success (Secondary)
4. Time to Ambulation (Secondary)
5. Treatment Success (Secondary)
6. Procedure Time (Secondary)

The following Safety Endpoints will be evaluated for the MANTA device, definitions are provided in Section 4 above:

1. The percentage of subjects with one or more Major Complications within 30 days following procedure (Primary)
2. The percentage of subjects with one or more Minor Complications within 30 days following procedure (Secondary)
3. The percentage of subjects with one or more VARC-2 Major Vascular Complications within 30 days following procedure (Secondary)

### **8.3.2 Interim Analysis**

No formal interim analysis is planned.

### **8.3.3 Final Analysis**

The primary effectiveness endpoint, Time to Hemostasis, will be tested by placing an exact one-sided upper 97.5% confidence bound on the mean Time to Hemostasis. If this upper confidence bound is less than 10 minutes the study will have met its primary effective objective. Time to Hemostasis will not be truncated. In the event that Time to Hemostasis cannot be evaluated because a surgical repair must be performed, Time to Hemostasis for that subject will be imputed using the longest Time to Hemostasis from any subject for whom that datapoint exists. There are no statistical tests of the secondary effectiveness endpoints.

The crude rate of the primary safety endpoint, Major Complications, will be presented as the proportion of subjects with one or more Major Complications, along with its exact one-sided upper 97.5% confidence bound. If a significant number of subjects 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 Armitage. 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.

The secondary safety endpoint, Minor Complications, will be presented as the proportion of subjects with one or more Minor Complications. Minor Complications will be qualitatively assessed against a Clinical Acceptance Criterion of 20%. This CAC will not be statistically tested.

VARC-2 Major Vascular Complications will be reported as another second safety endpoint but will not be statistically tested against a PG or qualitatively assessed against a CAC.

### **8.3.4 Subgroup Analysis**

Subgroup analyses of the primary effectiveness and primary safety endpoints will be performed on the following subgroups.

- Gender
- Race/Ethnicity
- Procedure Type (e.g., TAVI, EVAR, etc.)

Time to Hemostasis will be analyzed by a one-way analysis of variance that includes the effect of the subgroup. 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 will be analyzed by Pearson's chi square to assess if the Major Complication rates differ between the levels of the subgroup. If the subgroup rates 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.

### **8.3.5 Poolability Analysis**

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 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 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.

### **8.3.6 Missing Data**

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 endpoints are missing, the worst value observed for any subject at the same study site will be imputed for the missing value.

## **8.4. *Minimum and Maximum Subject Recruitment for Analysis***

Study enrollment will be competitive. There is no minimum number of subjects that can be enrolled per site. However, no single site will be permitted to enroll more than 20% of the Analysis Cohort enrollment (i.e., 50 treated subjects).

There is also no minimum or maximum number of subjects defined in order to be included in the statistical analysis.

## 9 Adverse Events

### 9.1. Definitions

Refer to Section 4 for the definitions of the following terms associated with adverse events:

- Adverse Event
- Adverse Device Effect
- Device Deficiency
- Serious Adverse Event
- Serious Adverse Device Effect
- Unanticipated Adverse Device Effect
- Unanticipated Serious Adverse Device Effect

### 9.2. Potential Adverse Events and Adverse Device Effects

Potential Adverse Events and Adverse Device Effects associated with any large bore intervention, including the use of the MANTA VCD, include but are not limited to:

- Arterial damage
- Arterio-venous fistula
- Bleeding complications
- Bradycardia
- Closure device failure (lack of hemostasis)
- Compartment syndrome
- Death related to the procedure
- Deep vein thrombosis
- Dissection
- Ecchymosis
- Embolization
- Hematoma
- Infection at the puncture site which may require antibiotics or extended hospitalization
- Late arterial bleeding
- Limb ischemia
- Nerve injury or neuropathy
- Perforation
- Pressure in groin/access site region
- Pseudoaneurysm
- Retroperitoneal bleed
- Stenosis
- Transfusion due to blood loss resulting from the femoral arteriotomy procedure, or vascular repair
- Thrombus formation
- Ultrasound guided compression
- Vascular occlusion or repair
- Vessel laceration or trauma
- Wound dehiscence

### **9.3. Relationship of Adverse Event to Device/Procedure**

Each reported AE will be assessed by the Investigator for its primary suspected relationship to the closure device or to the interventional procedure.

- MANTA Study AEs related to the interventional procedure (e.g., TAVI, EVAR procedure) or closure of a non-target access site are considered Procedure-Related AEs.
- MANTA Study AEs related to the MANTA closure device and/or its deployment (in total, the closure procedure) are considered Device-Related AEs.
- MANTA Study AEs that are related to neither the interventional procedure nor the MANTA device 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: An AE which cannot be attributed to the study device or initial study procedure.
- 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.

### **9.4. Severity of Adverse Events**

The following categories will be used to describe the severity of an AE:

- 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.

### **9.5. Reporting of Adverse Events**

#### **9.5.1 SAE and AE Reporting to Sponsor**

All SAEs, irrespective of potential causal relationship to the device, procedure or study, that occur from the point of attempted MANTA placement onwards will be reported to the Sponsor within 24 hours of the Investigator’s first knowledge of the event. Suspected SAEs also should be reported.

The Investigator will forward information, via the eCRF system, about an SAE promptly, even if the information is incomplete or it is obvious that more data will be needed to form any

conclusions. This information will be available to the sponsor and CRO in the database. Additional information regarding the SAE will be recorded on the follow-up AE form forwarded to the Sponsor.

All AEs should be reported on the eCRF as soon as practicably possible. AEs will be recorded by their final medical diagnosis and not by each separate symptom. All AEs categorized by the Investigator as associated with the target artery and/or the ipsilateral leg, and all contralateral access site and systemic AEs categorized by the Investigator as possibly, probably or definitely device-related, will be reviewed by the Clinical Events Committee for a final adjudication. The information for the event will include the date of onset and resolution, the action taken, the corrective treatment and how the subject recovered with or without sequelae. In case of death, the relationship of death to the investigational device and/or the study procedure will be well documented. The date on which subject expired, what attempts were made to treat the event that led to death, the performance and functioning of the device during the event will be noted.

### **9.5.2 SAE Reporting to IRB and FDA – US**

The Investigator is responsible for reporting SAEs, in the required timeframe, to his/her IRB as required by the IRB.

The Sponsor is responsible for reporting UADEs to the U.S FDA in accordance with the IDE regulations (21 CFR Part 812). The results of any UADE evaluation will be reported to FDA and all reviewing IRBs and participating investigators within 10 working days after receiving notice of the UADE, per 812.150(b)(1).

The Sponsor will notify device-related SAE information to all active study Investigators as it becomes available.

### **9.5.3 SAE Reporting to EC and CA – EU**

As the MANTA device is CE-marked, device-related AEs and SAEs will be recorded by the Sponsor as complaints, in accordance with the Sponsor's Quality System. Such complaints will be analyzed to determine if vigilance reporting is required and any required vigilance reports filed in accordance with EU medical device vigilance requirements. AEs and SAEs that are not device-related will be handled only within the clinical study database and will not be reported as complaints.

### **9.5.4 SAE Reporting to IRB and CA – Canada**

The Investigator is responsible for reporting SAEs, in the required timeframe, to his/her IRB as required by the IRB. The investigator is also responsible for notifying Health Canada of any events that meet the definition of an "incident" under the Canadian Medical Device Problem Reporting requirements.

The Sponsor is responsible for reporting device-related incidents to Health Canada in accordance with the Canadian Medical Device Problem Reporting requirements.

### **9.6. Device Deficiencies**

The Investigator will record any device deficiencies, as defined in Section 4, in the eCRF. A device deficiency has occurred if an investigational device used in the study procedure failed to meet its performance specifications whether due to mechanical failure, malfunction or defects. Device deficiencies also include use errors and inadequate labeling. This applies to:

- devices used in the subject; or
- devices in which the package was opened, but the device was not used on the subject; or
- devices with which at least one insertion attempt was made, but the device did not remain in the subject.

If the device deficiency was associated with an AE, the reporting provisions for AE, ADE, SAE, SADE, UADE and USADE as outlined in above apply. Any device deficiency that did not lead to an AE but could have led to a SADE, if suitable action had not been taken, if intervention had not been made, or if circumstances had been less fortunate, must be reported to the Sponsor within 24 hours of the event using the eCRF. Reporting will follow the guidelines above. All device deficiencies will be recorded on the eCRF. Device deficiencies which could not have led to a SADE must be reported to the Sponsor within 3 business days. All devices alleged to be deficient must be returned to the Sponsor within 5 business days.

### **9.7. Clinical Events Committee (CEC)**

An independent Clinical Events Committee (CEC) will be established for this study. The CEC will have at least two members who are qualified to review adverse event data from this study. The CEC will be established and operate according to a charter defined prior to the initiation of the trial. The CEC (Baim Institute) 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.

For each AE reviewed, the CEC may adjudicate its device-relatedness. 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.

### **9.8. Data & Safety Monitoring Committee (DSMC)**

A Data and 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: a statistician, an interventional cardiologist and a vascular surgeon; the latter two members must have extensive experience with large-bore cardiovascular interventions. 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, either by phone or face-to-face, at least 2 times during the study in order to assure close and timely monitoring of adverse events and outcomes.

## 10 Medication

There are no prohibited medications for this clinical investigation.

Only the following medications will be recorded on the eCRF: cardiovascular medications (e.g., anti-hypertensives, anti-arrhythmics, etc.), anti-coagulants, anti-thrombotics and anti-platelets. This includes such medications being taken at baseline through 60-day follow-up, inclusive of medications given in the cath lab.

For these medications, the following information will be recorded:

- Name of medication
- Indication
- Being taken prior to study enrollment (Yes/No)
- Being taken due to study adverse event (Yes/No)
- Ongoing at study end (yes or no)

## **11 Vulnerable Population**

The intended patient population of this clinical investigation does not meet the criteria of vulnerable population as defined in ISO 14155, Section 3.44.

## **12 Data Management**

### **12.1. Case Report Forms**

The Investigator is responsible for ensuring the completeness and accuracy of all study documentation, including the eCRFs. All clinical study data must be reported on electronic case report forms (eCRF) provided by the Sponsor.

The investigator must review, and electronically sign off the eCRFs as indicated on the form; these responsibilities cannot be delegated to another person. It is the investigator's responsibility to comply with regulatory requirements including, but not limited to, the maintenance of accurate, complete and current records relating to the eCRFs.

Queries may be generated by the data management department of the CRO or by the monitor during a monitoring visit directly in the eCRF. In general, queries should be resolved by making additions or corrections to the eCRF.

### **12.2. Data Management**

The CRO's monitors will review the data against the original source documents and ensure any noted discrepancies are resolved by the investigational site. Subject data will be compared to information originally recorded on source documents related to the trial (i.e. professional notes, laboratory reports, investigation-specific worksheets, etc.).

All information collected in the eCRFs will be entered directly into a secure database. The database design and installation will be validated prior to use.

The details of data review, database cleaning and data querying are described in a Data Management Plan (DMP). This plan may be updated throughout the investigation as amended data management requirements and investigation-specific data conventions are determined.

A comprehensive eCRF Completion Guideline for participating investigational sites will be developed to describe general instructions on eCRF completion.

Data entered by investigational sites will be reviewed on an ongoing basis to ensure adequate query resolution and identify and query adverse events, protocol deviations, and any other ambiguous data points.

### **12.3. Data Retention**

Record retention period will be determined by country and/or site-specific requirements. At a minimum, records must be retained for at least 2 years beyond the date of PMA approval of the MANTA device or 2 years beyond the termination of this study, in the case of the Sponsor's decision not to pursue a PMA.

### **12.4. Other Aspects of Clinical Quality Assurance**

The study will be conducted and monitored by the CRO under the sponsorship of Essential Medical, Inc. (see next section).

The Sponsor, or the Sponsor's representative, may conduct audits at the investigational sites. Audits may include, but are not limited to, device supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. The investigator agrees to participate with audits conducted at a reasonable time, in a reasonable manner.

The U.S. Food and Drug Administration may inspect investigational sites if warranted. The EU and Canadian ECs and competent authorities may also audit investigational sites that are involved in this study.

## **13 Clinical Monitoring**

### **13.1 Clinical Research Organization**

Study monitoring functions will be performed by clinical monitors from a qualified independent clinical research organization (CRO) in compliance with recognized applicable U.S. regulations (21 CFR Part 812 [Investigational Device Exemptions], 21 CFR Part 50 [Protection of Human Subjects] and 21 CFR Part 56 [Institutional Review Boards]), Good Clinical Practice, ISO 14155:2011 and recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964. The CRO will oversee progress of the investigation and work with research coordinators to ensure adherence to the study protocol and informed patient consent obligations.

### **13.2 Monitoring**

The Sponsor/CRO has responsibility for performing site visits prior to the start of and during the study to monitor data collection forms for accuracy and completion and for verifying the report of any adverse events. The monitor will also review the site device inventory, storage conditions and device dispensing records to verify device accountability.

On-site monitoring visits include a pre-study visit, periodic visits, and a final visit at the close of the study.

The pre-study visit is intended to review the Investigational Plan with the investigator and to assure that the investigator has:

- Appropriate training, facilities, patient load, time, and willingness to comply with study requirements.
- Approval of the IRB for the Investigational Plan.
- All study documentation and required records on site.
- Assumed responsibility for the investigation at her/his center.

Periodic visits are intended to assess:

- Investigator's adherence to the Investigational Plan.
- Maintenance and tracking of records, reports and investigational devices.
- Source documents for accuracy, completeness, and legibility.

During these periodic visits, the monitor is required to: 1) assess the progress of the study toward meeting study objectives, 2) identify any concerns that stem from observations of device performance and/or review of the investigator's subject records, 3) review study management and informed consent documents, and 4) ensure accountability of all investigational devices and subjects that have been treated under the study. The monitor's final on-site visit at completion of the study is intended to assure that all the data and investigational devices have been properly collected and to have a closing meeting with the investigator and her/his staff members.

Reports of the on-site visits will be made by the monitor and should include resolution of concerns, completion of appropriate follow-up activities, completion of assigned tasks, and any necessary corrective actions. At the close of the study, the monitor will prepare a final monitoring report.

### **13.3 Initial Procedures**

The monitor and/or company representatives may attend the initial procedures utilizing the device to provide assistance with device training, study management issues, including compliance with credentialing, study documentation, product inventory, and specific record keeping and reporting requirements. A data review with the investigator by the study monitor will be held after a few initial procedures to assure adherence to the study protocol.

### **13.4 Review of Study Documents**

The monitor will review completed data forms and study documentation for accuracy, completeness, and protocol compliance. The following documents will be audited:

- (1) Investigator Agreement signed by the investigator, indicating his/her agreement to participate in the investigation and willingness to comply with all study requirements.
- (2) Case Report Forms will be reviewed for errors, omissions, internal consistency, and signature and dates in the appropriate sections. The monitor will assume responsibility for any follow-up activities that result from review of these forms. Subject informed consent documents will be reviewed for completeness.
- (3) Study Monitor Reports, including pre-study visits, initial procedure visits, on-site visits or final visits reports, submitted by a monitor-designate will be reviewed by the monitor. The monitor will assume responsibility for any corrective action.
- (4) Study Master File, including initial and ongoing IRB approvals, will be reviewed for completeness and updated as necessary. Study Master File will contain all study documents and correspondences.
- (5) Source Documents will be reviewed and compared against electronic case report forms to ensure the accuracy of the eCRFs. Source documents will also be reviewed for adverse events not reported by the investigators.

### **13.5 Device Accountability**

The Sponsor will supply each Investigator with an adequate number of investigational devices for completion of the study. The study devices may only be used for subjects enrolled into this study under the supervision of the Investigator and under the terms of the clinical protocol. The Investigator may not provide the devices to any person not authorized to use it. The Investigator will also ensure that the device components are maintained under secure storage and that the device accountability record is maintained. When instructed by the sponsor, the investigator will return any remaining devices to the sponsor. Device accountability will be checked at routine monitoring visits. This will include:

- product code
- lot number
- receipt dates
- dates and quantities dispensed including subject number
- return date to the Sponsor or destruction date (if any)

All mechanical failures, malfunctions and defects of the MANTA VCD will be recorded on the eCRF and should be reported to the Sponsor. Do not dispose of any device that malfunctions. Any used devices that have malfunctioned should be treated as biohazardous; investigational

sites will be provided with specific instructions and supplies for returning such devices. Devices may not be re-sterilized and reused. The following will be reported:

- All situations where the device physically deforms or breaks even if caused by user error.
- All situations where the device fails to move or perform as it was intended to function according to the instructions for use.
- All situations where the device is physically defective.



## **14 Protocol Deviations and Amendments**

### **14.1. Protocol Adherence and Deviations**

The study will be conducted as described in this protocol. Investigators are not permitted to deviate from this protocol except to protect the subject's rights, safety or well-being. Any deviations from this protocol must be documented by the Investigator. If an emergency situation arises in which the rights, safety or well-being of a subject may require immediate alternative intervention, the Investigator should act in the best interests of the subject. Sponsor and the site's IRB/EC must be notified immediately if this occurs. This should be followed with written confirmation that describes the emergency action and outcomes to Sponsor and the IRB/EC within 10 working days. Protocol deviations will be reviewed during monitoring visits; as appropriate, Investigators will be required to identify corrective and preventive actions to prevent further deviations. An Investigator may be disqualified from the study for repeated and/or egregious protocol deviations.

This protocol may be amended as necessary by the Sponsor. Any protocol amendments will be documented via an incremented version of this protocol with the relevant revision history. Amendments to the protocol must undergo the same approval process by the Sponsor, Investigators, IRB/ECs and regulatory authorities as the original protocol.

### **14.2. Corrective and Preventive Actions**

The Sponsor or its representatives will evaluate protocol deviations during monitoring visits. Individual event corrective and preventive actions may be recommended at that time. In addition, deviations occurring across investigational sites will be reviewed by the Sponsor on a periodic basis to determine if more global preventive actions may be required.

### **14.3. Investigator Disqualification Criteria**

The Sponsor reserves the right to terminate an investigator/investigational site for any of the following reasons:

- Failure to secure subject informed consent, including protection of personal data, prior to enrollment.
- Failure to report safety events within 24 hours of discovery to the Sponsor after learning of the event.
- Failure to report serious adverse device effects within 24 hours of discovery.
- Repeated investigational plan deviations.
- Repeated failure to appropriately complete eCRFs.
- Failure to enroll an adequate number of subjects.
- Loss of or unaccounted for investigational product inventory.

## **15 Statements of Compliance**

This clinical investigation will be conducted in compliance with the principles that have their origin in the latest version of the Declaration of Helsinki; this clinical investigation plan; U.S. 21 CFR Parts 50, 56 and 812; requirements of the approving IRBs/EC and competent authorities, including the U.S. FDA; ISO 14155:2011; the EU Medical Devices Directive 93/42/EEC Annex X – Clinical Evaluation; and other applicable regulatory requirements, whichever provides the greater protection of the individual.

This clinical investigation will not be initiated until approval has been obtained from the IRB/EC and the regulating competent authority at each site. Any additional requirements imposed by the IRB/EC or regulatory authority will be followed. No changes to the protocol will be implemented without the prior review and approval of the IRB/EC and the regulatory authority.

This protocol conforms to all the standards of Medicare coverage requirements. The MANTA subject characteristics are consistent with the Medicare population, and the results are expected to be generalizable to the Medicare population.

## **16 Publication Policy**

### **16.1. *Publication by Essential Medical, Inc.***

Essential Medical, Inc. may at any time publish the results of and information pertaining to the investigation subject only to compliance with regulatory requirements pertaining to subject protected health information.

### **16.2. *Publication by Investigational Sites***

The conditions under which an investigator may publish results from this clinical investigation in any form are defined in detail in the clinical trial agreement.

## 17 References

1. Abbott Vascular international labeling:  
<http://www.abbottvascular.com/int/products/vessel-closure/perclose-proglide.html>;  
<http://www.abbottvascular.com/int/products/vessel-closure/prostar-xl.html>
2. Refer to Essential Medical MANTA Literature Review, version 1.1.
3. Ben-Dor I, Looser P, Bernardo N, Maluenda G, Torguson R, Xue Z, Lindsay J, Pichard AD, Satler LF, Waksman R. Comparison of closure strategies after balloon aortic valvuloplasty: suture mediated versus collagen based versus manual Catheter Cardiovasc Interv. 2011 Jul 1 ;78(1 ):119-24.
4. Nelson PR, Kracjer Z, Kansal N, Rao V, Bianchi C, Hashemi H, Jones P, Bacharach JM. A multicenter, randomized, controlled trial of totally percutaneous access versus open femoral exposure for endovascular aortic aneurysm repair (the PEVAR trial). J Vasc Surg. 2014 May;59(5):1181-93.
5. Kadakia MB, Herrmann HC, Desai ND, Fox Z, Ogbara J, Anwaruddin S, Jagasia D, Bavaria JE, Szeto WY, Vallabhajosyula P, Li R, Menon R, Kobrin DM, Giri J. Factors associated with vascular complications in patients undergoing balloon-expandable transfemoral transcatheter aortic valve replacement via open versus percutaneous approaches. Circ Cardiovasc Interv. 2014 Aug;7(4):570-6.
6. 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.