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

NCT Number: NCT03330002

Document Date: September 26, 2019

CLINICAL REGISTRY STUDY

Title:	Post-Market Clinical Registry to Evaluate the Safety and Performance of MANTA Vascular Closure Device Under Real World Conditions in the European Union
Short Title	MARVEL - "**MA**nta **R**egistry for **V**ascular Large-bor**E** C**L**osure"
Protocol Number:	PSD-212
Device:	MANTA 14F and 18F Vascular Closure Devices
Study Type:	International, multi-center prospective post-market registry
Date:	September 26, 2019
Version:	C
Sponsor:	Essential Medical, Inc., a wholly owned subsidiary of Teleflex, Inc. 260 Sierra Drive Suite 120 Exton, PA 19341, U.S.A.
Sponsor Contact:	Darra Bigelow Clinical Trial Manager Telephone: +1 610 331 7299 Email: darra.bigelow@teleflex.com
European Authorized Representative:	MedPass SAS 95b Boulevard Pereire 75017 – Paris France

This protocol has been prepared in compliance with 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 Ethics Committee or Institutional Review Board.

Agreed to by Investigator:

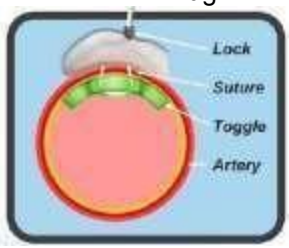
Principal Investigator	Date
Principal Investigator (print)	

Agreed to by Sponsor:

Chris Buller	09-27-2019
Chris Buller, MD Medical Director, Interventional Sponsor – Teleflex, Inc.	Date

Protocol Synopsis

Protocol Element	Details
Title	Post-Market Clinical Registry to Evaluate the Safety and Performance of MANTA Vascular Closure Device Under Real World Conditions in European Union.
Short Title	MARVEL - “MAnta Registry for Vascular Large-borE CLosure”
Protocol ID	PSD-212
Conformité Européene (European Conformity)	MANTA Vascular Closure Device 18-July-2016 BSI NL Certificate No. CE 650543
Device	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).
Trial Type	Post market observational
Clinical Design	Prospective, international, multi-center, observational, non-randomized study
Clinical Registry Purpose	The aim of this observational post market study is to compile real world outcome data on the use of the CE marked MANTA Vascular Closure Device following percutaneous cardiac or peripheral procedures for large bore (10-18F ID) interventional devices. This study also fulfills EU regulatory requirements for post-market clinical follow-up.
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). Procedures include transfemoral TAVI, EVAR and TEVAR; however all participants must meet indications for use and contra-indications as described in the Instructions for Use and sites must adhere to registry requirements.
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.

Protocol Element	Details	
Device Illustration	MANTA Plug 	MANTA Handle 
Number of Subjects	Up to 500 patients implanted with MANTA VCD which will consist of 2 cohorts. • Cohort 1 restricted to TAVI procedures (T Group) - T Group will require CT at baseline and femoral angiogram post-MANTA deployment. • Cohort 2 includes all other on-label CE-marked medical devices in accordance with MANTA device IFU excluding TAVI procedures (NT Group) - such as mechanical circulatory support (MCS), EVAR and TEVAR procedures. ET Group does not require MSCT at baseline or invasive angiography post-MANTA deployment.	
Location of Sites	Experienced sites in EU and Canada currently implanting the MANTA VCD, signed off by local MANTA distributors or Sponsor Geography may include: Switzerland, Netherlands, Finland, Denmark, Sweden, Norway, Canada and the United States with any sites that meet the experience and interest requirement. The registry may include up to 20 participating sites.	
User Experience	Individual operators with 10 or greater MANTA implants signed off by local distributors or Sponsor.	
Duration of the Registry	Approximately 6-18 months for enrollment. A subset of 100-120 patients will undergo follow-up at 12M post-procedure. Approximately 36 months for entire duration of study.	
Device	14F and 18F MANTA Vascular Closure Devices	
Primary Objectives	1. Major and Minor access site related Complications (as described below): within 30 days of procedure. Adapted from the VARC-2 definitions 1: Major femoral vascular complications: Femoral access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) leading to death, life-threatening or major bleeding; OR, downstream distal embolization (lower extremities) requiring surgery or resulting in amputation; OR, the use of unplanned endovascular or surgical intervention associated with death, major femoral bleeding; OR, any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased	

[1] Kappetein AP, Head SJ, Généreux P et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: The Valve Academic Research Consortium-2 consensus document. J Thorac Cardiovasc Surg

2013;145:6-23.

Protocol Element	Details
	or absent blood flow on lower extremity angiogram; OR, surgery for femoral access site-related nerve injury; OR, permanent femoral access site-related nerve injury. Minor femoral vascular complications: Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneuysms, hematomas, percutaneous closure device failure) not leading to death, life-threatening or major bleeding; OR, downstream distal embolization (lower extremities) treated with embolectomy and/or thrombectomy and not resulting in amputation; OR, any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication; OR, vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft); OR, percutaneous closure device failure*. *Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning). 2. 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).
Clinical Visits/Testing	▪ Baseline evaluation: Informed consent, history and physical, CT Angiographic Scan ▪ Index Procedure: Adverse Events ▪ Pre-MANTA Closure Procedure: Target Femoral Access Site Visual Assessment ▪ MANTA Closure Procedure: ACT/Systolic Blood Pressure ▪ Post-MANTA Closure Procedure: Femoral Angiography, Target Femoral Access Site Visual Assessment, Time to Hemostasis, Adverse Events ▪ Post procedure: Target Femoral Access Site Visual Assessment, Adverse Events ▪ Discharge: Target Femoral Access Site Visual Assessment, Time to Ambulation, Adverse Events ▪ 30D (+/- 7 days): Clinical Exam, Target Femoral Access Site Visual Assessment, Adverse Events • 30 Day Follow-Up may be done via phone if not SOC/ per site SOC timing (6 weeks) ▪ 12M (+/- 30 days): Clinical Exam, Target Femoral Access Site Visual Assessment, Adverse Events (subset only)
Indications	1. The 14F MANTA is indicated for closure of femoral arterial access sites following the use of 10-14F devices or sheaths (maximum OD/profile of 18F) 2. The 18F MANTA device is indicated for closure of femoral arterial access sites following the use of 15-18F devices or sheaths (maximum OD/profile of 25F).

Contraindications	1. Severe calcification of the access vessel. 2. Severe peripheral artery disease. 3. Puncture in the origin of the profundal femoral artery. 4. Sheath insertion in vessel other than the femoral artery. 5. Marked tortuosity of the femoral or iliac artery. 6. Marked obesity or Cachexia (BMI >40 or <20). 7. Blood pressure > 180 mmHg.

Protocol Element	Details
Statistical Analysis:	Statistical analysis will consist of descriptive statistics using standard methods, such as mean, standard deviation, minimum/maximum, proportions, counts, etc. Data will be qualitatively compared to VARC-2 endpoints in the literature.

Schedule of Assessments

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

1. Medications (only Aspirin, Clopidogrel, Vitamin K Antagonists and, NOAC"s: [eloxaban, rivaroxaban, dabigatran, apixaban] will be collected)
2. Screening Visit CT Scan to assess both limbs for presence/absence of calcium, atherosclerotic disease, tortuosity, and acceptable flow rates.
3. Prior to MANTA closure, record ACT and systolic BP (per contraindications BP<180; recommend ACT below 250 seconds prior to closure)
4. Post-MANTA closure, perform target (ipsilateral) common femoral angiography from contralateral access site to ensure patency into the ipsilateral common femoral artery
   * #2 CT Angiographic Scan and #4 Post MANTA femoral angiogram are required in cohort 1
5. A subset of study enrollment, 100-120 subjects at up to 7 sites, will complete the 12M follow-up visit.

Abbreviations/Acronyms

Abbreviation/ Acronym	Definition
ACT	Activated clotting time
ADE	Adverse device effect
AE	Adverse event
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
EC	Ethics committee
CRF	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
ID	Inner diameter
INR	International normalized ratio
IRB	Institutional review board
ISO	International Organization for Standardization

MCS	Mechanical Circulatory Support
NT Group	Non-TAVI Cohort
OD	Outer diameter
PG	Performance goal
PMA	Pre-market approval
SAE	Serious adverse event
SADE	Serious adverse device effect
SOC	Standard of care
SOPs	Standard operating procedures
T Group	TAVI Only Cohort
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	14 Nov 2017	Initial Release
B	13 Aug 2019	• Include 12M follow-up visit for 100-120 out of the 500 total enrolled subjects. • 30D follow-up window clarification per site SOC • Include site selection criteria for 12M visit and minimization of bias • Updated study duration timeline • Updated Schedule of Assessments to include 12M follow-up procedures • Clarified definition of adverse event (AE) • Clarified AE adjudication for 12M • General administrative updates
C	26 Sep 2019	• Updated study duration timeline and location of sites • Included Canadian sites to site selection criteria for 12M visit • Updated number of sites criteria for 12M visit • Clarified adverse event (AE)/ serious adverse event (SAE) terminology under reporting SAE/AE for this study • General administrative updates

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1. Introduction

1.1 Large Bore Vascular Interventions

Closure of large bore (10-24F) arteriotomies after interventional procedures (e.g., transcatheter aortic valve replacement, endovascular aneurysm repair, implantation of a percutaneous left ventricular assist device, etc.) continues to be 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 have been reported at up to 20%. [1]

1.2 MANTA Large Bore Vascular Closure Device

The MANTA VCD is innovative in that it is specifically designed to close large bore (10-18F) 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.

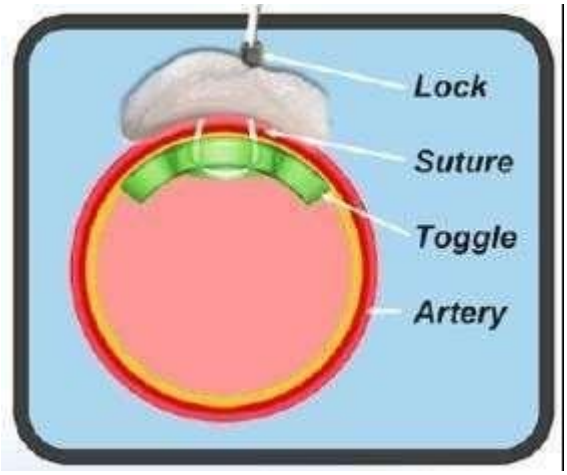

Figure 1: Illustration of the MANTA Vascular Closure Device

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 Clinical Experience

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

First in Human (FIH) Trial (November 2014-July 2015, Asuncion, Paraguay):

18F FIH Cohort
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 for an example post-procedure Doppler ultrasound and image of the access site, see Figure 2 below. 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 Cohort
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

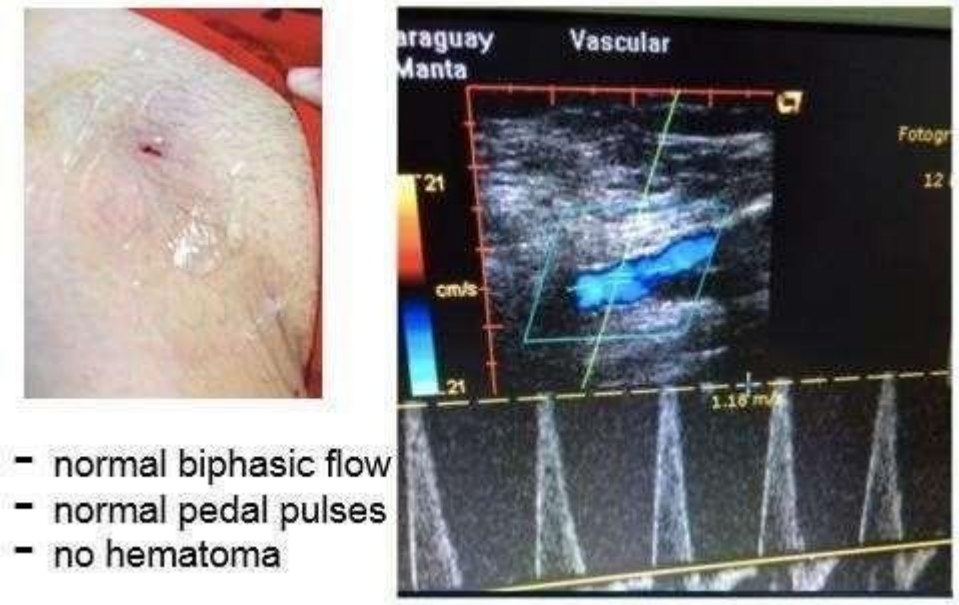

Figure 2: FIH Puncture Site and Duplex Ultrasound Photos

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 ± 8.3 years, mean weight was 75.4 ± 15.6 kg, mean height was 164.1 ± 10.0 cm, and mean Body Mass Index was 27.8 ± 4.4 kg/m^2.

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 ± 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 [2], 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 ± 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 ≤ 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 stenosis 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^2. 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.

Pivotal Clinical Study to Evaluate the Safety and Effectiveness of MANTA Vascular Closure Device:
The purpose of this study is 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. A total of 341 subjects were enrolled in the study and follow-up is now complete. Study was closed in December 2017. The study met its endpoints. U.S. PMA approval for the MANTA device was received, on the basis of this Pivotal Study, in February 2019.

1.5 Study Rationale

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

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.

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

The Legal Manufacturer of the MANTA vascular closure device is:
Essential Medical, Inc.
260 Sierra Drive, Suite 120
Exton, PA 19341, U.S.A.

1.8 Regulatory Classification

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 registry is adequate experience with large-bore interventions and the MANTA VCD, commitment to safety, and consistency in adherence to the clinical protocol. Prior to performing the MANTA procedures for this registry, 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 must have personally performed at least 10 MANTA implants and 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 (e.g., local distributor).

Prior to performing the MANTA procedures for this registry, training materials will be reviewed with each Investigator and clinical coordinator. The study protocol, appropriate patient selection and enrollment will be reviewed.

Up to seven sites will be asked to participate in the 12M follow-up visit. Sites who will be invited to participate in the 12M subset will be selected based on number of subjects enrolled, study staff support and SOC procedures at site regarding 12-month follow-up post-procedure. The qualification process of site selection for the 12M subset will begin with the highest enrolling site(s). Other factors taken into consideration for site selection are availability of study staff support and standard of care procedures done at the 12-month visit. Sites selected for the 12M follow-up visit will be considered from all actively participating sites who enrolled subjects .

2. Justification of the Design of the Registry Study

The First in Human study in Paraguay and the EU Pre-Market Clinical Study in the Netherlands and Italy demonstrated that the MANTA VCD is safe and has excellent performance in achieving hemostasis. Due to the favorable feasibility and safety results of these studies, the MANTA VCD was CE marked in 2016. Over 1,000 MANTA large bore vascular closure devices have been successfully deployed globally; however, there has been limited data collection on the performance of the device under real world conditions.

3. Risks and Benefits of the Device and Registry Study

3.1. Anticipated Clinical Benefits

For subjects undergoing procedures requiring large bore sheaths (10-18 F), the potential benefit is that the MANTA device has been successful at closing these arteriotomies without additional complications compared to the suture-mediated closure devices. The method is simple and easy to use and it reduces 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 - Anticipated Adverse Events and Adverse Device Effects.

Risks from the registry itself are negligible. All of the registry 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 no additional risk. Therefore, the registry 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 medical device. For the purpose of this protocol, AEs to be recorded include AEs associated with the MANTA device, AEs related to the non-MANTA access site, and additional outcomes either associated or not associated with the MANTA device. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to devices. For the subjects followed up at 12M, only AEs related to the MANTA access site or the ipsilateral leg will be collected.

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

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

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

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

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

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

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

- Femoral access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) leading to death, life-threatening or major bleeding; OR,
- Downstream distal embolization (lower extremities) requiring surgery or resulting in amputation; OR,
- The use of unplanned endovascular or surgical intervention associated with death, major femoral bleeding; OR,
- Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram; OR,
- Surgery for femoral access site-related nerve injury; OR,
- Permanent femoral access site-related nerve injury (lasting>30 days).

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

- Femoral access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneuysms, hematomas, percutaneous closure device failure) not leading to death, life-threatening or major bleeding; OR,
- Downstream distal embolization (lower extremities) treated with embolectomy and/or thrombectomy and not resulting in amputation; OR,
- Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication; OR,
- Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft); OR,
- Percutaneous closure device failure*; OR,
- Any other adverse event that is definitely or probably device-related or access-site related.

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

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

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

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

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

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

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

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

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

Severe Peripheral Vascular Disease: Any of the following:

- Severe claudication when ambulating <30 meters
- Weak or absent pulses in the affected limb
- Known stenosis >50% in the iliac or femoral artery on the affected side
- Prior vascular bypass surgery involving the affected femoral artery

Significant Calcium: Visible calcium on fluoroscopy or CTA.

Document calcium on MFACS scale (MFACS is not exclusionary)

- Manta Femoral Artery Calcification Score (MFACS)
  - 0 - No calcification
  - 1 - Minor calcification
  - 2 – Moderate anterior and posterior wall calcification
  - 3 – Significant posterior wall calcification
  - 4 – Significant anterior wall calcification
  - 5 – Circumferential wall calcification

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

Time to Ambulation: The elapsed time between post-MANTA deployment (time suture cut away from body) and when ambulation is achieved (patient standing and walking at least 6 meters without re-bleeding).

Time to Hemostasis: The elapsed time between MANTA deployment (withdrawal of sheath from artery) and first observed and confirmed arterial hemostasis (no or minimal subcutaneous oozing and the absence of expanding or developing hematoma).

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

Procedure Success: A patient will be considered a Procedure Success if he/she has **no** Major Complications (as defined above).

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 following Performance Endpoints will be evaluated for the MANTA device (definitions are provided in Section 4):

1. Time to Hemostasis (Primary)

The following Safety Endpoints will be evaluated for the MANTA device (definitions are provided in Section):

1. The percentage of patients with one or more VARC-2 Major femoral vascular complications within 30±7 days following procedure (Primary)
2. The percentage of patients with one or more VARC-2 Minor femoral vascular complications within 30±7 days following procedure (Secondary)

6. Study Design

6.1. General

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

6.2. Minimization of bias

Potential for bias during this registry has been minimized by design of a well-controlled registry, expected conduct under the terms of an approved study protocol, use of specific device indications and contraindications per IFU, careful definitions for study procedures and outcomes and prospectively defined methods of data analysis.

6.3. Randomization

There is no randomization in this investigation.

6.4. Subject Replacement

Only patients who exit the study before device implantation will be replaced by new subjects. Up to 500 subjects will receive the MANTA vascular closure device. Patients that exit the study after implantation but before study completion will not be replaced by new patients.

6.5. Study Population

6.5.1 Number of Subjects

Up to 500 subjects will receive 14F MANTA or 18F MANTA. The registry will consist of 2 cohorts; cohort 1 will be restricted to TAVI procedures only (with a mandatory CT at baseline and angiogram performed post MANTA closure); cohort 2 will include all other on-label CE-marked medical devices in accordance with MANTA device IFU excluding TAVI procedures.

6.5.2 MANTA Device Indications

To participate in this registry, the subject must meet all the following indications/contraindications per device IFU.

1. The 14F MANTA is indicated for closure of femoral arterial access sites following the use of 10-14F devices or sheaths (maximum OD/profile of 18F)
2. The 18F MANTA device is indicated for closure of femoral arterial access sites following the use of 15-18F devices or sheaths (maximum OD/profile of 25F).

6.5.3 MANTA Device Contraindications

Subjects are not eligible for registry participation if they meet any of the following seven contraindications: (per judgment of operator)

1. Subject with calcification severity of the access vessel
2. Subject with severe peripheral artery disease
3. Subject with puncture in the origin of the profundal femoral artery
4. Subject with sheath insertion in vessel other than the femoral artery
5. Subject with marked tortuosity of the femoral or iliac artery
6. Subject with marked obesity or cachexia (BMI >40 or <20)
7. Subject with systolic blood pressure > 180 mmHg prior

6.5.4 Subject Withdrawal or Discontinuation

Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled. Withdrawal from the study will not jeopardize their future medical care or relationship with the investigator. Subjects will be asked to specify the reason for their termination, but have the right not to answer.

The investigator may decide to withdraw a subject from the study at any time with reasonable rationale. The subject's future care will not be influenced by a decision, voluntary or otherwise, to withdraw from the study. All reasonable efforts should be made to retain the subject in the study until completion of the study.

Reasons for subject withdrawal include, but are not limited to:

- Subject withdraws consent
- Subject refuses to continue their participation
- Subject does not meet the inclusion/exclusion criteria
- Subject is deceased (event or symptoms pertaining to outcome of death must be documented on an Adverse Event CRF)
- Subject's participation is terminated by the investigator, although the subject consented, since participation is no longer medically appropriate
- Subject is „lost to follow up" (subject does not adhere to the scheduled follow up visits but has not explicitly requested to be withdrawn from the study)
- Site personnel should make reasonable efforts to locate and communicate with the subject in order to achieve subject compliance to the scheduled follow up visits

If a subject withdraws from the study, the site will record the subject's reasons for withdrawal on the End of Study CRF.

6.5.5 Enrollment

A patient is considered enrolled in the clinical registry after he/she has provided written informed consent, meets all device indication and contraindications and where an attempt to use the MANTA device has been made. Patients 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.

6.5.6 Duration of the Study

All enrolled subjects will be expected to complete the 30-Day Follow-Up visit. One hundred (100) to 120 subjects from up to 7 investigational sites will also, after informed consent is obtained, complete a 12M follow-up visit.

Anticipated Study Duration Timeline	
First Patient In	January 2018
Last Patient In	July 2019
Endpoint Analysis	October 2019
Study Close	September 2020

7. Study Procedures

7.1. Pre-Screening

Per site standard of care, the Investigator or his/her designee (e.g., study coordinator) will pre-screen the patient's medical record to determine if the patient is a potential candidate for the registry. Any information existing in the medical record may be reviewed and compared to the device indications/contraindications.

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 or his or her designee is responsible for obtaining informed consent 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/EC-approved consent form before continuing with the study screening process. Failure to obtain written informed consent excludes the patient from the study. It must be reported to Essential Medical as soon as possible and to the reviewing site's EC consistent with the site/s EC reporting requirements, A notation that the subject consented to participate in the study, including the date and time of consent will be recorded on the CRF and in the patient's medical record.

7.3. Assignment of Subject Number

A unique identification number will be given to study subjects. Subject numbers will be assigned in sequential order by site. 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 01-001 will be the first subject at site 01; 01-002 will be the second subject at site 1, etc.). The Investigator will maintain a log that relates 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.

7.4. Baseline Evaluation

Informed consent will be obtained from the subject prior to conducting any registry-related activities. Data available in the patient's medical record for standard of care exams and tests may be utilized to fill in CRFs. Computed Tomography scan with angiography (CTA) may be performed per site standard of care.

Computed Tomography Angiography (CTA) Scan
All patients in cohort 1must 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.

The following baseline data and assessments will be performed per site standard of care:

Demographics
- Demographic data including gender, height, weight, BMI and date of birth
- STS Adult Cardiac Surgery Risk Score (TAVI cases only)

The following baseline tests will be performed during the index interventional procedure and prior to attempted MANTA deployment.

Angiogram
All patients will have an intra-procedural angiographic evaluation of the target

(ipsilateral) femoral artery immediately prior to sheath dilation. If bilateral MANTA deployments are planned, angiographic evaluation of both femoral arteries will be performed prior to sheath dilation. Per the device contraindications, fluoroscopically visible calcium, vessel diameter <6 mm, vascular stenosis, the position of the femoral

bifurcation and the presence of significant calcification will be assessed. The operator should access the target (ipsilateral/contralateral) femoral vessel using angiographic or ultrasound control to ensure precise anterior wall entry placement preferably using micropuncture approach. The 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 5 minutes of) sheath removal.

7.5. Procedure

At the start of the interventional procedure, it is recommended that the operator should gain arterial access of the target (ipsilateral and contralateral-if bilateral MANTA deployments are planned) femoral vessel using angiographic or ultrasound control to ensure precise anterior wall entry placement preferably using micropuncture approach. There should be no evidence of significant peripheral vascular disease or calcification in the region of the arteriotomy.

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).

Prior to use, refer to the MNATA Device Instructions for Use (Appendix 1) for a complete description of the indications, contraindications, cautions, precautions, and warnings.

If the subject has two femoral access sites that are 10-18F (ex. EVAR), both may be closed with the MANTA device; however proper data collection must be captured on CRF.

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.

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 judgment 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.

7.6. Post-Procedure Evaluations

Site Checks should be performed 3 hours, 24 hours and pre discharge.

The following guidelines are provided for ambulation following the MANTA deployment procedure; however, specific ambulation regimes should follow standard hospital procedures and or clinician practices.

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.
2. If the patient successfully stands with no or minimal oozing, the patient should be asked to walk 6 meters. If the patient ambulates successfully, record the ambulation time on the CRF.
3. If the patient is unable to walk 6 meters, the patient should be returned to bed. Attempt to ambulate the patient at the earliest possible time when the risk of bleeding is minimal. When the patient ambulates successfully, record the ambulation time on the CRF.
4. When the patient is ready for discharge (defined as ability to walk 6 meters, freedom from orthostatic hypotension [defined as stable blood pressure and heart rate after ambulating], ability to void and a stable groin site without bleeding or expansion of a prior hematoma), record the date and time on the CRF.

7.7. Subject Follow-up

All patients will undergo an in-office follow-up examination at 30±7 days post procedure to assess for any major or minor femoral vascular complications based on VARC-2 definitions or other device-related adverse events. After the 30-day follow-up is completed, subjects will be exited from the study and return to receiving medical care per their physician's recommendations.

One hundred (100) to 120 subjects will undergo an in-office examination at 12M ±30 days post procedure to assess for any major or minor femoral vascular complications based on VARC-2 definitions or other device-related adverse events. Subjects who were previously exited from the study will be contacted to assess interest in participating in the 12M visit. All subjects interested in the 12M visit must voluntarily sign the informed consent form addendum for the 12M visit. Subjects completing the 12M

follow-up visit will be exited from the study and return to receiving medical care per their physician's recommendations.

7.8 Sponsor Representatives

Trained Sponsor personnel may perform certain study activities to ensure compliance to the clinical protocol and may provide technical expertise. Monitoring may be performed by Essential Medical and/or authorized designees according to the International Organization for Standardization (ISO) 14155 and MEDDEV guidelines for post market studies; and applicable Essential Medical standard operating procedures and work instructions. Qualified monitors will ensure investigators comply with this clinical protocol and ISO 14155 and MEDDEV post market requirements.
To ensure study personnel accept, understand and complete their assigned responsibilities, monitors, or field clinical personnel may perform periodic site visits during the course of the study. These actions will help to ensure the continued acceptability of the facilities, compliance to the clinical protocol and relevant regulations, and the maintenance of complete records.

Monitoring will include review and resolution of missing or inconsistent results and source document verification (i.e. comparison of submitted study results to original reports) to assure the accuracy of the reported data.

8. Statistical Methods

8.1. Study Hypothesis

This is a single arm study, and no formal hypothesis will be tested.

8.2. Sample Size Considerations

Up to 500 subjects are considered a meaningful sample size to assess real-world use of the MANTA device. There is no statistical basis for the sample size.

8.3. Data Analysis

8.3.1 Endpoints

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

1. Time to Hemostasis (Primary)

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

1. The percentage of patients with one or more VARC-2 Major femoral vascular complications within 30±7 days following procedure (Primary)
2. The percentage of patients with one or more VARC-2 Minor femoral vascular complications within 30±7 days following procedure (Secondary)

8.3.2 Final Analysis

Statistical analysis will consist of descriptive statistics using standard methods, such as mean, standard deviation, minimum/maximum, proportions, counts, etc. Two-sided 95% confidence

intervals will be calculated, when relevant. Comparison to published literature results will be descriptive only; there will be no comparative statistics.

8.4. Interim Analysis

Interim analysis may be performed throughout the duration of the registry.

8.5. Minimum and Maximum Patient Recruitment for Analysis

Study enrollment will be competitive. There is no minimum or maximum number of patients that can be enrolled per site.

8.6 12M Follow-Up Analysis and Minimization of Bias

A minimum of 100 and up to a maximum of 120 subjects will be re-enrolled into the registry to complete the 12M follow-up visit. Bias will be minimized by contacting subjects who were treated within a specific timeframe designated by the Sponsor (for example, September 2018 to July 2019). Sites will be extended an invitation to participate in the study if they have enrolled at least 10 subjects within the identified timeframe in order to justify study costs incurred to keep the site open, submit amendments to the appropriate ethics committee, bandwidth of the site research team, etc.

The subset followed to one year is expected to be similar to the overall cohort in baseline patient characteristics. Baseline data for the 12M subset will be analyzed and compared to the overall cohort to demonstrate that the subset is representative of the overall cohort. If there are differences in the baseline characteristics of the subset and the overall cohort, these will be further evaluated and assessed as to their potential impact on the 12M results.

To test for generalizability of 12-month outcomes, patients undergoing 12-month follow-up will be compared to patients not undergoing 12-month follow-up in a pre-specified analysis of baseline demographics, clinical characteristics, procedural variables and in-hospital/30-day end-point outcomes.

Only AEs related to the MANTA access site or the ipsilateral leg will be collected at the 12M visit. AE data from the 12M visit will be analyzed separately from the primary safety endpoint, as 12M data will only be available on a subset of the study cohort and the primary safety endpoint is events through 30-days.

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 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:

- Failed hemostasis.
- Damage to the superficial femoral artery.
- Local trauma to the femoral artery wall.
- Damage to the inguinal ligament, causing retroperitoneal bleeding.
- Accidental positioning of collagen plug within the femoral artery, leading to ischemia or stenosis.
- Other access site complications leading to bleeding, hematoma, pseudoaneurysm, etc., possibly requiring blood transfusion and/or surgical intervention.

9.3. Relationship of Adverse Event to Device

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

- MANTA Study AEs related to the MANTA closure device and/or its deployment (in total, the closure procedure) are considered Device-Related AEs.

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

- Not Related: An AE which cannot be attributed to the MANTA device or initial study procedure.
- Possible: The clinical event occurs within a reasonable time sequence to 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 and the event is such that the relationship is likely or patient's condition or concomitant therapy could have caused the AE
- Definite: The clinical event occurs in a plausible time relationship to 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 patient's usual activity or is transient, resolved without treatment and with no sequelae
- Moderate: interferes with the patient's usual activity and/or requires symptomatic treatment
- Severe: symptom(s) causing discomfort and requires transfusion of 2 or more units of whole blood/RBC

9.5. Reporting of Adverse Events

9.5.1 SAE and AE Reporting to Sponsor

Safety Surveillance within this registry and the safety reporting performed by both the investigator and Sponsor starts from the point of attempted MANTA placement and onward. The safety surveillance and the safety reporting will continue until the last visit has been performed, the subject is deceased. The subject/investigator concludes their participation in the study or the subject/investigator withdraws the subject from the study. All device-related SAEs from the point of attempted MANTA placement and onward will be reported to the Sponsor within 24 hours of the Investigator's first knowledge of the event. Suspected SAEs also should be reported. Investigators should also report AEs or SAEs that are known to be unrelated to the device on eCRF.

The Investigator will forward information about a device-related SAE promptly and complete the AE and SAE report forms provided by the Sponsor, even if the information is incomplete or it is obvious that more data will be needed to form any conclusions. Additional information regarding the SAE will be recorded on the follow-up SAE form and forwarded to the Sponsor.

All MANTA device-related AEs, and AE's associated with non-MANTA access sites, and additional outcomes not associated with MANTA device should be reported on the eCRF as soon as practicably possible. Such AEs will be recorded by their final medical diagnosis and not by each separate symptom. All AEs categorized by the Investigator as associated with MANTA leg and 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 intervention/treatment and how the subject recovered with or without sequelae. In case of death, the relationship of death to the MANTA 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.

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 with EU competent authorities in accordance with EU medical device vigilance requirements.

9.6 Device Deficiencies

The Investigator will record any device deficiencies, as defined in Section 4, in the CRF. A device deficiency has occurred if a 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 AEs, ADEs, SAEs, SADEs and USADEs 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 CRF. Reporting to the EC and/or Competent Authority will follow EU vigilance requirements. All device deficiencies will be recorded on the CRF. 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 will review individual adverse events that meet the following criteria:

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

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

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

AEs identified in the subset of patients completing the 12M extended follow-up will not be adjudicated,

as the safety endpoints are through 30 days.

10. Medication

There are no prohibited medications for this clinical investigation.

Only the following medications will be recorded on the CRF: Aspirin, Clopidogrel, Vitamin K Antagonists, and NOAC‟s (eloxaban, rivaroxaban, dabigatran, apixaban) at baseline through 30-day follow-up, inclusive of medications given in the cath lab.

11. Vulnerable Population

The intended patient population of this post-market registry does not meet the criteria of vulnerable population as defined in ISO 14155, Section 3.44.

12. Outsourcing

The Sponsor may transfer some duties and functions related to the clinical study, such as monitoring, data management, etc. to an external organization (such as a contract research organization or individual contractor). When outsourcing does occur, the ultimate responsibility for the quality and integrity of the clinical study will reside with the Sponsor. All requirements applying to the Sponsor will also apply to the external organization inasmuch as this organization assumes the clinical study related duties and functions of the Sponsor.

13. Data Management

The Sponsor/designee will be responsible for data handling. The Sponsor will be responsible for compiling and submitting all required reports to governmental agencies.
Data will be analyzed by the Sponsor/designee and may be transferred to the Sponsor's locations outside of Europe.

Essential Medical respects and protects personally identifiable information that is collected or maintained. As part of its commitment, Essential Medical's designee is aware of the U.S. - European Union Framework and U.S. – Swiss Safe Harbor Framework Agreements regarding human resources and subject clinical trial personal information. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data. Confidentiality of data will be observed by all parties involved at all times throughout the clinical study. All data will be secured against unauthorized access.

CRFs will be used in this study, as noted below and in the data management plan. Informed consent documents will be translated to each country's language, as applicable. If additional documentation is required for any reason (e.g. procedural notes for an adverse event), it is to be appropriately redacted/de-identified prior to being sent to Essential Medical. Source documents will be collected and translated, as needed, for CEC meetings, reporting, etc.

The principal investigator or institution will provide direct access to source data during and after the clinical study for monitoring, audits, EC review and regulatory authority inspections.

13.1 Data Management Plan

A detailed data management plan (DMP) will be established to ensure consistency of the collected data. This document will include procedures used for data review, database cleaning, and issuing and resolving data queries. If appropriate, the DMP may be updated throughout the study duration. All revisions will be tracked and document controlled.

13.2 Document and Data Control

The investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the Sponsor on the CRFs and in all required reports.

13.3 Recording data

Source documents will be maintained by the investigational site throughout the clinical study. Data reported on the CRFs will be derived from, and be consistent with, these source documents, and any discrepancies will be explained in writing.
The CRFs will be signed and dated by the authorized site personnel, as specified in the Data Management Plan.

13.4 Data Retention

Record retention period will be determined by country and/or site-specific requirements.

13.5 Clinical Quality Assurance

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

The ECs and competent authorities may also audit investigational sites that are involved in this registry. The investigator and/or delegate should contact Essential Medical immediately upon notification of a governmental agency inspection at the site. A clinical monitor or designee will assist the investigator and/or delegate in preparing for the audit.

An investigator, or any person acting on behalf of such a person with respect to the study, will permit authorized governmental agency employees, at reasonable times and in reasonable manner, to inspect and copy all records relating to the study.

An investigator will permit authorized governmental agency employees to inspect and copy records that identify subjects, upon notice that governmental agency has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator, to the Sponsor or EC have not been submitted or are incomplete, inaccurate, false or misleading.

14. Clinical Monitoring

14.1 Monitoring

It is the responsibility of Essential Medical as the Sponsor of the study to ensure the study is conducted, recorded, and reported according to the approved protocol, subsequent amendment(s), applicable regulations, and guidance documents. Monitoring may be conducted according to the Essential Clinical Monitoring Plan and standard operating procedure.
This monitoring is designed to identify missing and inconsistent data, data outliers, and potential protocol deviations that may be indicative of site non-compliance. On-site monitoring may occur at the discretion of the Sponsor if significant concerns arise. The investigator shall make subject and study records available to the clinical monitor for monitoring.

15. Protocol Deviations and Amendments

15.1. Protocol Adherence and Deviations

The registry will be conducted as described in this protocol. Investigators are not permitted to deviate from this protocol except to protect the patient'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 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 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, ethics committees and regulatory authorities as the original protocol.

15.2. 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.

15.3. Investigator Suspension or Termination

The Sponsor reserves the right to stop the study at any stage, with appropriate written notice to the investigator.
Possible reasons for early termination of the study by the Sponsor, either at local, national or international level, may include, but are not limited to:

- 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 Essential Medical, Inc.) 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 case report forms.
- Sponsor's decision.

In such events, the study will be terminated according to applicable regulations. The investigator may also discontinue participation in the clinical study with appropriate written notice to the Sponsor. Should either of these events occur, the investigator should provide a written statement as to why the premature termination has taken place, and notify the EC and/or the CA (if applicable). Follow-up for all enrolled subjects will be per center standard of care.

A principal investigator, EC, or regulatory authority may suspend or prematurely terminate participation in a clinical study at the investigational sites for which they are responsible.

15.4 Study Conclusion

The study will be concluded when:

- All follow up visits have been completed and subjects withdrawn AND
- All sites are closed AND
- The final report generated by Essential Medical has been provided to sites or Essential Medical has provided formal documentation of study closure

16. Statements of Compliance

This clinical registry 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, requirements of the approving ethics committees, ISO 14155:2011, MEDDEV post market re requirements and any regional and/or national regulations and will be compliant to these International Standards and any regional and national regulations, as appropriate.

This clinical registry will not be initiated until approval has been obtained from the ethics committee. EC approval, if applicable, and authorization from the Sponsor in writing for the study. The subject must sign the study informed consent form prior to any study-related procedures.

Any additional requirements imposed by the ethics committee will be followed. No deviation from the protocol will be implemented without the prior review and approval of the ethics committee except where it may be necessary to eliminate an immediate hazard to a subject.

As the Sponsor, Essential Medical will hold general liability insurance in accordance with the requirements of applicable local laws if required. Appropriate country representatives will be utilized to interpret the requirements regarding the type of insurance that will be provided to subjects, and such information will be incorporated into the informed consent form, as applicable. If required, additional subject coverage or study specific insurance may also be provided by the Sponsor.

17. Publication Policy

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.

18. References

1. Refer to Essential Medical MANTA Literature Review, version 1.1.
2. 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.
3. 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.

Appendix 1. Instructions for Use