Essential Medical

CLINICAL STUDY PROTOCOL

Title: Prospective Multicenter MANTA™ Vascular Closure Device Ultrasound Guided Closure Study

Short Title: MANTA ULTRA Closure

Protocol Number: ST-3370

Study Type: Prospective, North American, Multi-center, Non-randomized Study

Date: August 03, 2022

Version: C

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This protocol has been prepared in compliance with U.S. 21 CFR Part 812 and current International Standard BS EN ISO 14155:2020, Clinical Investigations of medical devices for human subjects – Good Clinical Practices; Annex A (normative) Clinical Investigation Plan (CIP).

Protocol Signature Page

The Principal 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 Research Ethics Board.

Agreed to by Principal Investigator:

_____ _____

Principal Investigator Date

_____

Principal Investigator (print)

Agreed to by Sponsor:

20-Sep-2022

_____ _____

Christopher Buller, MD Date
Medical Director- Interventional
For and on behalf of Essential Medical, Inc.

Protocol Synopsis

Title	Prospective Multicenter MANTA™ Vascular Closure Device Ultrasound Guided Closure Study
Short Title	MANTA ULTRA Closure
Protocol ID	ST-3370
Study Type	Interventional
Clinical Design	Prospective, Multicenter, Non-randomized
Clinical Purpose	Demonstrate the safety of MANTA Vascular Closure Device (VCD) ultrasound (U/S) guided closure (without dependence on the pre-procedural depth locator measurements) in patients undergoing elective TAVR procedures with planned percutaneous femoral arterial access. The primary safety endpoint of any Large Bore Access-site Related VARC-2 Major Vascular (LBAR VARC-2 Major) complication (adapted from VACR-2 criteria[1]) will be compared to a Performance Goal (PG) which is based on clinical judgment regarding prior performance of MANTA VCD in published literature. The study will also evaluate time to hemostasis, technical success, ambulation success, treatment success, procedure time, and the rate of any large bore access-site-related VARC-2 Minor vascular (LBAR VARC-2 Minor) complications, adapted from VARC-2 criteria.[1]
Number of Subjects	Primary Analysis Cohort (PAC): A total of 150 subjects, with a maximum of 30 subjects per PI and/or site, undergoing elective TAVR procedures utilizing a femoral arterial access site with a MANTA VCD closure device will be evaluated. Roll-in Cohort: Additionally, up to 2 roll-in subjects per operator per site will be enrolled to allow investigators to learn how to use MANTA VCD ultrasound guided closure technique.
Number and Location of Sites	A minimum of 5 and up to 15 sites with experienced MANTA VCD users in the U.S. and Canada
User Experience	Individual operators must have the following experience to participate (limit up to 2 operators per site): • ≥25 successful closures with the MANTA VCD verified by sponsor. Must include at least 10 sponsor training cases • Currently using ultrasound for femoral access in large bore procedures, with an operator experience of at least 50 ultrasound-guided access cases
Duration of the Study	Approximately 2 months for start-up and 12 months for enrollment. Additional 12 months for 12 month (additional analysis) follow-up and 2 months for close out. Approximately 28 months for entire duration of study.
Closure Methods	• 14F MANTA Vascular Closure Device • 18F MANTA Vascular Closure Device
Primary Safety Endpoint	Any Large Bore Access-site Related VARC-2 Major Vascular (LBAR VARC-2 Major) complication within 30 days (adapted from VARC-2 Criteria)[1]: • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) leading to death, life threatening or major bleeding, visceral

	ischemia, or neurological impairment OR • Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR • The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia or neurological impairment OR • Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR • Surgery for access site-related nerve injury OR • Permanent access site-related nerve injury
Secondary Endpoints	Effectiveness Endpoints • Time to Hemostasis: The elapsed time between MANTA deployment (withdrawal of sheath from artery) and first observed and confirmed arterial hemostasis (no or minimal subcutaneous oozing and the absence of expanding or developing hematoma). Time to Hemostasis should be inclusive of any time that manual or mechanical pressure is applied specifically to stop arterial bleeding. Do not include time spent when light digital or mechanical pressure is done to treat oozing, or if short manual compression is done as a preventative measure as part of standard of care. • Technical Success: A subject will be considered a Technical Success if percutaneous vascular closure is obtained with the MANTA VCD without the use of unplanned endovascular or surgical intervention. • Ambulation Success: A subject will be considered an Ambulation Success if a previously ambulatory patient (until day of TAVI) is able to ambulate for at least 20 feet/6 meters without re-bleeding. • Time to Ambulation: The elapsed time between MANTA VCD deployment (withdrawal of MANTA VCD sheath from artery) and when ambulation is achieved (subject standing and walking at least 20 feet/6 meters without re-bleeding). • Treatment Success: A subject will be considered a Treatment Success if he/she has Time to Hemostasis ≤10 minutes and has no LBAR VARC-2 Major complications within 30 days. • Procedure Time: Defined as elapsed time from initial skin break (first needle insertion) to time when the post-deployment angiogram is completed. Safety Endpoint • Any Large Bore Access-site Related VARC-2 Minor Vascular (LBAR VARC-2 Minor) complication within 30 days (adapted from VARC-2 Criteria): o Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysms, hematomas, percutaneous closure device failure) not leading to death, life-threatening or major bleeding, visceral ischemia, or neurological impairment OR o Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR o Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR o Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft) OR o 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)
Additional Analyses	• Any long-term LBAR VARC-2 Major and Minor complications (>30 days though 12 months post-procedure) • Quantify Procedural and Post-procedural Characteristics such as: o Readmission rates within 30 days o Delayed ambulation for subjects attributable to large bore access site problems or complications (site investigator assessment) o Delayed discharge for subjects attributable to large bore access site problems or complications. (site investigator assessment) o Use of adjunctive devices required at large bore access site to address bleeding or other access site complications (e.g., bare or covered stent, balloon or surgical repair) o VARC-3 Major and Minor Vascular Complications within 30 days (adapted from VARC-3 criteria)[2] • Subsequent Secondary Intervention(s) (For example, any new surgical or percutaneous interventions post the index large bore procedure that occurred on the femoral artery of the MANTA (ipsilateral) leg, such as percutaneous coronary intervention (PCI), through the 12 month follow-up phone call.)
Clinical Visits	See 'Schedule of Assessments' below
Inclusion Criteria	1. Candidate for elective or planned (i.e., not emergent or urgent) percutaneous transcatheter valve replacement (TAVR) via a 10-20F device or sheath (12-25F OD) with common femoral artery approach 2. Vessel size would allow for access for the MANTA VCD based on vessel size as determined by baseline CTA: minimum vessel diameter of 5mm for the 14F MANTA VCD and 6mm for the 18F MANTA VCD 3. Understand and sign the study specific written informed consent form and PHI authorization 4. Able and willing to fulfill the follow-up requirements 5. Age ≥21 years
Exclusion Criteria	1. Patients known to be pregnant or lactating 2. Patients who have a systemic infection or a local infection at or near the access site 3. Patients with significant anemia (hemoglobin ≤10 g/DL) 4. Patients who are morbidly obese or cachectic (BMI >40 or <20kg/m2) 5. Patients with a known bleeding disorder including thrombocytopenia (platelet count <100,000 cells/UL), thrombasthenia, hemophilia, or von Willebrand disease 6. Patients with allergy to bovine materials or any other device material, including collagen and/or collagen products, polyglycolic or polylactic acid, stainless steel or nickel 7. Patients with a femoral artery puncture in target groin within the prior 30 days, prior vascular closure device placement in the target common femoral artery within 3 months, or any prior target femoral artery access-related complication 8. Patients who have undergone use of an intra-aortic balloon pump (IABP) through

	the arterial access site within 30 days prior to the baseline evaluation. 9. Patients who have a Common Femoral Artery (CFA) with visible calcium and/or tortuosity, as determined by baseline CTA, precluding safe access and likely to impede large bore access site arteriotomy, as determined by investigator. 10. Patients with 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 in whom oral anticoagulation therapy cannot be stopped for the peri procedural period or patients with INR >1.8 at the time of the procedure 12. Patients who are unable to ambulate at least 6 meters without assistance at baseline 13. Patients with renal insufficiency (serum creatinine >2.5 mg/dl) or on dialysis therapy 14. Patients with existing nerve damage in the ipsilateral leg 15. Patients with a further planned endovascular procedure within the next 30 days 16. Patients who have already participated in this IDE study 17. Patients who are currently participating in another clinical study of an unapproved investigational device or drug that has not concluded the follow-up period or patient currently participating in another clinical study likely to influence hemostasis and vascular complications 18. Patients who cannot adhere to or complete the investigational protocol for any reason including but not limited to geographical residence, psychiatric condition or life threatening disease 19. Patients who have a common femoral artery <5mm in diameter for the 14F MANTA VCD or <6 mm in diameter for the 18F MANTA VCD, common femoral artery stenosis resulting in a vessel diameter <5mm in diameter for the 14F MANTA VCD or <6 mm in diameter for the 18F MANTA VCD, or > 50% diameter femoral or iliac artery stenosis 20. Patients in whom, during initial access of the artery, arteriotomy and surrounding anatomy cannot be visualized and identified clearly under U/S imaging and/or if the vertical depth from the surface of the skin to target area of the common femoral artery measures greater than 6cm
Analysis & Reporting:	The primary safety analysis will be performed on the first 75 chronologically enrolled subjects in the PAC where an attempt to use the MANTA VCD is made (see Section 15) (enrolled subjects without an attempt will not be included). The complete study results will be analyzed and reported. The PAC and the Roll-in Cohort will be analyzed separately.

Schedule of Assessments

Table 1: Schedule of Assessments

Assessment	Screening Visit	TAVR Procedure	Closure Procedure			Post-procedure	Discharge	Follow-up (FUP)	
			Pre-closure	Closure	Post-closure			30-day office visit (±7 Days)	12-month Phone (±30 Days)
Subject Eligibility / Informed Consent / Applicable PHI Authorization form*	X								
Medical History	X								
Medications[1]	X	X	X	X	X	X	X	X	X
Laboratory Tests	X[2]								
Pregnancy Test	X[9]								
CT Angiographic Scan	X[3]								
Ultrasound[4] (access and assessment)		X		X					
ACT / SBP			X[5]						
Adjunctive Devices				X	X				
Target Femoral angiography					X[6]				
Target Femoral access site assessment					X	X	X	X	X[7]
Time to Hemostasis					X[8]				
Delayed Ambulation/Discharge						X	X		
Adverse Events			X	X	X	X	X	X	X[7]
Subsequent Secondary Intervention[10]							X	X	X

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

1. The following medications will be recorded on the eCRF for each subject: cardiovascular medications (e.g., anti-hypertensives, anti-arrhythmic, etc.), anti-coagulants, anti-thrombotic and anti-platelets. Any changes to these medications should be documented throughout the course of the 12 month follow up.
2. Considered standard of care and are to be done according to the site's standard of care practice for pre-procedure labs for the TAVR procedure (hemoglobin, creatinine, and platelet count, International Normalized Ratio (INR))
3. Screening Visit CT Scan to assess both limbs for presence/absence/severity of calcium, atherosclerotic disease, tortuosity, and acceptable flow rates
4. Ultrasound for access SOC; Ultrasound data collection during closure
5. Prior to all closure methods, record ACT and systolic BP (per MANTA VCD warnings SBP<180mmHg; recommend ACT<250 seconds prior to closure but these targets are not mandatory per protocol; capturing ACT and SBP prior to closure is mandatory)
6. Post-closure, perform target (ipsilateral) femoral angiography from contralateral access site to ensure patency into the ipsilateral common femoral artery
7. At 12m follow-up, target femoral access site assessment will be questions completed via phone; adverse events will only pertain to target access site

8. The elapsed time between MANTA deployment (withdrawal of sheath from artery) and first observed and confirmed arterial hemostasis (no or minimal subcutaneous oozing and the absence of expanding or developing hematoma).
9. Female subjects of child bearing potential only. Test to be conducted within 7 days of TAVR procedure or according to standard of care for TAVR procedures requiring contrast and angiography. Urine pregnancy test is acceptable.
10. Any new surgical or percutaneous interventions post the index large bore procedure that occurred on the femoral artery of the MANTA (ipsilateral) leg, such as percutaneous coronary intervention (PCI), through the 12 month phone follow-up.

Abbreviations

Table 2: Abbreviations

Abbreviation/ Acronym	Definition
ACT	Activated clotting time
ADE	Adverse device effect
AE	Adverse event
BAV	Balloon aortic valvuloplasty
BMI	Body mass index
BP	Blood Pressure
CA	Competent authority
CE	Conformité Européene (European Conformity)
CEC	Clinical events committee
CFA	Common Femoral Artery
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 safety monitoring 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

Abbreviation/ Acronym	Definition
IRB	Institutional review board
ISO	International Organization for Standardization
LBAR VARC-2 Major	Large Bore Access-site Related VARC-2 Major Vascular complication
LBAR VARC-2 Minor	Large Bore Access-site Related VARC-2 Minor Vascular complication
OD	Outer diameter
PAC	Primary Analysis Cohort
PHI	Protected Health Information
PG	Performance goal
PMA	Pre-market approval
REB	Research ethics board
SADE	Serious adverse device effect
SAE	Serious adverse event
SBP	Systolic blood pressure
SOC	Standard of care
TAVR/TAVI	Transcatheter aortic valve replacement / transcatheter aortic valve implantation
TTA	Time to ambulation
TTH	Time to hemostasis
UADE	Unanticipated adverse device effect
U.S.	United States
U/S	Ultrasound
UADE	Unanticipated adverse device effect
USADE	Unanticipated serious adverse device effect
VARC	Valve Academic Research Consortium
VCD	Vascular closure device

Revision History

Table 3: Revision History

Rev	Description of Change	CO#
A	Initial Release	CO55669
B	Section 15.3.3: Removed, “Additionally, 95% confidence intervals may be calculated.” Section 12 and 13: Clarified two members from these committees will be the same. Fixed grammatical errors and depersonalized text throughout the document.	CO56845
C	Protocol Synopsis: • Added *VARC-2* to LBAR Major and LBAR Minor to clarify LBAR Major and Minor are tied to VARC-2 and the primary and secondary safety endpoints; they now read LBAR *VARC-2* Major and LBAR *VARC-2* Minor (also updated throughout entire document) • Added additional analysis of VARC-3 (also updated in sections 6.3 and 15.3.4) • Add *PI and/or* to the sentence ‘A total of 150 subjects, with a maximum of 30 subjects per *PI and/or* site’ to ensure an individual PI cannot enroll more than 30 subjects in the study (also updated in section 5.5) Schedule of Assessments • Added to key #5 that specific targets of SBP<180mmHg and ACT<250 are not mandatory per protocol but ACT and SBP must be captured prior to closure (also updated in Section 8.3) Section 1, 3, 15.2: Updated citations Section 2.4, 5.1: Updated to reflect Canada’s current regulatory status Added Section 7.4: Prescreening to clarify prescreening procedures Section 12: Added a sentence to state that the CEC will also classify each AE whether it is a VARC-3 Major or VARC-3 Minor complication or neither References: Added two references for BACR and VARC-3 Appendix A – Definitions • Added VARC-3 bleeding definitions • Added BARC definition to align with VARC-2/3 Vascular Complication Definitions • Added VARC-3 Major and Minor Vascular Complications definitions	CO60413

Table of Contents

Table of Tables:

1. Introduction

Percutaneous cardiac and peripheral procedures performed through large bore arteriotomies, such as transcatheter aortic valve replacement (TAVR), endovascular aneurysm repair (EVAR), balloon aortic valvuloplasty (BAV), and extracorporeal membrane oxygenation (ECMO) demonstrate a continued need for safe and effective access site closure. TAVR is arguably the most common large bore arterial intervention and vascular complications in patients are fairly common.[3,4] Nearly two-thirds of TAVR adverse events are related to arteriotomy closure failure, with larger sheath size being one predictor of increased risk.[3] Even minor complications like hematoma, pseudoaneurysm, and arteriovenous fistula can be devastating and contribute to morbidity and mortality.[5]

Prospective pivotal studies of the MANTA™ Vascular Closure Device (VCD) have yielded historically favorable VACR-2 major vascular complications rates of 2% to 4% in selected patients undergoing TAVR or EVAR.[6-8] These results have subsequently been supported by real world investigator-initiated prospective studies enrolling less selected TAVR and EVAR populations.[9-12] Yet, in retrospective investigator led MANTA VCD patient registries, VARC-2 major vascular complications rates ranging up to 11% have been seen.[13-17] Hence, residual complications attributable to the large bore arterial access sites that enable these procedures remain important targets for improving outcomes and reducing health care costs.[5,18]

The use of ultrasound (U/S) simply to guide initial arterial puncture is itself associated with reduced vascular complications and has become a recommended practice for interventional procedures requiring femoral arterial access.[19-21] Accordingly, interventionalists and surgeons performing these procedures have generally become familiar with real-time imaging of femoral artery access sites, and ultrasound equipment is now commonly available in cardiac catheterization laboratories, cardiovascular surgical suites and so-called hybrid operating rooms.

The current method for MANTA VCD deployment is obtaining a pre-measurement to measure the depth of the artery using the dedicated MANTA Depth Locator (DL); recently, investigator-driven studies have emerged that suggest the use of U/S to guide MANTA VCD deployment (as opposed to the MANTA DL) may result in even fewer complications than seen in the pivotal studies cited above. A retrospective review of over 150 TAVR patients demonstrated that access-site major vascular complications occurred significantly less frequently in patients where U/S was used to guide MANTA VCD deployment in comparison to those without the use of U/S-guided MANTA VCD deployment (1.5% vs. 7.4%; p=.03), with significantly lower incidence of access-site life-threatening or major bleeding complication (1.5% vs. 8.9%; p=.008).[22] A separate pilot study involving 25 consecutive patients undergoing TAVR assessed the safety and feasibility of U/S-guided closure of MANTA VCD. Placement of the MANTA VCD was based solely on direct visualization of the anchor as it came in contact with the anterior wall of the artery. Technical success was achieved in 100% of patients and there were no VARC-2 major or minor vascular complications.[23]

These encouraging results are nevertheless limited. Both reports are based on single center experiences that may not be generalizable and may be prone to publication bias. The larger series was retrospective, and the report by Wood and Sathananthan includes just 25 patients.

Accordingly, we propose to examine a prospective, multicenter study to evaluate the safety of ultrasound guided deployment of MANTA VCD, which can serve as a safe alternative method to using the dedicated MANTA DL.

2. MANTA Large Bore Vascular Closure Device

2.1. Device Description

The MANTA VCD consists of a 14F or 18F MANTA Closure Device, a 14F or 18F Sheath with Introducer, and an 8F Depth Locator. The MANTA VCD is composed of a delivery handle containing the implantable closure unit, which consists of an absorbable collagen hemostat, and an absorbable polymer anchor (also known as a toggle) that are connected by a suture. The closure unit is deployed using the depth locator, sheath, introducer and delivery handle. Hemostasis is achieved primarily by the mechanical means of the anchor-arteriotomy-collagen sandwich, which is supplemented by the coagulation-inducing properties of the collagen. An extra-vascular radiopaque lock secures and marks the location of the absorbable unit for future identification on fluoroscopy. The delivery handle features a tension indicator and orientation markings to facilitate proper deployment of the absorbable unit.

2.2. Indications for Use

In the U.S., the MANTA Vascular Closure Device is indicated for closure of femoral arterial access sites while reducing time to hemostasis following the use of 10-20F devices or sheaths (12-25F OD) in endovascular catheterization procedures.

In the EU, 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), and 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).

2.3. Manufacturer / Sponsor Name and Address

The Legal Manufacturer of the MANTA Vascular Closure Device and the Sponsor of this study is:
Essential Medical, Inc. (a wholly owned subsidiary of Teleflex, Inc.)
260 Sierra Drive, Suite 120
Exton, PA 19341, U.S.A.

2.4. Regulatory Classification

In the U.S., the MANTA Vascular Closure Device is a class 3 device, which received Pre-Market Approval (PMA) from the U.S. FDA in February 2019 (P180025).

In the EU, the MANTA Vascular Closure Device is classified as a Class III device per rule 17 of Annex IX of the Medical Devices Directive 93/42/EEC.

The MANTA VCD was approved by Health Canada in May 2022. MANTA is classified as a Class IV device per rule 14 of Schedule 1 of the Medical Devices Regulation SOR/98-282. This study will be conducted under an Investigational Testing Authorization (ITA).

3. MANTA VCD Clinical Experience

Four manufacturer-sponsored studies have been conducted on the MANTA VCD. Three studies were done for purposes of market clearance in the EU and United States. One post market registry has also been performed.

Brief summaries are provided below.

Two investigator-led reviews of the MANTA VCD were completed to gather information on U/S-guided closure with the MANTA VCD. These two studies are summarized in the earlier introduction section.[22,22]

3.1. First In Human (FIH) Study

The FIH study, conducted in Asuncion Paraguay was broken into two cohorts to evaluate both the 18F and 14F sizes.

3.1.1. *18F Cohort*

This was a prospective, non-randomized, single-site, non-blinded feasibility study to evaluate the initial safety and preliminary efficacy of the 18F MANTA VCD. Six subjects undergoing balloon aortic valvuloplasty (BAV) were enrolled, and 5 subjects were treated with the 18F MANTA VCD; the MANTA VCD 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 the MANTA VCD. There were no device-related adverse events. 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 U/S to evaluate flow for all subjects.

3.1.2. *14F Cohort*

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

In 1 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 VCD deployment with a challenging puncture locating step. This subsequently resulted in suboptimal MANTA VCD 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 U/S, a pseudoaneurysm was seen at the puncture site. A Femo-Stop™ compression device (Abbott) was applied for 3 hours, which resolved the pseudoaneurysm. The subject was discharged without further sequelae.

3.2. EU Pre-Market Clinical Study

This was a prospective, non-randomized, multi-site, non-blinded study to evaluate the safety and performance of the 14F and 18F MANTA VCD 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[6]. Fifty subjects were enrolled and treated with the MANTA VCD; 16 subjects were treated with the 14F MANTA VCD (32%) and 34 subjects were treated with the 18F MANTA VCD (68%).

The primary performance endpoint was evaluation of Hemostasis Success, defined as hemostasis at the puncture site within 10 minutes of cutting the MANTA VCD suture without need for manual or mechanical compression and without later re-bleeding. 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.

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 published surgical closure results[24] demonstrated strong evidence that rate of Major Complications was non- inferior to the published surgical closure results ($p < 0.05$).

CE Mark was obtained for the MANTA VCD on July 18, 2016 (BSI NL Certificate No. CE 650543) and was renewed by BSI NL on January 8, 2020.

3.3. SAFE MANTA U.S. Pivotal Study

The SAFE MANTA Pivotal Study[7] was a prospective, single arm, multicenter investigation performed under a U.S. Food and Drug Administration-approved IDE for purposes of supporting a U.S. pre-market approval (PMA). A total of 341 patients were enrolled in the study at 20 investigational sites in the United States and Canada. Forty-one operators performed at least one roll-in case before entering patients into the IDE Primary Analysis Cohort (PAC).

The primary effectiveness outcome was Time to Hemostasis (TTH) defined as the elapsed time between MANTA VCD deployment and first observed and confirmed arterial hemostasis (no or minimal subcutaneous oozing and the absence of expanding or developing hematoma).
A single MANTA VCD was deployed in 262 (99.6%) of cases with a median TTH of 24 seconds.

The primary safety outcomes of site-related vascular injury or bleeding complications occurred in 14 (5.3 %) subjects. Major bleeding in 6 subjects (2.3%), covered stent in 4 subjects (1.5%), balloon inflation in 2 subjects (0.8%), and surgical repair in 2 subjects (0.8%). Major bleeding was treated with manual pressure and transfusion. One major bleeding event resulted in a procedural death related to retroperitoneal hemorrhage from the contralateral (non-MANTA VCD related) access site. A separate major bleeding event was judged by the operator to have been caused by perforation of an inferior epigastric artery and unrelated to the successful MANTA VCD closure.

U.S. PMA approval for the MANTA VCD was received in February 2019.

3.4. MANTA EU Registry (MARVEL Study)

This prospective registry was a post-market, single-arm, observational study[9] including 500 patients from 10 sites in the European Union and Canada. Operators were required to have performed more than 10 MANTA VCD cases to participate in this study. The primary endpoint was 30-day follow-up through outpatient clinic visit with safety endpoints (major and minor vascular complications) and performance endpoint (time to hemostasis).

At 30 days, the primary safety endpoint for major vascular complications, as defined by Valve Academic Research Consortium (VARC)-2, was 4.0%, and minor vascular complication rate (VARC-2) was 5.8%. Median time to hemostasis was 50 seconds.

A subset of subjects (n=81) was followed for long-term safety assessment through 12 months post-closure . Long-term (12-month) follow-up indicates that VARC-2 Major or Minor complications occurring between the standard follow-up post-TAVR (30 days) and one year, the lifetime of the device, are rare (1/81, 1.2%).

4. Study Rationale / Objective

The rationale for this study is to establish the safety of U/S-guided closure with MANTA VCD following TAVR procedures utilizing large bore sheaths as an alternative method to using the MANTA DL.

5. Study Design

5.1. Design

The MANTA ULTRA Closure Study is a prospective, North American, multi-center, non-randomized study. The MANTA VCD is commercially available in the U.S. (approved via PMA No. P180025) and in Canada (license No 107711), but the U/S-guided closure method is investigational.

5.2. 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

5.3. Randomization

There is no randomization in this investigation.

5.4. Subject Replacement

See Section 14.2 below. Sixty nine (69) subjects will provide adequate power to reject the null hypothesis for the primary safety endpoint. To ensure an adequate sample size of subjects meeting the 30-day primary safety endpoint, and to account for patient attrition, data from the first 75 consecutive subjects in the PAC will be analyzed and submitted to support a PMA supplement for revised labeling to include the U/S-guided method.

5.5. Study Population Scale and Duration

A total of 150 subjects, with a maximum of 30 subjects per site and/or PI, undergoing elective TAVR procedures utilizing a femoral arterial access site with a MANTA VCD closure device will be evaluated. Additionally, up to 2 roll-in subjects per operator will be enrolled to allow investigators to learn how to use MANTA VCD ultrasound guided closure technique. A minimum of 5 and up to 15 sites with experienced MANTA VCD users in the U.S. and Canada will be included.

Data from the first 75 consecutive Primary Analysis Cohort (PAC) subjects enrolled, in whom an attempt to use the MANTA VCD was made, may be submitted to support a PMA supplement for revised labeling (see Section 15).

5.6. Justification of Study Design

The safety and effectiveness of the MANTA VCD has been demonstrated in previous clinical trials in support of CE Mark[5] and FDA approval.[6] This MANTA ULTRA clinical investigation is designed as a cohort trial to prospectively evaluate the safety of U/S-guided closure with the MANTA VCD in patients undergoing large bore procedures, specifically in TAVR procedures, which are arguably the most common large bore procedures, as an alternate to the depth measurement method using the MANTA DL.

The primary safety hypothesis will evaluate the rate of LBAR VARC-2 Major complications within 30 days of the procedure compared to a Performance Goal (PG) which is based on clinical judgment regarding prior performance of MANTA VCD in three manufacturer-sponsored clinical studies and eight published studies (Section 15.2). Data from the first 75 consecutive subjects in the PAC will be analyzed in support of a PMA supplement for revised labeling to include the U/S-guided method.

Upon completion of the study, the full dataset will be analyzed and reported.

6. Study Endpoints

6.1. Primary Safety

Primary safety will be evaluated by comparing the rate of any Large Bore Access-site Related VARC-2 Major Vascular complications within 30 days to a Performance Goal (PG) which is based on clinical judgment regarding prior performance of MANTA VCD in published literature (see Section 15.2):

Any Large Bore Access-site Related VARC-2 Major Vascular (LBAR VARC-2 Major) complication within 30 days is defined as (adapted from VARC-2 Criteria[1]):

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

6.2. Secondary Endpoints

The following secondary endpoints will be evaluated:

Effectiveness Endpoints

- 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). Note: Time to Hemostasis should be inclusive of any time that manual or mechanical pressure is applied specifically to stop arterial bleeding. Do not include time spent when light digital or mechanical pressure is done to treat oozing, or if short manual compression is done as a preventative measure as part of standard of care.
- Technical Success: A subject will be considered a Technical Success if percutaneous vascular closure is obtained with the MANTA VCD without the use of unplanned endovascular or surgical intervention.
- Ambulation Success: A subject will be considered an Ambulation Success if a previously ambulatory patient (until day of TAVI) is able to ambulate for at least 20 feet/6 meters without re-bleeding.
- Time to Ambulation: The elapsed time between MANTA VCD deployment (withdrawal of MANTA sheath from artery) and when ambulation is achieved (subject standing and walking at least 20 feet/6 meters without re-bleeding).
- Treatment Success: A subject will be considered a Treatment Success if he/she has Time to Hemostasis ≤10 minutes and has no LBAR Major complications within 30 days.
- Procedure Time: Defined as elapsed time from initial skin break (first needle insertion) to time when the post-deployment angiogram is completed.

Safety Endpoint

- Any large Bore Access-site Related VARC-2 Minor Vascular (LBAR VARC-2 Minor) complication within 30 days is defined as (adapted from VARC-2 Criteria[1]):
  - Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysms, hematomas, percutaneous closure device failure) not leading to death, life-threatening or major bleeding, visceral ischemia, or neurological impairment OR
  - Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR
  - Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR
  - Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft) OR
  - Percutaneous closure device failure – Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning).

6.3. Additional Analyses

The following outcomes will also be analyzed:

- Any long-term LBAR VARC-2 Major and Minor complications (>30 days through 12 months post-procedure)
- Quantify Procedural and Post-procedural Characteristics such as:
  - Readmission rates within 30 days
  - Delayed ambulation (beyond the institution's ambulation protocol) for subjects with LBAR VARC-2 Major or LBAR VARC-2 Minor complications
  - Delayed discharge (beyond institution's discharge protocol), for subjects with LBAR VARC-2 Major or LBAR VARC-2 Minor complications
  - Use of adjunctive devices at large bore access site to address bleeding or other access site related complications (e.g., bare or covered stent, balloon, or surgical repair)
  - VARC-3 Major and Minor Vascular Complications within 30 days (adapted from VARC-3 criteria)[2]
- Subsequent Secondary Intervention(s) (for example, any new surgical or percutaneous interventions post the index large bore procedure that occurred on the femoral artery of the MANTA (ipsilateral) leg, such as percutaneous coronary intervention (PCI), through the 12 month follow-up phone call.)

7. Selection and Enrollment

7.1. Subject Identification

Patients scheduled to undergo elective TAVR procedure with planned percutaneous femoral arterial access will be considered for inclusion into the study. Each new patient expressing interest in study participation must sign the informed consent form and authorization or other form required by applicable U.S. or Canadian laws governing the use and disclosure of individually identifiable health information (referred to hereafter as "Protected Health

Information" or PHI), and meet the inclusion eligibility requirements outlined in the following sections.

7.2. Inclusion Criteria

Subjects enrolled in this clinical study must meet all of the following criteria:

1. Candidate for elective or planned (i.e., not emergent or urgent) percutaneous transcatheter valve replacement (TAVR) via a 10-20F device or sheath (12-25F OD) with common femoral artery approach
2. Vessel size would allow for access for the MANTA VCD based on vessel size as determined by baseline CTA: minimum vessel diameter of 5mm for the 14F MANTA VCD and 6mm for the 18F MANTA VCD
3. Understand and sign the study specific written informed consent form and PHI authorization
4. Able and willing to fulfill the follow-up requirements
5. Age ≥21 years

7.3. Exclusion Criteria

Subjects will be excluded from the study if any of the following conditions apply:

1. Patients known to be pregnant or lactating
2. Patients who have a systemic infection or a local infection at or near the access site
3. Patients with significant anemia (hemoglobin ≤10 g/DL)
4. Patients who are morbidly obese or cachectic (BMI >40 or <20 kg/m2)
5. Patients with a known bleeding disorder including thrombocytopenia (platelet count <100,000 cells/UL), thrombasthenia, hemophilia, or von Willebrand disease
6. Patients with allergy to bovine materials or any other device material, including collagen and/or collagen products, polyglycolic or polylactic acid, stainless steel or nickel
7. Patients with a femoral artery puncture in target groin within the prior 30 days, prior vascular closure device placement in the target common femoral artery within 3 months, or any prior target femoral artery access-related complication
8. Patients who have undergone use of an intra-aortic balloon pump (IABP) through the arterial access site within 30 days prior to the baseline evaluation
9. Patients who have a Common Femoral Artery (CFA) with visible calcium and/or tortuosity, as determined by baseline CTA, precluding safe access, and likely to impede large bore access site arteriotomy, as determined by investigator
10. Patients with 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 in whom oral anticoagulation therapy cannot be stopped for the peri procedural period or patients with INR >1.8 at the time of the procedure
12. Patients who are unable to ambulate at least 6 meters (20 feet) without assistance

at baseline

13. Patients with renal insufficiency (serum creatinine >2.5 mg/dl) or on dialysis therapy
14. Patients with existing nerve damage in the ipsilateral leg
15. Patients with a further planned endovascular procedure within the next 30 days
16. Patients who have already participated in this IDE study
17. Patients who are currently participating in another clinical study of an unapproved investigational device or drug that has not concluded the follow-up period or patient currently participating in another clinical study likely to influence hemostasis and vascular complications
18. Patients who cannot adhere to or complete the investigational protocol for any reason including but not limited to geographical residence, psychiatric condition or life-threatening disease
19. Patients who have a common femoral artery <5mm in diameter for the 14F MANTA VCD or <6 mm in diameter for the 18F MANTA, VCD common femoral artery stenosis resulting in a vessel diameter <5mm in diameter for the 14F MANTA VCD or <6 mm in diameter for the 18F MANTA VCD, or > 50% diameter femoral or iliac artery stenosis
20. Patients in whom, during initial access of the artery, arteriotomy and surrounding anatomy cannot be visualized and identified clearly under U/S imaging and/or if the vertical depth from the surface of the skin to the target area of the common femoral artery measures greater than 6cm

7.4. 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 patients is a potential candidate for the study.

7.5. Informed consent

Subject participation in this clinical study is voluntary. Informed Consent and authorization to use and disclose PHI is required from all subjects agreeing to participate in the study. The investigator or trained designee will discuss the study background along with the benefits and risks of the study. Ample time and opportunity for candidate to inquire about details of the study in order to decide whether or not to participate in the study should be given.

For this study, the potential subject must sign the informed consent form that has been approved by the study site's Institutional Review Board (IRB) / Research Ethics Board (REB). A copy of the signed and dated written consent form shall be given to the subject, an original shall be filed in the subject's medical record, and a copy maintained with the site's research documentation.

Subjects should sign the informed consent prior to undergoing any non-standard of care testing required by this study protocol.

Throughout the study, should there be important updates to the protocol and/or additional risks identified, a new IRB/REB approved consent form will require the subject's signature and date.

7.6. Enrollment

All subjects that sign an informed consent, undergo the TAVR procedure, and an attempt (insertion of MANTA VCD sheath) to close the arteriotomy with the MANTA VCD will be considered enrolled and will be followed until study conclusion. If a subject signs the informed consent, but does not undergo the TAVR procedure or if no attempt is made to use the MANTA device, the subject will be withdrawn from the study and will not count toward total population analyzed.

7.7. Withdrawal

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.

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

Possible reasons for withdrawal include:

- Adverse Event
- Subject is unwilling or unable to comply with follow up requirements
- Explantation of device
- Subject withdraws consent and/or PHI authorization
- Subject is Lost to Follow up after 3 attempts to reach out to the subject with final attempt documented on a registered letter.
- Investigator determines that the subject should no longer continue in the study
- Death

8. Study Procedures

8.1. Screening and Baseline Visit Data Collection

Informed consent and authorization to use and disclose PHI 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 according to the site's standard of care practice for pre-procedure labs prior to the TAVR procedure.

8.1.1. *Computed Tomography Angiography (CTA) Scan and Core Lab*

All subjects must have a high-quality baseline CTA within 180 days of procedure, to assess both limbs for presence and absence of calcium, atherosclerotic disease, tortuosity and flow rates. Patients noted to have calcification as defined in the exclusion criteria will be excluded from the study following the CTA and considered screen failures.

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

It is the responsibility of each site to perform the local interpretation of the CTA scans 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. If the Core Lab determines that the data are unreadable, the site will be responsible for having the subject return for another assessment.

8.1.2. *Medical History*

Medical history including demographic information will be collected on each subject and updated as necessary throughout the study.

8.1.3. *Laboratory Tests*

- Hemoglobin, creatinine, and platelet count
- International normalized ratio (INR)

8.1.4. *Pregnancy Test*

- Female subjects of child bearing potential only. Test to be conducted within 7 days prior to TAVR procedure or according to standard of care for TAVR procedures requiring contrast and angiography. Urine pregnancy test is acceptable.

8.1.5. *Medications*

The following medications will be recorded on the eCRF for each subject: cardiovascular medications (e.g., anti-hypertensives, anti-arrhythmic, etc.), anti-coagulants, anti-thrombotic and anti-platelets. Any changes to these medications will be documented throughout the course of the 12 month follow up.

8.2. TAVR Procedure

At the start of the interventional procedure, it is mandatory that the operator access the target (ipsilateral) femoral vessel using U/S to ensure precise anterior wall entry placement, preferably

using micropuncture approach. The TAVR procedure should be performed per Standard of Care until time for vessel closure.

8.3. Closure Procedure

Just prior to access site closure, document ACT and systolic BP (ACT should be <250 seconds prior to closure, Systolic BP should be <180mmHg per MANTA VCD IFU but these targets are not mandatory per protocol; capturing ACT and SBP prior to closure is mandatory).

The operator should refer to the study specific U/S-Guided Closure Procedure Instructions located in the site binder for details pertaining to the specific steps for closing the femoral access site using the MANTA VCD. The closure procedure must be performed by an authorized operator.

8.3.1. *Time to Hemostasis Measurement*

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

As Time to Hemostasis is an important secondary endpoint for this study, it is critical to measure and document it accurately.

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

8.3.2. *Additional Procedure and Post-closure Required Documentation*

The following items are to be recorded on the eCRF:

- Use of certain medications:
  - Cardiovascular medications (e.g., anti-hypertensives, anti-arrhythmic, etc.), anti-coagulants, anti-thrombotic and anti-platelets
- Use of any adjunctive devices or methods (e.g., lidocaine/epinephrine or thrombin injection beyond institution's standard of care protocol) to obtain hemostasis
- Target Femoral angiogram
- Assessment of adverse events

8.4. Post Procedure

The following assessments will take place post procedure (within 3-12 hours of closure):

- Medication changes
- Target Femoral access site assessment
- Recording of any adverse events

- Ambulation: 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.
    - It is recommended that 6 hours after removal of the MANTA sheath, if the femoral access site is suitable for ambulation and if medically indicated, the subject should be asked to stand at bedside.
    - If the patient successfully stands with no or minimal oozing, the patient should be asked to walk 6 meters (20 feet). If the patient ambulates successfully, record the ambulation time on the CRF.
    - If the patient is unable to walk 6 meters (20 feet), 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 eCRF.

8.5. Discharge

The subject is ready for discharge when the subject has ability to walk 6 meters (20 feet), is free from orthostatic hypotension [defined as stable blood pressure and heart rate after ambulating], has the ability to void, and has a stable groin site without bleeding or expansion of a prior hematoma. However, discharge should follow standard hospital procedures and or clinician practices.

The following assessments will take place just prior to discharge:

- Documentation of any changes to medications
- Target Femoral access site assessment
- Recording of any adverse events
- Any subsequent secondary interventions since post procedure (For example, any additional surgical or percutaneous interventions post the index large bore procedure that occurred on the femoral artery of the MANTA (ipsilateral) leg, such as percutaneous coronary intervention (PCI), through the 12 month follow-up phone call.)

The date and time of discharge for each subject should be recorded in the eCRF.

9. Study Follow up Visits

9.1. 30 Day Office Visit

The following evaluations will be performed in the office/clinic at 30 days (± 7 days) post procedure:

- Assess any changes to medications
- Adverse events
- Target Femoral access site assessment
- Any subsequent secondary interventions since discharge (For example, any new surgical or percutaneous interventions post the index large bore procedure that occurred on the femoral artery of the MANTA (ipsilateral) leg, such as percutaneous coronary intervention (PCI), through the 12 month follow-up phone call.)

9.2. 12-month Phone Assessments

The following assessments will be collected via phone at 12 months (± 30 days) post procedure:

- Assess any changes to medications
- Adverse event inquiry (specific to adverse events related to the MANTA leg and/or a MANTA related adverse event between 30 days and 12 months)
- Target Femoral access site assessment question
- Any subsequent secondary interventions since the 30-day visit (For example, any new surgical or percutaneous interventions post the index large bore procedure that occurred on the femoral artery of the MANTA (ipsilateral) leg, such as percutaneous coronary intervention (PCI), through the 12 month follow-up phone call.)

10. Data Management

10.1. Electronic Case Report Form (eCRF) Entry

Data from study site medical records and source worksheets will be entered into an online electronic data capture (EDC) system. Qualified study staff at each site will perform primary data collection drawn from source document (hospital chart) review. Sponsor designated monitors will perform clinical monitoring, including review of eCRFs with verification to the source documentation.

Data entry should occur in a timely manner for accuracy, but additionally for complying with regulations if unanticipated or serious adverse event occurs.

10.2. Data Management

The Sponsor or its designee will review the data against the original source documents and ensure any noted discrepancies are resolved by the investigational site, in accordance with the separate data management and monitoring plan(s). Subject data will be compared to information originally recorded on source documents related to the trial (e.g., professional notes, laboratory reports, investigation-specific worksheets, etc.). The extent of source document verification may be risk-based.

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.

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.

10.3. 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 supplement approval or 2 years beyond the termination of this study, in the case of the Sponsor's decision not to pursue a PMA supplement.

10.4. Confidentiality

The investigators and Sponsor (and its parent company, Teleflex Incorporated) commit to maintaining the confidentiality of individual data of subjects involved in the study. All data collection forms and related documents will be submitted using unique, confidential subject identification numbers. All documents submitted to the Sponsor will be maintained in strict confidence.

Each subject's data will be completely de-identified in the final reports and subsequent publications in order to maintain subject confidentiality. All investigators and study site staff must comply with the requirements of all applicable U.S. (e.g., HIPAA) or Canadian laws and local regulations with regards to the collection, storage, processing and disclosure of personally identifying medical information.

10.5. Protocol Deviations

A protocol deviation is defined as any instance during the conduct of the study in which the investigator or other site personnel changed or failed to adhere to the study design or procedures specified by this protocol. Examples of protocol deviations may include (but are not limited to):

- Enrollment of a study subject who does not meet all of the inclusion/exclusion criteria specified in this protocol;
- Failure to obtain a specified data element or endpoint (e.g., lab test results, TTH, safety events, etc.); or
- Enrollment of a patient during a lapse in IRB/REB approval of the study.

All relevant protocol deviations should be submitted by the site on the applicable eCRF, and will be reviewed and assessed for their impact on subject safety and data analysis by the sponsor or its designee. Investigational sites are expected to comply with this study protocol except where necessary to protect the life or physical well-being of a subject in an emergency (in cases of medical emergency, the Sponsor should be notified within 24 hours of the occurrence of the event).

Investigational sites should report deviations to their IRBs/REBs per their local requirements.

10.6. 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 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.

11. Adverse Events

11.1. Definitions

All of the following adverse event terms are defined in Appendix A-Definitions:

- Adverse Event (AE)
- Adverse Device Effect (ADE)
- Device Deficiency (DD)
- Serious Adverse Event (SAE)
- Serious Adverse Device Effect (SADE)
- Unanticipated (Serious) Adverse Device Effect (UADE/USADE)

11.2. Potential Adverse Events and Adverse Device Effects

The following potential adverse events are related to the deployment of VCDs:

- Ischemia of the leg or stenosis of the femoral artery
- Local trauma to the femoral or iliac artery wall, such as dissection
- Retroperitoneal bleeding, and its consequences, as a result of failed closure in the setting of an access above the inguinal ligament or the most inferior border of the epigastric artery
- Perforation of iliofemoral arteries, causing bleeding or hemorrhage
- Thrombosis formation or embolism
- Adjacent nerve damage or neuropathy
- Other access site complications leading to bleeding, hematoma, pseudoaneurysm, or arterio-venous fistula, possibly requiring blood transfusion and/or surgical intervention

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
- Bradycardia
- Compartment Syndrome
- Death related to procedure
- Deep vein thrombosis
- Ecchymosis
- Edema
- Infection at the puncture site which may require antibiotics or extended hospitalization
- Inflammatory response
- Late arterial bleeding
- Oozing from the puncture site
- Pressure in groin/access site region

- Vessel laceration or trauma
- Wound dehiscence

11.3. Adverse Event (AE) Assessment

Starting at the time an attempt is first made to use the MANTA VCD (including U/S use post TAVR valve deployment and prior to MANTA VCD use) and at each subsequent evaluation, the investigator will determine if any AEs have occurred in any subject. Subjects are encouraged to report AEs freely or in response to general, non-directed questioning. The subject may volunteer information that appears to be an AE anytime during the study. If an AE is determined to have occurred, the investigator should obtain all the required information and document findings on the eCRF.

In general, a primary diagnosis for the event should be reported instead of each symptom. Only exacerbated conditions or new onset qualify as an AE, but if patient history is in question, report AE conservatively.

11.4. Relatedness to Device or Procedure

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

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

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

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

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;
- the event has no temporal relationship with the use of the investigational device or the procedures;
- the event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the event;
- the event involves a body-site or an organ not expected to be affected by the device or procedure
- the event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- harms to the subject are not clearly due to use error;

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

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

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

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

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

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

11.5. 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.

11.6. AE and Serious Adverse Event (SAE) Reporting to Sponsor

All SAEs, irrespective of potential causal relationship to the device, procedure or study, that occur from the point of attempted MANTA VCD placement (including U/S use post TAVR completion and prior to MANTA VCD use) 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. The information for the event will include the date of awareness, 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.

11.7. IRB and Regulatory Agency Reporting of Adverse Events

11.7.1. *U.S. Sites*

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 evaluation that has determined a UADE has occurred 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.

11.7.2. *Canadian Sites*

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

11.7.3. *Device Deficiencies*

The Investigator will record any device deficiencies, as defined in Appendix A, 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 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.

12. Clinical Events Committee

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

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

- All Adverse Events that are categorized by the investigator on the eCRF as “associated with the target artery and/or the ipsilateral leg (not the contralateral side)”;
- All Adverse Events marked on the eCRF that are categorized by the investigator as having a possible, probable or causal relationship with the MANTA device.

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

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

Lastly, the CEC will also classify each AE whether it is a VARC-3 Major or VARC-3 Minor complication or neither.

13. Data & Safety Monitoring Committee

A Data & Safety Monitoring Committee (DSMC) will be established for this study. The DSMC will be independent from the Sponsor and the study investigators. It will consist of at least three (3) members: two interventional cardiologist physicians that will also act on the CEC and an independent statistician; the two physicians must have extensive experience with large-bore cardiovascular interventions, preferably experience using the MANTA VCD. The DSMC will be established and operate according to a charter defined prior to the initiation of the trial. The DSMC will review cumulative adverse event data and will recommend study termination if safety

concerns warrant such action. If the DSMC believes it is possible to predict adverse events, guideline criteria for recommending study termination will be established before enrollment in the study begins. The DSMC will meet by phone or face-to-face, at least 2 times during the study in order to assure close and timely monitoring of adverse events and outcomes.

14. Risks and Benefits

14.1. Anticipated Clinical Benefits

There are no guaranteed benefits from participation in this study. The MANTA VCD is FDA approved and has received CE Mark in Europe, allowing the device to be marketed in the United States and Europe. The MANTA VCD is investigational in Canada. In published clinical studies, the MANTA VCD has shown to be safe and effective in closing large bore arteriotomies with low rates of vascular complications.[5-7]

The U/S technique used for closure is not currently part of the approved labeling for the MANTA VCD but has been used at some hospitals as part of standard practice.[21] It is thought that U/S closure may decrease rates of vascular complications in patients whose access sites are closed with the MANTA VCD.[21]

Information gained from this study may be used to benefit future MANTA patients and help guide their therapy.

14.2. Anticipated Risks

14.2.1. *Risks of Study Required Assessments*

Data collected for this study includes mostly standard of care assessments. Assessments that may be specific to this protocol include additional U/S evaluations at the time of the closure procedure.

The U/S evaluations are noninvasive and do not expose subjects to harmful radiation. There are no risks associated with this test, and most people feel little to no discomfort during use of U/S.

14.2.2. *Anticipated Adverse Device Effects*

Use of the U/S-guided MANTA VCD deployment carries risk from procedural error, inherent use hazards, and device failure. This method does not pose any new or increased risks compared to using the MANTA VCD without U/S. A complete list of anticipated adverse device effects can be found in Section 11.2 - Potential Adverse Events and Adverse Device Effects.

14.2.3. *Risk Mitigation*

Clinical risks will be minimized by careful assessment of the subject prior to, during, and after the procedure. Careful follow-up will help minimize risks associated with changing conditions of the subject. Subjects will be selected in accordance with the subject inclusion and exclusion criteria.

All Investigators selected to participate will have performed at least 25 successful cases with a MANTA VCD and have currently used U/S for access in at least 50 large bore procedures. Additionally, prior to enrolling in the study, all investigators will have completed formal training and documented up to 2 roll-in cases.

The study sites selected will have adequate personnel, resources and facilities to safely conduct the study in compliance with this protocol and the study agreement.

14.2.4. *Risk to Benefit Rationale*

The potential benefits of U/S-guided MANTA VCD closure 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.

15. Statistical Analysis

15.1. Study Hypothesis

15.1.1. *Safety*

The primary safety analysis will be performed on the first 75 chronologically enrolled PAC (non roll-in) subjects where an attempt to use the MANTA VCD is made (enrolled subjects without an attempt will not be included). 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 PAC. The primary safety endpoint is any Large Bore Access-site Related VARC-2 Major Vascular complication (LBAR VARC-2 Major) within 30 days as defined in Section 6 and adjudicated by the CEC.

The primary safety hypothesis is that the LBAR VARC-2 Major complication rate (proportion of subjects with one or more) is less than the Performance Goal of 14.2%, as follows:

H_O: $\pi \geq 0.142$
vs.
H_A: $\pi < 0.142$,
where π is the population LBAR VARC-2 Major complication rate within 30 days.

The primary safety hypothesis is that the rate of LBAR VARC-2 Major complications within 30 days of the procedure is less than the performance goal of 14.2%. Derivation of the performance goal is described below.

Stated in words, the hypothesis is:

Null hypothesis: The rate of LBAR VARC-2 Major complications within 30 days after the procedure is not less than the performance goal of 14.2%

Alternate hypothesis: The rate of LBAR VARC-2 Major complications within 30 days after the procedure is less than the performance goal of 14.2%

15.2. Sample Size Considerations

The performance goal and the postulated event rate in the prospective study population are based upon clinical judgment supported by outcomes from comparable published studies in Table 4 below; in particular rows pertaining to studies of similar size to the proposed 75 patients are shown in bold. Results for all studies shown used VARC-2 definitions.

Table 4: Safety Performance of the MANTA VCD from Published Literature

		VARC-2 Major Complication			95% Confidence Interval*
Reference	**N MANTA VCD subjects**	**Essential Medical Sponsored**	**Independent MANTA VCD Studies**	**Overall**	
Van Mieghem 2017 (CE Mark)[6]	**50**	**2.0%**		**2.0%**	**0.0%, 10.6%**
Wood 2019 (IDE Study)[7]	263	4.2%		4.2%	2.1%, 7.4%
Van Mieghem 2020 (MARVEL)[9]	500	4.0%		4.0%	2.5%, 6.1%
Biancari 2018[13]	**107**		**9.3%**	**9.3%**	**4.6%, 16.5%**
DePalma 2018[11]	**89**		**1.1%**	**1.1%**	**0.0%, 6.1%**
Gheorghe 2019[14]	169		0.6%	0.6%	0.0%, 3.3%
Hoffman 2018[15]	**75**		**10.7%**	**10.7%**	**4.7%, 19.9%**
Moccetti 2019[16]	**100**		**7.0%**	**7.0%**	**2.8%, 13.9%**
Moriyama 2019[17]	**111**		**7.0%**	**7.0%**	**3.2%, 13.7%**
Van Wiechen 2021[12]	**102**		**1.9%**	**1.9%**	**0.2%, 6.9%**
Moccetti 2021[10]	**100**		**1.0%**	**1.0%**	**0.2%, 5.4%**
Weighted Average	**1666**	**3.9%**	**4.4%**	**4.2%**	**2.0, 8.4%**

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

Based on these results, the population LBAR VARC-2 Major complication rate is hypothesized to be 4.2%, the weighted average of the above rates. Examining the confidence intervals above, the upper confidence limits for comparably-sized studies range from 5.4% to 19.9%, corresponding to point estimates of 1.0% to 10.7%. A performance goal of 14.2%, which is based on clinical judgment regarding device performance, falls well within this range, indicating that it is constructed in a fashion consistent with prior findings in the literature.

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

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

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

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

15.3. Data Analysis

15.3.1. *Cohort Definitions*

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

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

15.3.2. *Primary Safety Endpoint*

The rate of LBAR VARC-2 Major complications within 30 days (based on CEC-adjudicated data) following procedure will be presented along with the exact one-sided upper 97.5% confidence bound for subjects with one or more events. If this upper confidence bound is less than 14.2%, the study will have met its primary objective.

15.3.3. *Secondary Endpoints*

Secondary endpoints will be summarized using descriptive statistics including mean, standard deviation, median, range for continuous data and frequency and proportions for categorical data.

The following secondary endpoints will be evaluated for the MANTA VCD, definitions are provided in Section 6.

- Time to Hemostasis (effectiveness)
- Technical Success (effectiveness)
- Ambulation Success (effectiveness)
- Time to Ambulation (effectiveness)
- Treatment Success (effectiveness)
- Procedure Time (effectiveness)
- Any Large Bore Access-site Related VARC-2 Minor Vascular (LBAR VARC-2 Minor) complication within 30 days (based on CEC-adjudicated data) (safety)

15.3.4. *Additional Analyses*

The following outcomes will be analyzed using descriptive statistics:

- Any long-term LBAR VARC-2 Major and Minor complications (>30 days to 12 months post procedure)
- Procedural and Post-procedural Characteristics such as:
    - Readmission rates within 30 days
    - Delayed ambulation (beyond institution's ambulation protocol) for subjects

with LBAR VARC-2 Major or LBAR VARC-2 Minor complications
- Delayed discharge (beyond institution's discharge protocol) for subjects with LBAR VARC-2 Major or LBAR VARC-2 Minor complications
- Use of adjunctive devices required at large bore access site (Angio-Seal, ProGlide, Prostar XL, balloon, stent, covered stent or surgical repair)
- VARC-3 Major and Minor Vascular Complications within 30 days (adapted from VARC-3 criteria)
- Subsequent Secondary Intervention(s) (For example, any new surgical or percutaneous interventions post the index large bore procedure that occurred on the femoral artery of the MANTA (ipsilateral) leg, such as percutaneous coronary intervention (PCI), through the 12 month follow-up phone call.)

15.3.5. *Timing of Reports*

IDE annual progress reports will be submitted as required per applicable law and regulations. A primary analysis report will be submitted to FDA to support a PMA supplement for revised labeling when the first 75 PAC subjects have completed their 30 day follow-up visit. A final clinical study report will be submitted once all 150 PAC subjects have been enrolled, completed all follow-up visits and have exited the study.

15.4. Poolability Analysis

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

LBAR VARC-2 Major complications will be analyzed by Fisher's Exact test to assess if the LBAR VARC-2 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.

15.5. Missing Data

Every effort will be undertaken to limit premature discontinuations and ascertain completeness of data collection throughout the course of the study. It is unlikely that there would be missing data for the LBAR VARC-2 Major complication endpoint as a 30 day follow-up visit is typically standard of care for TAVR patients; therefore all subjects with an attempted procedure are expected to be followed for at least 30 days. The 12 month follow up assessment will be conducted via phone; sites will ensure that subject contact details are on file correctly when concluding the 30 day visit.

Missing data will not be imputed, and all available data will be summarized.

16. Sponsor responsibilities

16.1. Site and Investigator Selection

The primary consideration in operator and site selection for this trial is adequate experience with the MANTA VCD, using U/S routinely and conducting clinical trials, commitment to safety, and consistency in adherence to the clinical protocol. Prior to performing the U/S-guided MANTA

closure procedure, 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 trained on the U/S-guided MANTA VCD closure procedure during cases proctored by a previously trained Investigator or by a company representative.

All investigators selected for the MANTA ULTRA Closure study (up to 2 operators per site) will have undergone MANTA training programs and must have the following to participate:

- Experienced operators with 25 or greater (≥25) MANTA VCD closures (Verified by Sponsor. Must include at least 10 Sponsor training cases)
- Currently using U/S for femoral access in large bore procedures, with an operator experience of at least 50 U/S-guided access cases

16.2. Site Training

The training of appropriate clinical site personnel on this study protocol and the study procedures will also be the responsibility of Sponsor or their designee. The Investigator is responsible for ensuring that study site staff conduct the study according to this protocol and are qualified to perform their delegated study activities.

To ensure uniform data collection, adherence to Sponsor procedures and understanding of this protocol, the Sponsor or its representative(s) will present a formal training session to study site personnel before study recruitment commences.

16.3. Monitoring

It is the responsibility of the Sponsor is to ensure proper monitoring of study. Qualified Sponsor clinical monitors or their designee will perform on site and/or remote auditing of study records to ensure accuracy and compliance. A monitoring plan will be established in advance of study initiation. On site or remote monitoring visits will be performed on a site-by-site basis, as warranted by the findings of previous monitoring visits.

The Investigator and study staff are expected to cooperate and provide all relevant study documentation to the monitor upon request, including access to the study data, such as electronic or paper medical records.

If a monitor finds that an Investigator is not complying with the executed study agreement, this protocol, applicable laws and regulations, or the requirements of the reviewing IRB/REB, prompt action will be taken to secure compliance.

By signing this protocol, the Investigator grants permission to Sponsor, and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all required study documentation.

16.4. Initial Procedures

The Sponsor or its designee(s) may attend the initial procedures utilizing the U/S-guided MANTA VCD closure method 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

Sponsor may be held after a few initial procedures to assure adherence to the study protocol and data collection requirements.

16.5. Review of Study Documents

The Sponsor or its designee 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 will be reviewed by the Sponsor.

(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.

16.6. Device Accountability

The Sponsor will supply each Investigator with an adequate number of 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 perform as it was intended to function according to the instructions for use.
- All situations where the device is physically defective.

17. Investigator Responsibilities

The investigator is responsible for ensuring the study is conducted according to all signed agreements, this protocol, applicable local, state, federal and other national laws and regulations and Good Clinical Practice requirements. Investigators will be trained on the appropriate records and reports to maintain and file. Sponsor and Investigators will maintain records relating to the study for a minimum period of two years after study termination or as required by applicable local, state, federal and other national laws and regulations. No Investigator may dispose of any of these records until receipt of written notification to do so from Sponsor.

It is the responsibility of the Investigator to provide each subject with full and adequate verbal and written information before inclusion in the study using the IRB/REB approved informed consent document, including the objective and procedures of the study and the possible risks involved. The Investigator shall also ensure that subjects sign an authorization or other form required by applicable U.S. or Canadian laws governing the use and disclosure of individually identifiable health information to permit access to and disclosure to such information to the Investigator, Study Staff, Sponsor, Sponsor's authorized employees and representatives, study auditors and monitors, the FDA, Health Canada and/or other applicable regulatory agencies involved in approving use of the study device. For HIPAA purposes, the authorization may be combined with the informed consent form approved by the Sponsor and the IRB/IEC.

In cases of withdrawal or lost to follow up, the study Investigator should document the contact attempts and reasons for subject withdrawal or loss to follow up with other supporting information as requested on the appropriate eCRFs.

18. Vulnerable Population

The intended patient population of this study does not meet the criteria of vulnerable population as defined in BS EN ISO 14155:2020.

19. Statement of Compliance

This study 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/REB and regulatory authorities, including the U.S. FDA and Health Canada; BS EN ISO 14155:2020 and other applicable regulatory requirements, whichever provides the greater protection of the individual.

This study will not be initiated until approval has been obtained from the regulatory authority in the country where the site is located and from the IRB/REB governing that site. Any additional requirements imposed by the IRB/REB or regulatory authority will be followed. No changes to this protocol will be implemented without the prior review and approval of the IRB/REB and the regulatory authority.

This protocol conforms to all the standards of U.S. Medicare coverage requirements. The MANTA VCD subject characteristics are consistent with the Medicare population, as the

average age of subjects undergoing TAVR is approximately 80 years, and the results are expected to be generalizable to the Medicare population based on age of the included subjects.

This study will be registered with the National Institutes of Health National Library of Medicine's ClinicalTrials.gov, as required for studies seeking Medicare coverage.

20. Publication Policy

The conditions under which a study site and/or Investigator may publish results from this study in any form are defined in detail in the clinical study agreement.

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22. Appendix A: Definitions

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

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

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

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

Bleeding Academic Research Consortium (BARC)[25]: Standardize bleeding definitions for cardiovascular clinical trials.

Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek treatment
Type 2	Any clinically overt sign of hemorrhage that "is actionable" and requires diagnostic studies, hospitalization, or treatment by a health care professional
Type 3	a) Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL (provided hemoglobin drop is related to bleed); transfusion with overt bleeding b) Overt bleeding plus hemoglobin drop < 5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring IV vasoactive agents c) Intracranial hemorrhage confirmed by autopsy, imaging, or lumbar puncture; intraocular bleed compromising vision
Type 4	CABG-related bleeding within 48 hours
Type 5	a) Probable fatal bleeding b) Definite fatal bleeding (overt or autopsy or imaging confirmation)

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

Life-threatening or disabling bleeding:

- Fatal bleeding (BARC type 5) OR
- Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) OR

- Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) OR
- Overt source of bleeding with drop in hemoglobin ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units* (BARC type 3b)

Major bleeding (BARC type 3a):

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

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

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

Bleeding VARC-3: : Definitions used in conjunction with VARC-3 Major complications and VARC-3 Minor complications. As defined in the VARC-3 Clinical Guidelines:

Type 1

- Overt bleeding that does not require surgical or percutaneous intervention, but does require medical intervention by a health care professional, leading to hospitalization, an increased level of care, or medical evaluation (BARC 2)
- Overt bleeding that requires a transfusion of 1 unit of whole blood/red blood cells (BARC 3a)

Type 2

- Overt bleeding that requires a transfusion of 2–4 units of whole blood/red blood cells (BARC 3a
- Overt bleeding associated with a haemoglobin drop of >3 g/dL (>1.86 mmol/L) but <5 g/d (<3.1 mmol/L) (BARC 3a)

Type 3

- Overt bleeding in a critical organ, such as intracranial, intraspinal, intraocular, pericardial (associated with haemodynamic compromise/tamponade and necessitating intervention), or intramuscular with compartment syndrome (BARC 3b, BARC 3c)
- Overt bleeding causing hypovolemic shock or severe hypotension (systolic blood pressure <90 mmHg lasting >30 min and not responding to volume resuscitation) or requiring vasopressors or surgery (BARC 3b)
- Overt bleeding requiring reoperation, surgical exploration, or re-intervention for the purpose of controlling bleeding (BARC 3b, BARC 4)
- Post-thoracotomy chest tube output ≥2 L within a 24-h period (BARC 4)
- Overt bleeding requiring a transfusion of ≥5 units of whole blood/red blood cells (BARC 3a)
- Overt bleeding associated with a haemoglobin drop ≥5 g/dL (≥3.1 mmol/L) (BARC 3b).

Type 4

- Overt bleeding leading to death. Should be classified as:
  - Probable: Clinical suspicion (BARC 5a)
  - Definite: Confirmed by autopsy or imaging (BARC 5b)

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

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

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

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

Hemostasis (Time to): The elapsed time between MANTA deployment (withdrawal of sheath from artery and first observed and confirmed arterial hemostasis (no or minimal subcutaneous oozing and the absence of expanding or developing hematoma). Time to Hemostasis should be inclusive of any time that manual or mechanical pressure is applied specifically to stop arterial bleeding. Do not include time spent when light digital or mechanical pressure is done to treat oozing, or if short manual compression is done as a preventative measure as part of standard of care.

Large Bore Access-site Related VARC-2 Major Vascular (LBAR VARC-2 Major) Complications: Adapted from the VARC-2 Clinical Guidelines -– Standardized endpoints for transcatheter aortic valve implantation[1]:[a]

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

Large Bore Access-site Related VARC-2 Minor Vascular (LBAR VARC-2 Minor) Complication: Adapted from VARC-2 Clinical Guidelines – Standardized endpoints for transcatheter aortic valve implantation:

- Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysms, hematomas, percutaneous closure device failure) not leading to death, life-threatening or major bleeding, visceral ischemia, or neurological impairment OR

[a] 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

- Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR
- Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR
- Vascular repair or the need for vascular repair (via surgery, U/S-guided compression, transcatheter embolization, or stent-graft) OR
- Percutaneous closure device failure - Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)

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

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

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

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

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

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

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

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

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

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

Severe Peripheral Vascular Disease: Any of the following:

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

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

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

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

Time to Hemostasis: The elapsed time between MANTA deployment (withdrawal of sheath from artery) and first observed and confirmed arterial hemostasis (no or minimal subcutaneous oozing and the absence of expanding or developing hematoma). Time to Hemostasis should be inclusive of any time that manual or mechanical pressure is applied specifically to stop arterial bleeding. Do not include time spent when light digital or mechanical pressure is done to treat oozing, or if short manual compression is done as a preventative measure as part of standard of care.

Treatment Success: A subject will be considered a Treatment Success if he/she has Time to Hemostasis ≤10 minutes and has **no** LBAR VARC-2 Major complications within 30 days.

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

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

Valve Academic Research Consortium 3 (VARC-3): updated endpoint definitions for Aortic Valve Clinical Research

VARC-3 Major Vascular Complications:

One of the following:

- Aortic dissection or aortic rupture
- Vascular (arterial or venous) injury (perforation, rupture, dissection, stenosis, ischaemia,

arterial or venous thrombosis including pulmonary embolism, arteriovenous fistula, pseudoaneurysm, haematoma, retroperitoneal haematoma, infection) or compartment syndrome resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment

- Distal embolization (non-cerebral) from a vascular source resulting in death, amputation, limb or visceral ischaemia, or irreversible end-organ damage
- Unplanned endovascular or surgical intervention resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment
- Closure device failure‡ resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment
  A failure to achieve hemostasis at the access site, resulting in alt. treatment (other than manual compression or adjunctive endovascular ballooning)

VARC-3 Minor Vascular Complications

One of the following:

- Vascular (arterial or venous) injury (perforation, rupture, dissection, stenosis, ischaemia, arterial or venous thrombosis including pulmonary embolism, arteriovenous fistula, pseudoaneurysm, haematoma, retroperitoneal haematoma, infection) not resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment
- Distal embolization treated with embolectomy and/or thrombectomy, not resulting in death, amputation, limb or visceral ischaemia, or irreversible end-organ damage
- Any unplanned endovascular or surgical intervention, ultrasound guided compression, or thrombin injection, not resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment
- Closure device failure‡ not resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment
  A failure to achieve hemostasis at the access site, resulting in alt. treatment (other than manual compression or adjunctive endovascular ballooning)