Vortex Temporary Percutaneous Transvalvular Circulatory Support System Feasibility Study

Vortex Feasibility Study

S2465

CLINICAL INVESTIGATION PLAN

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Original Release: 10-Feb-2020

Current Version: 21-May-2021

Revision History

Revision Number	Release Date	Template Version	Reason for Change
A	10-Feb-2020	90702637 Rev/Ver AL	Not Applicable
B	13-Nov-2020	90702637 Rev/Ver AM	See Table 25.1-1

Revision History

Revision Number	Release Date	Template Version	Reason for Change
C	3-Mar-2021	90702637 Rev/Ver AO	Change in Inclusion Criteria 3. LVEV is changed from left ventricular ejection fraction (LVEF) ⩽ 35% into left ventricular ejection fraction (LVEF) ≤ 50% to be consistent with the inclusion criteria of other contemporary mechanical circulatory support device studies and the labelling of the commercially approved (Abiomed) device
C	3-Mar-2021	90702637 Rev/Ver AO	In Table 18.4-1 is the Serious Health Threat removed to follow the new protocol template where this is no longer required for the Investigator Reportings.
D	21-May-2021	90702637 Rev/Ver AP	See Table 25.1-1

2. Protocol Synopsis

<table>
<tr><th colspan="2">Vortex Temporary Percutaneous Transvalvular Circulatory Support System Feasibility Study: Vortex Feasibility Study</th></tr>
<tr><td>Study Objective(s)</td><td>To evaluate the feasibility and safety of the Vortex Temporary Percutaneous Transvalvular Circulatory Support System (Vortex System) in subjects undergoing elective high-risk percutaneous coronary intervention (HR-PCI)</td></tr>
<tr><td>Planned Indication(s) for Use</td><td>The Vortex System is indicated to provide temporary (≤ 4 hours) circulatory support in subjects undergoing elective high-risk percutaneous coronary intervention (HR-PCI).</td></tr>
<tr><td>Test Device</td><td>The Vortex System is a minimally invasive device that is in direct contact with the heart while in use. Components are summarized below.
<table>
<tr><th>Component</th><th>Description</th></tr>
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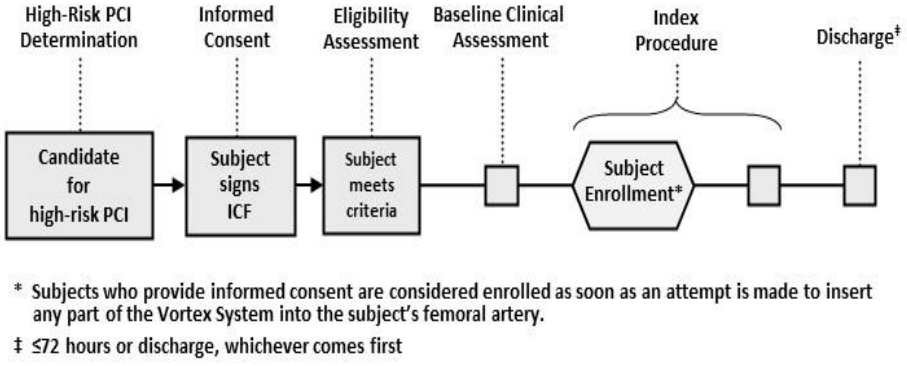
Vortex Temporary Percutaneous Transvalvular Circulatory Support System Feasibility Study: Vortex Feasibility Study	
Study Design	The Vortex Feasibility Study is a prospective, open-label, single-arm study designed to assess the safety and feasibility of the Vortex System to provide temporary (≤ 4 hours) circulatory support in subjects undergoing HR-PCI. The study design is summarized in the figure below.  **Vortex Feasibility Study Design Overview** The Vortex study will be conducted in accordance with the International Standard ISO 14155:2020 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice; European Medical Device Regulations; ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country/state/local laws and regulations. The study shall not begin until the required approval/favorable opinion from the Independent Ethics Committee (IEC)/Human Research Ethics Committee (HREC) and/or regulatory authority has been obtained, if appropriate.
Planned Number of Subjects / Investigational Centers / Countries	There will be up to 10 subjects enrolled in up to 3 centers in Australia and Europe.
Primary Endpoint	The primary endpoint consists of Technical Success and Clinical Success, defined as follows. <u>Technical Success</u> • Successful delivery of the device to the correct anatomical position; and

Vortex Temporary Percutaneous Transvalvular Circulatory Support System Feasibility Study: Vortex Feasibility Study	
	• Successful operation and removal of the Vortex circulatory support system Clinical Success • No conversion to open heart surgery; and • No in-hospital mortality
Additional Measurements	Safety events will be collected through 72 hours post-procedure or hospital discharge, whichever comes first, as listed below. • Stroke/transient ischemic attack (TIA; see **Note 1** below) • Cardiac tamponade • Cardiac death (see **Note 1** below) • Myocardial infarction (MI) • Bleeding complications: Type 3–5 based on the Mechanical Circulatory Support Academic Research Consortium (MCS-ARC) definitions[a] (see **Note 1** below) • Acute kidney injury (AKI; based on the AKIN System Stage 3 [including renal replacement therapy] or Stage 2) • Major vascular complications (see **Note 1** below) • Any device-related adverse event (adverse device effect [ADE]/serious adverse device effect [SADE]) • Any procedure-related adverse event • Any adverse event related to management practices • Any adverse event related to patient specific adherence • Any unanticipated serious adverse device effect (USADE) **Note 1:** Death, stroke, bleeding complications, and major vascular complications are adjudicated by an Independent Medical Reviewer (IMR). a: Kormos RL, et al. *J Heart Lung Transplant* 2020;39:735-50
Method of Assigning	Subjects who provide written informed consent and are confirmed eligible for the study are considered enrolled in the study as soon as an

Vortex Temporary Percutaneous Transvalvular Circulatory Support System Feasibility Study: Vortex Feasibility Study	
Patients to Treatment	attempt is made to insert any part of the Vortex System into the subject's femoral artery (e.g., Vortex sheath).
Follow-up Schedule	Follow up will occur through 72 hours or hospital discharge, whichever comes first.
Study Duration	Enrollment/total study duration may be completed in approximately 12 months.
Participant Duration	The study duration for each subject is expected to be through 72 hours or hospital discharge, whichever comes first.
Inclusion Criteria	A subject will be considered for enrollment if all of the following inclusion criteria are met, provided no exclusion criteria are met. IC1. Subject provides signed informed consent. IC2. Subject is ≥ 18 years and < 90 years of age. IC3. Subject is indicated for NON-emergent PCI of at least one *de novo* or restenotic lesion in a native coronary vessel or coronary artery bypass graft (CABG) and has left ventricular ejection fraction (LVEF) ≤ 50% with the following: • Unprotected left main -OR- • Last remaining vessel -OR- • Three vessel disease (≥ 50% diameter stenoses by visual estimate or total occlusion)
Exclusion Criteria	A subject will be excluded from the study if any of the following exclusion criteria are met. EC1. Subject has had ST-elevation myocardial infarction (STEMI) within 24 hours. EC2. Subject has had pre-procedure cardiac arrest requiring cardiopulmonary resuscitation (CPR) within 24 hours of enrollment. EC3. Subject is in shock, defined as follows: • Cardiac index (CI) < 2.2 L/min/m^2 and pulmonary capillary wedge pressure (PCWP) > 15 mmHg -AND- • Hypotension (systolic blood pressure < 90 mmHg for > 30 minutes) -OR-

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	• Need for supportive measures (i.e., inotropes or mechanical support) to maintain systolic blood pressure ≥ 90 mmHg and end organ hypoperfusion (cool extremities or urine < 30 mL/hour and a heart rate > 60 beats per minute) EC4. Subject has left ventricular mural thrombus. EC5. Subject has a prosthetic aortic valve. EC6. Subject has pericarditis or constrictive heart disease (constrictive pericarditis or restrictive cardiomyopathy). EC7. Subject has moderate or greater aortic valve stenosis[b] or moderate or greater aortic valve insufficiency[b] (by echocardiographic assessment, graded as ≥ 2+). EC8. Subject has abnormalities of the aorta that preclude safe delivery of the device, including severe calcification, tortuosity, aneurysm, or prior surgery. EC9. Subject has peripheral vessel disease (PVD) preventing passage of the device (e.g., calcification, small caliber) or tortuosity that would preclude safe placement of the 16 Fr introducer sheath. **Note 2:** Minimum required vessel diameter is > 5.5 mm. EC10. Subject has advanced renal dysfunction (AKIN Stage 3). EC11. Subject has a history of liver dysfunction (Childs Class C) with elevation of liver enzymes and bilirubin > 3× upper limit of normal (ULN) or international normalization ratio (INR) ≥ 2. EC12. Subject has had a recent (within 1 month) stroke or TIA. EC13. Subject has known hypersensitivity to intravenous contrast agents that cannot be adequately pre-medicated or has known hypersensitivity to heparin, aspirin, ADP receptor inhibitors or nitinol. EC14. Subject has current or a history of heparin induced thrombocytopenia (HIT). EC15. Subject has uncorrected abnormal coagulation or platelet count ≤ 75,000/mm³ or INR ≥ 2.0. EC16. Subject has significant right heart failure (right atrial pressure [RAP] > 15 mmHg, right ventricular stroke work index

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	[RVSWI] < 0.30 mmHg·L/m², pulmonary vascular resistance [PVR] > 3.6 Woods units). EC17. Subject requires mechanical ventilation. EC18. Subject has an atrial or ventricular septal defect (including post-infarct ventricular septal defect [VSD]). EC19. Subject has left ventricular rupture. EC20. Subject has cardiac tamponade. EC21. Subject has severe pulmonary disease (FEV1 < 1L). EC22. Subject has sustained or non-sustained ventricular tachycardia. EC23. Subject is breast feeding or is pregnant. EC24. Subject has other disease condition(s) resulting in the subject being unsuitable for participation in the clinical trial (e.g. advanced malignancy with limited expected survival) EC25. Subject has other disease condition(s) which the Investigator has determined may cause non-compliance to the study requirements. b: Nishimura RA, et al. *J Am Coll Cardiol* 2014;63:e57-185.
Index Procedure	The Vortex sheath will be inserted percutaneously into the femoral artery. The Vortex wire and Vortex pump will pass though this sheath during the procedure and will be advanced through the aorta, across the aortic valve, and into the left ventricle. The wire will be withdrawn before the pump is turned on, but the sheath and pump will stay in place throughout the HR-PCI procedure and will be withdrawn as soon as the mechanical circulatory support is deemed to be unnecessary.
Statistical Methods	
Primary Statistical Hypothesis	There is no formal statistical hypothesis in this observational feasibility study.
Statistical Test Method	Descriptive statistics will be used for baseline, procedure, and follow-up data collected during the study. The primary endpoint and additional measurements will be analyzed on an intention-to-treat (ITT) basis and a per-protocol basis. Analysis sets

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	are listed below. Subjects are considered enrolled in the study as soon as an attempt is made to insert any part of the Vortex System into the subject's femoral artery. • ITT: This population includes all subjects who sign an Informed Consent Form (ICF) and are enrolled in the study, whether or not a study device is successfully inserted and used. • Per-protocol: This population includes all ITT subjects in whom the device is successfully advanced across the aortic valve into the left ventricular outflow tract and turned on.
Sample Size Parameters	This is a prospective, multicenter, non-randomized feasibility study with no formal pre-specified hypothesis and therefore sample size estimates are not applicable. In order to support the stated objectives of this feasibility study, the study sample size has been limited to a maximum of up to 10 subjects enrolled.

3. Table of Contents

3.1. *Table of Figures*

3.2. *Table of Tables*

4. Introduction

4.1. *Background*

Coronary artery disease (CAD) is a leading cause of morbidity and mortality globally[1]. Treatments to reduce adverse clinical events and improve quality of life in patients with symptomatic CAD include guideline-directed medical therapy, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG)[2,3]. As PCI technology has evolved, an expanded population eligible for percutaneous treatment has emerged, including high-risk patients who are older, have complex anatomic lesions, and/or have multiple comorbidities that preclude surgical revascularization[4,5].

4.1.1. High-Risk Percutaneous Coronary Intervention

High-risk percutaneous coronary intervention (HR-PCI) has become a valuable therapeutic approach for the growing patient population referred to as "complex high-risk and indicated patients" (CHIP)[6]. This patient group is characterized by technically complex CAD (multivessel or left main disease, anatomically complex coronary lesions, target vessel providing collateral supply to an occluded second vessel supplying > 40% of the myocardium [anticipated high ischemic burden during the procedure or last remaining conduit]), adverse hemodynamics (including abnormal ventricular/valvular function), and/or significant medical comorbidities (including advanced age, diabetes, peripheral vascular disease, heart failure, acute coronary syndromes, or previous cardiac surgery)[4]. While registry data and retrospective analysis of randomized trials suggest that complete revascularization results in the best patient outcomes[7,8], members of the CHIP population often undergo incomplete revascularization or staged PCI. This is due to prolonged procedure times and/or procedural complications owing to multiple balloon inflations or atherectomy and can lead to a higher incidence of adverse clinical outcomes[7,9]. Patients with severe CAD and reduced left ventricular ejection fraction (LVEF) are especially prone to peri-procedural complications and often have poorer long-term outcomes[10,11]. Among these patients, temporary mechanical circulatory support (MCS) may improve short- and long-term results[12].

4.1.2. Mechanical Circulatory Support

Percutaneous MCS devices are designed to temporarily decrease the load on the heart and ensure adequate organ perfusion[12-15]. They are increasingly used prophylactically or as part of an anticipatory strategy for HR-PCI patients to enable more complex procedures and provide protection from adverse events until the benefits of reperfusion are achieved (protected PCI)[12,16]. There are several percutaneous MCS devices available, with variable impact on cardiovascular hemodynamics[13,15,17]. They include the intra-aortic balloon pump (IABP), centrifugal pumps, venous arterial extracorporeal membrane oxygenation devices, and micro-axial pumps[6,15,17]. Society guidelines state that elective insertion of an appropriate hemodynamic support device as an adjunct to PCI may be reasonable in carefully selected high-risk patients[14,18].

The IABP has been studied extensively and used most widely in HR-PCI[15]. It displaces blood volume in the descending aorta by inflating during diastole and producing a potential space during systole that supports cardiac filling of the aorta. The effect is to reduce myocardial work and oxygen demand. It provides a modest increase in cardiac index (cardiac output from 0.5 to 1.0 L/min).

The Impella® device (Abiomed, Inc., Danvers, MA, USA) is a catheter-mounted, nonpulsatile, microaxial pump that continuously pulls oxygenated blood from the left ventricle and propels it into the ascending aorta[15]. This extraction unloads the left ventricle and reduces myocardial wall stress, pulmonary capillary wedge pressure, and myocardial oxygen demand. The increased unloading results in ventriculoarterial uncoupling[19]. In the presence of critical stenoses, use of Impella improves distal coronary pressure and coronary perfusion pressure, thereby lessening the ischemic burden[20]. The Impella LD®, Impella 5.0®, and Impella 2.5® received CE Mark in 2002, 2003, and 2004, respectively. The Impella 2.5, Impella CP®, and Impella CP® with SmartAssist® are CE marked for treatment of HR-PCI and acute myocardial infarction cardiogenic shock patients for up to 5 days. The United States Food and Drug Administration approved the Impella 2.5® and Impella CP® Systems as temporary (≤6 hours) ventricular support devices indicated for use during HR-PCI performed in elective or urgent, hemodynamically stable patients with severe CAD, when a heart team, including a cardiac surgeon, has determined HR-PCI is the appropriate therapeutic option[21].

Safety and effectiveness of Impella support in HR-PCI was examined in the prospective, single-arm PROTECT I feasibility study[22]. Patients (N=20) had LVEF ≤35% and underwent PCI on an unprotected left main coronary artery or last patent coronary conduit. Patients with recent ST-elevation myocardial infarction (STEMI) or cardiogenic shock were excluded. The Impella 2.5 device was implanted successfully in all patients; mean duration of circulatory support was 1.7±0.6 hours (range of 0.4 to 2.5 hours) with a mean pump flow during PCI of 2.2±0.3 L/min. Through 30 days, there were 2 deaths, 2 cases of periprocedural myocardial infarction (MI) and no cases of aortic valve injury, cardiac perforation, or limb ischemia. No patient developed hemodynamic compromise during PCI.

The 1:1 randomized PROTECT II trial compared outcomes during nonemergent HR-PCI with Impella 2.5 versus IABP in symptomatic patients with complex 3-vessel disease or unprotected left main CAD and severely depressed left ventricular function[23]. The primary end point was the 30-day incidence of major adverse events; there was also a protocol-mandated 90-day follow-up. After an interim data review, the trial was stopped prematurely for futility (69% of planned enrollment). The prespecified per-protocol analysis set included patients who met the protocol-mandated eligibility criteria (N=216 for Impella, N=211 for IABP). At 30 days, mortality in the per protocol population was similar between the 2 groups (6.9% with Impella vs. 6.2% with IABP, *P*=0.744). The 30-day primary endpoint was also not different between the groups (34.3% for Impella vs. 42.2%, *P*=0.092), but the 90-day rate of major adverse events was significantly lower with Impella (40.0% vs. 51.0%, *P*=0.023). Notably, the Impella 2.5 provided significantly better hemodynamic support compared to the IABP; maximal decrease in cardiac power was 0.04±0.24 W with Impella vs. 0.14±0.27 W with IABP (*P*=0.001). The duration of hemodynamic support was also significantly shorter with Impella (1.9±2.7 hours vs. 8.4±21.8 hours, *P* <0.001).

The safety, feasibility, and hemodynamic usefulness of Impella in HR-PCI have been examined in various registries. In the multicenter USpella registry (N=175), mortality was 3.4% in-hospital; the 30-day rate of major adverse cardiac events (MACE) was 8%[24]. Angiographic revascularization was successful in 99% of patients and ejection fraction improved significantly from 31±15% to 36±14% (P <0.001). Median support time was 1.0 hour (range 0.1–72 hours) and the average pump flow was 2.1±0.2 L/min. Among 144 consecutive patients receiving Impella support in the Europella Registry[25] there was 1 intraprocedural death and 30-day mortality was 5.5%. The duration of hemodynamic support was 87.8±50.7 minutes and placement/retrieval of the device was considered easy/suitable in >99% of cases. In the multicenter German Impella registry (N=154), Impella was successfully placed in 99.4% of cases and removed in the cath lab in 87.0%[26]. In-hospital mortality was 2.6%. Among 86 patients treated with Impella in the Roma-Verona registry, there was 1 procedural death[27]. The median value for duration of Impella support was 104 minutes (range 55–3151 minutes).

In conclusion, the success of performing HR-PCI has become increasingly dependent on the availability and improvement of MCS devices to provide hemodynamic support and left ventricular unloading. The use of MCS as an adjunct to HR-PCI may, therefore, be an important component for improvement in clinical outcomes.

4.2. *Study Rationale*

The Vortex System is intended to support stable subjects undergoing HR-PCI by temporarily decreasing the load on the heart and ensuring adequate organ perfusion. Prophylactic use of the Vortex System during HR-PCI procedures should improve patient hemodynamics and may improve patient outcomes. The Vortex design provides a therapeutic approach and mechanism of action like that of commercially available devices but may also provide improved conformation to subject anatomy and a less complex arrangement during the interventional procedure. The Vortex design has been assessed in animals, in benchtop models, and via computational simulations. However, there are currently no animal or bench models that can adequately represent the disease state of subjects undergoing HR-PCI. Therefore, a first-human-use study is required to assess and confirm device safety, and technical feasibility of device use during the HR-PCI procedure to aid in optimization of device functionality and design.

5. Device Description

The Vortex System is a minimally invasive, temporary device that is in direct contact with the heart while in use. It is intended to run for up to 4 hours to support subjects undergoing HR-PCI as determined by an appropriately trained medical team. The Vortex design provides a therapeutic approach and mechanism of action similar to that of the commercially available Impella® devices (Abiomed, Inc., Danvers, MA, USA). A summary of the device is provided below. Additional information on the device can be found in the Investigator's Brochure and Instructions For Use (IFU).

5.1. *Vortex System*

[redacted]

Table 5.1-1: Summary of Vortex System Components

Component	Description[a]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

a: Detailed information is provided in the Investigator's Brochure.

5.1.1. Vortex Pump

[redacted]

[redacted]

5.1.2. Vortex Delivery System

[redacted]

[redacted]

5.1.3. Vortex Console

[redacted]

5.2. *Device Labeling*

A copy of the Vortex IFU is included in the study Manual of Operations.

Packaging includes peelable, self-adhesive labels applied to both the sterile barrier pouch and the carton for each unit shipped. The labels on the shelf cartons and sterile pouch include the following information.

- Product name
- Product number
- Lot number or serial number
- Expiration date (use by) date (labeled as month/year, device not to be used after the last day of the indicated month)

The following statement appears on the study device product labeling:

Exclusively for Clinical Investigations.

5.3. *Ancillary Devices and Procedures*

The Vortex System requires the use of several medical instruments to ensure correct delivery and positioning of the pump and other devices to characterize pump performance during use. Please see the Investigator's Brochure for a list of devices that may be used with the Vortex System.

6. Study Objectives and Endpoints

6.1. *Objectives*

The objective of the Vortex feasibility study is to evaluate the feasibility and safety of the Vortex Temporary Percutaneous Transvalvular Circulatory Support System (Vortex System) in subjects undergoing elective HR-PCI.

6.2. *Primary Endpoint*

The primary endpoint consists of Technical Success and Clinical Success, defined as follows.

Technical Success

- Successful delivery of the device to the correct anatomical position; and
- Successful operation and removal of the Vortex circulatory support system

Clinical Success

- No conversion to open heart surgery; and

- No in-hospital mortality (see ***Note 1*** in Section **6.3**)

6.3. *Additional Measurements*

Safety events will be collected through 72 hours post-procedure or hospital discharge, whichever comes first, as listed below.

- Stroke/transient ischemic attack (TIA; see ***Note 1*** below)
- Cardiac tamponade
- Cardiac death (see ***Note 1*** below)
- Myocardial infarction (MI)
- Bleeding complications: Type 3–5 based on the Mechanical Circulatory Support Academic Research Consortium (MCS-ARC)[28] definitions (see ***Note 1*** below)
- Acute kidney injury (AKI; based on the AKIN[29,30] System Stage 3 [including renal replacement therapy] or Stage 2)
- Major vascular complications (see ***Note 1*** below)
- Any device-related adverse event (adverse device effect [ADE]/serious adverse device effect [SADE])
- Any procedure-related adverse event
- Any adverse event related to management practices
- Any adverse event related to patient specific adherence
- Any unanticipated serious adverse device effect (USADE)

Note 1: Death, stroke, bleeding complications, and major vascular complications are adjudicated by an Independent Medical Reviewer (IMR).

6.4. *Overview of Objectives and Endpoints*

Table 6.4-1 provides an overview of the aforementioned study objectives and endpoints and a justification for the specific endpoints.

Table 6.4-1: Overview of Objectives and Endpoints

Objective	Endpoint	Rationale for Endpoint
Primary Endpoint		
Evaluate feasibility and safety of the device and the procedure	Technical success (successful delivery of the device to the correct anatomical position and successful operation and removal of the Vortex circulatory support system) and clinical success (no conversion to open heart surgery and no in-hospital mortality).	Assess the ability of the device to be delivered and removed as intended and operate as intended without in-hospital mortality or conversion to open heart surgery during HR-PCI. Mortality events are adjudicated by an IMR.

Table 6.4-1: Overview of Objectives and Endpoints

Objective	Endpoint	Rationale for Endpoint
Additional Measurements		
Evaluate safety of the device and procedure	Safety events collected through 72 hours post-procedure or hospital discharge, whichever comes first.	Evaluate safety using event definitions based on MCS-ARC recommendations[28]. Mortality, stroke, bleeding complications, and major vascular complications are adjudicated by an IMR.

Abbreviations: HR-PCI=high-risk percutaneous coronary intervention; IMR=independent medical reviewer; MCS-ARC=Mechanical Circulatory Support Academic Research Consortium

7. Study Design

The Vortex Feasibility Study is a prospective, multicenter, open-label, single-arm study to assess the safety and feasibility of the Vortex System in subjects undergoing elective high-risk percutaneous coronary intervention (HR-PCI).

7.1. *Scale and Duration*

The Vortex Feasibility Study will be conducted at up to 3 centers in Australia and Europe with planned enrollment up to 10 subjects. All subjects will be screened according to the protocol inclusion and exclusion criteria. Follow-up will occur through 72 hours or hospital discharge, whichever comes first. The study design is summarized below in **Figure** 7.1-1.

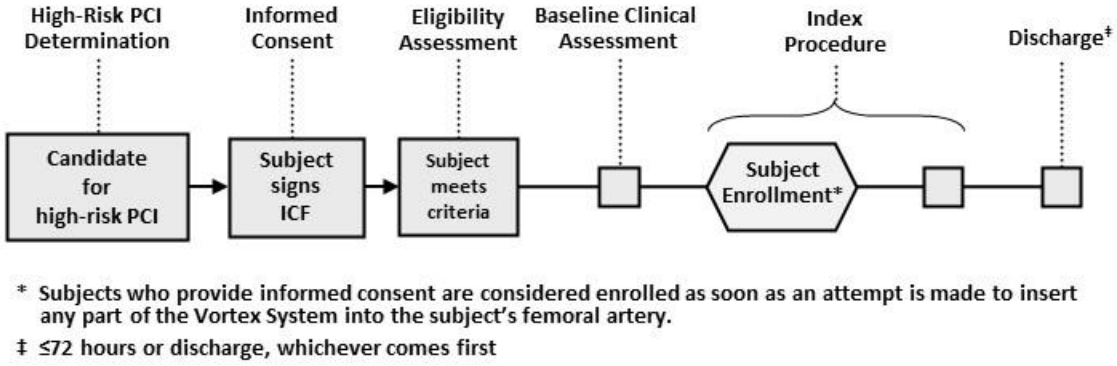


Figure 7.1-1: Vortex Feasibility Study Design Overview

7.2. *Treatment Assignment*

7.3. *Subjects who are candidates for high-risk percutaneous coronary intervention, provide written informed consent, and are eligible to be treated with the Vortex System will be evaluated for enrollment in this study. Prior to being eligible for*

the study, a subject must meet all of the inclusion criteria (Section 8.2) and none of the exclusion criteria (Section 8.3). Justification for the Study Design

In order to provide an assessment of safety and performance of the Vortex System while also limiting the potential exposure of study subjects to risk, the sample size in this feasibility study has been limited to up to 10 subjects at up to 3 investigative centers in Australia and Europe. Technical Success, Clinical Success, and safety results will be reported on all enrolled subjects through 72 hours or hospital discharge, whichever comes first.

8. Subject Selection

8.1. *Study Population and Eligibility*

Subjects who are candidates for high-risk percutaneous coronary intervention, provide written informed consent, and are eligible to be treated with the Vortex System will be evaluated for enrollment in this study. Prior to being eligible for the study, a subject must meet all of the inclusion criteria (Section 8) and none of the exclusion criteria (Section 8.2).

8.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see **Table 8.2-1**) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 8.2) is met.

Table 8.2-1: Inclusion Criteria

IC1. Subject provides signed informed consent.
IC2. Subject is ≥ 18 years and < 90 years of age.
IC3. Subject is indicated for NON-emergent PCI of at least one *de novo* or restenotic lesion in a native coronary vessel or coronary artery bypass graft and has left ventricular ejection fraction (LVEF) ≤ 50% with the following: • Unprotected left main -OR- • Last remaining vessel -OR- • Three vessel disease (≥ 50% diameter stenoses by visual estimate or total occlusion)

Abbreviations: LVEF=left ventricular ejection fraction; PCI=percutaneous coronary intervention

8.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (**Table 8.3-1**) cannot be included in this study or will be excluded from this clinical study.

Table 8.3-1: Exclusion Criteria

EC1. Subject has had STEMI within 24 hours.

EC2. Subject has had pre-procedure cardiac arrest requiring CPR within 24 hours of enrollment.

EC3. Subject is in shock, defined as follows:

- CI < 2.2 L/min/m^2 and PCWP > 15 mmHg -AND-
- Hypotension (systolic blood pressure < 90 mmHg for > 30 minutes) -OR-
- Need for supportive measures (i.e., inotropes or mechanical support) to maintain systolic blood pressure ≥ 90 mmHg and end organ hypoperfusion (cool extremities or urine < 30 mL/hour and a heart rate > 60 beats per minute)

EC4. Subject has left ventricular mural thrombus.

EC5. Subject has a prosthetic aortic valve.

EC6. Subject has pericarditis or constrictive heart disease (constrictive pericarditis or restrictive cardiomyopathy).

EC7. Subject has moderate or greater aortic valve stenosis[31] or moderate or greater aortic valve insufficiency[31] (by echocardiographic assessment, graded as ⩾ 2+).

EC8. Subject has abnormalities of the aorta that preclude safe delivery of the device, including severe calcification, tortuosity, aneurysm, or prior surgery.

EC9. Subject has PVD preventing passage of the device (e.g., calcification, small caliber) or tortuosity that would preclude safe placement of the 16 Fr introducer sheath.

Note: Minimum required vessel diameter is > 5.5 mm.

EC10. Subject has advanced renal dysfunction (AKIN[29,30] Stage 3).

EC11. Subject has a history of liver dysfunction (Childs Class C) with elevation of liver enzymes and bilirubin > 3× ULN or INR ≥ 2.

EC12. Subject has had a recent (within 1 month) stroke or TIA.

EC13. Subject has known hypersensitivity to intravenous contrast agents that cannot be adequately pre-medicated or has known hypersensitivity to heparin, aspirin, ADP receptor inhibitors or nitinol.

EC14. Subject has current or a history of heparin induced thrombocytopenia.

EC15. Subject has uncorrected abnormal coagulation or platelet count ≤ 75,000/mm^3 or INR ≥ 2.0.

EC16. Subject has significant right heart failure (RAP > 15 mmHg, RVSWI < 0.30 mmHg·L/m^2, PVR > 3.6 Woods units)[32].

EC17. Subject requires mechanical ventilation.

EC18. Subject has an atrial or ventricular septal defect (including post-infarct VSD).

EC19. Subject has left ventricular rupture.

EC20. Subject has cardiac tamponade.

EC21. Subject has severe pulmonary disease (FEV1 < 1L).

EC22. Subject has sustained or non-sustained ventricular tachycardia.

EC23. Subject is breast feeding or is pregnant.

EC24. Subject has other disease condition(s) resulting in the subject being unsuitable for participation in the clinical trial (e.g. advanced malignancy with limited expected survival)

Table 8.3-1: Exclusion Criteria

EC25.	Subject has other disease condition(s) which the Investigator has determined may cause non-compliance to the study requirements.

Abbreviations: CI=cardiac index; CPR=cardiopulmonary resuscitation; FEV=forced expiratory volume; INR=international normalization ratio; PCWP=pulmonary capillary wedge pressure; PVD=peripheral vessel disease; PVR=pulmonary vascular resistance; RAP=right atrial pressure; RVSWI=right ventricular stroke work index; STEMI=ST-elevation myocardial infarction; TIA=transient ischemic attack; ULN=upper limit of normal; VSD=ventricular septal defect

9. Subject Accountability

9.1. *Point of Enrollment*

Subjects who provide written informed consent and are confirmed eligible for the study are considered enrolled in the study as soon as an attempt is made to insert any part of the Vortex System into the subject's femoral artery (e.g., Vortex sheath).

9.2. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

While all efforts should be made to minimize attrition, subjects may withdraw from the study at any time, with or without reason and without prejudice to further treatment. Withdrawn subjects will not undergo any additional study follow-up, nor will they be replaced. The investigator may discontinue a subject from participation in the study if the investigator feels that the subject can no longer fully comply with the requirements of the study or if any of the study procedures are deemed potentially harmful to the subject. Data that have already been collected on withdrawn subjects will be retained and used for analysis, but no new data will be collected after withdrawal. All applicable case report forms up to the point of subject withdrawal and an "End of Study" form for the subject must be completed.

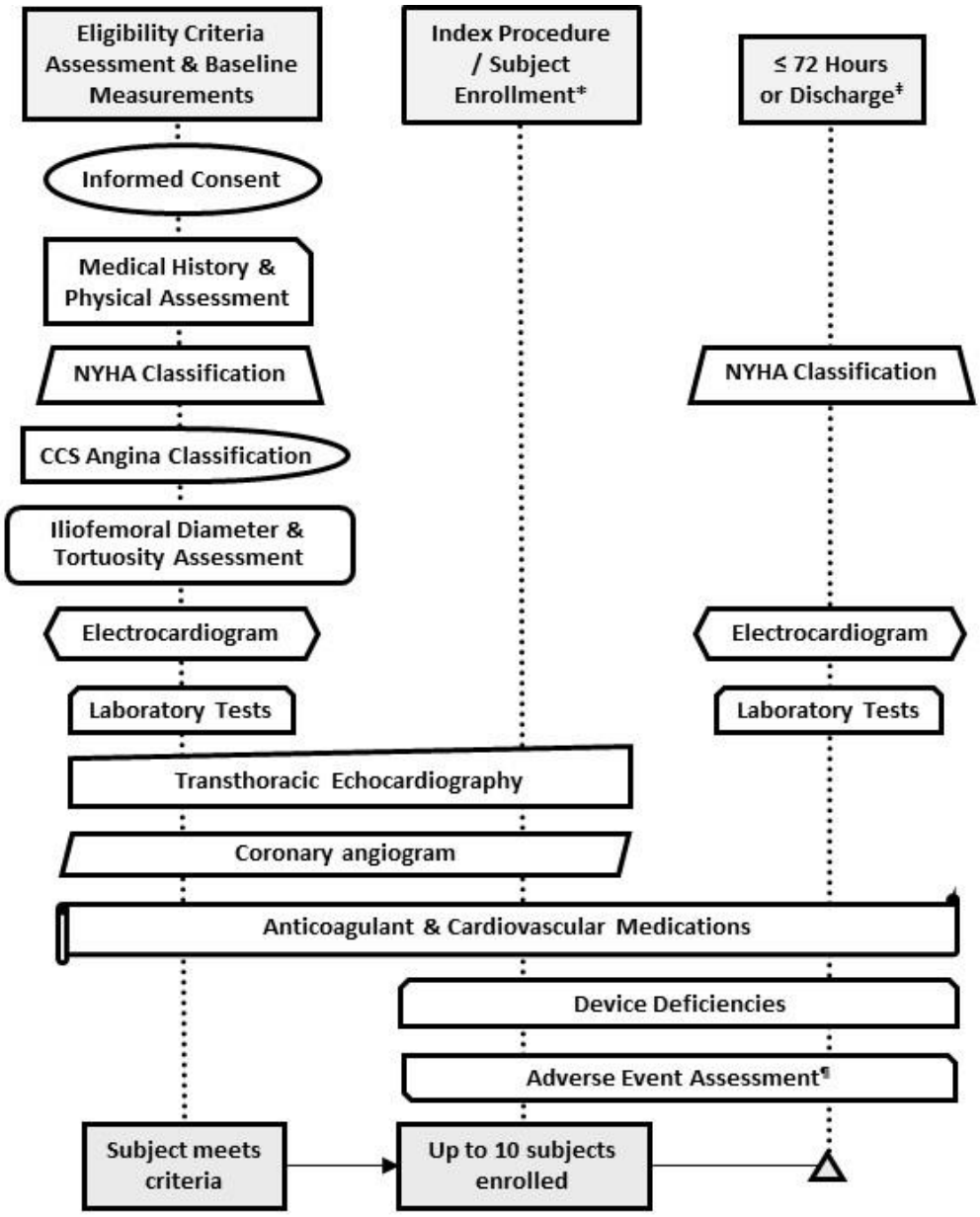
9.3. *End-of-Study Definition*

This clinical study will be considered completed when subjects are no longer being examined or the last subject's last study visit as outlined in the data collection schedule (**Table 10.1-1**) has occurred.

10. Study Methods

10.1. *Data Collection*

This section indicates the data needed to fulfill the objectives of this clinical study. Boston Scientific Corporation (BSC) considers data collected from clinical trial subjects to be personal data (see definitions of different data categories in **Table 24.2-1**) and compliance with privacy and data protection laws and regulations (for example, the General Data Protection Regulation [GDPR], see **Table 24.2-1**) to be critically important. Data collection for this clinical study has been carefully considered to comply with data privacy laws. The data collection schedule is shown in **Figure 10.1-1** and **Table 10.1-1**. Additional information on data collection can be found in Sections 10.3 through 10.10.



* Subjects who provide informed consent and are confirmed eligible are considered enrolled in the study as soon as an attempt is made to insert any part of the Vortex System into the subject's femoral artery.

‡ ≤72 hours or discharge, whichever comes first

¶ Includes AE, SAE, ADE, SADE, USADE, and IMR events

Figure 10.1-1: Vortex Study Data Collection Schedule

See **Table 10.1-1** for additional information.

Table 10.1-1: Data Collection Schedule

Assessment	Baseline	Index Procedure	≤72 Hours / Discharge[a]
Signed Informed Consent Form	X	–	–
Demographics and medical history[b]	X	–	–
Physical assessment[c]	X	–	–
New York Heart Association classification	X	–	X
CCS Angina classification	X	–	–
Electrocardiogram[d]	X	–	X
Laboratory tests[e]	X	O	X
Assessment of iliofemoral diameter and tortuosity[f]	X	–	–
Anticoagulant medications	X	X	X
Other cardiovascular medications	X	X	X
Transthoracic echocardiography[g,h]	X	X	–
Coronary angiogram[h,i]	X	X	–
Intracardiac echocardiography[h]	–	O	–
Activated clotting time	–	X	–
Device deficiencies[j]	–	X	X
Adverse event assessment[k]	–	X	X

Note: X = required; O = optional; – = not required.

Additional information on data collection can be found in Sections 10.3 through **10.10**.

a: Data collected through 72 hours or hospital discharge, whichever comes first.

b: Including cardiac, neurological, renal, and peripheral vascular disease.

c: Including weight, height, and vital signs.

d: 12-lead ECG; baseline ECG should be done within 30 days prior to the index procedure; post-procedure timing is per standard of care for HR-PCI.

e: Laboratory tests at baseline include CBC with platelets, serum creatinine, plasma-free hemoglobin, and cardiac enzymes. Post-procedure, cardiac enzymes (CK or troponin is required, CK-MB or troponin if CK is elevated) must be collected once per standard of care within 6–24 hours; if readings are abnormal, a second collection per standard of care is required. Plasma-free hemoglobin must be collected pre-discharge (≥ 6 hours post procedure). Plasma-free hemoglobin may be collected during the index procedure per the standard of care.

f: Minimum required iliofemoral diameter is > 5.5 mm; any assessment technique to determine diameter and tortuosity is permitted; assessment must be done within 365 days prior to the index procedure.

g: TTE assessment should be done within 180 days prior to the index procedure.

h: Deidentified copies of the imaging assessments should be provided to Boston Scientific.

i: Coronary angiogram should be done within 365 days prior to the index procedure per standard of care for HR-PCI.

j: Information on device deficiencies for the test device will be monitored and reported to Boston Scientific.

k: The adverse event assessment includes AE, SAE, ADE, SADE, USADE, and IMR events, which will be collected from the time of enrollment through 72 hours post-procedure or hospital discharge, whichever comes first, in all subjects. Please refer to Section 18.1 for reportable events, including a list of IMR events, and to **Table 24.2-1** for definitions of these events, which specify data required for IMR adjudication.

Abbreviations: AE=adverse event; ADE=adverse device effect; CBC=complete blood count; CCS=Canadian Cardiovascular Society; CK=creatine kinase; CK-MB=creatine kinase myoglobin band; ECG=electrocardiogram; HR-PCI=high risk percutaneous coronary intervention; IMR=independent medical

Table 10.1-1: Data Collection Schedule

Assessment	Baseline	Index Procedure	≤72 Hours / Discharge[a]

reviewer; SADE=serious adverse device effect; SAE=serious adverse event; USADE=unanticipated serious adverse device effect

10.2. *Study Candidate Screening*

Subjects will be evaluated for eligibility by the center's heart team.

10.3. *Informed Consent*

Before any study specific tests or procedures are performed, subjects who meet eligibility criteria will be asked to sign the study Informed Consent Form (ICF) that was approved by the Independent Ethics Committee (IEC)/Human Research Ethics Committee (HREC). Subjects must be given ample time to review the ICF and have questions answered before signing.

Study personnel should explain to the subject that even if the subject agrees to participate in the study and signs the ICF, screening tests and procedures may demonstrate that the subject is not a suitable candidate for the study.

10.4. *Screening Assessments*

The screening tests and procedures listed below must be performed to confirm a subject's eligibility for the study. Specific data points will be collected in the electronic Case Report Forms (eCRFs) as shown below.

- Clinical assessments
  - Demographics including age and gender
  - Medical history, including cardiac, neurological, renal disease, peripheral disease and other medical conditions
  - Physical assessment, including weight, height, and vital signs
  - New York Heart Association (NYHA) classification
  - Canadian Cardiovascular Society (CCS) angina classification
  - 12-lead electrocardiogram (ECG; see ***Note 1*** below)
  - Current anticoagulant and other cardiovascular medications
- Imaging assessments (see ***Note 1*** and ***Note 2*** below)
  - Transthoracic echocardiography (TTE)
  - Coronary angiogram

- Evaluation of iliofemoral diameter and tortuosity (any assessment technique is permitted)

Note 1: Baseline ECG should be done within 30 days prior to the index procedure, TTE within 180 days prior to the index procedure, coronary angiogram per standard of care for HR-PCI, and iliofemoral diameter/tortuosity assessment within 365 days prior to the index procedure.

Note 2: Imaging assessments should include basic cardiac measurements, including ventricular dimensions, function of the left and right ventricle, and function of all cardiac valves. Deidentified copies of the imaging assessments should be provided to Boston Scientific.

10.5. *Baseline Assessments*

The following assessments must be completed prior to the index procedure. The eCRFs identify the specific data points to be collected.

- Confirmation of eligibility criteria
- NYHA classification
- Laboratory tests
  - Cardiac enzymes (CK [creatine kinase] or troponin is required, CK-MB [creatine kinase myoglobin band] or troponin if CK is elevated)
  - Plasma-free hemoglobin
  - Complete blood count (CBC) with platelets
  - Serum creatinine

10.6. *Pre-procedure/Procedural Medications*

Subjects should be treated with heparin during the procedure. Activated clotting time (ACT) should be measured as standard of care with a recommended target of >250 and <400 seconds for the duration of the procedure.

10.7. *Index Procedure*

The preparation of the subject for the percutaneous procedure will be performed following standard techniques.

10.7.1. Vortex System Procedure

The investigational device will be delivered on a guidewire through a Vortex introducer sheath catheter from the femoral artery access site to the aorta and positioned across the aortic valve. During the transcatheter approach, the subject is under conscious sedation.

Please refer to the Vortex IFU and investigator training materials (see Section 15.4.1) for detailed instructions on procedural steps.

Note 1: All Vortex procedures will be performed with the support/presence of trained BSC personnel.

Note 2: Plasma-free hemoglobin may be collected during the index procedure per the standard of care.

The following information will be collected during the procedure. Additional data to be collected will be outlined in the eCRF.

- Date of procedure
- Time of first vascular puncture (femoral) and vascular closure (skin-to-skin time)
- Vortex System insertion and removal time
- Additional information regarding use of the Vortex System
    - Descriptive information on Vortex System insertion procedure
    - Descriptive information on Vortex System positioning and retrieval
    - Descriptive information on the impact of the Vortex System on cardiac anatomy and physiology
    - Impact of Vortex System usage on HR-PCI procedure success
- ECG changes (per standard of care)
- Adverse event assessment; see Section 18
- Device deficiencies assessment

10.7.2. Intraprocedural Cardiac Imaging

Subjects will undergo heart catheterization with radiographic imaging as per standard of care. Imaging may include fluoroscopy, ventriculography, and/or sonography before and after placement of the Vortex System to assess the left ventricle and verify freedom from coronary interference. Minimization of contrast media injected into subjects with compromised renal function is recommended.

Deidentified copies of the imaging assessments should be provided to Boston Scientific.

10.7.3. Intraprocedural Hemodynamic Measurements

Intraprocedural hemodynamic assessment is primarily based on TTE (or intracardiac echocardiography[33] as per standard of care) and catheter-based pulmonary artery measurements. Cardiac output (CO), pulmonary artery (PA) pressure, pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), mean arterial pressure (MAP), and right atrial pressure (RAP) should be measured before and after the pump is placed and switched on via the pulmonary artery catheter and also when the pump is switched off and

removed (post-procedure). Left ventricular pressure may be measured via the pigtail catheter.

10.8. *Post-procedure (≤ 72 Hours)/Prior to Hospital Discharge*

Within 72 hours post procedure or before discharge (whichever comes first), the following assessments must be performed.

- 12-lead ECG
- Laboratory tests
  - Cardiac enzymes (CK or troponin required, CK-MB or troponin if CK is elevated) must be collected once per standard of care within 6–24 hours post-procedure; if readings are abnormal, a second collection per standard of care is required.
  - Plasma-free hemoglobin must be collected ≥ 6 hours post procedure (before discharge)
- NYHA classification
- Anticoagulation therapy and other cardiovascular medications
- Adverse event assessment (see Section 18)
- Device deficiencies assessment

10.9. *Study Completion*

All subjects will be evaluated through 72 hours or hospital discharge, whichever comes first. A subject's participation in the study will be considered complete after 72 hours or hospital discharge (whichever comes first).

10.10. *Source Documents*

It is preferable that original source documents, when available, are maintained at the investigative center. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. Source documentation includes but is not limited to those items noted in **Table 10.10-1**. Source documentation provided to the Sponsor for assessment/adjudication will be deidentified per local law and regulations.

Table 10.10-1: Source Documentation Requirements

Requirement	Disposition
Printed, optical, or electronic document containing source data. Examples may include but are not limited to hospital records, laboratory notes, device accountability records, photographic negatives, radiographs, records kept at the investigation center, at the laboratories and at the medico-technical departments involved in the clinical investigation.	Retain at center.

Note: Please see Table 24.2-1 for definitions of "source data" and "source document."

10.11. *Local Laboratory/Vendor Documentation*

This study requires local laboratory results. Appropriate certifications and documentation records are required to be maintained at the center.

11. Statistical Considerations

Event definitions can be found in **Table 24.2-1**.

11.1. *Endpoints*

11.1.1. Primary Endpoint

The primary endpoint consists of Technical Success and Clinical Success. Technical Success is defined as successful delivery of the device to the correct anatomical position and successful operation and removal of the Vortex System. Clinical Success is defined as no conversion to open heart surgery or in-hospital mortality.

11.1.1.1. Hypotheses

There is no formal statistical hypothesis in this observational feasibility study.

11.1.1.2. Sample Size

This is a prospective non-randomized feasibility study with no formal pre-specified hypothesis and therefore sample size estimates are not applicable. To support the stated objective of this feasibility study, while also limiting the potential exposure to risk of study subjects, the study sample size has been arbitrarily set at a maximum of 10 subjects enrolled.

11.1.1.3. Statistical Methods

Descriptive statistics will be used for baseline, procedure, and follow-up data collected during the study. See Section 11.2.1 for a discussion of analysis sets.

11.1.2. Additional Measurements

Additional measurements are listed in Section **6.3**. There are no statistical hypotheses for the additional measurements.

11.2. *General Statistical Methods*

All statistical analyses will be performed using the SAS System software, version 9.2 or later (Copyright© 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved).

All statistical analyses will be conducted according to applicable Standard Operating Procedures, Work Instructions, and the study-specific statistical analysis plan.

11.2.1. Analysis Sets

The primary endpoint and additional measurements will be analyzed on an intention-to-treat (ITT) basis and a per-protocol basis. Analysis sets are listed below. Subjects are considered enrolled in the study as soon as an attempt is made to insert any part of the Vortex System into the subject's femoral artery.

- ITT: This population includes all subjects who sign an ICF and are enrolled in the study, whether or not a study device is successfully inserted and used.
- Per-protocol: This population includes all ITT subjects in whom the device is successfully advanced across the aortic valve into the left ventricular outflow tract and turned on.

11.2.2. Control of Systematic Error/Bias

The selection of subjects will be made from the Investigator's usual case load. Subjects who are candidates for HR-PCI, provide written informed consent, and are eligible to be treated with the Vortex System will be evaluated for enrollment in this study. The study center's heart team assessments and imaging measurements before device placement will contribute to the determination of subject eligibility for the study.

To control for inter-observer variability, an independent IMR (see Section **20.2**) will adjudicate mortality, stroke, major vascular complications, and bleeding endpoints.

11.3. *Data Analyses*

Baseline data, procedural data, and follow-up data (72 hours post procedure or hospital discharge, whichever comes first) collected for the ITT subjects will be summarized using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency tables or proportions for discrete variables. Data will be collected as detailed in the clinical study schedule (**Table 10.1-1**).

12. Data Management

12.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

The clinical database will reside on a production server hosted by Medidata EDC System. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor or its representative. The associated Rave software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the Medidata EDC system and will be issued to the center for appropriate response. Center staff will be responsible for resolving all queries in the database.

All access to the clinical database will be changed to “Read Only” after all data are either “Hard Locked” or “Entry Locked.” Once acceptance of the final study report or finalization of publications (as applicable) is received, final database storage and archiving activities can begin. When all closeout activities are completed, a request to the BSC Information Technology department is submitted to have the database locked or decommissioned and all database access revoked.

12.2. *Data Retention*

The Principal Investigator or his/her designee or Investigational site will maintain all essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements.

The Principal Investigator or his/her designee will take measures to prevent accidental or premature destruction of these documents. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Centers are required to inform BSC in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

13. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing IEC/HREC, and regulatory authorities if applicable, of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to BSC using the EDC eCRF. Centers may also be required to report deviations to the IEC/HREC, and the regulatory authority, per local guidelines and national/government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including IEC/HREC notification, center re-training, or center discontinuation/termination) will be put into place by the sponsor.

The sponsor will not approve protocol waivers.

14. Device Accountability for Products Labelled Investigational

The investigational devices shall be securely maintained, controlled, and used only in this clinical study. Equipment shall be returned in the condition in which it was provided, reasonable wear and tear excepted.

For items labelled "investigational," the principal investigator or an authorized designee shall do the following:

- Securely maintain and control access to these items to ensure they are used only in this clinical study and only per the protocol.
- Ensure the storage environment for these items is appropriate for maintaining conditions per the items' labeling (e.g., temperature, humidity, etc., as applicable)
- Return remaining items upon sponsor request and in the condition in which they were provided, reasonable wear and tear excepted.

The sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices from BSC or designated facility to the investigation centers until return or disposal.

Records shall be kept by the sponsor to document the physical location and conditions of storage of all investigational devices/equipment.

The principal investigator or an authorized designee shall maintain accurate and timely records, providing copies to BSC upon request. These records shall document the receipt,

use, return, and disposal of the investigational devices, and shall include minimally the following content.

- Name(s) of person(s) who received, used, returned, or disposed of each item;
- Date of receipt;
- Identification and quantity of each item (examples of identification include batch number, serial number or unique code);
- Expiry date for each item (or batch of items), as applicable;
- Date or dates of use;
- Subject identification;
- Date on which the item was returned, if applicable;
- Date of return (and number) of unused, expired, no longer needed, and/or malfunctioning items, as applicable;
- Date and documentation of item disposal, as directed by sponsor, if applicable.

15. Compliance

15.1. *Statement of Compliance*

This clinical investigation is financed by the study sponsor. Before an investigational center can be considered "Authorized to Enroll," the investigational center must enter into a Clinical Study Agreement with the sponsor that details the financing of the study as well as the rights and obligations of the investigational center and the investigator.

This study will be conducted in accordance with the International Standard ISO 14155:2020 Clinical Investigation of Medical Devices for Human Subjects-Good Clinical Practices (GCP), European Medical Device Regulations, ethical principles that have their origins in the Declaration of Helsinki, and applicable individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IEC/HREC and/or regulatory authority has been obtained, if appropriate. Also, the study shall not begin prior to issuance of the center Authorization to Screen/Enroll, as provided by the sponsor. Any additional requirements imposed by the IEC/HREC or regulatory authority shall be followed, if appropriate.

15.2. *Investigator Responsibilities*

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan, ISO 14155:2020, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IEC/HREC, and prevailing

local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Investigator Brochure Signature Page and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the case report forms and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency.
- Report to sponsor, per the protocol requirements, all reportable events.
- Report to the IEC/HREC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE, if required by applicable laws or regulations or this protocol or by the IEC/HREC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Maintain the device accountability records and control of the device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions for use.
- Allow the sponsor to perform monitoring and auditing activities and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IEC/HREC when performing auditing activities.

- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IEC/HREC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the ICF.
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the investigational device when it is used/operated by the subject.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.

All investigators will provide their qualifications and experience to assume responsibility for their delegated tasks through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.

15.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training, so the delegate is competent to perform the tasks they have been delegated, and adequate supervision of those to whom tasks are delegated. Where there is a sub-investigator at a center, the sub-investigator should not be delegated the primary

supervisory responsibility for the site. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

15.3. *Independent Ethics Committee / Human Research Ethics Committee*

The investigational center will obtain the written and dated approval/favorable opinion of the IEC/HREC for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required.

A copy of the written IEC/HREC and/or competent authority (CA) approval of the protocol (or permission to conduct the study) and ICF, must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product/equipment.

Any amendment to the protocol and/or ICF will require review and approval by the IEC/HREC and the Swedish Medical Products Agency (MPA) before changes to the study are implemented. All changes to the ICF will be IEC/HREC approved; a determination will be made regarding whether a new ICF needs to be obtained from subjects who provided consent using a previously approved ICF. Annual IEC/HREC approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IEC/HREC requirements. Copies of the study reports and the IEC/HREC continuance of approval must be provided to the sponsor.

15.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC and will be kept confidential in accordance with all applicable laws and regulations. Only authorized BSC personnel and/or a BSC representative including, but not limited to, a Contract Research Organization (CRO), will have access to this information. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes, such as overseeing and improving the performance of its device, new medical research, and proposals for developing new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

15.4.1. Training

The Sponsor is responsible for providing Investigators with the information and training they need to conduct the study properly. The Sponsor is also responsible for maintaining documentation of attendance at each of the training sessions provided.

Training for operators includes the following elements.

- Detailed description of all Vortex System components

- Detailed description of the step-by step procedure on how to use the Vortex System, including insertion, positioning, pump operation, and retrieval
- Hands-on demonstration and use of the Vortex System: deliver the device across the aortic valve, switch the device on and then off, withdraw the device.

15.4.2. Role of Boston Scientific Representatives

Boston Scientific personnel who are trained in the use of the investigational device can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during the procedure and testing required by the protocol. Support may include HCP training (see Section 15.4.1), addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices (including programmers, analyzers, and other support equipment).

At the request of the investigator and while under investigator supervision, BSC personnel may operate equipment during the procedure, assist with the conduct of testing specified in the protocol, and interact with the subject to accomplish requested activities.

Typical tasks may include the following.

- Providing instructions for the safe return of investigational products; for potentially hazardous items, providing specialized instructions and materials, as applicable.
- Interrogating the device or programming device parameters to investigator-requested settings as well as operating investigational equipment
- Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel
- Providing technical expertise/support to the principal investigator or delegated center staff

In addition, BSC personnel may perform certain activities to ensure study quality. These activities may include the following.

- Observing testing or medical procedures to provide information relevant to protocol compliance
- Reviewing collected data and study documentation for completeness and accuracy

Boston Scientific personnel will not do the following.

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject’s condition or treatment with a subject
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

15.5. *Insurance*

Where required by local/country regulation, proof and type of insurance coverage for subjects in the study will be obtained by BSC.

16. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The sponsor will put a plan in place to document the specific monitoring requirements. A general outline of the monitoring plan is described below -

Site Initiation Visits
All sites participating in the study will have Site Initiation Visits (SIVs). A live, online training session with slides will be conducted virtually via the Web. A checklist of activities (as specified in the monitoring plan: e.g. protocol training, ICH/GCP, monitoring expectations, PI responsibilities, safety reporting requirements, documentation requirements, local law requirements such as: data protection, EC reporting) will be conducted and confirmed complete, prior to site authorization to enroll to ensure preparedness of the investigator and site staff. Additional training may be done on an as-needed basis throughout the study for study procedures and updates, clinical events, unanticipated adverse device effect reporting process, regulatory requirements, CRF completion, and compliance issues noted during monitoring.

Interim Monitoring Visits
Interim Monitoring Visits (IMVs) will be conducted for each site. Each visit will require a written confirmation letter, a monitoring visit report, and a follow up letter.
At each interim monitoring visit, the monitor will assess:

- Regulatory documents and contents of the Investigator Site File to ensure that they are complete, accurate and current.
- Accuracy of data: the monitor will compare subject medical records and other supporting documents with the CRFs to determine that they are complete, accurate, and legible.
- Informed consent forms: monitor will review the ICFs and documentation of the consent process in the source documents.
- Safety reporting: monitor will verify and/or discuss that all reportable events and device deficiencies are reported and recorded in accordance with the protocol and the local regulatory requirements and ensures necessary source documents are obtained.

- Site resources, adequacy of facilities, any changes in study personnel, location, etc.
- Device accountability to ensure the log is complete and accurate

Site compliance to the study protocol will be assessed over the life of the study.

Closeout Visits
A Closeout monitoring visit (COV) will be performed for each site. Closeout activities can be performed separately or in conjunction with an interim monitoring visit. When preparing the site for closure, the monitor will verify and/or discuss that:

- All essential documents are complete and up to date
- All CRFs are completed
- All outstanding queries are resolved
- The current status of all ongoing adverse events is documented and protocol compliant.
- All CRF pages are signed by the designated investigator
- Device reconciliation is accurate and documented
- Arrangements are made for archiving and record retention.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

17. Potential Risks and Benefits

17.1. *Anticipated Adverse Events and Adverse Device Effects*

Adverse events/adverse device effects (in alphabetical order) potentially associated with use of the Vortex System during HR-PCI include but may not be limited to the risks listed in **Table 17.1-1**. These potentially fatal complications may require the subject to undergo medical, percutaneous, or surgical intervention.

As the Vortex System is an investigational device, uncertainty remains over risks of experiencing some or all of the complications listed below. There may be risks that are unknown at this time.

Table 17.1-1: Risks Associated with Use of the Vortex System During High-Risk Percutaneous Coronary Intervention

Access site complications (including hematoma, lymph vessel damage, pseudoaneurysm, arteriovenous fistula [myocardial contusion or rupture])
Acute kidney injury
Allergic reaction or unfavorable response to procedure medications (including to medications, anesthesia, contrast, or device materials)
Aneurysm

Table 17.1-1: Risks Associated with Use of the Vortex System During High-Risk Percutaneous Coronary Intervention

Angina
Aortic or mitral valve insufficiency or injury
Arrhythmia or new conduction system injury (including need for pacemaker insertion)
Bleeding
Blood loss resulting in anemia
Cardiac failure and pulmonary edema
Cardiac ischemia possibly requiring surgical intervention
Cardiogenic shock from low cardiac output
Death
Device malfunction
Device related thrombus
Dislodgement of the pump or interventional equipment from operating position
Embolization (device, thrombus or other)
Failure to achieve angiographic success
Hemodynamic instability or shock
Hemolysis
Inability to complete coronary procedure
Infection (including sepsis and endocarditis)
Organ failure (including kidney, lungs and liver)
Perforation or rupture of the heart or blood vessels including dissection or spasm
Pericardial effusion/cardiac tamponade
Peripheral ischemia or infarction
Repeat revascularization
Stroke/cerebrovascular accident/transient ischemic attack
Thrombocytopenia

17.2. *Risks Associated with the Study Device*

Overall, there are no incremental risks expected with the investigational device compared to similar mechanical circulatory support system devices on the market.

17.3. *Risks Associated with Participation in the Clinical Study*

Risks associated with HR-PCI and participation in this clinical study are listed above in **Table 17.1-1**.

17.4. *Possible Interactions with Concomitant Medical Treatments*

Medications to be used in the Vortex Feasibility Study constitute standard of care for subjects undergoing HR-PCI as described in society guidelines[3].

17.5. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

The aforementioned risks are mitigated with the following approaches.

- Estimation of risks associated with the investigational device in accordance with ISO 14971 prior to conducting the clinical investigation
- Preclinical testing and bench testing of the Vortex System to establish safety and performance
- Selection of investigators who are experienced and skilled in interventional HR-PCI procedures supported by mechanical circulatory support devices
- Completion of training provided by the sponsor
- Clearly defining the inclusion/exclusion criteria to ensure only appropriate subjects are enrolled
- Confirmation of eligible subjects by investigators experienced in HR-PCI with MCS procedures
- Performing all procedures in accordance with the Vortex System IFU
- Ensuring that treatment of subjects is consistent with current medical practices, including adjunctive pharmacologic therapy
- On-site support by BSC representatives during the procedure
- Dynamic safety review processes, with Independent Medical Reviewer (IMR) adjudication

Anticoagulation medication (e.g., heparin) will be administered during the procedure per standard of care to reduce the risk of thrombosis, embolism, and stroke.

Cardiac enzyme, serum creatinine and plasma free hemoglobin measurements and electrocardiograms will be performed post-procedure to detect cardiac or renal injury.

Subjects will be carefully monitored during the procedure, and through 72 hours or hospital discharge, whichever comes first.

Data will be monitored as they are submitted to BSC.

In addition, BSC has implemented specific design and clinical mitigations to address observations from prior preclinical and clinical studies. Please refer to the Investigator Brochure for a detailed description of risk mitigations.

17.6. *Anticipated Benefits*

The Vortex System is intended to support stable subjects undergoing HR-PCI by temporarily decreasing the load on the heart and ensuring adequate organ perfusion. The benefit of mechanical circulatory support devices is that they provide support in the event the subject becomes hemodynamically unstable during a procedure. Society guidelines state that elective insertion of an appropriate hemodynamic support device as an adjunct to PCI may be reasonable in carefully selected high-risk patients[18]. The Vortex design provides mechanical circulatory support and a mechanism of action similar to that of the commercially available Impella® devices (Abiomed, Inc., Danvers, MA, USA). Both designs use a cannula and impeller to move blood from the left ventricle into the aorta. The Vortex System may provide improved conformation to subject anatomy and a less complex arrangement during the interventional procedure.

Please see the Investigator Brochure for existing clinical data regarding use of mechanical circulatory support devices and additional information on the Vortex design. Prophylactic use of the Vortex System during HR-PCI procedures should improve patient hemodynamics and may improve patient outcomes.

17.7. *Risk to Benefit Rationale*

Review of the aforementioned clinical benefits versus risks takes into account the known risks/benefits that have been identified in the published literature on other mechanical circulatory support devices. Risks associated with the investigational device have been estimated, risk controls have been implemented, and an evaluation of residual risk (individual risks and overall risk) has been performed. When used according to the IFU, investigator training, and proctoring, all risks have been reduced as low as possible, and the medical benefits of the investigational device have been determined to outweigh the residual risk.

18. Safety Reporting

18.1. *Reportable Events by Investigational Center to Boston Scientific*

It is the responsibility of the investigator to assess and report to BSC any event which occurs in any of following categories from time of enrollment through end of study (see definitions in **Table 18.2-1**).

- All serious adverse events (SAE)
- All adverse events (AE)
- All serious adverse device effects (SADE)
- All adverse device effects (ADE)
- All investigational device deficiencies
- All unanticipated serious adverse device effects (USADE)

- All IMR events
- New findings/updates in relation to already reported events

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and/or device deficiency.

Any reportable AE required by the protocol and experienced by the study subject after informed consent and once considered enrolled in the study (see Section **9.1**), whether during or subsequent to the study procedure, must be recorded in the eCRF.

Underlying diseases and chronic conditions are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE but should only be reflected as an outcome of one (1) specific SAE (see **Table 18.2-1** for AE definitions).

Refer to Section 16 for the known risks associated with the study device.

18.2. *Definitions and Classification*

Adverse event definitions are provided in **Table 18.2-1**. Administrative edits were made on the safety definitions from applicable regulations and guidance including (but not limited to) ISO 14155 and EU MDR 2017/745/MDCG 2020-10/1 Guidance on Safety Reporting in Clinical Investigations for clarification purposes.

Table 18.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational medical device and whether anticipated or unanticipated. **NOTE 1:** This includes events related to the investigational medical device or comparator. **NOTE 2:** This definition includes events related to the procedures involved. **NOTE 3:** For users or other persons, this definition is restricted to events related to the investigational medical device. **NOTE 4:** This definition includes events related to management practices **NOTE 5:** This definition includes patient related events
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event related to the use of an investigational medical device **NOTE 1:** This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the procedural treatment, the installation, the operation, or any malfunction of the investigational medical device.

Table 18.2-1: Safety Definitions

Term	Definition
	NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. **NOTE 3:** This includes "comparator" if the comparator is a medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event that led to any of the following: a) Death, b) Serious deterioration in the health of the subject, users or other persons as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic diseases, or 3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) Foetal distress, foetal death, or a congenital abnormality or birth defect including physical or mental impairment. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment. **NOTE 1:** Anticipated serious adverse device effect (ASADE) is an effect which by its nature incidence, severity or outcome has been identified in the risk assessment.
Serious Health Threat *Ref: ISO 14155*	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health of subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. **NOTE 1:** This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.
Device Deficiency *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	An inadequacy of a medical device related to its identity, quality, durability, reliability, usability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. **NOTE 2**: This definition includes device deficiencies related to the investigational medical device or the comparator.
The following definitions will be used for defining hospitalization or prolongation of hospitalization for SAE classification purposes:	

Table 18.2-1: Safety Definitions

Term	Definition
Hospitalizations	Hospitalization does not include: • Emergency room visit that does not result in in-patient admission **NOTE 1:** Although an emergency room visit does not itself meet the definition for hospitalization, it may meet other serious criteria (e.g., medical or surgical intervention to prevent permanent impairment or damage) • Elective and pre-planned treatment/surgery for a pre-existing condition that is documented in the subject's record at the time of consent/enrollment • Admission for social reasons and/or respite care in the absence of any deterioration in the subject's general condition (e.g., subject is homeless, caregiver relief) • Pre-planned, protocol-specified admission related to the clinical study (e.g., procedure required by protocol)
Prolongation of Hospitalization	In-patient admission to the hospital that is prolonged beyond the expected standard duration for the condition under treatment. **NOTE** 1: New adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criterion.

18.3. *Relationship to Study Device(s) and/or Study Procedure*

The Investigator must assess the relationship of the reportable adverse events to the study device or study procedure. See criteria in **Table 18.3-1:**

Table 18.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Not Related *Ref: MDCG 2020-10/1*	Relationship to the device, comparator, or procedures can be excluded when: • the event has no temporal relationship with the use of the investigational device or the procedures related to the use of the investigational device; • the serious 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 serious event; • the event involves a body-site or an organ that cannot be affected by the device or procedure; • the serious 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);

Table 18.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
	• the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; 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 serious event.
Possibly Related *Ref: MDCG 2020-10/1*	The relationship with the use of the investigational device or comparator or the relationship with procedures is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/clinical condition and/or 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.
Probably Related *Ref: MDCG 2020-10/1*	The relationship with the use of the investigational device, comparator, or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause.
Causal Relationship *Ref:* ***MDCG 2020-10/1***	The serious event is associated with the investigational device or comparator or with procedures beyond 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 procedures are applied to; - the investigational device or procedures have an effect on; • the serious 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 serious 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; • the event depends on a false result given by the investigational device used for diagnosis, when applicable In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

18.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in **Table 18.4-1**.

Table 18.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline (Pre-market Studies)** (MDCG 2020-10/1)
Unanticipated Serious Adverse Device Effects (USADE)	Complete AE electronic case report form (eCRF) page with all available new and updated information.	• Within 1 business day of first becoming aware of the event • Terminating at the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor
Serious Adverse Events (SAE) and IMR events[a]	Complete AE eCRF page with all available new and updated information.	• Immediately but not later than 3 calendar days of first becoming aware of the event or as per local/regional regulations • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified /pseudonymized) for reported event.	• Upon request of sponsor
Serious Adverse Device Effects (SADE)	Complete AE eCRF page with all available new and updated information.	• Immediately but not later than 3 calendar days of first becoming aware of the event or as per local/regional regulations • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon request of sponsor
Device Deficiencies (including but not limited to , malfunctions, use errors and inadequacy in information supplied by the manufacturer, including labeling) **Note:** Any Device Deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, circumstances had	Complete Device Deficiency eCRF with all available new and updated information.	• Immediately but not later than 3 calendar days of first becoming aware of the event. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor

Table 18.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline (Pre-market Studies) (MDCG 2020-10/1)
been less fortunate is considered a reportable event.		
Adverse Event (AE) including Adverse Device Effects (ADE)	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device. Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Adverse Device Effects: In a timely manner but not later than 10 business days after becoming aware of the information • Adverse Events: In a timely manner but recommend within 10 business days after becoming aware of the information • Reporting required through the end of the study • Upon request of sponsor

a: All Independent Medical Reviewer (IMR) events must be reported using the timeframe for SAE, regardless of whether they meet serious criteria.

18.5. *Device Deficiencies*

Vortex System device deficiencies will be documented in the appropriate eCRF and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the investigational device(s) will be provided in the Manual of Operations. Device deficiencies should also be documented in the subject's source records.

Device deficiencies are not adverse events. However, an adverse event that results from a device deficiency would be recorded as an adverse event on the appropriate eCRF.

18.6. *Reporting to Regulatory Authorities / IECs / HRECs/ Investigators*

Boston Scientific Corporation is responsible for reporting adverse event information to all participating Principal Investigators, IECs/HRECs and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the IEC/HREC and regulatory authorities of USADEs and SAEs as required by local/regional regulations.

19. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, the relevant parts of ISO 14155:2020, any

applicable national regulations, and local Ethics Committee and/or Regulatory authority, as applicable. The ICF must be accepted by BSC or its delegate (e.g., CRO), and approved by the center's IEC/HREC, if applicable.

Boston Scientific Corporation will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative site's IEC/HREC. Any modification requires acceptance from BSC or authorized representative prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the center in obtaining a written consent translation. Translated consent forms must also have IEC/HREC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the center and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory authority according to their requirements. Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g., IEC/HREC), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date

an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IEC/HREC. The new version of the ICF must be approved by the IEC/HREC. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the center's IEC/HREC. The IEC/HREC will determine the subject population to be re-consented.

Study personnel should explain to the subject that even if the subject agrees to participate in the study and signs the ICF, screening tests and procedures may demonstrate that the subject is not a suitable candidate for the study.

20. Committees

20.1. *Safety Monitoring Process*

The BSC personnel from the Medical Safety and Safety Trial Operations team review safety data as the data are reported by the centers throughout the duration of the study. During scheduled monitoring activities, clinical research monitors will further support this review through their review of source documents and other data information. The BSC Medical Safety and Safety Trial Operations team include health care providers with expertise in HR-PCI and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

20.2. *Independent Medical Reviewer*

An Independent Medical Reviewer (IMR) will be used in this study. The IMR will review a safety event dossier which may include copies of subject source documents provided by study centers and adjudicate study endpoint related clinical events as per the IMR charter. The responsibilities, qualifications, and procedures of the IMR are outlined in the IMR charter.

21. Suspension or Termination

21.1. *Premature Termination of the Study*

Boston Scientific reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or business reasons and reasons related to protection of subjects. Investigators, associated IECs/HRECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

21.1.1. Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following.

- Suspicion of an unacceptable risk, including serious health threat. In this case, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed.
- Instructions by the IEC/HREC or regulatory authorities to suspend or terminate the clinical investigation.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development of the device.

21.2. *Termination of Study Participation by the Investigator or Withdrawal of IEC/HREC Approval*

Any investigator, or associated IEC/HREC or regulatory authority may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to BSC. Investigators, associated IECs/HRECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

21.3. *Requirements for Documentation and Subject Follow-up*

In the event of premature study termination, a written statement as to why the premature termination has occurred will be provided to all participating sites by BSC. The IEC/HREC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IEC/HREC terminates participation in the study, participating investigators, associated IECs/HRECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by BSC.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility, detailed information on how enrolled subjects will be managed thereafter will be provided by BSC.

The Principal Investigator or his/her designee must return all study-related documents and investigational product to BSC, unless this action would jeopardize the rights, safety, or welfare of the subjects.

21.4. *Criteria for Suspending/Terminating a Study Center*

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled or if the center has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of center participation, all study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IEC/HREC and regulatory authorities, as applicable, will be notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

22. Study Registration and Results

22.1. *Study Registration*

To comply with applicable laws and regulations, the study will be registered on a publicly accessible database before enrollment of the first subject.

22.2. *Clinical Investigation Report*

Study results will be made available in accordance with the legal requirements and the recognized ethical principles, in accordance with the Boston Scientific Policy. A Clinical Investigation Report will be made available to all investigators, IECs/HRECs, and regulatory authorities, as applicable in accordance with the Boston Scientific Policy and local requirements.

22.3. *Publication Policy*

Boston Scientific Corporation requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. Boston Scientific Corporation may submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific Corporation adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

The data, analytic methods, and study materials for this clinical trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (https://www.bostonscientific.com/).

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24. Abbreviations and Definitions

24.1. *Abbreviations*

Abbreviations are shown in **Table 24.1-1**.

Table 24.1-1: Abbreviations

Abbreviation/Acronym	Term
ACT	activated clotting time
ADE	adverse device effect
ADP	adenosine diphosphate
AE	adverse event
AKI	acute kidney injury
BP	blood pressure
BSC	Boston Scientific Corporation
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CCS	Canadian Cardiovascular Society
CHIP	complex high-risk and indicated patients
CI	cardiac index
CK	creatine kinase
CK-MB	creatine kinase-myoglobin band
CPR	cardiopulmonary resuscitation
CRF	case report form
CV	cardiovascular
CVP	central venous pressure
ECG	electrocardiogram
EDC	electronic data capture
FEV1	forced expiratory volume in the first second
GCP	Good Clinical Practices
HIT	heparin induced thrombocytopenia
HREC	Human Research Ethics Committee
HR-PCI	high risk percutaneous coronary intervention
IABP	intra-aortic balloon pump
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	international normalization ratio
IMR	Independent Medical Reviewer
ISO	International Organization for Standardization
LVEF	left ventricular ejection fraction
MI	myocardial infarction
MCS	mechanical circulatory support
MCS-ARC	Mechanical Circulatory Support Academic Research Consortium

Table 24.1-1: Abbreviations

Abbreviation/Acronym	Term
NYHA	New York Heart Association
PA	pulmonary artery
PCI	percutaneous coronary intervention
PCWP	pulmonary capillary wedge pressure
PVD	peripheral vessel disease
PVR	pulmonary vascular resistance
RAP	right atrial pressure
RVSWI	right ventricular stroke work index
SADE	serious adverse device effect
SAE	serious adverse event
STEMI	ST-elevation myocardial infarction
TIA	transient ischemic attack
TTE	transthoracic echocardiogram
ULN	upper limit of normal
URL	upper reference limit
USADE	unanticipated serious adverse device effect
VSD	ventricular septal defect

24.2. *Definitions*

Terms are defined in **Table 24.2-1**.

Table 24.2-1: Definitions

Term	Definition
ACUTE KIDNEY INJURY (AKI) (AKIN System[29,30])	Maximal change in serum creatinine from baseline through discharge or 72 hours post-procedure, whichever comes first. • Stage 1: Increase in serum creatinine to 150–199% (1.5–1.99 × increase compared with baseline) OR increase of ≥0.3 mg/dl (≥26.4 mmol/L), or urine output <0.5 ml/kg per hour for >6 but <12 hours • Stage 2: Increase in serum creatinine to 200–299% (2.0–2.99 × increase compared with baseline) or urine output <0.5 ml/kg per hour for >12 but <24 hours • Stage 3: Increase in serum creatinine to ≥300% (>3 × increase compared with baseline) OR serum creatinine of ≥4.0 mg/dL (≥354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) OR urine output <0.3 ml/kg per hour for ≥24 hours or anuria for ≥12 hours Note: Subjects receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.
ACUTE VESSEL OCCLUSION	The state of complete luminal obstruction with no antegrade blood flow.
ADVERSE EVENT (AE) *Ref: ISO 14155*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other

Table 24.2-1: Definitions

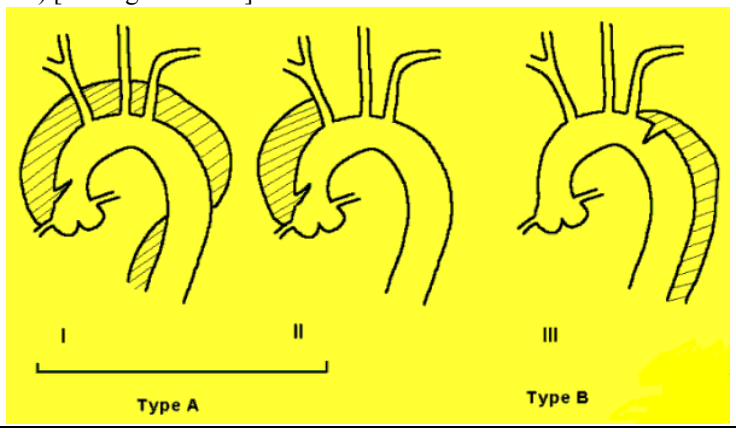
Term	Definition
Ref: MDCG 2020-10/1	persons, in the context of a clinical investigation, whether or not related to the investigational medical device and whether anticipated or unanticipated. Note 1: This includes events related to the investigational medical device or the comparator. Note 2: This definition includes events related to the procedures involved. Note 3: For users or other persons, this definition is restricted to events related to the investigational medical device. Note 4: This definition includes events related to management practices. Note 5: This definition includes patient related events.
ADVERSE EVENT BECOME AWARE DATE	The become aware date for an adverse event that requires reporting per the protocol is the date that study personnel listed on the Delegation of Authority Log identify or are notified of the event.
ADVERSE DEVICE EFFECT (ADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event related to the use of an investigational medical device Note 1: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the procedural treatment, the installation, the operation, or any malfunction of the investigational medical device. Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. Note 3: This includes "comparator" if the comparator is a medical device.
AORTIC DISSECTION	Intimal tear resulting in blood splitting the aortic media and producing a false lumen that can progress in an antegrade or retrograde direction. Aortic dissection is further classified using Stanford classification (Types A and B depending on whether ascending or descending aorta involved) or DeBakey classification (Types I, II and III) [see Figure below]. 

Table 24.2-1: Definitions

Term	Definition
ARRHYTHMIA[28]	**MCS-ARC Cardiac Arrhythmias** Any documented arrhythmia that results in clinical compromise (e.g., abnormal Vortex System function [e.g., diminished Vortex System flow or suction events], oliguria, pre-syncope or syncope, angina, dyspnea), or requires hospitalization or treatment (drug therapy, defibrillation, cardioversion, ICD therapy (e.g., shock or anti-tachycardia pacing) or arrhythmia ablation procedure). Cardiac arrhythmias are classified as 1 of 2 types. • Sustained ventricular arrhythmia resulting in clinical compromise, or requiring hospitalization or drug treatment, defibrillation, cardioversion, ICD therapy, or arrhythmia ablation procedure. • Sustained supraventricular arrhythmia resulting in clinical compromise, or requiring hospitalization or drug treatment, cardioversion, ICD therapy, or arrhythmia ablation procedure The association of the cardiac arrhythmia event should be classified as follows: • Patient-related (e.g., recurrence of pre-operative arrhythmia non-adherence with medications) • Management-related (e.g., related to uncorrected electrolyte imbalance, Swan Ganz malposition, secondary to cardiac tamponade) • Device-related (e.g., Vortex System malfunction, malposition of Vortex System or inflow cannula)
BLEEDING COMPLICATIONS[28]	**MCS-ARC Bleeding Adverse Event** • Type 1: Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional. This type is not relevant during a hospitalization. • Type 2: Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for Type 3, 4, or 5 but does meet at least one of the following criteria: 1) requiring nonsurgical medical intervention by a health care professional; 2) leading to hospitalization or increased level of care; or 3) prompting evaluation. • Type 3: - Type 3a: o Overt bleeding accompanied by hemoglobin drop of 3 to < 5 g/dl or (1.86−3.1 mmol/liter SI units) (provided hemoglobin drop is related to bleed) o Any transfusion with overt bleeding - Type 3b: o Overt bleeding plus hemoglobin drop 5 g/dl (3.1 mmol/liter) or greater (provided hemoglobin drop is related to bleed). o Cardiac tamponade o Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) o Bleeding requiring intravenous vasoactive agents

Table 24.2-1: Definitions

Term	Definition
	• Type 4: Vortex System-related bleeding (includes concomitant cardiac or non-cardiac surgical procedures) 1) Reoperation after the closure of incision or incisions used to place the Vortex System to control bleeding. 2) ≥ 50 kg: ≥ 4 U packed red blood cells (PRBC) within any 48 hours through discharge or 72 hours post-procedure (whichever comes first). 3) < 50 kg: ≥ 20 cm^3/kg PRBC within any 24 hours through discharge or 72 hours post-procedure (whichever comes first). 4) Chest tube output > 2 liters within 24 hours. • Type 5: Fatal bleeding - Type 5a: Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious - Type 5b: Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation The association of the bleeding event should be classified as follows: • Patient-related (e.g., coagulopathy unrelated to surgical technique such as non-adherence with anti-coagulation medication resulting in an inappropriately high level of anti-coagulation, hepatic failure) • Management-related (e.g., related to surgical technique; hypertension; bleeding in the setting of inappropriate levels of anti-coagulation or to mismanagement of anti-coagulants) • Device-related (e.g., bleeding from the outflow graft, apical connector, or other internal components) Note: The forms recording the presence of bleeding will continue to record the key sources of bleeding as outlined in the INTERMACS[34] User Manual. These include mediastinal: chest wall; mediastinal: outflow-aorta anastomosis; mediastinal: outflow conduit; mediastinal: inflow conduit; mediastinal: cardiopulmonary bypass cannulation site; mediastinal: coagulopathy with no surgical site; mediastinal: other surgical sites; pump or implanted component pocket (battery or controller); mediastinal: unspecified; pleural space; intra-abdominal; retroperitoneal; pulmonary; genitourinary tract; GI: upper gastrointestinal (esophagus, stomach, duodenum, and small bowel); GI: lower gastrointestinal (colon, rectum, and anus); GI: unknown, but guaiac positive stools; ENT/dental; other.
CARDIAC TAMPONADE	Evidence of a new pericardial effusion associated with hemodynamic instability and clearly related to the procedure. Clinical syndrome caused by the accumulation of fluid in the pericardial space, resulting in reduced ventricular filling and subsequent hemodynamic compromise.
CARDIOGENIC SHOCK	An insufficient forward cardiac output to maintain adequate perfusion of vital organs to meet ongoing demands for oxygenation and metabolism. Cardiogenic shock is due to either inadequate left ventricular pump function (such as in congestive heart failure) or inadequate left ventricular filling (such as in cardiac tamponade). Cardiogenic shock is defined as sustained hypotension (>30 minutes) with evidence of tissue hypoperfusion including oliguria (<30 mL/h), cool extremities, cyanosis, and altered mental status.
CLINICAL SUCCESS	Clinical success is defined as follows: • No conversion to open heart surgery; and • No in-hospital mortality

Table 24.2-1: Definitions

Term	Definition
DATA CATEGORIES	Data categories as defined by General Data Protection Regulation (GDPR) are listed below. Personal Data: GDPR defines "Personal Data" to be any information relating to an identified or identifiable natural person ('data subject'); an identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person. Sensitive Personal Data: GDPR defines "Sensitive Personal Data" as a subset of Personal Data, which, due to their nature have been classified as deserving additional privacy and security protections because their processing may create a risk for an individual's fundamental right and freedom. This subset includes but is not limited to the following: racial, ethnic origin or ethnicity; political opinions; religious or philosophical beliefs; trade union membership; genetic data; biometric data for the purpose of uniquely identifying a natural person; health data (including gender, family medical history, etc.); sex life or sexual orientation; criminal records or allegations of crimes (requires an even higher standard of protection). Identifiers: "Identifiers" are Personal Data that can be used alone or in combination with other identifiers to identify an individual. Identifiers include but are not limited to the following: • All government-issued identification numbers (including but not limited to names, social security number, certificate/license numbers, passport, national ID) • All financial account numbers (including but not limited to bank account numbers, payment numbers, bank or credit card numbers) • All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP code, and their equivalent geocodes, except for the initial three digits of the ZIP code if, according to the current publicly available data from the Bureau of the Census, the geographic unit formed by combining all ZIP codes with the same three initial digits contains more than 20,000 people and/or the initial three digits of a ZIP code for all such geographic units containing 20,000 or fewer people is changed to 000 • All elements of dates (except year) for dates that are directly related to an individual, including birth date, admission date, discharge date, death date, and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older • Telephone numbers • Fax numbers • Device identifiers and serial numbers • E-mail addresses • Web Universal Resource Locators (URLs) • Internet Protocol (IP) addresses • Medical record numbers • Biometric identifiers, including finger and voice prints

Table 24.2-1: Definitions

Term	Definition
	• Health plan beneficiary numbers • Full-face photographs and any comparable images • Any other unique identifying number, characteristic, or code (including subject ID number)
DEATH	<u>All-cause Death</u> Death from any cause after percutaneous coronary intervention using circulatory support. Death is categorized as cardiac or non-cardiac. <u>Cardiac Death</u> Cardiac death is defined as death due to any of the following. • Acute myocardial infarction • Cardiac perforation/pericardial tamponade • Arrhythmia or conduction abnormality • Cerebrovascular accident (CVA) through hospital discharge or CVA suspected of being related to the procedure • Death due to complication of the procedure, including bleeding, vascular repair, transfusion reaction, or bypass surgery • Any death in which a cardiac cause cannot be excluded <u>Non-cardiovascular Death</u> Non-cardiac death is defined as a death not due to cardiac causes as defined above.
DEVICE DEFICIENCY *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	An inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. <u>Note 1</u>: Device deficiencies include malfunctions, use errors, or inadequacy in the information supplied by the manufacturer.
DEVICE MALFUNCTION[28]	**Major Device Malfunction** Major device malfunction, otherwise known as failure, occurs when one or more of the components of the Vortex System either directly causes or could potentially induce a state of inadequate circulatory support (low cardiac output state) or death. A failure that was iatrogenic or recipient-induced will be classified as an Iatrogenic/Recipient-Induced Failure. A device malfunction or failure is categorized as Major when one of the following conditions occurs: • Death • Hospitalization, emergency room visit or prolongation of hospitalization, or escalation of the level of care in an ongoing hospitalization (i.e., transfer to the intensive care unit) • Life-threatening event (i.e., stroke or transient ischemic attack, cardiac arrest, heart failure, syncope or near syncopal event, arrhythmia, etc.) • Results in significant disability or incapacity • Requires an intervention to prevent impairment/injury including: o Urgent transplantation listing (immediate urgent listing for the transplant) o Pump replacement o Pump explant o Pump deactivation without explant or partial explant of components o Breach of integrity of percutaneous lead requiring repair

Table 24.2-1: Definitions

Term	Definition
	○ Operation to repair or replace any internal component of the circulatory support system ○ Procedure to repair or stent an outflow graft • Suspected or confirmed device thrombus Note: Replacement of the external controller that is done in an inpatient setting for logistical reasons, in an otherwise stable patient, should be considered a minor device malfunction rather than major. **Minor Device Malfunction** Minor device malfunction includes inadequately functioning external components that require repair or replacement but do not result in the conditions listed above for major device malfunctions. Device malfunction does not apply to routine maintenance including replacement of external controller, pneumatic drive unit, electric power supplies, batteries, and interconnecting cables that are not related to a failed component. **The association of the device malfunction should be classified as follows:** • Patient-related (i.e., non-adherence with care of device or its peripheral components, or the Instructions for Use, or non-adherence with the anti-coagulation regimen, or pro-coagulation abnormalities) • Management-related (i.e., surgical protocol deviation, suboptimal anti-coagulation) • Device-related (i.e., detected in a device at explant or on contrast studies or associated with hemolysis or other controller data consistent with device malfunction)
DEVICE RELATED COMPLICATIONS	Complications associated with the device as it relates to delivery, placement, efficacy or durability; these may involve the temporarily inserted device or the delivery system.
DEVICE THROMBOSIS	Device thrombosis, defined as any thrombus attached to or near the temporarily inserted device, subclassified as: • Major: occludes part of the blood flow path, interferes with valve function (e.g., immobility of 1 or more leaflets), is symptomatic, • or is sufficiently large to warrant treatment, or • Minor: incidental finding on echocardiography or other imaging test that is not major
EMBOLISM	Examples include a free-flowing blood clot or lesion material that is located in the systemic or pulmonary circulation. Embolism may be manifested by a neurological event or a noncerebral embolic event.
GENERAL DATA PROTECTION REGULATION	The General Data Protection Regulation (GDPR) is a legal framework that sets guidelines for the collection and processing of personal information of individuals within the European Union.
INTENT TO TREAT (ITT) ANALYSIS SET	This population includes all subjects who sign an informed consent form and are enrolled in the study, whether or not a study device is successfully inserted and used.
INTRACRANIAL HEMORRHAGE	Collection of blood between the brain and skull; subcategorized as epidural, subdural, and subarachnoid bleeds.
MYOCARDIAL INFARCTION/INJURY (MI)[35]	**Universal Definitions of Myocardial Injury and Myocardial Infarction** • Criteria for Myocardial Injury

Table 24.2-1: Definitions

Term	Definition
	The term myocardial injury should be used when there is evidence of elevated cardiac troponin values (cTn) with at least one value above the 99th percentile upper reference limit (URL). The myocardial injury is considered acute if there is a rise and/or fall of cTn values. • Criteria for Acute Myocardial Infarction (types 1, 2 and 3 MI) The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL and at least one of the following: o Symptoms of myocardial ischaemia; o New ischaemic electrocardiogram (ECG) changes; o Development of pathological Q waves; o Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology; o Identification of a coronary thrombus by angiography or autopsy (not for type 2 or 3 MIs). *Type 1 MI:* Post-mortem demonstration of acute athero-thrombosis in the artery supplying the infarcted myocardium meets criteria for *type 1 MI*. *Type 2 MI:* Evidence of an imbalance between myocardial oxygen supply and demand unrelated to acute athero-thrombosis meets criteria for *type 2 MI*. *Type 3 MI:* Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumed new ischaemic ECG changes before cTn values become available or abnormal meets criteria for *type 3 MI*. • Criteria for Coronary Procedure-Related Myocardial Infarction (types 4 and 5 MI) Percutaneous coronary intervention (PCI) related MI is termed type 4a MI. Coronary artery bypass grafting (CABG) related MI is termed type 5 MI. Coronary procedure-related MI ≤ 48 hours after the index procedure is arbitrarily defined by an elevation of cTn values > 5 times for type 4a MI and > 10 times for type 5 MI of the 99th percentile URL in patients with normal baseline values. Patients with elevated pre-procedural cTn values, in whom the pre-procedural cTn level are stable (≤ 20% variation) or falling, must meet the criteria for a > 5- or > 10-fold increase and manifest a change from the baseline value of > 20%. In addition, with at least one of the following: o New ischaemic ECG changes (this criterion is related to type 4a MI only); o Development of new pathological Q waves; o Imaging evidence of loss of viable myocardium that is presumed to be new and, in a pattern, consistent with an ischaemic aetiology; o Angiographic findings consistent with a procedural flow-limiting complication such as coronary dissection, occlusion of a major epicardial artery or graft, side-branch occlusion-thrombus, disruption of collateral flow or distal embolization. *Type 4a MI or Type 5 MI:* Isolated development of new pathological Q waves meets the *type 4a MI* or *type 5 MI* criteria with either revascularization procedure if cTn values are elevated and rising but less than the pre-specified thresholds for PCI and CABG.

Table 24.2-1: Definitions

<table>
<tr><th>Term</th><th>Definition</th></tr>
<tr><td></td><td>Type 4b MI and Type 4c MI: Other types of 4 MI include type 4b MI stent thrombosis and type 4c MI criteria.
Type 4a MI and Type 4b MI: Post-mortem demonstration of a procedure-related thrombus meets the type 4a MI criteria or type 4b MI criteria if associated with a stent.
• <u>Criteria for Prior or Silent/Unrecognized Myocardial Infarction</u>
Any one of the following criteria meets the diagnosis for prior or silent/ unrecognized MI:
o Abnormal Q waves with or without symptoms in the absence of nonischaemic causes
o Imaging evidence of loss of viable myocardium in a pattern consistent with ischaemic aetiology
o Patho-anatomical findings of a prior MI</td></tr>
<tr><td>NEUROLOGICAL EVENT</td><td>Any central, new neurological deficit, whether temporary or permanent and whether focal or global, that occurs after the subject emerges from anesthesia</td></tr>
<tr><td>NEW YORK HEART ASSOCIATION CLASSIFICATION (NYHA)</td><td>Classification system for defining cardiac disease and related functional limitations into four broad categorizations:
<table>
<tr><td>Class I</td><td>Subject with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.</td></tr>
<tr><td>Class II</td><td>Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.</td></tr>
<tr><td>Class III</td><td>Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.</td></tr>
<tr><td>Class IV</td><td>Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.</td></tr>
</table></td></tr>
<tr><td>PER-PROTOCOL ANALYSIS SET</td><td>This population includes all subjects who sign an ICF, are enrolled in the study, and in whom the device is successfully advanced across the aortic valve into the left ventricular outflow tract and turned on.</td></tr>
<tr><td>PROCEDURE-RELATED EVENTS</td><td>Events occurring during or as a direct result of the index procedure.</td></tr>
<tr><td>SERIOUS ADVERSE DEVICE EFFECT (SADE)
Ref: ISO 14155
Ref: MDCG 2020-10/1</td><td>Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event</td></tr>
<tr><td>SERIOUS ADVERSE EVENT (SAE)
Ref: ISO 14155
Ref: MDCG 2020-10/1</td><td>Adverse event that led to any of the following:
a) Death,
b) Serious deterioration in the health of the subject, users or other persons as defined by either:</td></tr>
</table>

Table 24.2-1: Definitions

Term	Definition
	1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic diseases, or 3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) Foetal distress, foetal death, or a congenital abnormality or birth defect including physical or mental impairment. Note 1: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
SERIOUS HEALTH THREAT *Ref: ISO 14155*	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health of subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. Note 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.
SOURCE DATA *(per ISO 14155)*	All information in original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation
SOURCE DOCUMENT *(per ISO 14155)*	Original or certified copy of printed, optical or electronic document containing source data.
STROKE	Stroke is defined as an acute symptomatic episode of neurological dysfunction attributed to a vascular cause lasting more than 24 hours or lasting 24 hours or less with a brain imaging study or autopsy showing infarction. **Stroke Classification** • Ischemic Stroke: an acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue. • Hemorrhagic Stroke: an acute symptomatic episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage • Undetermined Stroke: a stroke with insufficient information to allow categorization as ischemic or hemorrhagic An event that lasts < 24 hours may be adjudicated as a stroke if the following treatments were used: • Pharmacologic, i.e., thrombolytic drug administration, or • Non-pharmacologic, i.e., neuro-interventional procedure (e.g., intracranial angioplasty)
TECHNICAL SUCCESS	Technical success is defined as follows: • Successful delivery of the device to the correct anatomical position; and • Successful operation and removal of the Vortex circulatory support system
TRANSIENT ISCHEMIC ATTACK (TIA)	A TIA is a focal ischemic neurological deficit of abrupt onset and of presumed vascular etiology that resolves completely within 24 hours of onset.

Table 24.2-1: Definitions

Term	Definition
UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT *Ref: ISO 14155* (USADE)	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 1: An anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity, or outcome has been identified in the risk analysis report.
VASCULAR COMPLICATION - MAJOR (MCS-ARC[28])	Major vascular complications include any of the events below that require a diagnostic investigation to be confirmed and require surgical or endovascular intervention. • Pseudo-aneurysm • Arteriovenous fistula • Vessel thrombosis/Distal embolization • Vessel dissection, perforation or rupture • Vessel stenosis • Cannulation site bleeding (would have to fulfill durable device bleeding definition) • Limb ischemia • Vascular access site infection
VESSEL PERFORATION	Unexpected puncture of the vessel with evidence of extravasation into extraluminal surrounding tissue or space requiring treatment using interventional or surgical techniques

Abbreviations: ADE=adverse device effect; AE=adverse event; CABG=coronary artery bypass graft; CK-MB=creatine kinase-myoglobin band; CT=computed tomography; cTn=cardiac troponin; ECG=electrocardiogram; GDPR=General Data Protection Regulation; ICD=implantable cardioverter-defibrillators; LVEF=left ventricular ejection fraction; MI=myocardial infarction; MRI=magnetic resonance imaging; NYHA=New York Heart Association; PCI=percutaneous coronary intervention; PRBC=packed red blood cells; SADE=serious adverse device effect; SAE=serious adverse event; TIA=transient ischemic attack; ULN=upper limit of normal; URL=upper reference limit (defined as 99th percentile of normal reference range); USADE=unanticipated serious adverse device effect

25. Revision History

25.1. *Summary of Protocol Revision History*

Protocol revision history is provided in **Table 25.1-1**.

Table 25.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
A	10-Feb-2020	90702637 Rev/Ver AL	Not applicable.	Not applicable.	Not applicable.
B	13-Nov-2020	90702637 Rev/Ver AM	Page 1	Vortex Temporary Percutaneous… ~~National Clinical Trial (NCT) Identification Number: TBD~~ European Authorized Representative Boston Scientific International S.A. Le Val Saint-Quentin 2 rue René Caudron, 78960 Voisins le Bretonneux, France Australian Representative Boston Scientific Pty. Ltd. Building 1, Level 6 191 O'Riordan Street Mascot, NSW 2020, Australia	Added for clarity Registration number to be determined later BSC representative in Australia and Europe added because the study centers will be there.
			Page 2, Coordinating Principal Investigator	Antony Walton, MBBS Deputy Director and Head of Catheter Laboratory Department of Cardiology, The Alfred Hospital 55 Commercial Road, Melbourne VIC 3004 Australia **Current Version**: ~~10-Feb-~~12-Nov-2020 Updated revision table	Coordinating principal investigator Updated to reflect new protocol version
			Section 2, Synopsis, Title	Vortex Temporary Percutaneous…	Added for clarity
			Section 2, Synopsis, Study Objective(s)	To evaluate the feasibility and safety~~, clinical success, and technical success~~ of the Vortex Temporary Percutaneous Transvalvular Circulatory Support System (Vortex System) in	

Table 25.1-1: Protocol Revision History

<table>
<tr><th>Revision Version</th><th>Protocol Date</th><th>Template Number and Version</th><th>Protocol Sections Modified</th><th>Summary of Changes</th><th>Justification for Changes</th></tr>
<tr><td></td><td></td><td></td><td></td><td>subjects undergoing elective high-risk percutaneous coronary intervention (HR-PCI)</td><td></td></tr>
<tr><td></td><td></td><td></td><td>Section 2, Synopsis, Planned Indication for Use</td><td>The Vortex System is indicated to provide temporary (≤ 4 hours) circulatory support in subjects undergoing elective high-risk…</td><td></td></tr>
<tr><td></td><td></td><td></td><td>Section 2, Synopsis, Test Device ~~and Sizes if Applicable~~</td><td>~~Vortex temporary percutaneous, transvalvular circulatory support system.~~
The Vortex System ~~includes a starter tube, introducer sheath, and 0.018” wire that are used to position the pump. A controller is used to run the pump and collect and display data on pump performance; it is connected to the pump using a sterile extension cable~~ is a minimally invasive device that is in direct contact with the heart while in use. Components are summarized below.
<table>
<tr><th>Component</th><th>Description</th></tr>
<tr><td>Vortex Pump</td><td>- Axial flow pump magnetically coupled to the impeller with an expandable flexible cannula in a membrane-covered pre-shaped braid and a proximal catheter
- Introduced percutaneously via femoral artery access; advanced across the aortic valve into the left ventricular outflow tract; outlet ports are near the sinotubular junction</td></tr>
<tr><td>Vortex Delivery System</td><td>- Starter tube
- Introducer sheath with 16 Fr profile, 35-cm length
- Dilator (compatible with 0.035” wire)
- Cannula delivery tool</td></tr>
<tr><td>Vortex Wire</td><td>- 0.018” diameter, 300-cm length, shapeable tip</td></tr>
</table></td><td></td></tr>
</table>

Table 25.1-1: Protocol Revision History

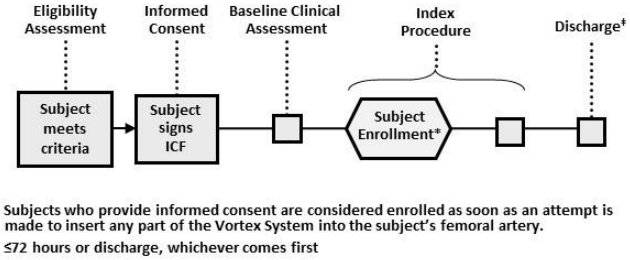
Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				Vortex Console: - Interface to control/monitor the pump; connected to the pump using a sterile extension cable, which is plugged into the wall and controls power to the pump	
			Section 2, Synopsis, Study Design	The Vortex Feasibility Study is a prospective, open-label, single-arm study designed to assess the safety and feasibility of the Vortex System to provide temporary (≤ 4 hours) circulatory support in subjects undergoing HR-PCI. The study design is summarized in the figure below.  * Subjects who provide informed consent are considered enrolled as soon as an attempt is made to insert any part of the Vortex System into the subject's femoral artery. ‡ ≤72 hours or discharge, whichever comes first **Vortex Feasibility Study Design Overview** The Vortex study will be conducted in accordance with the International Standard ISO 14155 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice; European Medical Device Regulations; ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country/state/local laws and regulations. The study shall not begin until the required approval/favorable opinion from the Independent Ethics Committee (IEC)/Human Research Ethics Committee (HREC) and/or regulatory authority has been obtained, if appropriate.	
			Section 2, Synopsis, Planned Number…	There will be up to 10 subjects enrolled in up to 3 centers in ~~Asia Pacific~~ Australia and Europe.	

Table 25.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 2, Synopsis Primary Endpoint	The primary endpoint consists of Technical Success and Clinical Success, defined as follows. Technical Success • Successful delivery… Clinical Success • ~~Without~~ No conversion to open heart surgery ~~or~~; and • No in-hospital mortality ~~and freedom of procedural Q-wave MI~~	
			Section 2, Synopsis Additional ~~Endpoints~~ Measurements	Safety events will be collected through 72 hours post-procedure or hospital discharge… • Stroke/transient ischemic attach (TIA; see Note 1 below)… • Cardiac death~~: all cause~~ (see Note 1 below)… • Bleeding complications: Type 3–5 based on the Mechanical Circulatory Support Academic Research Consortium (MCS-ARC) definitions[a] (see Note 1 below) • Acute kidney injury (AKI; based on the AKIN System Stage 3 [including renal replacement therapy] or Stage 2 ~~or 3~~)… ~~• Procedure time~~ • Any device-related adverse event (adverse device effect [ADE]/serious adverse device effect [SADE])… • Any unanticipated serious adverse device effect (USADE)… ~~• Device deficiencies~~ **Note 1:** Death, stroke, bleeding complications, and major vascular complications are adjudicated by an Independent Medical Reviewer (IMR). a: Kormos RL, et al. J Heart Lung Transplant 2020;39:735-50 ~~Note 1: Death, stroke, MI and cardiac tamponade will be based on theVARC-2 definitions and endpoints.~~ ~~Note 2: Bleeding events will be based on the BARC definitions~~	

Table 25.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 2, Synopsis Study Duration	Enrollment/total study duration may ~~is expected to~~ be completed in approximately 12~~–3~~ months.	
			Section 2, Synopsis Participant Duration	The study duration for each subject is expected to be through 72 hours or hospital discharge, whichever comes first.	
			Section 2, Synopsis Inclusion Criteria	IC1. Subject provides signed informed consent. IC2. Subject is ≥ 18 years and < 90 years of age. IC3. Subject is indicated for NON-emergent PCI of at least one de novo or restenotic lesion in a native coronary vessel or coronary artery bypass graft (CABG) and has left ventricular ejection fraction (LVEF) ≤ 35% with the following: • Unprotected left main ~~or last remaining vessel and LVEF≤ 35%~~ -OR- • Last remaining vessel -OR- • Three vessel disease (≥ 50% diameter stenoses by visual estimate or total occlusion) ~~and LVEF ≤ 35%~~	
			Section 2, Synopsis Exclusion criteria	EC1. Subject has had ST-elevation myocardial infarction (STEMI) within 24 hours. EC2. Subject has had pre-procedure cardiac arrest requiring cardiopulmonary resuscitation (CPR) within 24 hours of enrollment. EC3. Subject is in ~~cardiogenic~~ shock, defined as follows: • Cardiac index (CI) < 2.2 L/min/m^2 and pulmonary capillary wedge pressure (PCWP) > 15 mmHg -AND- • Hypotension… EC5. Subject has a ~~Presence of mechanical or~~ prosthetic aortic valve. EC6. Subject has pericarditis or constrictive heart disease (constrictive pericarditis or restrictive cardiomyopathy), ~~moderate or greater aortic valve stenosis (effective orifice area < 1.5 cm^2), severe aortic calcification~~.	

Table 25.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				EC7. Subject has moderate ~~to severe~~ or greater aortic valve stenosis[b] or moderate or greater aortic valve insufficiency[b] (by… EC8. Subject has abnormalities of the aorta that preclude safe delivery of the device, including severe calcification, tortuosity, aneurysm, or prior surgery. EC9. Subject has ~~severe~~ peripheral vessel disease (PVD) preventing passage of the device (e.g., calcification, small caliber) or ~~severe~~ tortuosity that would preclude safe placement of the 16 Fr introducer sheath. Note 2: Minimum required vessel diameter is > 5.5 mm. EC10. Subject has ~~with~~ advanced renal ~~failure~~ dysfunction (~~creatinine ≥~~AKIN Stage 3 ~~mg/dL~~)… EC13. Subject has known ~~allergy~~ hypersensitivity to intravenous contrast agents that cannot be adequately pre-medicated or has known hypersensitivity to heparin… EC17. Subject requires mechanical ventilation ~~combined cardiorespiratory failure…~~ ~~• Participation in another clinical trial that has not reached it is primary endpoint~~ EC21. Subject has severe pulmonary disease (FEV1 ~~≥~~ < 1L). EC22. Subject has sustained or non-sustained ventricular tachycardia. EC23. Subject is breast feeding or is pregnant. b: Nishimura RA, et al. J Am Coll Cardiol 2014;63:e57-185	
			Section 2, Synopsis ~~Multiple Interventions During~~ Index Procedure	The Vortex sheath… pump will pass though this sheath ~~at various times throughout~~ during the procedure… as soon as the mechanical circulatory support is deemed to be unnecessary	
			Section 2, Synopsis Primary Statistical Hypothesis	There is no formal statistical hypothesis in this observational feasibility study. ~~No formal sample size calculation will be performed. Descriptive summaries will be provided.~~	

Table 25.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 2, Synopsis Statistical Test Method	Descriptive statistics will be used for baseline, procedure, and follow-up data collected ~~through~~ during the study. The primary endpoint and additional measurements will be analyzed on an intention-to-treat (ITT) basis and a per-protocol basis. Analysis sets are listed below. Subjects are considered enrolled in the study as soon as an attempt is made to insert any part of the Vortex System into the subject's femoral artery. • ITT: This population includes all subjects who sign an Informed Consent Form (ICF) and are enrolled in the study, whether or not a study device is successfully inserted and used. • Per-protocol: This population includes all ITT subjects in whom the device is successfully advanced across the aortic valve into the left ventricular outflow tract and turned on.	
			Section 2, Synopsis Sample Size Parameters	This is… and therefore sample size estimates are not applicable. In order to support the stated objectives of this feasibility study, the study sample size has been limited to a maximum of up to 10 subjects enrolled.	
			Sections 3–25	Sections 3–25 are all new.	Added the rest of the protocol information to the Synopsis
C	5-Mar-2021	90702637 Rev/Ver AO	Section 2, Protocol Synopsis, Inclusion Criteria 3 Section 8.2; Table 8.2-1	A subject will be considered for enrollment if all of the following inclusion criteria are met, provided no exclusion criteria are met. IC1. Subject provides signed informed consent. IC2. Subject is ⩾ 18 years and < 90 years of age. IC3. Subject is indicated for NON-emergent PCI of at least one *de novo* or restenotic lesion in a native coronary vessel or coronary artery bypass graft (CABG) and has left ventricular ejection fraction (LVEF) ⩽ ~~35~~50% with the following:	LVEV is changed from left ventricular ejection fraction (LVEF) ⩽ 35% into left ventricular ejection fraction (LVEF) ≤ 50% to be consistent with the inclusion criteria of other contemporary mechanical circulatory support

Table 25.1-1: Protocol Revision History

<table>
<tr><th>Revision Version</th><th>Protocol Date</th><th>Template Number and Version</th><th>Protocol Sections Modified</th><th colspan="3">Summary of Changes</th><th>Justification for Changes</th></tr>
<tr><td></td><td></td><td></td><td></td><td colspan="3">• Unprotected left main -OR-
• Last remaining vessel -OR-
Three vessel disease (⩾50% diameter stenoses by visual estimate or total occlusion)</td><td>device studies and the labelling of the commercially approved (Abiomed) device</td></tr>
<tr><td rowspan="2">C</td><td rowspan="2">5-Mar-2021</td><td rowspan="2">90702637 Rev/Ver AO</td><td rowspan="2">Section 18.4; Table 18.4-1</td><td>~~Serious Health Threat~~</td><td>~~Complete applicable eCRF page with all available new and updated information.~~</td><td>~~• Within 1 business day of first becoming aware of the event.~~
~~Terminating at the end of the study~~</td><td rowspan="2">In Table 18.4-1 is the Serious Health Threat removed to follow the new protocol template where this is no longer required for the Investigator Reportings</td></tr>
<tr><td></td><td>~~Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.~~</td><td>~~Upon request of sponsor~~</td></tr>
<tr><td>D</td><td>21-May-2021</td><td>90702637 Rev/Ver AP</td><td>Contact Information</td><td colspan="3"><table><tr><th>Role</th><th>Contact</th><th></th></tr><tr><td>Clinical Contact</td><td>Arjun Bhat, MBBS, MBA
Sr. Clinical Trial Manager,
Interventional Cardiology
Boston Scientific
300 Boston Scientific Way
Marlborough, MA 01752
E-mail: arjun.bhat@bsci.com</td><td></td></tr><tr><td>Coordinating Principal</td><td>Antony Walton, MBBS
Deputy Director and Head of Catheter Laboratory</td><td></td></tr></table></td><td>Clinical contact updated to reflect Arjun Bhat as new trial manager for the study.

List of investigation sites with corresponding names of their principal investigators added per MPA request.</td></tr>
</table>

Table 25.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				Investigator and Site Principal Investigator: Department of Cardiology The Alfred Hospital 55 Commercial Road Melbourne VIC 3004 Australia **Site Principal Investigator**: Matthias Götberg, MD, PhD Director, Cardiac Catheterization Laboratory University Hospital of Lund Getingevagen Department of Coronary Heart Disease SE-221 85 Lund, Sweden	
			Section 2; Protocol Synopsis	**Vortex Feasibility Study Design Overview** The Vortex study will be conducted in accordance with the International Standard ISO 14155:2020 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice; European Medical Device Regulations; ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country/state/local laws and regulations. The study shall not begin until the required approval/favorable opinion from the Independent Ethics Committee (IEC)/Human Research Ethics Committee (HREC) and/or regulatory authority has been obtained, if appropriate	For clarity; to specify which version of the GCP standard that is applied for this clinical investigation.

Table 25.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 8.3; Table 8.3 1, Protocol Synopsis	A subject will be excluded from the study if any of the following exclusion criteria are met. EC1. Subject has had ST-elevation myocardial infarction (STEMI) within 24 hours. EC2. Subject has had pre-procedure cardiac arrest requiring cardiopulmonary resuscitation (CPR) within 24 hours of enrollment. EC3. Subject is in shock, defined as follows: • Cardiac index (CI) < 2.2 L/min/m^2 and pulmonary capillary wedge pressure (PCWP) > 15 mmHg -AND- • Hypotension (systolic blood pressure < 90 mmHg for > 30 minutes) -OR- • Need for supportive measures (i.e., inotropes or mechanical support) to maintain systolic blood pressure ≥ 90 mmHg and end organ hypoperfusion (cool extremities or urine < 30 mL/hour and a heart rate > 60 beats per minute) EC4. Subject has left ventricular mural thrombus. EC5. Subject has a prosthetic aortic valve. EC6. Subject has pericarditis or constrictive heart disease (constrictive pericarditis or restrictive cardiomyopathy). EC7. Subject has moderate or greater aortic valve stenosis[b] or moderate or greater aortic valve	Per MPA request, EC24 and EC25 added to include other disease conditions resulting in the patient being unsuitable to participate in the clinical trial or non-compliant per protocol requirements.

Table 25.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				insufficiency[b] (by echocardiographic assessment, graded as ≥ 2+). EC8. Subject has abnormalities of the aorta that preclude safe delivery of the device, including severe calcification, tortuosity, aneurysm, or prior surgery. EC9. Subject has peripheral vessel disease (PVD) preventing passage of the device (e.g., calcification, small caliber) or tortuosity that would preclude safe placement of the 16 Fr introducer sheath. **Note 2:** Minimum required vessel diameter is > 5.5 mm. EC10. Subject has advanced renal dysfunction (AKIN Stage 3). EC11. Subject has a history of liver dysfunction (Childs Class C) with elevation of liver enzymes and bilirubin > 3× upper limit of normal (ULN) or international normalization ratio (INR) ≥ 2. EC12. Subject has had a recent (within 1 month) stroke or TIA. EC13. Subject has known hypersensitivity to intravenous contrast agents that cannot be adequately pre-medicated or has known hypersensitivity to heparin, aspirin, ADP receptor inhibitors or nitinol. EC14. Subject has current or a history of heparin induced thrombocytopenia (HIT). EC15. Subject has uncorrected abnormal coagulation or platelet count ≤ 75,000/mm³ or INR ≥ 2.0.	

Table 25.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				EC16. Subject has significant right heart failure (right atrial pressure [RAP] > 15 mmHg, right ventricular stroke work index [RVSWI] < 0.30 mmHg·L/m², pulmonary vascular resistance [PVR] > 3.6 Woods units). EC17. Subject requires mechanical ventilation. EC18. Subject has an atrial or ventricular septal defect (including post-infarct ventricular septal defect [VSD]). EC19. Subject has left ventricular rupture. EC20. Subject has cardiac tamponade. EC21. Subject has severe pulmonary disease (FEV1 < 1L). EC22. Subject has sustained or non-sustained ventricular tachycardia. EC23. Subject is breast feeding or is pregnant. EC24. Subject has other disease condition(s) resulting in the subject being unsuitable for participation in the clinical trial (e.g. advanced malignancy with limited expected survival) EC25. Subject has other disease condition(s) which the Investigator has determined may cause non-compliance to the study requirements. b: Nishimura RA, et al. *J Am Coll Cardiol* 2014;63:e57-185.	

Table 25.1-1: Protocol Revision History

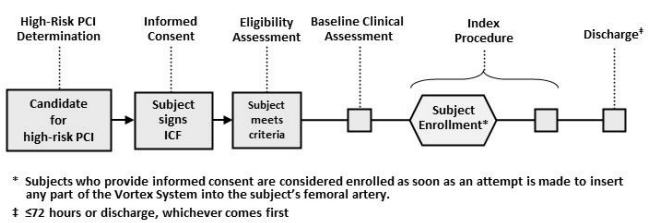
Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 2; Protocol Synopsis, Section 7.1; Figure 7.1 1		Figure 7.1 1 updated per MPA request to match study enrollment definition.
			Section 7.2	Subjects who are candidates for high-risk percutaneous coronary intervention, provide written informed consent, and are eligible to be treated with the Vortex System will be evaluated for enrollment in this study. Prior to being eligible for the study, a subject must meet all of the inclusion criteria (Section 8.2) and none of the exclusion criteria (Section 8.3).	Section 7.2 (treatment assignment) updated to match language in Section 8.1 (Study Population and Eligibility) per MPA request.

Table 25.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 15.2	The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan, ISO 14155:2020, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IEC/HREC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.	For clarity; to specify which version of the GCP standard that is applied for this clinical investigation.
			Section 15.3	Any amendment to the protocol and/or ICF will require review and approval by the IEC/HREC and the Swedish Medical Products Agency (MPA) before changes to the study are implemented. All changes to the ICF will be IEC/HREC approved; a determination will be made regarding whether a new ICF needs to be obtained from subjects who provided consent using a previously approved ICF. Annual IEC/HREC approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IEC/HREC requirements. Copies of the study reports and the IEC/HREC continuance of approval must be provided to the sponsor.	Language modified per MPA request.

Table 25.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 16	Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities. The sponsor will put a plan in place to document the specific monitoring requirements. A general outline of the monitoring plan is described below - **Site Initiation Visits** All sites participating in the study will have Site Initiation Visits (SIVs). A live, online training session with slides will be conducted virtually via the Web. A checklist of activities (as specified in the monitoring plan: e.g. protocol training, ICH/GCP, monitoring expectations, PI responsibilities, safety reporting requirements, documentation requirements, local law requirements such as: data protection, EC reporting) will be conducted and confirmed complete, prior to site authorization to enroll to ensure preparedness of the investigator and site staff. Additional training may be done on an as-needed basis throughout the study for study procedures and updates, clinical events, unanticipated adverse device effect reporting process, regulatory requirements, CRF completion, and compliance issues noted during monitoring. **Interim Monitoring Visits**	General outline of monitoring plan included per MPA request.

Table 25.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				Interim Monitoring Visits (IMVs) will be conducted for each site. Each visit will require a written confirmation letter, a monitoring visit report, and a follow up letter. At each interim monitoring visit, the monitor will assess: • Regulatory documents and contents of the Investigator Site File to ensure that they are complete, accurate and current. • Accuracy of data: the monitor will compare subject medical records and other supporting documents with the CRFs to determine that they are complete, accurate, and legible. • Informed consent forms: monitor will review the ICFs and documentation of the consent process in the source documents. • Safety reporting: monitor will verify and/or discuss that all reportable events and device deficiencies are reported and recorded in accordance with the protocol and the local regulatory requirements and ensures necessary source documents are obtained. • Site resources, adequacy of facilities, any changes in study personnel, location, etc. • Device accountability to ensure the log is complete and accurate Site compliance to the study protocol will be assessed over the life of the study. **Closeout Visits** A Closeout monitoring visit (COV) will be performed for each site. Closeout activities can be performed separately or in	

Table 25.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				conjunction with an interim monitoring visit. When preparing the site for closure, the monitor will verify and/or discuss that: • All essential documents are complete and up to date • All CRFs are completed • All outstanding queries are resolved • The current status of all ongoing adverse events is documented and protocol compliant. • All CRF pages are signed by the designated investigator • Device reconciliation is accurate and documented • Arrangements are made for archiving and record retention. The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.	

Table 25.1-1: Protocol Revision History

<table>
<tr><th>Revision Version</th><th>Protocol Date</th><th>Template Number and Version</th><th>Protocol Sections Modified</th><th>Summary of Changes</th><th>Justification for Changes</th></tr>
<tr><td></td><td></td><td></td><td>Section 18, Table 18.2-1, Section 18.3, Table 18.3-1, Section 18.4, Table 18.4-1</td><td>Adverse event definitions are provided in Table 18.2-1. Administrative edits were made on the safety definitions from applicable regulations and guidance including (but not limited to) ISO 14155 and EU MDR 2017/745/MDCG 2020-10/1 Guidance on Safety Reporting in Clinical Investigations for clarification purposes.

Table 25.1-2: Safety Definitions
<table><tr><th>Term</th><th>Definition</th></tr><tr><td>Adverse Event (AE)
Ref: ISO 14155
Ref: MDCG 2020-10/1</td><td>Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational medical device and whether anticipated or unanticipated.
NOTE 1: This includes events related to the investigational medical device or comparator.
NOTE 2: This definition includes events related to the procedures involved.
NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.
NOTE 4: This definition includes events related to management practices
NOTE 5: This definition includes patient related events</td></tr></table></td><td></td></tr>
</table>

Table 25.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes		Justification for Changes
				Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event related to the use of an investigational medical device **NOTE 1:** This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the procedural treatment, the installation, the operation, or any malfunction of the investigational medical device. **NOTE 2:** This definition includes any event resulting from use error or from intentional misuse of the investigational medical device. **NOTE 3:** This includes "comparator" if the comparator is a medical device.	
				Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event that led to any of the following: a) Death, b) Serious deterioration in the health of the subject, users or other persons as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic diseases, or	

Table 25.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes		Justification for Changes
					3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) Foetal distress, foetal death, or a congenital abnormality or birth defect including physical or mental impairment. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.	
				Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.	
				Unanticipated Serious Adverse	Serious adverse device effect which by its nature, incidence, severity, or outcome has	

Table 25.1-1: Protocol Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes		Justification for Changes
				Device Effect (USADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	not been identified in the current risk assessment. **NOTE 1:** Anticipated serious adverse device effect (ASADE) is an effect which by its nature incidence, severity or outcome has been identified in the risk assessment.	
				Serious Health Threat *Ref: ISO 14155*	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health of subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. **NOTE 1:** This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.	
				Device Deficiency *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	An inadequacy of a medical device related to its identity, quality, durability, reliability, usability, safety or performance. **NOTE 1**: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. **NOTE 2**: This definition includes device deficiencies related to the investigational medical device or the comparator.	

Table 25.1-1: Protocol Revision History

<table>
<tr><th>Revision Version</th><th>Protocol Date</th><th>Template Number and Version</th><th>Protocol Sections Modified</th><th>Summary of Changes</th><th>Justification for Changes</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
The following definitions will be used for defining hospitalization or prolongation of hospitalization for SAE classification purposes:
<table>
<tr><td>Hospitalizations</td><td>Hospitalization does not include:
Emergency room visit that does not result in in-patient admission
NOTE 1: Although an emergency room visit does not itself meet the definition for hospitalization, it may meet other serious criteria (e.g., medical or surgical intervention to prevent permanent impairment or damage)
Elective and pre-planned treatment/surgery for a pre-existing condition that is documented in the subject’s record at the time of consent/enrollment
Admission for social reasons and/or respite care in the absence of any deterioration in the subject’s general condition (e.g., subject is homeless, caregiver relief)
Pre-planned, protocol-specified admission related to the clinical study (e.g., procedure required by protocol)</td></tr>
<tr><td>Prolongation of</td><td>In-patient admission to the hospital that is prolonged beyond the expected standard duration for the condition under treatment.</td></tr>
</table>
</td><td></td></tr>
</table>

Table 25.1-1: Protocol Revision History

<table>
<tr><th>Revision Version</th><th>Protocol Date</th><th>Template Number and Version</th><th>Protocol Sections Modified</th><th>Summary of Changes</th><th>Justification for Changes</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>Hospitalization</td><td>NOTE 1: New adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criterion.</td></tr>
</table>

The Investigator must assess the relationship of the reportable adverse events to the study device or study procedure. See criteria in Table 18.3-1:

Table 25.1-3: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event
<table>
<tr><th>Classification</th><th>Description</th></tr>
<tr><td>Not Related
Ref: MDCG 2020-10/1</td><td>Relationship to the device, comparator, or procedures can be excluded when:
the event has no temporal relationship with the use of the investigational device or the procedures related to the use of the investigational device;
the serious 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</td></tr>
</table>
</td><td></td></tr>
</table>

Table 25.1-1: Protocol Revision History

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					reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; • the event involves a body-site or an organ that cannot be affected by the device or procedure; • the serious 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); • the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; 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 serious event.	
				Possibly Related *Ref: MDCG 2020-10/1*	The relationship with the use of the investigational device or comparator or the relationship with procedures is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/clinical condition and/or an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been	

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					obtained should also be classified as possible.	
				Probably Related *Ref: MDCG 2020-10/1*	The relationship with the use of the investigational device, comparator, or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause.	
				Causal Relationship *Ref: **MDCG 2020-10/1***	The serious event is associated with the investigational device or comparator or with procedures beyond 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 procedures are applied to; - the investigational device or procedures have an effect on; • the serious event follows a known response pattern to the medical device (if the response pattern is previously known);	

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				• 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 serious 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; • the event depends on a false result given by the investigational device used for diagnosis, when applicable In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event. The communication requirements for reporting to BSC are as shown in **Table 18.4-1**.	

Table 25.1-4: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline (Pre-market Studies) (MDCG 2020-10/1)
Unanticipated Serious Adverse Device Effects (USADE)	Complete AE electronic case report form (eCRF) page with all available new and updated information.	• Within 1 business day of first becoming aware of the event • Terminating at the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor
Serious Adverse Events (SAE) and IMR events[a]	Complete AE eCRF page with all available new and updated information.	• Immediately but not later than 3 calendar days of first becoming aware of the event or as per local/regional regulations • Reporting required through the end of the study
	Provide all relevant source documentation	• Upon request of sponsor

Table 25.1-1: Protocol Revision History

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					(de-identified /pseudonymized) for reported event.		
				Serious Adverse Device Effects (SADE)	Complete AE eCRF page with all available new and updated information.	• Immediately but not later than 3 calendar days of first becoming aware of the event or as per local/regional regulations • Reporting required through the end of the study	
					Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • Upon request of sponsor	
				~~Serious Health Threat~~	~~Complete applicable eCRF page with all available new and updated information.~~	~~• Within 1 business day of first becoming aware of the event.~~ ~~• Terminating at the end of the study~~	
					~~Provide all relevant source documentation~~	~~• Upon request of sponsor~~	

Table 25.1-1: Protocol Revision History

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					~~(de-identified/ pseudonymized) for reported event.~~		
				Device Deficiencies (including but not limited to , malfunctions, use errors and inadequacy in information supplied by the manufacturer, including labeling) **Note:** Any Device Deficiency that might have led to a serious adverse event if appropriate action had	Complete Device Deficiency eCRF with all available new and updated information.	• Immediately but not later than 3 calendar days of first becoming aware of the event. • Reporting required through the end of the study	
					Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor	

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				not been taken, intervention had not occurred, circumstances had been less fortunate is considered a reportable event.			
				Adverse Event (AE) including Adverse Device Effects (ADE)	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• Adverse Device Effects: In a timely manner but not later than 10 business days after becoming aware of the information • Adverse Events: In a timely manner but recommend within 10 business days after becoming aware of the information • Reporting required through the end of the study • Upon request of sponsor	
					Provide all relevant source documentation (de-identified/ pseudonymized		

Table 25.1-1: Protocol Revision History

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				) for reported event. a: All Independent Medical Reviewer (IMR) events must be reported using the timeframe for SAE, regardless of whether they meet serious criteria.	
			Section 18.5	***18.5 Device Deficiencies*** Vortex System device deficiencies will be documented in the appropriate eCRF and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the investigational device(s) will be provided in the Manual of Operations. Device deficiencies should also be documented in the subject's source records. Device deficiencies are not adverse events. However, an adverse event that results from a device deficiency would be recorded as an adverse event on the appropriate eCRF.	For clarity