Abbott	Clinical Investigation Plan Cover Page [redacted]

NCT Number: NCT02468778
SHIELD II
Supporting Patients Undergoing High-Risk PCI Using a High-Flow PErcutaneous Left Ventricular Support Device
Study Document No: [redacted]
Version [redacted]
Date: 19-Aug-2020

Sponsor Abbott [redacted]

[redacted]

[redacted]

SHIELD II Clinical Investigation Plan

Supporting Patients Undergoing High-Risk PCI Using a High-Flow Percutaneous Left Ventricular Support Device (SHIELD II)

Version Number	[redacted]
Date	August 19, 2020
Study Principal Investigator:	[redacted]
Planned Number of Sites and Regions	Up to 120 sites in the United States
Clinical Investigation Type	Prospective, randomized, open-label, multi-center clinical investigation
Abbott Medical Expert	[redacted] Chief Medical Officer
Sponsor	Abbott [redacted]
Registration/Randomization Service	Abbott Web-based Randomization System
Electronic Data Capture Software	Oracle Clinical Remote Data Capture
Echocardiographic Core Laboratory	[redacted]
Angiographic Core laboratory	

[redacted]

	[redacted]
Clinical Events Committee Administration	[redacted]
Data Safety Monitoring Board Administration	[redacted]
CIP Author of Current Version	[redacted]

TABLE OF CONTENTS

COMPLIANCE STATEMENT:

This clinical investigation will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki, and applicable Good Clinical Practices and regulations (e.g., US 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 812, 21 CFR Part 54, and 21 CFR Part 11). The conduct of the clinical investigation will be approved by the Food and Drug Administration (FDA) and the appropriate Institutional Review Board (IRB) of the respective investigational site.

CLINICAL INVESTIGATION PLAN (CIP) SUMMARY

Clinical Investigation Name and Number	SHIELD II Clinical Investigation CRD_834
Title	Supporting Patients Undergoing High-Risk PCI Using a High-Flow Percutaneous Left Ventricular Support Device (SHIELD II)
Objective	Assess the safety and effectiveness of the HeartMate PHP™ (Percutaneous Heart Pump) System compared to Impella® in supporting patients with severe symptomatic coronary artery disease but with stable cardiovascular function, who are undergoing elective or urgent high-risk percutaneous coronary intervention (PCI), and a heart team, including a cardiac surgeon, has determined high-risk PCI is an acceptable therapeutic option
Investigational Device	The HeartMate PHP System
Control Device	Any Abiomed Impella device approved for use in high-risk PCI
Clinical Investigation Design	Prospective, randomized, open-label, multi-center clinical investigation
Number of Subjects Required for Inclusion in Clinical Investigation	This clinical investigation is divided into two phases, a feasibility phase and a pivotal phase. • Feasibility Phase: Includes 75 roll-in and 120 randomized subjects registered under the CIP versions 2-4 at 48 sites in the United States (U.S.) prior to January 30, 2017 • Pivotal Phase: Includes subjects to be registered under version F or a later version of the CIP at up to 120 sites in the U.S. Non-randomized Roll-in Cohort: Up to 480 subjects with the HeartMate PHP Randomized Cohort: A minimum of 473 and a maximum of 716 subjects will be randomized in a 2:1 ratio to the HeartMate PHP and Impella.
Subject Follow-up	All registered subjects will be followed for 90 days post-device removal. The 90-day (± 30 days) follow-up will include a clinical follow-up and an echocardiographic follow-up.
Subject Enrollment and Registration	• Enrollment: Subjects are considered enrolled in this clinical investigation after signing the Informed Consent Form (ICF). • Registration:

<table>
<tr><td></td><td>

Roll-in Cohort: Only after the subjects sign the ICF, meet all eligibility criteria and receive a HeartMate PHP device, the subjects are considered registered in this clinical investigation.
Randomized Cohort: Only after the subjects sign the ICF, meet all eligibility criteria and are randomized, the subjects are considered registered in this clinical investigation.

Registration is the point when the subjects enter this clinical investigation, and registered subjects must follow all CIP requirements. All registered subjects will need to be followed until 90 days post device removal. Enrolled but not registered subjects are considered screen failures and will not need to be followed.

</td></tr>
<tr><td>Time Points of Data Collection</td><td>Data will be collected at baseline, during the index procedure, post-procedure, at discharge, and at 90 days post-device removal.</td></tr>
<tr><td>Primary Endpoint</td><td>The primary endpoint is a composite endpoint at 90 days, including the following:

Cardiovascular Death
Myocardial infarction (MI)
Stroke
Any unplanned repeat revascularization (PCI or CABG)
Bleeding (BARC 3 or 5) up to 14 days post-device removal
Severe hypotension, defined as: systolic blood pressure (SBP) or augmented diastolic pressure (whichever is greater) <90 mmHg while on device support requiring (1) more than one administration of OR (2) continuous infusion of inotropic/pressor medications to restore hemodynamics
Change in aortic insufficiency from baseline to 90 days by echocardiographic assessment and defined as:

<table>
<tr><th>Baseline Assessment</th><th>90 Day Assessment</th></tr>
<tr><td>None</td><td>Moderate OR Severe</td></tr>
<tr><td>Trace</td><td>Moderate OR Severe</td></tr>
<tr><td>Mild</td><td>Moderate OR Severe</td></tr>
</table>
</td></tr>
</table>

Descriptive Endpoints	[redacted]

	
Exploratory Endpoints	• Quality of Life questionnaires including EQ-5D-5L and Seattle Angina Questionnaire (SAQ) at baseline and 90 days
Inclusion Criteria	**General Inclusion Criteria:** 1. At least 18 years of age 2. Subject is undergoing elective or urgent high-risk PCI procedure and is hemodynamically stable. 3. Subject is indicated for a revascularization of at least one *de novo* or restenotic lesion in a native coronary vessel or bypass graft. 4. A heart team, including a cardiac surgeon, has determined high-risk PCI is an acceptable therapeutic option. 5. Subject must provide written informed consent prior to any clinical investigation related procedure. **Imaging Inclusion Criteria:** 1. The presence of complex coronary artery disease (CAD) makes hemodynamic instability resulting from repeat episodes of reversible myocardial ischemia during PCI likely. Complex CAD is defined as an ejection fraction of <50% by

	echocardiographic assessment AND at least one of the following: a. Intervention of the last patent coronary conduit, OR b. Intervention of an unprotected left main artery, OR c. Intervention on patient presenting with triple vessel disease defined as at least one significant stenosis (at least 50% diameter stenosis on visual assessment) in all three major epicardial territories
Exclusion Criteria	**<u>General Exclusion Criteria:</u>** 1. Emergency PCI 2. Any prior coronary revascularization within the last 6 months 3. Any MI with elevated cardiac biomarker (creatinine kinase-MB (CK-MB) or troponin >1X upper limit of normal (ULN)) and no evidence of at least 1 consecutive CK-MB or troponin value trending downward from previous value (at least 4 hours apart) OR ST Elevation MI (STEMI) within 72 hours prior to the index procedure regardless of the level of cardiac biomarker 4. Cardiac arrest within 24 hours of procedure requiring cardiopulmonary resuscitation (CPR) or defibrillation 5. Any use of a mechanical circulatory support device within 14 days prior to the index procedure (Note: Subjects must be hemodynamically stable without any hemodynamic support to be eligible for this clinical investigation.) 6. Hemodynamic support with a mechanical circulatory support device (e.g., the HeartMate PHP, Impella, intra-aortic balloon pump (IABP), or extracorporeal membrane oxygenation (ECMO)) post-PCI is anticipated. 7. Any condition that requires discontinuation of antiplatelet and/or anticoagulant therapy within 90 days following the index procedure (e.g., planned noncardiac surgery). 8. Any use of vasopressors or inotropes within 24 hours prior to the index procedure 9. Staged PCI is planned within 90 days following device removal. 10. Cardiogenic shock (SBP <90 mmHg for >1 hour with either cool clammy skin OR oliguria OR altered sensorium AND cardiac index <2.2 L/min/m^2) 11. History of aortic valve replacement or repair

	12. Severe peripheral vascular disease that will preclude the use of a 14F access sheath, which is required for the insertion of the HeartMate PHP catheter (If the investigator is unsure of the presence or severity of the peripheral vascular diseases for study device access, an appropriate imaging assessment (e.g., duplex ultrasound, angiogram or computerized tomography) should be performed to verify the access before randomization.) 13. Known abnormalities of the aorta that would preclude surgery, including aneurysms and significant tortuosity or calcifications 14. Subject is on hemodialysis. 15. Liver dysfunction with elevation of liver enzymes and bilirubin levels to ≥ 3X ULN or Internationalized Normalized Ratio (INR) ≥1.6 or lactate dehydrogenase (LDH) > 2.5X ULN 16. Abnormal coagulation parameters (platelet count ≤75000/mm^3 or INR ≥1.6 or fibrinogen ≤1.5 g/l) 17. Active systemic infection requiring treatment with antibiotics 18. Subject had active COVID-19 symptoms and/or a positive test result within the prior 2 months. 19. Stroke or transient ischemic attack (TIA) within 6 months of procedure 20. Any allergy or intolerance to ionic and nonionic contrast media, anticoagulants (including heparin), or antiplatelet therapy drugs that cannot be adequately premedicated 21. Subject is pregnant (For a female subject of childbearing potential, a pregnancy test must be performed within 14 days (≤14 days) prior to the index procedure per site standard test). 22. Participation in another clinical study of an investigational drug or device that has not met its primary endpoint 23. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results 24. Life expectancy <1 year **Imaging Exclusion Criteria:** 1. Mural thrombus in the left ventricle

	2. Documented presence of aortic stenosis (orifice area of 1.5cm^2 or less) 3. Moderate to severe aortic insufficiency by echocardiographic assessment

1.0 INTRODUCTION

1.1 Background

Percutaneous coronary intervention (PCI) has provided a significantly less invasive alternative than traditional cardiothoracic surgery to treat patients with severe coronary artery disease. A subset of patients undergoing PCI may require the use of hemodynamic support devices such as intra-aortic balloon pumps (IABP) or percutaneous left ventricular support devices in cases of complex coronary anatomy or depressed left ventricular function as a result of acute myocardial infarction (AMI) and/or cardiogenic shock. These patients are at risk of hemodynamic collapse during PCI due to decrease in coronary perfusion during balloon inflations or in the event of complications such as vessel occlusion or dissection. With advances in PCI technology and improvement in PCI outcomes, an increasing number of patients with severe coronary disease and comorbidities are undergoing PCI[1].

Since the 1960's, the IABP has been the most frequently and widely used circulatory support device in patients with cardiogenic shock. The first use of the IABP in these patients was reported by Kantrowitz in 1968[2]. Since that time, the IABP has been used for circulatory support due to its low cost and easy percutaneous insertion technique. The IABP is able to provide hemodynamic and metabolic benefits such as augmentation of diastolic aortic pressure, reduction of systolic aortic pressure, a decrease in heart rate, and increase in cardiac output[3]. The IABP has also been widely utilized in cases of high-risk PCI. Numerous non-randomized studies have reported on the use of IABP in PCI[4-8]. A prospective, randomized, controlled clinical investigation of over 300 patients with severe left ventricular dysfunction and complex coronary disease was performed in 17 tertiary care clinical centers to evaluate elective IABP use in high-risk PCI. Although no statistically significant differences were found in the rate of major cardiac and cerebral events and mortality between the IABP and no IABP groups, significantly less procedural complications occurred in the IABP group. Twelve percent of patients in the no IABP group had "rescue" IABP placement during the procedure[9].

The need for devices that are able to provide better hemodynamic support than that allowed by the IABP resulted in the development of percutaneous support devices such as the TandemHeart™ and Impella®. The TandemHeart is a percutaneously inserted left atrial-to-femoral artery bypass system comprising a transseptal cannula, arterial cannula, and a centrifugal blood pump intended for short-term circulatory support. Over 200 cases of TandemHeart use have been reported in the literature to treat patients in cardiogenic shock, AMI, and those undergoing high-risk PCI[10-17]. Many of these publications have demonstrated the safe use and effectiveness of this percutaneously placed device.

The Impella devices are likewise percutaneously placed and are catheter-mounted, axial flow devices which are advanced across the aortic valve into the left ventricle. The devices provide circulatory support by advancing blood from the left ventricle to the aorta. These devices have been reported to provide 2.5 to 5.0 liters per minute of flow[1].

Numerous publications have reported on the use of Impella devices in patients with AMI, cardiogenic shock, and those undergoing high-risk PCI in both randomized and registry studies[18-22]. Studies comparing IABP with the above mentioned percutaneous devices during PCI have been performed and have reported varying results in terms of improved hemodynamics, complications and mortality[23-26].

The HeartMate PHP™ (Percutaneous Heart Pump) System is a catheter-based, axial-flow, percutaneous heart pump manufactured by Thoratec (now Abbott). It was designed to provide a high forward flow with rapid insertion for hemodynamic support during high-risk PCI and cardiogenic shock, and it can provide an average flow of over 4.0 liters per minute against a pressure gradient of 60 mmHg. The safety of the HeartMate PHP was initially tested in a prospective, nonrandomized, single-center, open label study with the objective to assess the safety of the HeartMate PHP in supporting cardiovascular hemodynamics in subjects undergoing PCI. In this first-in-human study, 8 subjects were registered and no device-related adverse events were reported.

The SHIELD I clinical investigation was conducted to evaluate the use of the HeartMate PHP in patients with reduced left ventricular function who were at risk of hemodynamic compromise while undergoing high-risk PCI. SHIELD I was a prospective, nonrandomized, multi-center, open-label trial registering up to 50 high-risk subjects in Europe and South America. The primary endpoints of the clinical investigation were freedom from hemodynamic compromise during PCI and a composite measure of major adverse events. Subjects were followed for 30 days. No subjects met the primary performance endpoint. Six safety endpoints in 5 subjects occurred, including 1 access site complication requiring intervention, 1 cerebrovascular accident, 2 major bleeding complications, and 2 cases of new or worsening aortic insufficiency. No cardiac deaths, myocardial infarction, or surgical interventions occurred. Hemodynamic stability was achieved in all subjects with a low incidence of adverse events[27].

1.2 Rationale for Conducting SHIELD II

Although the safety and performance of the HeartMate PHP have been demonstrated in SHIELD I, its performance compared to the approved Impella device still remains to be determined. SHIELD II is a prospective, randomized, open-label, multi-center clinical investigation at up to 120 sites in the United States (U.S.). The objective of SHIELD II is to assess the safety and effectiveness of the HeartMate PHP compared to Impella in supporting patients with severe symptomatic coronary artery disease but with stable cardiovascular function, who are undergoing elective or urgent high-risk PCI, and a heart team, including a cardiac surgeon, has determined high-risk PCI is an acceptable therapeutic option. Any Abiomed Impella device approved for use in high-risk PCI can be used as the control device.

This clinical investigation will be conducted in accordance with this Clinical Investigational Plan (CIP). All investigators involved in the conduct of the clinical

investigation will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

2.0 CLINICAL INVESTIGATION OVERVIEW

2.1 Clinical Investigation Objective

The objective of the SHIELD II clinical investigation is to assess the safety and effectiveness of the HeartMate PHP compared to Impella in supporting patients with severe symptomatic coronary artery disease but with stable cardiovascular function, who are undergoing elective or urgent high-risk PCI, and a heart team, including a cardiac surgeon, has determined high-risk PCI is an acceptable therapeutic option.

2.2 Devices to Be Used in SHIELD II

2.2.1 Investigational Device

The investigational device is the HeartMate PHP System, consisting of a catheter pump and a catheter pump console, which are serial-controlled. The manufacturer is Thoratec Corporation at 6035 Stoneridge Drive, Pleasanton, CA 94588, USA.

2.2.2 Intended Indication for Use

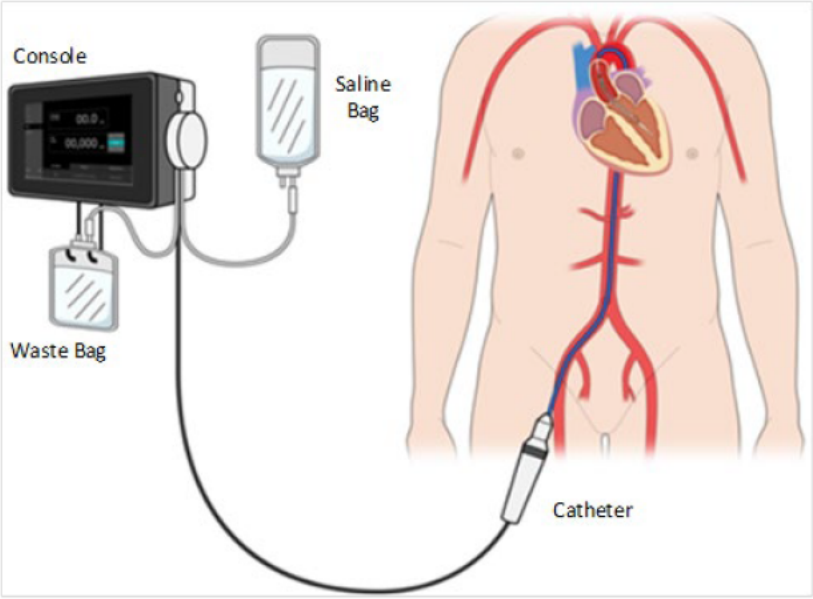
The HeartMate PHP System is a temporary (<6 hours) ventricular assist device indicated for use during high-risk percutaneous coronary interventions (PCI) performed electively or urgently in hemodynamically stable patients with severe coronary artery disease, when a heart team, including a cardiac surgeon, has determined high-risk PCI is the appropriate therapeutic option. Use of the HeartMate PHP System in these patients may prevent hemodynamic instability, which can result from repeat episodes of reversible myocardial ischemia that occur during planned temporary coronary occlusions and may reduce peri- and post-procedural adverse events.

2.2.3 Description of the Device Under Investigation

The HeartMate PHP System is a catheter-based axial flow pump designed to provide partial left ventricular hemodynamic support. The key feature of the HeartMate PHP System is its ability for percutaneous delivery. [redacted]

[redacted]

Figure 1 – HeartMate PHP System in Use



[redacted]

[redacted]

[redacted]

2.2.4 Summary of Preclinical Studies

A summary of preclinical studies for the device under investigation can be found within the IDE application or Investigator Brochure (IB).

2.2.5 Description of the Control Devices

Any Abiomed Impella device approved for use in high-risk PCI can be used as the control device in this clinical investigation. Similar to the HeartMate PHP, Impella is also a catheter-based, axial-flow, percutaneous heart pump. Currently, Impella 2.5 and Impella CP are approved for high-risk PCI. Please refer to the Impella IFUs from Abiomed for additional information.

2.2.6 Device Handling

Sponsor requires all investigational products to be stored according to the labeling and IFU in a secure area to prevent unauthorized access or use.

3.0 CLINICAL INVESTIGATION DESIGN

SHIELD II is a prospective, randomized, open-label, multi-center clinical investigation that will register subjects at up to 120 sites in the U.S. The objective of SHIELD II is to assess the safety and effectiveness of HeartMate PHP compared to Impella in supporting patients with severe symptomatic coronary artery disease but with stable cardiovascular function, who are undergoing elective or urgent high-risk PCI, and a heart team, including a cardiac surgeon, has determined high-risk PCI is an acceptable therapeutic option. Subjects in this clinical investigation will be randomly assigned to the HeartMate PHP or Impella in a 2:1 ratio. The primary endpoint is a composite endpoint at 90 days, including cardiovascular death, myocardial infarction (MI), stroke, unplanned repeat revascularization, bleeding of BARC 3 or 5 up to 14 days post-device removal, severe hypotension and change in aortic insufficiency from baseline to 90 days by echocardiographic assessment. HeartMate PHP will be tested for non-inferiority in the primary endpoint compared to Impella. Any Impella device approved for use in high-risk PCI can be used as the control device. All registered subjects will be followed for 90 days. This clinical investigation is conducted to support the pre-market approval of the HeartMate PHP for the indication of high-risk PCI.

The SHIELD II clinical investigation is divided into two phases chronologically: a feasibility phase, [redacted] and a pivotal phase, [redacted]. Both phases consist of a non-randomized roll-in

[redacted]

cohort and a randomized cohort. The roll-in cohort is designed to prevent a learning curve from biasing the clinical investigation results.

There were 195 subjects, including 75 HeartMate PHP roll-in and 120 randomized subjects, registered at 48 U.S. sites in SHIELD II prior to January 30, 2017, and these subjects are now considered in the feasibility phase of the clinical investigation. All registered subjects in the feasibility phase were already beyond the time point of the 90-day follow-up visit, and the feasibility phase of the clinical investigation reached its end in 2017.

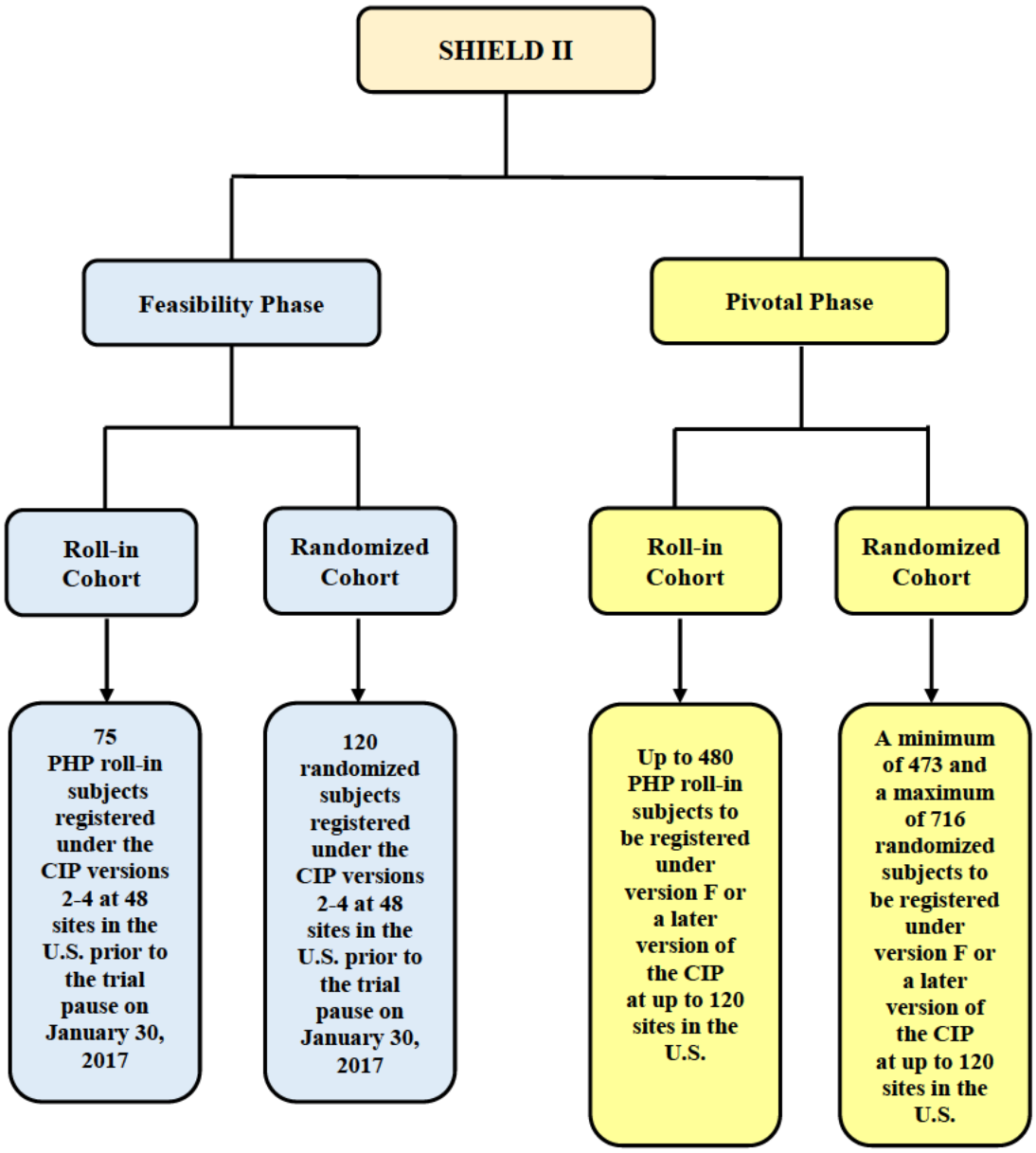
In the pivotal phase, each operator will be required to actively participate in treating a minimum of 1 and up to 2 HeartMate PHP subjects first before becoming qualified to randomize subjects. Since only sites experienced in the use of Impella will be invited to participate in this clinical investigation, no roll-in subjects using Impella will be required in the pivotal phase. With an estimation of 2 operators per site, up to 480 HeartMate PHP roll-in subjects will be registered at up to 120 sites in the U.S. in the roll-in cohort. For the randomized cohort of the pivotal phase, a minimum of 473 subjects will be randomized. [redacted] Each site will be allowed a maximum of 60 randomized subjects. The overall design of the SHIELD II clinical investigation is shown in **Figure 3.**

[redacted] Both roll-in and randomized subjects will follow all the clinical investigation procedures outlined in this CIP. The results of the roll-in cohort will be analyzed as adjunctive data, separate from the results of the randomized cohort. In addition, data in the feasibility phase of the clinical investigation will also be analyzed separately from data in the pivotal phase of the clinical investigation. Hypothesis testing of the primary endpoint will be performed for the randomized cohort in the pivotal phase to support regulatory approval.

The clinical investigation has been designed to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects. Refer to the Risk Analysis section of this clinical investigation plan for details.

Figure 3: Overall Design of the SHIELD II Clinical Investigation

The SHIELD II trial Pivotal Phase will not enroll patients in Europe.



* The feasibility phase of the clinical investigation has already completed the 90-day follow-up and reached its end as of the release of Revision F of this CIP.

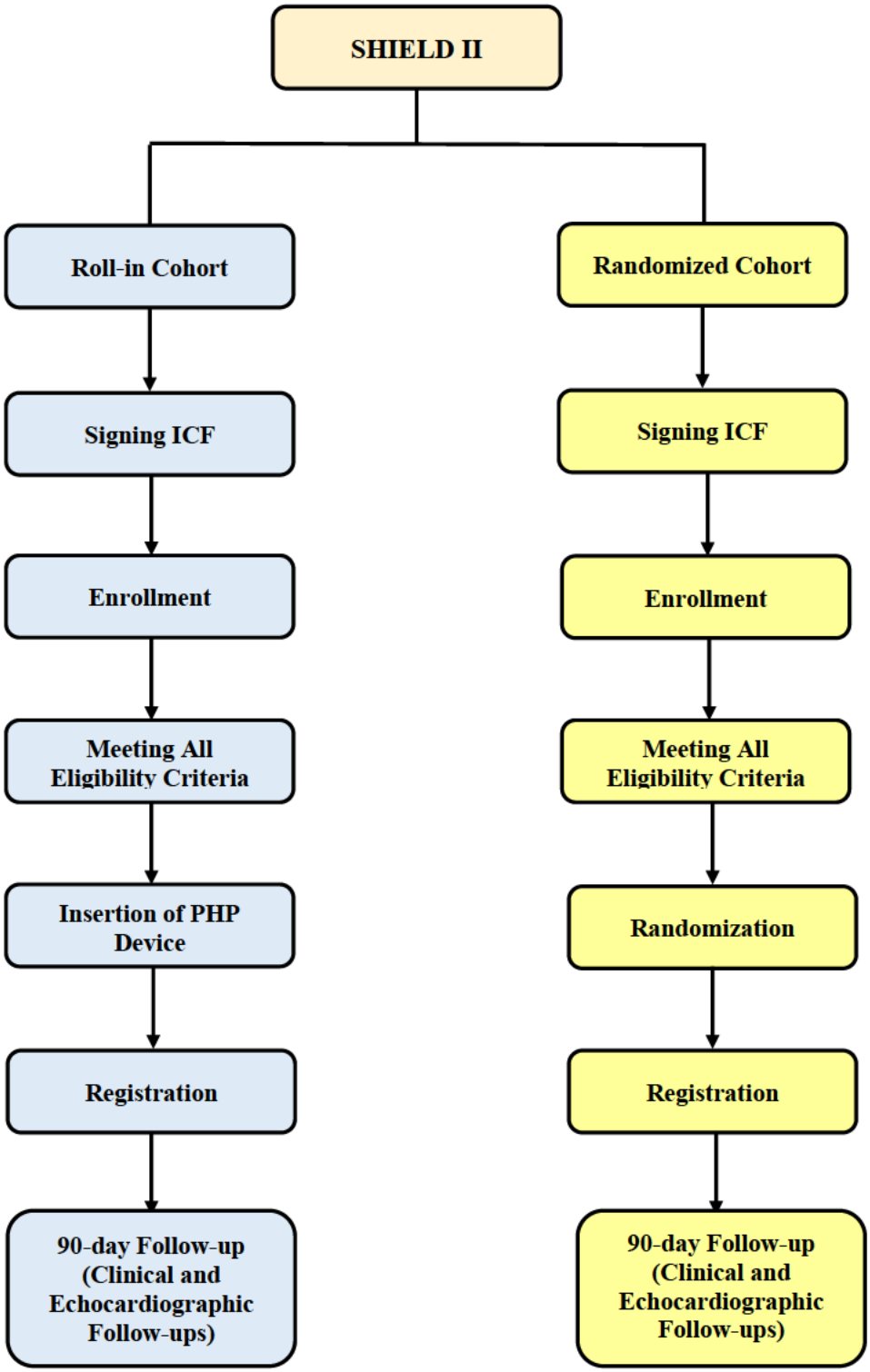
[redacted]

3.1 Clinical Investigation Procedures and Follow-up Schedule

Subjects will be considered enrolled in this clinical investigation when signing the Informed Consent Form (ICF). For subjects in the roll-in cohort, only after the subjects sign the ICF, meet all eligibility criteria and receive a HeartMate PHP device, will the subjects be considered registered in this clinical investigation. For subjects in the randomized cohort, only after the subjects sign the ICF, meet all eligibility criteria and are randomized, will the subjects be considered registered. Registration is the point when the subjects enter this clinical investigation, and registered subjects must follow all CIP requirements. All registered subjects will need to be followed until 90 days post-device removal. Enrolled but not registered subjects are considered screen failures and will not need to be followed. Further details on registration and screen failure can be found in **Sections 5.2.1 and 5.4**. (Note: Although the feasibility phase has already reached its end, for a consistent data analysis, the terms and definitions of enrollment and registration will also apply to the subjects in the feasibility phase.)

Data will be collected at baseline, during the index procedure, post-procedure, at discharge, and at 90 days post-device removal. The 90-day (± 30 days) follow-up visit includes both clinical follow-up and echocardiographic follow-up. The 90-day follow-up must be completed even if the subject is hospitalized. A flowchart of the process and follow-up is shown in **Figure 4** below.

Figure 4: Process of Enrollment, Randomization, Registration and Follow-up



3.2 Measures Taken to Avoid and Minimize Bias

Several measures will be taken to avoid and minimize bias in this clinical investigation, including randomization, blinding, having an independent Clinical Events Committee (CEC) for key adverse event adjudication as well as having an independent echocardiographic core laboratory and an independent angiographic core laboratory for imaging data analyses. Blinding to minimize bias will be discussed in **Section 3.2.1** below. Details on randomization, CEC, and core laboratories can be found in **Sections 6.2**, **10.8.3**, and **6.10**, respectively.

3.2.1 Blinding

This is an open-label clinical investigation. The subjects and the investigators will not be blinded to the treatment assignment. Nevertheless, measures of blinding will be taken to minimize bias and will be applied to the randomized cohorts of both the feasibility and pivotal phases.

[redacted]

[redacted]

3.3 Suspension or Early Termination of the Clinical Investigation

While no formal statistical rule for early termination of the clinical investigation for either overwhelming or insufficient effectiveness of the device under investigation is defined, the Sponsor reserves the right to discontinue the clinical investigation at any stage or reduce the follow-up period with suitable written notice to the investigators. Possible reasons may include, but are not limited to:

- Unanticipated adverse device effect (e.g., UADE) occurs and it presents an unreasonable risk to the participating subjects
- Any oversight committee (e.g., Data Safety Monitoring Board) makes a recommendation to stop or terminate the clinical investigation (such as higher frequency of anticipated adverse device effects)
- Further product development is cancelled

[redacted]

Should the clinical investigation be discontinued by the Sponsor, subjects will be followed per routine hospital practice with device-related adverse events (AEs) reported to the Sponsor as per vigilance/commercial reporting requirements.

If the sponsor suspends or prematurely terminates the clinical investigation at an individual site in the interest of safety, the Sponsor will inform all other Principal Investigators.

Should the clinical investigation be terminated, the investigator shall return all clinical investigation materials (including devices) to the Sponsor, and provide a written statement as to why the premature termination has taken place to the Institutional Review Board (IRB) (if applicable). All applicable clinical investigation documents shall be subject to the same retention policy as detailed in **Section 11.5** of the CIP.

A Principal Investigator, IRB or regulatory authority may suspend or prematurely terminate participation in a clinical investigation at the investigational sites for which they are responsible. The investigators will notify the Sponsor and follow the requirements specified in the Clinical Investigation Agreement.

If suspension or premature termination occurs, the Sponsor will remain responsible for providing resources to fulfill the obligations from the CIP and existing agreements for following the subjects registered in the clinical investigation, and the Principal Investigator or authorized designee will promptly inform the registered subjects at his/her site, if appropriate.

4.0 ENDPOINTS

4.1 Primary Endpoint

The primary endpoint of the clinical investigation is a composite endpoint at 90 days, including the following components representing important safety and effectiveness endpoints:

- Cardiovascular Death
- Myocardial infarction (MI)
- Stroke
- Any unplanned repeat revascularization (PCI or CABG)
- Bleeding (BARC 3 or 5) up to 14 days post-device removal
- Severe hypotension, defined as: systolic blood pressure (SBP) or augmented diastolic pressure (whichever is greater) <90 mmHg while on device support requiring (1) more than one administration of OR (2) continuous infusion of inotropic/pressor medications to restore hemodynamics

- Change in aortic insufficiency from baseline to 90 days by echocardiographic assessment and defined as:

Baseline Assessment	90 Day Assessment
None	Moderate OR Severe
Trace	Moderate OR Severe
Mild	Moderate OR Severe

4.2 Descriptive Endpoints

[redacted]

[redacted]

4.3 Exploratory Endpoints

- Quality of Life questionnaires including EQ-5D-5L and Seattle Angina Questionnaire (SAQ) at baseline and 90 days

5.0 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This clinical investigation will enroll male and female subjects from the general interventional cardiology population. Subjects must meet all eligibility criteria and provide written informed consent prior to conducting any clinical investigation-specific procedures not considered standard of care.

5.2 Subject Screening and Informed Consent

5.2.1 Subject Screening

Assessment for general eligibility criteria is based on medical record review and interview with a candidate subject. Potential subjects presenting at the clinical sites will be fully informed about the clinical investigation. Subjects meeting general inclusion criteria and no exclusion criteria will be asked to sign an ICF if they wish to participate in the clinical investigation. Once a duly dated and signed ICF is obtained following the

established Informed Consent process as described in **Section 5.2.2**, the clinical investigation-specific, non-standard of care screening procedures may begin. Subjects must be screened for clinical investigation eligibility by a member of the site's clinical investigation team previously trained to the CIP.

In case the subject does not meet all inclusion criteria or meets any of the exclusion criteria, the subject is considered a screen failure. The Principal Investigator or the delegated clinical investigation personnel will record the screening failure in the hospital records and the electronic data capture (EDC) EDC as required.

5.2.2 Informed Consent

The Investigator or his/her authorized designee (if applicable) will conduct the Informed Consent process, as required by applicable regulations and the center's IRB. This process will include a verbal discussion with the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate, such as details of clinical investigation procedures, anticipated benefits, and potential risks of clinical investigation participation. Subjects must be informed about their right to withdraw from the clinical investigation at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled. Withdrawal from the clinical investigation will not jeopardize their future medical care or relationship with the investigator.

During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the subject and will respect subject's legal rights. Financial incentives will not be given to the subject. Subjects may be compensated for time and travel directly related to participating in the clinical investigation. The subject shall be provided with the ICF written in a language that is understandable to the subject and has been approved by the center's IRB. The subject shall have adequate time to review, ask questions and consider participation. The Principal Investigator or his/her authorized designee will make efforts to ensure that the subject understands the information provided. If the subject agrees to participate, the ICF must be signed and dated by the subject and thereafter by the person obtaining the consent prior to any clinical investigation-specific procedures. The signed original will be filed in the subject's hospital or research charts, and a copy will be provided to the subject. Once the subject signs the ICF, the subject is considered enrolled in the clinical investigation.

Failure to obtain informed consent from a subject prior to clinical investigation registration should be reported to Sponsor within 5 working days and to the reviewing center's IRB according to the IRB's reporting requirements. Revisions to the informed consent will be approved by the Sponsor and the IRB prior to re-consenting subjects.

If during the clinical investigation, new information becomes available that can significantly affect a subject's future health and medical care, the Principal Investigator or his/her authorized designee will provide this information to the subject. If relevant, the subject will be asked to confirm their continuing informed consent in writing.

In addition, an authorization for use and disclosure of the subject's protected health information, in accordance with the Health Insurance Portability and Accountability Act (HIPAA), must be obtained from the subject or their legally authorized representative in applicable geographies.

For live cases at congresses, the subjects need to sign a specific Live Case ICF, approved by the IRB and by the Sponsor, as well as by the competent authorities (e.g., FDA), as applicable. The investigator must request Sponsor approval prior to performing a Live Case.

Vulnerable Populations

No vulnerable populations will be recruited for this clinical investigation. Vulnerable patients are defined as patients whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. Incapacitated individuals, defined as persons who are mentally ill, mentally handicapped, or individuals without legal authority, are excluded from the study population. Additionally, pregnant women are excluded from the study population.

Individuals unable to read or write may be enrolled in this clinical investigation. Informed consent will be obtained through a supervised oral process. An independent witness will be present throughout the Informed Consent process. The written ICF and any other information will be read aloud and explained to the prospective subject and he/she will sign and personally date the ICF. The witness will also sign and personally date the ICF attesting that the information was accurately explained, and that informed consent was freely given.

5.3 Eligibility Criteria

Subjects must meet all of the inclusion criteria to be considered for the clinical investigation. If any of the exclusion criteria are met, the subject is excluded from the clinical investigation and cannot be registered. Assessment for general eligibility criteria is based on medical records of the site and interview with a candidate subject. If some of the clinical and laboratory tests are not included in site standard tests, they must be done but after written informed consent is obtained.

5.3.1 Inclusion Criteria

5.3.1.1 General Inclusion Criteria:

1. At least 18 years of age

2. Subject is undergoing elective or urgent high-risk PCI procedure and is hemodynamically stable.
3. Subject is indicated for a revascularization of at least one *de novo* or restenotic lesion in a native coronary vessel or bypass graft.
4. A heart team, including a cardiac surgeon, has determined high-risk PCI is an acceptable therapeutic option.
5. Subject must provide written informed consent prior to any clinical investigation related procedure.

5.3.1.2 Imaging Inclusion Criteria:

1. The presence of complex coronary artery disease (CAD) makes hemodynamic instability resulting from repeat episodes of reversible myocardial ischemia during PCI likely. Complex CAD is defined as an ejection fraction of <50% by echocardiographic assessment AND at least one of the following:
    a. Intervention of the last patent coronary conduit, OR
    b. Intervention of an unprotected left main artery, OR
    c. Intervention on patient presenting with triple vessel disease defined as at least one significant stenosis (at least 50% diameter stenosis on visual assessment) in all three major epicardial territories

5.3.2 Exclusion Criteria

5.3.2.1 General Exclusion Criteria:

1. Emergency PCI
2. Any prior coronary revascularization within the last 6 months
3. Any MI with elevated cardiac biomarker (creatinine kinase-MB (CK-MB) or troponin >1X upper limit of normal (ULN)) and no evidence of at least 1 consecutive CK-MB or troponin value trending downward from previous value (at least 4 hours apart) OR ST Elevation MI (STEMI) within 72 hours prior to the index procedure regardless of the level of cardiac biomarker
4. Cardiac arrest within 24 hours of procedure requiring cardiopulmonary resuscitation (CPR) or defibrillation
5. Any use of a mechanical circulatory support device within 14 days prior to the index procedure (Note: Subjects must be hemodynamically stable without any hemodynamic support to be eligible for this clinical investigation.)
6. Hemodynamic support with a mechanical circulatory support device (e.g., the HeartMate PHP, Impella, intra-aortic balloon pump (IABP) or extracorporeal membrane oxygenation (ECMO)), post-PCI is anticipated.

7. Any condition that requires discontinuation of antiplatelet and/or anticoagulant therapy within 90 days following the index procedure (e.g., planned noncardiac surgery).
8. Any use of vasopressors or inotropes within 24 hours prior to the index procedure
9. Staged PCI is planned within 90 days following device removal.
10. Cardiogenic shock (SBP <90 mmHg for >1 hour with either cool clammy skin OR oliguria OR altered sensorium AND cardiac index <2.2 L/min/m^2)
11. History of aortic valve replacement or repair
12. Severe peripheral vascular disease that will preclude the use of a 14F access sheath, which is required for the insertion of the HeartMate PHP catheter (If the investigator is unsure of the presence or severity of the peripheral vascular diseases for study device access, an appropriate imaging assessment (e.g., duplex ultrasound, angiogram or computerized tomography) should be performed to verify the access before randomization.)
13. Known abnormalities of the aorta that would preclude surgery, including aneurysms and significant tortuosity or calcifications
14. Subject is on hemodialysis.
15. Liver dysfunction with elevation of liver enzymes and bilirubin levels to ≥ 3X ULN or Internationalized Normalized Ratio (INR) ≥1.6 or lactate dehydrogenase (LDH) > 2.5X ULN
16. Abnormal coagulation parameters (platelet count ≤75000/mm^3 or INR ≥1.6 or fibrinogen ≤1.5 g/l)
17. Active systemic infection requiring treatment with antibiotics
18. Subject had active COVID-19 symptoms and/or a positive test result within the prior 2 months.
19. Stroke or transient ischemic attack (TIA) within 6 months of procedure
20. Any allergy or intolerance to ionic and nonionic contrast media, anticoagulants (including heparin), or antiplatelet therapy drugs that cannot be adequately premedicated
21. Subject is pregnant (For a female subject of childbearing potential, a pregnancy test must be performed within 14 days (≤14 days) prior to the index procedure per site standard test).
22. Participation in another clinical study of an investigational drug or device that has not met its primary endpoint
23. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's

ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results

24. Life expectancy <1 year

5.3.2.2 Imaging Exclusion Criteria:

1. Mural thrombus in the left ventricle
2. Documented presence of aortic stenosis (orifice area of 1.5cm^2 or less)
3. Moderate to severe aortic insufficiency by echocardiographic assessment

5.4 Subject Registration

Registration is the point when the subjects enter the clinical investigation, and registration for the roll-in and the randomized cohorts in the clinical investigation will be defined differently as described below.

A. Roll-in Cohort

Subjects in the roll-in cohort will not be randomized. A roll-in subject will be considered registered only after signing an ICF, meeting all eligibility requirements, and after a HeartMate PHP device is inserted.

Roll-in screen failures are further defined as:

1. Roll-in subjects who sign consent and subsequently fail any inclusion or exclusion criteria. No follow-up is required.
2. Roll-in subjects who sign consent and meet initial inclusion and exclusion criteria but who subsequently do not undergo device insertion due to previously undiagnosed anatomic abnormalities (e.g., peripheral vascular disease) which preclude device insertion or unforeseen clinical conditions that preclude device insertion. No follow-up is required.

B. Randomized Cohort

Subjects in the randomized cohort will be randomized only after the subjects have signed the ICF and met all eligibility requirements. Randomization assignments will be given through the EDC Study Site Portal. Subjects will be considered registered in the clinical investigation once randomized and must follow all CIP requirements. Randomized subjects who do not undergo device placement due to previously undiagnosed anatomic abnormalities (e.g. peripheral vascular disease) which precludes device placement, will still be considered registered and must follow all CIP requirements. Once a subject is randomized, PCI should be performed as soon as possible.

5.4.1 Medicare Beneficiaries

This clinical investigation will recruit Medicare beneficiaries and therefore conforms to all standards of Medicare coverage requirements. The Risks and Benefits section describes how all registered subjects, including Medicare beneficiaries, may be affected by the device under investigation.

A portion of the subjects registered in the clinical investigation display characteristics consistent with the Medicare population based on age. The clinical investigation results will be analyzed by age (<65 years and ≥65 years) and compared to ensure that the outcomes are similar between the Medicare and non-Medicare populations.

5.4.2 Historically Under-Represented Demographic Subgroups

The Sponsor intends to implement FDA's guidance on sex-specific data in medical device clinical investigations to ensure adequate representation of women and other traditionally under-represented demographic subgroups in this clinical investigation. As noted in the guidance, some barriers to participation of women and ethnic minorities in clinical investigations have traditionally been:

- Lack of understanding about main obstacles to participation of such subgroups in clinical research
- Inclusion/exclusion criteria potentially not needed to define the clinical investigation population may unintentionally exclude specific subgroups
- Under diagnosis of disease etiologies and pathophysiology leading to under referral of demographic subgroups
- Avoidance of specific subgroups by investigators and Sponsors due to the perception that it takes more time and resources to recruit them
- Fear of fetal consequences (for female participants)
- Family responsibilities limiting women's ability to commit time for follow-up requirements

The Sponsor will take the following steps to ensure adequate representation of women and racial or ethnic minorities in this clinical investigation:

- The Sponsor will provide training to investigational site personnel to ensure adequate representation of these demographic subgroups
- The Sponsor will approach sites without bias or consideration for specific demographic subgroups

5.5 Subject Discontinuation

Each registered subject shall remain in the clinical investigation until completion of the required 90-day (± 30 days) follow-up visit however, a subject's participation in any clinical investigation is voluntary and the subject has the right to withdraw at any time

without penalty or loss of benefits. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Subject death
- Subject voluntary withdrawal
- Subject withdrawn by the Investigator
- Subject lost-to follow-up as described below
- Subject's follow-up is terminated according to **Section 3.3**.

The Sponsor must be notified of the reason(s) for subject discontinuation. The site will provide this information to the Sponsor. Investigators must also report this to their respective IRB as defined by their institution's procedure(s).

No additional follow–up will be required or data recorded from subjects once discontinued from the clinical investigation, except for the status (deceased/alive).

In case of subject withdrawal of consent, the site should make attempts to schedule the subject for a final clinical investigation visit prior to withdrawal. At this final follow-up visit, the subject will undergo the following assessments:

- Clinical assessment
- Echocardiographic assessment

Lost-to-Follow-up

There will be only one scheduled follow-up visit at 90 days (±30 days) in this clinical investigation. If the subject misses the scheduled 90-day follow-up visit and the attempts at contacting the subject detailed below are unsuccessful, then the subject is considered lost-to-follow-up. Site personnel shall make all reasonable efforts to locate and communicate with the subject (and document these efforts in the source documents), including the following:

- A minimum of two telephone calls on different days over the specified follow-up window to contact the subject should be recorded in the source documentation, including date, time and initials of site personnel trying to make contact.
- If these attempts are unsuccessful, a letter (certified, if applicable) should be sent to the subject.

Note: Telephone contact with general practitioner, non-clinical investigation cardiologist or relative without the presence of the subject or indirect documentation obtained via discharge letters will not be considered as subject contact.

[redacted]

5.7 Expected Duration of Each Subject's Participation

The expected duration of each subject's participation in the clinical investigation is 90 days following the removal of the study device.

5.8 Number of Subjects

In the feasibility phase of the clinical investigation, 195 subjects, including 75 HeartMate PHP roll-in and 120 randomized subjects, were registered.

In the pivotal phase of the clinical investigation, up to 480 HeartMate PHP roll-in subjects and a minimum of 473 and a maximum of 716 randomized subjects will be registered.

5.9 Estimated Time Needed to Register the Required Number of Subjects

The time needed to register the required number of subjects for the pivotal phase of this clinical investigation is estimated to be up to 39 months.

6.0 TREATMENT AND EVALUATION OF ENDPOINTS

In this clinical investigation, data will be collected at baseline, during the index procedure, post-procedure, at discharge, and at 90 days post-device removal to assess subject eligibility as well as to evaluate the safety and effectiveness of the study devices. The clinical investigation-required assessments and the timing of data collection for each assessment will be described below. A complete listing of the clinical investigation-required assessments and schedule can be found in **Table 2**: Clinical Investigation Assessment Schedule in **Section 6.9**.

6.1 Baseline Assessments

The following data will be collected at baseline to assess the subjects' eligibility to participate in this clinical investigation or for baseline reference.

- Subject demographics
- Subject medical history
- COVID-19 Assessment: If the patient had a COVID-19 test at any point before enrollment in the study, details of the test, date conducted, and outcome should be captured in the COVID-19 Assessment Log Form.
- Physical examination/Vital signs

[redacted]

- Laboratory tests except for cardiac biomarkers (within 14 days prior to the index procedure; refer to **Table 2** for required baseline laboratory tests)
- Cardiac biomarkers: CK-MB and troponin (NO high-sensitivity troponin) are both required within 48 hours prior to the index procedure.
- 12-lead electrocardiogram (ECG) (within 48 hours prior to the index procedure)
- Echocardiogram (within 60 days prior to the index procedure). Images need to be uploaded to the Echocardiographic Core Laboratory via Bioclinica website. For a baseline echocardiogram performed prior to the subject signing informed consent, the investigators will need to assess whether the available baseline echocardiogram captures the appropriate images of aortic valve required for a quantitative assessment of aortic regurgitation by the Echocardiographic Core Laboratory per the Echocardiographic Core Laboratory guidance. If not, a baseline echocardiogram will need to be repeated per the Echocardiographic Core Laboratory guidance before the index procedure.
- Diagnostic angiogram (within 60 days prior to the index procedure). Images need to be uploaded to the Angiographic Core Laboratory via Bioclinica website along with the information on the size of the diagnostic catheter to obtain the SYNTAX score.
- Health assessments (Euroscore II, Society of Thoracic Surgery (STS) mortality score and New York Heart Association (NYHA) heart failure class) (within 30 days prior to the index procedure)
- Quality of life questionnaires (SAQ and EQ-5D-5L) (within 30 days prior to the index procedure)
- Concomitant use of anticoagulant and antiplatelet medications

For physical examination, vital signs, laboratory tests and echocardiogram, refer to **Section 6.8** for further details.

6.2 Randomization

6.2.1 Stratified Randomization

Subjects will be randomly assigned in a 2:1 fashion to either HeartMate PHP or Impella in SHIELD II. [redacted]

6.2.2 Timing of Randomization

Randomization assignments will be given through EDC Study Site Portal after subjects have signed the ICF and met all eligibility requirements. Subjects will be considered registered in the clinical investigation once randomized and must follow all CIP

[redacted]

requirements. Randomized subjects who do not undergo device placement due to previously undiagnosed anatomic abnormalities (e.g. peripheral vascular disease) which precludes device placement, will be considered registered and in the intent-to-treat (ITT) population, and they must follow all CIP requirements. Once a subject is randomized, PCI should be performed as soon as possible.

6.3 Index Procedure

6.3.1 Right Heart Catheterization

Right heart catheterization is required to obtain hemodynamic measurements, and the placement of the catheter for the right heart catheterization will need to be done before inserting the study device and performing the PCI procedure for revascularization. In this CIP, the beginning of the index procedure is defined as the insertion of the first vascular access during the index procedure, and the end of the index procedure is defined as the removal of the last vascular access during the index procedure or the exit from the catherization laboratory, whichever occurs first. In addition, the beginning of the PCI procedure is defined as the insertion of the first guiding catheter for the lesion(s) to be revascularized during this index procedure, and the end of the PCI procedure is defined as the removal of the last guiding catheter for the lesion(s) to be revascularized during this index procedure.

Hemodynamic Assessments

Hemodynamic assessments will be performed at the following four time points:

1) Prior to device insertion
2) Prior to the PCI procedure while on device support
3) Immediately prior to weaning for the preparation of device shutdown and removal
4) 10 to 30 minutes after device removal

The following hemodynamic measurements at each of the time points above and the corresponding study pump parameters at time points 2) and 3) above need to be collected and recorded:

- Right atrial pressure (RAP)
- Pulmonary artery pressure (PAP)
- Pulmonary capillary wedge pressure (PCWP)
- Cardiac output (CO)*
- Cardiac index (CI)*
- Cardiac power output (CPO)
- Mean arterial pressure (MAP)
- Heart rate
- Corresponding pump speed of PHP or Impella at time points 2) and 3)

[redacted]

- Corresponding estimated pump flow of PHP or Impella at time points 2) and 3)

***Note**: The Fick method is required to measure CO and CI. A second method using thermodilution can be optional.

Hemolysis Biomarker Assessment

Hemolysis biomarkers include plasma free hemoglobin and lactate dehydrogenase (LDH). Two blood draws during the index procedure are required for the assessment.

1. Pre-device draw: Blood will be collected before device insertion via a vascular access sheath (could be venous or arterial, and with no other catheter/device simultaneously inserted in the sheath) in the catheterization laboratory during the index procedure for the assessment of both plasma free hemoglobin* and LDH.

2. Post-device draw: Blood will be collected after device removal via a vascular access sheath (could be venous or arterial, and with no other catheter/device simultaneously inserted in the sheath) in the catheterization laboratory during the index procedure for the assessment of both plasma free hemoglobin* and LDH.

* **Caution**: Special attention must be paid to blood draw and processing before laboratory analysis to avoid hemolysis during or after blood draw, which will cause falsely elevated values in the plasma free hemoglobin test. 1) Collect blood from a vascular access sheath for both pre-device and post-device draws to avoid the shearing of red blood cells through a small-gauge (<18 gauge) needle. 2) Centrifuge immediately or as soon as possible to separate plasma or serum from red blood cells following blood collection.

6.3.2 Procedures Involved in the Use of the Study Device

HeartMate PHP and Impella are both temporary ventricular assist devices indicated for support during high-risk PCI. The study device (HeartMate PHP or Impella) will be inserted before the PCI procedure starts and will be removed after the PCI procedure ends. The preparation and use of the HeartMate PHP and Impella devices will be according to their respective IFUs.

HeartMate PHP and Impella device parameters will be collected and recorded on the appropriate electronic case report form (eCRF) in EDC. For the HeartMate PHP device, the data can be found on the console. For the Impella device, the data can be found on the automated Impella controller. All pump data collected should be kept in the patient binder.

If any issues occur with the use of the HeartMate PHP during the index procedure, the HeartMate PHP must be returned to Abbott after use. A device deficiency must be recorded as appropriate and as described in Section 7.3.3. After device removal in the catheterization laboratory, sites will record any gross device abnormalities (e.g., thrombus, cuts, tears, etc.) on the eCRF prior to shipment of the device to Abbott.

6.3.3 PCI Procedure for Revascularization

Completeness of Revascularization

All ischemic myocardial areas should be revascularized. The approach is to perform PCI of all significant ischemia-producing lesions as opposed to all lesions which appear to be significant by angiographic visual assessment. Moreover, it is strongly recommended that PCI is performed only in ischemia-producing lesions, in most cases not treating non-ischemia-producing lesions.

Ischemia-producing lesions are defined as those which are:

1) ≥70% angiographic diameter stenosis (visually assessed), or
2) <70% diameter stenosis and:
   a) associated with noninvasive functional evidence of ischemia in the territory of the lesion (not explained by another coronary stenosis), and/or
   b) intra-procedure fractional flow reserve (FFR) ≤0.80 or an alternative intra-procedure physiological index (e.g., instantaneous wave free ratio (iFR) or resting full-cycle ratio (RFR) with the respective threshold defined per its IFU), and/or
   c) intravascular ultrasound (IVUS) minimal luminal area ≤6.0 mm^2 (for left main lesions)

All lesions which the investigator has targeted/planned for revascularization will be identified and recorded on the eCRF prior to randomization for subjects in the randomized cohort or prior to the index procedure for subjects in the roll-in cohort by the interventionalist performing the procedure. All lesions that are actually revascularized will also be recorded on the eCRF.

Angiography and PCI Information

Angiography and PCI information will be collected on the appropriate eCRF. Angiograms of all treated lesions pre- and post-PCI must be performed following the guidance in the Angiographic Protocol from the Angiographic Core Laboratory and submitted to the core laboratory via Bioclinica website for analysis. For each treated lesion, the total number of stents used, the relevant stent information, and the guiding catheter size must be recorded on the appropriate eCRF. Any pre-dilation, post-dilation, or atherectomy device use on the lesion and the total volume of contrast used during the procedure must also be recorded. If a baseline diagnostic angiogram is not available for submitting to the Angiographic Core Laboratory for analysis, diagnostic views of all three major epicardial coronary arteries (left anterior descending (LAD), left circumflex (LCX), and right coronary artery (RCA)) need to be repeated prior to PCI during the index procedure for the core laboratory to calculate the SYNTAX score.

Additional data related to the index procedure may also be collected.

6.4 Post-Index Procedure Assessments

- Vital signs
- Laboratory tests except for cardiac biomarkers (must be performed within 24 hours post device removal; refer to **Table 2** for required post-procedure laboratory tests)
- Cardiac biomarkers: Both CK-MB and troponin (NO high-sensitivity troponin) are required for the post-procedural assessment.
    1. First draw at 6 to 12 hours post-device removal
    2. If CK-MB is elevated > 1x ULN or troponin is elevated > 7x ULN in the first draw, a second draw of CK-MB and troponin is required at 18-24 hours post-device removal or at the time of discharge as long as discharge is at or after 16 hours post-device removal.

  Note: If CK-MB or troponin in the second draw is not stable and falling compared to the first draw, serial measurements of CK-MB and troponin every 12 hours or per site standard until a decline is noted are highly recommended.
- At least one 12-lead ECG (within 24 hours post device removal)
- Echocardiogram (must be performed within 48 hours post-device removal; may be performed during the procedure after device removal; performed per the Echocardiographic Core Laboratory guidance with images uploaded to the Echocardiographic Core Laboratory via Bioclinica website)
- Adverse event
- Concomitant use of anticoagulant and antiplatelet medications

For vital signs, laboratory tests and echocardiogram, refer to **Section 6.8** for further details.

6.5 Discharge Assessments

- Physical examination/Vital signs
- Adverse event
- COVID-19 Assessment: If the patient has a COVID-19 test at any point after enrollment in the study, details of the test, date conducted, and outcome should be captured in the COVID-19 Assessment Log Form.
- Concomitant use of anticoagulant and antiplatelet medications

For physical examination and vital signs, refer to **Section 6.8** for further details.

6.6 90-day Follow-up Assessments

All subjects are required to have an office visit for the 90-day (±30 days) clinical follow-up as well as echocardiographic follow-up. If a subject remains hospitalized 90 days post-

device removal, a 90-day follow-up form is still required. To aid in follow-up compliance, if necessary, an independent service (e.g. Hawthorne Effect) may be utilized to provide in-home visits for both the clinical and echocardiographic follow-up.

- Physical examination
- NYHA heart failure class
- Quality of life questionnaires (SAQ and EQ-5D-5L)
- Echocardiogram (performed per the Echocardiographic Core Laboratory Guidance with images uploaded to the Echocardiographic Core Laboratory via Bioclinica website)
- Adverse event
- COVID-19 Assessment: If the patient has a COVID-19 test at any point after enrollment in the study, details of the test, date conducted, and outcome should be captured in the COVID-19 Assessment Log Form.
- Concomitant use of anticoagulant and antiplatelet medications

For physical examination and echocardiogram, refer to **Section 6.8** for further details.

6.7 Unscheduled Visits

Additional subject visits, such as unscheduled visits, may occur as clinically warranted. The following information will be collected:

- Adverse Events
- COVID-19 Assessment: If the patient has a COVID-19 test at any point after enrollment in the study, details of the test, date conducted, and outcome should be captured in the COVID-19 Assessment Log Form.
- Concomitant use of anticoagulant and antiplatelet medications
- Details of any subsequent coronary interventions (e.g., repeat PCI or CABG), if applicable
- Any new valvular abnormalities (if suspected, an echocardiogram should be performed)

If an unscheduled visit is conducted due to a suspected ischemic cardiac event, troponin (NO high-sensitivity troponin) must be collected and ECG must be done. CK-MB is optional.

All efforts must be made to obtain follow-up information on subjects who have undergone procedures or have been treated for adverse events in a non-clinical investigation-related hospital(s).

6.8 Additional Information on Required Assessments

Neurological Assessments

In cases of suspected neurological dysfunction, appropriately trained individuals will perform standard neurological examinations and assessments. Subjects who exhibit signs/symptoms of cerebrovascular accident (CVA) or transient ischemic attack (TIA) should have a diagnosis confirmed by appropriate diagnostic imaging.

Echocardiographic Assessments

All subjects will have echocardiograms performed at the following time points:

1) Baseline – performed within 60 days prior to the index procedure; required for the analysis of the primary endpoint component (change in aortic insufficiency from baseline to 90 days) and the descriptive endpoints as well as for the assessment of the eligibility requirements (e.g. LVEF <50%, no moderate or severe aortic insufficiency, no aortic stenosis (stenosis as defined by the orifice area of 1.5cm^2 or less), and no mural thrombus in the left ventricle)
2) Post-device removal – no later than 48 hours post-device removal; required for and the descriptive endpoint
3) 90 days post-device removal (±30 days) – required for the analysis of the primary endpoint component (change in aortic insufficiency from baseline to 90 days) and the descriptive endpoint
4) Unscheduled – if new valvular abnormalities are suspected post device removal, an echocardiogram should be performed and the results documented on the eCRF.

Particular attention should be made to the presence of thrombus and any new abnormalities (or worsening of existing abnormalities) of the aortic valve.

IMPORTANT: All echocardiograms must have a focus on aortic valve (refer to the Echocardiographic Core Laboratory guidance) and must be submitted to the core laboratory for analysis. Both baseline and 90-day echocardiograms are required for the quantitative assessment of change in aortic insufficiency from baseline to 90 days, which is part of the primary endpoint in SHIELD II. For a baseline echocardiogram performed prior to the subject signing informed consent, the investigators will need to assess whether the available baseline echocardiogram captures the appropriate images of aortic valve required for a quantitative assessment of aortic regurgitation by the Echocardiographic Core Laboratory per the Echocardiographic Core Laboratory guidance. If not, a baseline echocardiogram will need to be repeated per the Echocardiographic Core Laboratory guidance before the index procedure.

Laboratory Assessments

The following laboratory assessments will be collected over the course of the clinical investigation. See **Table 2**: Clinical Investigation Assessment Schedule in **Section 6.9** for the required timing of these laboratory assessments.

Hematology:
Hemoglobin
Hematocrit
Red Blood Cells
White Blood Cells
Platelets

Cardiac Biomarkers:
Creatinine Kinase-MB (CK-MB)
Troponin (NO high-sensitivity troponin)

Hemolysis Biomarkers:
Plasma Free Hemoglobin (PfHgb)
Lactate Dehydrogenase (LDH)

Chemistries:
Aspartate Aminotransferase (AST)
Alanine Aminotransferase (ALT)
Total Bilirubin
Blood Urea Nitrogen (BUN)
Creatinine
Lactate
B-type Natriuretic Peptide (BNP) or NT-proBNP

Coagulation:
International Normalized Ratio (INR)
Activated Clotting Time (ACT)
Activated Partial Thromboplastin Time (APTT)/Partial Thromboplastin Time (PTT)

Physical Examination/Vital Signs

Physical examination will be completed and recorded at baseline, prior to hospital discharge, and at 90 days post-device removal. Any clinically significant findings during the physical examination should be reviewed by the investigator. Any clinically significant findings during the baseline physical examination should be reported in the subject medical history. Any clinically significant findings during physical examinations post-device insertion should be reported as adverse events. Physical examinations should be performed per the standard of care and may be completed by any qualified medical personnel.

Vital signs will be recorded at baseline, post procedure, and prior to hospital discharge.

Health Economics Data

Upon hospital discharge for the initial implant hospitalization and any subsequent rehospitalizations, redacted UB-04 bills (where it is applicable), or similar detailed

hospital billing data, will be requested to be entered into Abbott EDC. Duration of hospital stay and intensive care unit (ICU) duration will also be collected.

For rehospitalizations performed outside of the study center, clinical investigation staff should make their best effort to obtain the UB-04 bills (where it is applicable), or similar detailed hospital billing data and duration of stay information from the outside institution.

Concomitant Use of Anticoagulant and Antiplatelet Medications

The use of any oral anticoagulants, procedural anticoagulants, and post-procedural antiplatelet medications will be recorded.

6.9 Schedule of Events

The time windows and the schedule of the clinical investigation-required assessments are listed in **Table 1** and **Table 2**, respectively.

Table 1 – Time Windows for Select Clinical Investigation Assessments

Assessment	Time Window
Baseline Laboratory Testing (except for cardiac biomarkers)	Within 14 days prior to the index procedure
Baseline Cardiac Biomarkers: Both CK-MB and troponin (NO high-sensitivity troponin) are required.	Within 48 hours prior to the index procedure
Baseline 12-lead ECG	Within 48 hours prior to the index procedure
Baseline Echocardiogram	Within 60 days prior to the index procedure
Baseline Health Assessment and Quality of Life Questionnaires	Within 30 days prior to the index procedure
Diagnostic Angiogram	Within 60 days prior to the index procedure
Procedural Angiogram	During the index procedure
Pre-device Hemolysis Biomarkers	Before device insertion in the catherization laboratory during the index procedure
Post-device Hemolysis Biomarkers	After device removal in the catherization laboratory during the index procedure
Post-procedure Laboratory Testing (except for cardiac biomarkers)	Within 24 hours post device removal
Post-procedure Cardiac Biomarkers	Both CK-MB and troponin (NO high-sensitivity troponin) are required for the post-procedural assessment: 1. First draw at 6 to 12 hours post-device removal 2. If CK-MB is elevated > 1x ULN or troponin is elevated > 7x ULN in the first draw, a second draw of CK-MB and troponin is required at 18-24 hours post-device removal or at the time of discharge as long as discharge is at or after 16 hours post-device removal. Note: If CK-MB or troponin in the second draw is not stable and falling compared to the first draw, serial measurements of CK-MB and troponin every 12 hours or per site standard until a decline is noted are highly recommended.
Post-procedure 12-lead ECG	At least one within 24 hours post-device removal
Post-procedure Echocardiogram	Within 48 hours post device removal
90 Day Post-Device Removal Clinical Visit	± 30 days
90 Day Post-Device Removal Echocardiogram	± 30 days

[redacted]

Table 2 – Clinical Investigation Assessment Schedule

Clinical Test	Baseline[1]	Intraprocedure	Post-Procedure[10]	Discharge	90 Days Post Device Removal	Unscheduled Visit
LABORATORY ASSESSMENTS						
Hemoglobin	X		X			
Hematocrit	X		X			
Red Blood Cells (RBC)	X		X			
White Blood Cells (WBC)	X		X			
Platelets	X		X			
Plasma Free Hemoglobin		X[15]				
INR	X		X			
Activated Clotting Time (ACT)		X[16]	X			
APTT/PTT	X		X			
Aspartate Aminotransferase (AST)	X		X			
Alanine Aminotransferase (ALT)	X		X			
Total Bilirubin	X		X			
Blood Urea Nitrogen (BUN)	X		X			
Creatinine	X		X			
Lactate Dehydrogenase (LDH)	X	X[15]				
Creatine Kinase-MB (CK-MB)	X[2]		X[11]			Optional
Troponin (NO high-sensitivity troponin)	X[2]		X[11]			X[17]
Lactate	X		X			
B-type Natriuretic Peptide (BNP) or NT-proBNP	X					
Pregnancy Test	X[3]					
12-lead ECG						
12-lead ECG	X[4]		X[12]			X[17]
Health Assessment & Quality of Life Questionnaires						
Euroscore II	X[5]					
STS score	X[5]					
NYHA Heart Failure Class	X[5]				X	
Seattle Angina Questionnaire (SAQ)	X[5]				X	
EQ-5D-5L	X[5]				X	
IMAGING ASSESSMENTS						
Echocardiogram	X[6]	X[9]	X[9]		X	X[18]
Angiography Data	X	X				
HEMODYNAMIC ASSESSMENTS						
Hemodynamic Measurements (RAP/PAP/PCWP/CPO/CO/CI)		X[7]				
MAP	X	X[8]	X	X		
EXAMS						

[redacted]

[redacted]

Clinical Test	Baseline[1]	Intraprocedure	Post-Procedure[10]	Discharge	90 Days Post Device Removal	Unscheduled Visit
Physical Examination	X			X	X	
Vital Signs	X		X	X		
Follow-up Clinic Visit					X[14]	
Adverse Event Assessment		X	X	X	X	X[19]
COVID-19 Assessment	X			X	X	X
Neurological Assessment	**As required per event; See Section 6.7**					
DEVICE ASSESSMENTS						
Pump Flow/Speed		X[8]				
OTHER						
Health Economics Data				X[13]		
Concomitant Use of Anticoagulant and Antiplatelet Medications	X	X	X	X	X	X

1. All baseline laboratory tests except for cardiac biomarkers must be done within 14 days prior to the index procedure.
2. Baseline cardiac biomarkers, including CK-MB and troponin (NO high-sensitivity troponin), must be assessed within 48 hours prior to the index procedure.
3. Pregnancy test is required for female subjects of childbearing potential within 14 days prior to the index procedure.
4. Baseline 12-lead ECG is required within 48 hours prior to the index procedure.
5. Health assessment and quality of life questionnaires must be done within 30 days prior to the index procedure.
6. Baseline echocardiogram must be done within 60 days prior to the index procedure. In addition to scheduled echocardiograms, echocardiograms should be performed any time new aortic valve abnormalities are suspected.
7. Hemodynamic assessments will be performed four times during the index procedure:
   1) Prior to device insertion
   2) Prior to the PCI procedure while on device support
   3) Immediately prior to weaning for the preparation of device shutdown and removal
   4) 10 to 30 minutes after device removal
8. The corresponding MAP for the same four time points and the corresponding pump speed and estimated pump flow for the time points 2) and 3) as specified above will be also collected during the index procedure. Blood pressure should be also collected at the time of inotrope/vasopressor administration.
9. Echocardiogram must be performed no later than 48 hours post-device removal. This can be done either during or after the index procedure.
10. Post-procedure laboratory assessments except for cardiac biomarkers must be done within 24 hours after device removal.
11. Both CK-MB and troponin (NO high-sensitivity troponin) are required for the post-procedural assessment:
    1) First draw at 6 to 12 hours post-device removal
    2) If CK-MB is elevated > 1x ULN or troponin is elevated > 7x ULN in the first draw, a second draw of CK-MB and troponin is required at 18-24 hours post-device removal or at the time of discharge as long as discharge is at or after 16 hours post-device removal.

    Note: If CK-MB or troponin in the second draw is not stable and falling compared to the first draw, serial measurements of CK-MB and troponin every 12 hours or per site standard until a decline is noted are highly recommended.
12. At least one 12-ECG must be performed within 24 hours post device removal.
13. Upon hospital discharge for the initial index procedure hospitalization and for any subsequent re-hospitalization as described in Section 6.7.
14. Ninety-day Follow-Up Form is required even if subject is still hospitalized.
15. Pre-device (before device insertion) and post-device (after device removal) draws via vascular access sheath in the catherization laboratory during the index procedure
16. ACT must be checked after giving procedural anticoagulant and must be ≥250 seconds prior to the wire/device insertion and throughout the procedure.
17. If an unscheduled visit is conducted due to a suspected ischemic cardiac event, troponin (NO high-sensitivity troponin) must be collected and ECG must be done. CK-MB is optional.
18. An echocardiogram should be performed if any new valvular abnormalities is suspected in the event of an unscheduled visit.
19. Details of any subsequent coronary interventions (e.g., repeat PCI or CABG) must be recorded, if applicable, in the event of an unscheduled visit.

[redacted]

[redacted]

6.10 Angiographic and Echocardiographic Core Laboratories

The clinical investigation will utilize an independent angiographic laboratory and an independent echocardiographic core laboratory for the assessment and evaluation of all angiograms and echocardiograms required during the clinical investigation period. The angiographic core laboratory will also calculate SYNTAX scores.

All clinical investigation-required angiograms and echocardiograms should be submitted to the core laboratories by uploading the assessments directly to the core laboratories' database.

7.0 ADVERSE EVENTS

To comply with worldwide standards and guidelines on clinical investigation adverse event reporting, the Sponsor has adopted uniform and worldwide applicable standard definitions and reporting timelines to be used and adhered to by the investigators.

7.1 Definition

7.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device under investigation.

Note 1: This definition includes events related to the medical device under investigation 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 medical devices under investigation.

7.1.2 Serious Adverse Event

If the AE meets any of the criteria below, it is regarded as a serious adverse event (SAE).

a) Led to a death,

b) Led to a serious deterioration in health of the subject, that either resulted in

1. A life-threatening illness or injury, or
2. A permanent impairment of a body structure or a body function, 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.

5. Chronic disease

c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.

Note: A planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered to be an SAE.

7.1.3 Device Deficiency

Device deficiency is defined as an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling. This includes the failure of the device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling of the device.

7.2 Device Relationship

Determination of whether there is a reasonable possibility that an investigational product or device under investigation caused or contributed to an AE is to be **determined by the Investigator** and recorded on the appropriate CRF. Determination should be based on assessment of temporal relationships, evidence of alternative etiology, medical/biologic plausibility, and patient condition (pre-existing condition).

7.2.1 Unanticipated (Serious) Adverse Device Effect (U[S]ADE)

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

7.3 Adverse Event and Device Deficiency Reporting

7.3.1 Adverse Event Reporting

Safety surveillance and reporting starts as soon as the subject is registered in the clinical investigation. Safety surveillance and reporting will continue until the last follow-up visit has been performed, the subject is deceased, the subject concludes participation in the clinical investigation or the subject withdraws from the clinical investigation. All adverse event data, including deaths and device deficiencies, will be collected throughout the time period defined above and will be reported to the Sponsor on a CRF. Additional information with regard to an adverse event should be updated within the appropriate CRF.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be reported.

An offline form will be made available to allow the investigator to report SAEs in the event the entry cannot be made in the EDC. This does not replace the EDC reporting system. All information must still be entered in the EDC system as soon as feasible.

Non-cardiac related abnormal laboratory values will not be considered AEs unless:

1. The investigator determined that the value is clinically significant,
2. The abnormal lab value required intervention, or
3. The abnormal lab value required subject withdrawal from the clinical investigation.

In this clinical investigation, all adverse events, regardless of their relationship to the devices, are to be documented on the appropriate CRF throughout the 90-day follow-up visit. Anticipated adverse event definitions can be found in **Appendix II**.

SAE Reporting

The investigator should report all SAEs to the Sponsor as soon as possible but no later than the timelines outlined below.

Clinical Site	Reporting timelines
All Sites	SAEs must be reported to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined above.

The date the site staff became aware the event met the criteria of an SAE must be recorded in the source document. The Investigator will further report the SAE to the local IRB according to the institution's IRB reporting requirements.

7.3.2 Unanticipated Adverse Device Effect Reporting to Sponsor and IRB

The Sponsor requires the Investigator to report any UADE to the Sponsor within 3 calendar days of the Investigator's knowledge of the event, unless local requirements are more stringent, and to the IRB per IRB requirements.

7.3.3 Device Deficiency Reporting

All device deficiencies should be reported on the appropriate CRF.

The Investigator should report all device deficiencies to the Sponsor as soon as possible but no later than outlined below.

Clinical Sites	Reporting timelines
All Sites	Device deficiencies must be reported to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined above.

The defective device must be returned to the Sponsor.

Device deficiencies should be reported to the IRB per the investigative site's local requirements.

An offline form will be made available to allow the Investigator to report device deficiencies in the event that the entry cannot be made in the EDC system. This does not replace the EDC reporting system. All information must still be entered in the EDC system as soon as feasible.

7.3.4 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

The Sponsor will report SAEs and reportable device deficiencies to the country regulatory authority, per local requirements.

Note: Reportable device deficiencies include device deficiencies that might have led to an SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

8.0 STATISTICAL CONSIDERATIONS

The following section describes the statistical methods for the clinical investigation. Additional details on statistical analyses, including justification of clinical investigation design, sensitivity analyses, poolability analyses, subgroup analyses and analysis of descriptive endpoints, are maintained in a separate Statistical Analysis Plan (SAP).

8.1 Analysis Populations

[redacted]

8.1.1 Intent-to-Treat (ITT) Population

[redacted]

[redacted]

8.1.2 As-Treated (AT) Population

[redacted]

8.1.3 Per-Protocol (PP) Population

[redacted]

8.2 Statistical Analyses

8.2.1 Primary Endpoint Analyses

The primary endpoint, a composite of safety and effectiveness at 90 days as defined in **Section 4.1**, will be evaluated using the difference in event rates in the ITT population. The hypothesis test is designed to show non-inferiority of HeartMate PHP to Impella for the primary endpoint with one-sided alpha of 0.025. [redacted]

[redacted]

If non-inferiority is met, superiority testing will be performed with a two-sided alpha of 0.05. [redacted]

[redacted]

8.2.2 Descriptive and Exploratory Endpoint Analyses

Descriptive analysis will be performed on those descriptive and exploratory endpoints specified in **Sections 4.2 and 4.3,** respectively. Further details can be found in the SAP.

8.3 Sample Size Calculation and Assumptions

It is assumed that the Impella will have a 90-day composite endpoint rate of 20%. [redacted] the non-inferiority margin (δ) is assumed to be 10%.

[redacted]

[redacted] a total of 473 subjects (315 for the HeartMate PHP arm and [redacted]

[redacted]

[redacted]

8.4 Timing of Analysis

For the randomized cohort of the pivotal phase, the analyses will be performed after all registered subjects have reached their 90-day follow-up visit, the database is locked, and the clinical investigation becomes unblinded.

8.5 Subgroup Analysis

Details can be found in the SAP.

8.6 Multiplicity

There is a single primary endpoint and no powered secondary endpoints. Therefore, no adjustment will be made for multiple testing.

8.7 Pooling Assessment

[redacted]

8.8 Procedures for Accounting for Missing Data

All analyses will be based on available data with missing data excluded. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.12 Deviations from Statistical Plan

Any major changes to the SAP will be documented in an amendment to the SAP. Less significant changes to the planned analyses will be documented in the final report.

9.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator/Institution will permit direct access to source data/documents for the purpose of performing clinical investigation-related monitoring, audits, IRB review and regulatory inspections.

Subjects providing informed consent are agreeing to allow clinical investigation monitors or regulatory authorities, including foreign countries, to review, in confidence, any records identifying the subjects in this clinical investigation. This information may be shared with regulatory agencies; however, Sponsor undertakes not to otherwise release the subject's personal and private information.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Selection of Clinical Sites and Investigators

The Sponsor will select investigators qualified by training and experience to participate in the clinical investigation. Sites will be selected based upon review of a recent site assessment, if applicable, and the qualifications of the investigators who will participate in the clinical investigation.

10.2 Clinical Investigation Finances and Agreements

The clinical investigation is sponsored and funded by Abbott. Participating sites will enter into a Clinical Trial Agreement (CTA) with Abbott prior to the initiation of the clinical investigation at the site. The CTA includes a negotiated budget for the associated scope of work performed at the site and data submitted as part of this clinical investigation. Site reimbursement will follow the payment schedule in the agreement. Each site Investigator must understand and accept the obligations to conduct this clinical investigation according to the CIP and applicable regulations under the signed CTA.

The clinical investigation will be financed by Abbott. Investigational sites will be compensated by Abbott for participation in the clinical investigation per the conditions of agreement between the Sponsor and investigational site.

[redacted]

10.2 CIP Amendments

Approved CIP amendments will be provided to the Investigators by the Sponsor prior to implementing the amendment. The Principal Investigator is responsible for notifying the IRB or equivalent committee of the CIP amendment (administrative changes) or obtaining IRB's approval of the CIP amendment (changes in subject care or safety), according to the instructions provided by the Sponsor with the CIP amendment.

Acknowledgement/approval by the IRB of the CIP amendment must be documented in writing prior to implementation of the CIP amendment. Copies of this documentation must also be provided to the Sponsor.

10.3 Training

10.3.1 Site Training

All Investigators and clinical investigation personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit or other appropriate training sessions. Over-the-phone or self-training may take place as required. Training of Investigators and clinical investigation personnel will include, but is not limited to, the CIP requirements, investigational device usage, eCRF completion and clinical investigation personnel responsibilities. All Investigators and clinical investigation personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Investigators and clinical investigation personnel may not perform any CIP-related activities that are not considered standard of care at the site prior to documented training (as described previously).

10.4 Monitoring

Sponsor and/or designee will monitor the clinical investigation over its duration according to the CIP-specific monitoring plan which will include the planned extent of source data verification.

Prior to initiating any procedure, the Sponsor monitor (or delegate) will ensure that the following criteria are met:

- The Investigator understands and accepts the obligation to conduct the clinical investigation according to the CIP and applicable regulations, and has signed the Investigator Agreement and/or the Clinical Trial Agreement.
- The Investigator and his/her staff should have sufficient time and facilities to conduct the clinical investigation and should have access to an adequate number of appropriate subjects to conduct the clinical investigation.
- Source documentation (including original medical records) must be available to substantiate proper informed consent procedures, adherence to CIP procedures,

adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information.

- The Investigator/site will permit access to such records. A monitoring visit sign-in log will be maintained at the site. The Investigator will agree to dedicate an adequate amount of time to the monitoring process. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator will provide the monitor with a suitable working environment for review of clinical investigation-related documents.

10.5 Deviations from CIP

The Investigator should not deviate from the CIP for any reason except in cases of medical emergencies when the deviation is necessary to protect the rights, safety and well-being of the subject or eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify Sponsor immediately by phone or in writing.

No waivers for CIP deviations will be granted by the Sponsor. All deviations must be reported to the Sponsor using the Deviation CRF. The occurrence of CIP deviations will be monitored by the Sponsor for evaluation of investigator compliance to the CIP and regulatory requirements and dealt with according to written procedures. Investigators will inform their IRB or equivalent committee of all CIP deviations in accordance with their specific IRB or equivalent committee reporting policies and procedures.

In the event of repeated non-compliance, as determined by the Sponsor, a Sponsor's monitor or company representative may attempt to secure compliance by one or more of the following (and not limited to):

- Visiting the Investigator and/or delegate
- Telephoning the Investigator and/or delegate
- Corresponding with the Investigator and/or delegate

Repeated non-compliance with the signed agreement, the CIP or any other conditions of the clinical investigation may result in further escalation in accordance with the Sponsor's written procedures, including securing compliance or, at its sole discretion, Sponsor may terminate the Investigator's participation in the clinical investigation.

10.6 Quality Assurance Audit

A Sponsor representative or designee may request access to all clinical investigation records, including source documentation, for inspection during a Quality Assurance audit.

In the event that an investigator is contacted by a Regulatory Agency in relation to this clinical investigation, the Investigator will notify Sponsor immediately. The Investigator

and Research Coordinator must be available to respond to reasonable requests and audit queries made during the audit process. The Investigator must provide Sponsor with copies of all correspondence that may affect the review of the current clinical investigation (e.g., Form FDA 483, Inspectional Observations, Warning Letters, Inspection Reports, etc.). Sponsor may provide any needed assistance in responding to regulatory audits.

10.7 Sponsor Auditing

1. The Sponsor shall prepare an audit plan as well as the operating procedures for the related duties, and conduct audits in accordance with the audit plan and the operating procedures.
2. Individual engaged in auditing (hereinafter referred to as "auditor") shall be different than those in charge of medical device development or monitoring.
3. The auditor shall prepare an audit report documenting the matters confirmed in the audit to certify and verify that the audit has been conducted, and submit them to the Sponsor.

10.8 Committees

10.8.1 Publications Committee

A Publication Committee shall be established to oversee clinical investigations publications, including publication planning and authorship determinations. Publication Committee membership may include members of the Principal Investigators, a representative of the Sponsor and a statistician. The Publication Committee will determine policy and strategies regarding individual presentations and/or publications arising from clinical investigation-generated data. The committee will also review all external requests for accessing clinical investigation-related data and strategies aligning with the Sponsor's presentation and publication team expectations. The committee will also follow the Sponsor's applicable policies and Standard Operating Procedures.

10.8.2 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) is an independent multidisciplinary group restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. The DSMB is typically composed of at least two physicians with experience relevant to the clinical investigation and a biostatistician.

The DSMB will serve in an advisory role to the Sponsor to ensure safety by reviewing cumulative data from the clinical investigation at prescribed intervals for the purpose of safeguarding the interests of registered subjects and those subjects yet to be registered, as well as the continuing validity and scientific merit of the clinical investigation. The

composition, frequency of the meetings and the statistical monitoring guidelines are described in detail in the DSMB charter.

The DSMB may consider a recommendation for modifications or termination of the clinical investigation based on any perceived safety concerns regardless of statistical significance. The recommendations of the DSMB are not binding, and all final decisions related to clinical investigations modifications rest with the Sponsor.

10.8.3 Clinical Events Committee (CEC)

The Clinical Events Committee (CEC) is an independent adjudication body comprised of qualified physicians who are not participants in the clinical investigation. The CEC will review and adjudicate pre-specified events reported by investigators or identified by Safety personnel for the clinical investigation as defined in the CEC charter and according to definitions provided in this CIP.

11.0 DATA HANDLING AND RECORD KEEPING

Sponsor and/or its affiliates will maintain documentation of the systems and procedures used in data collection for the duration of the clinical investigation.

CRF data collection will be performed through a secure web portal and only authorized personnel will access the EDC system using a unique username and password to enter, review or correct data. Passwords and electronic signatures will be strictly confidential.

The data will be subjected to consistency and validation checks within the EDC system and supplemental review by the Sponsor.

At the conclusion of the clinical investigation, completed CRF images with the date-and-time stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be provided to the investigational sites, if requested.

For the duration of the clinical investigation, the Investigator will maintain complete and accurate documentation including, but not limited to, medical records, clinical investigation progress records, laboratory reports, CRFs, signed ICFs, device accountability records (if applicable), correspondence with the IRB and clinical investigation monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical investigation.

11.1 Protection of Personally Identifiable Information

The Sponsor respects and protects personally identifiable information collected or maintained for this clinical investigation.

The Sponsor implements technical and physical access controls to ensure that Personal Information is accessible only to and processed only on a 'need to know' basis, including periodic review of access rights, and revocation of access when an individual's employment is terminated or the individual transitions to a role that does not require access to Personal Information, and appropriate restrictions on physical access to premises, facilities, equipment, and records containing Personal Information.

The Sponsor requires the investigational sites to transfer into Sponsor's data management systems only pseudonymous Personal Information (key-coded) necessary to conduct the Clinical Investigation, such as the patient's medical condition, treatment, dates of treatment, etc. The Sponsor discloses as part of the clinical investigation informed consent process that some Sponsor representatives still may see Personal Information at the participating sites for technical support of the participating physicians on the device implant or procedures, monitoring and quality control purposes. Confidentiality of Personal Information will be observed by all parties involved at all times throughout the clinical investigation. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data.

The Sponsor data management systems and processes were designed, developed, and tested according to industry standards to appropriately safeguard Confidential Information (including any Personal Information) against unauthorized access and/or interference by third parties, intrusion, theft, destruction, loss or alteration. Clinical Investigation data are encrypted in transit and at rest.

The Sponsor maintains a Privacy Incident procedure that complies in all respects with Applicable Law and industry best practices.

11.2 Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data review, data cleaning, and issuing and resolving data discrepancies. If appropriate, the DMP may be updated throughout the duration of the clinical investigation. All revisions will be tracked and document controlled.

11.3 Source Documentation

Regulations and Good Clinical Practice (GCP) require the Investigator to maintain information in the subject's original medical records that corroborates data collected on the CRFs. In order to comply with these regulatory requirements/GCP, the following information should be included in the subject record at a minimum and if applicable to the clinical investigation:

- Medical history/physical condition of the subject before involvement in the clinical investigation sufficient to verify CIP entry criteria

- Dated and signed notes on the day of entry into the clinical investigation referencing the Sponsor, CIP number, subject ID number and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of procedures and exams)
- Adverse events reported and their resolution, including supporting documents, such as discharge summaries, catheterization laboratory or procedure reports, ECGs, and lab results including documentation of site awareness of SAEs and of investigator assessment of device relationship for SAEs.
- CIP-required laboratory reports and 12-lead ECGs, reviewed and annotated for clinical significance of out of range results (if applicable).
- Notes regarding CIP-required and prescription medications taken during the clinical investigation (including start and stop dates)
- Subject's condition upon completion of or withdrawal from the clinical investigation
- Any other data required to substantiate data entered into the CRF

11.4 Case Report Form Completion

Primary data collection based on source-documented hospital and/or clinic chart reviews will be performed clearly and accurately by site personnel trained on the CIP and CRF completion. The Investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the Sponsor on the CRFs and in all required reports.

Data on CRFs will be collected for all subjects that are enrolled into the clinical investigation.

Only authorized site personnel will be permitted to enter the CRF data through the EDC system deployed by the Sponsor. An electronic audit trail will be used to track any subsequent changes of the entered data.

11.5 Record Retention

The Sponsor and Investigator/Site will archive and retain all documents pertaining to the clinical investigation as per the applicable regulatory record retention requirements. The Investigator must obtain permission from Sponsor in writing before destroying or transferring control of any clinical investigation records.

11.6 Investigational Devices Accountability

The Sponsor ships investigational products only to the Principal Investigator (the responsible leader of the investigational site) or his/her authorized designee at each site, after sites meet the requirements of site activation and shipping authorization is complete.

The Investigator or an authorized designee must maintain adequate records of the receipt and disposition of each investigational device, including part number, batch number, and serial number (if applicable), date used, subject identification, and treating physician.

Storage locations for the devices at investigational sites must be locked with access restricted only to Investigators and authorized personnel.

All investigational devices that are associated with a device failure or device deficiency must be returned immediately to the Sponsor.

12.0 ETHICAL CONSIDERATION

12.1 Institutional Review Board Review and Approval

IRB approval for the CIP and ICF/other written information provided to the subject will be obtained by the Principal Investigator at each investigational site prior to consenting and registering subjects in this clinical investigation. The approval letter must be received prior to the start of this clinical investigation and a copy must be provided to the Sponsor.

Any amendments to the CIP as well as associated ICF changes will be submitted to the IRB and written approval obtained prior to implementation, according to each institution's IRB requirements.

No changes will be made to the CIP or ICF or other written information provided to the subject without appropriate approvals, including IRB, the Sponsor, and the regulatory agencies (if applicable).

Until the clinical investigation is completed, the Investigator will advise his/her IRB/EC of the progress of this clinical investigation, per IRB requirements. Written approval must be obtained from the IRB yearly to continue the clinical investigation, or according to each institution's IRB requirements.

No investigative procedures other than those defined in this CIP will be undertaken on the registered subjects without the written agreement of the IRB and the Sponsor.

13.0 CLINICAL INVESTIGATION CONCLUSION

The clinical investigation will reach its end when the last subject registered completes the 90-day follow-up visit. The Sponsor will submit the clinical investigation report within 6 months of the end of the investigation.

The clinical investigation will be concluded when:

- All sites are closed AND

- The final report has been provided to investigators or the Sponsor has provided formal documentation of clinical investigation closure.

14.0 PUBLICATION POLICY

The data and results from the clinical investigation are the sole property of the Sponsor. The Sponsor shall have the right to access and use all data and results generated during the clinical investigation. The Investigators will not use this clinical investigation-related data without the written consent of the Sponsor for any purpose other than for clinical investigation completion or for generation of publication materials, as referenced in the Clinical Trial Agreement. Single-center results are not allowed to be published or presented before the multi-center results. Any proposals for publications or presentations by the investigators must be reviewed and approved by the Sponsor in a timely manner to enable Sponsor review in compliance with the Sponsor's publication policy set forth in the Clinical Trial Agreement.

The Sponsor will register the clinical trial on www.clinicaltrials.gov, in accordance with the International Committee of Medical Journal Editors guidelines, or any other applicable guidelines. The Sponsor shall be responsible for any such registration and results posting as required by ClinicalTrials.gov. Investigational sites shall not take any action to register the trial. A full report of the pre-specified outcomes, including any negative outcomes, will be made public through the ClinicalTrials.gov website according to the requirements of Section 801 of the FDA Amendments Act. If this clinical investigation is terminated early, the Sponsor will make every effort to hasten the release of the pre-specified outcomes through ClinicalTrials.gov website.

15.0 RISK ANALYSIS

15.1 Anticipated Clinical Benefits

The HeartMate PHP may provide hemodynamic support during high-risk PCI by increasing output from the left ventricle to the ascending aorta at a flow rate of over 4.0 L/min against a differential pressure of 60 mmHg. The potential benefits of hemodynamic support using the HeartMate PHP include, but may not be limited to, the following:

- Reduced or eliminated periods of coronary ischemia
- More complete revascularization than would be possible without HeartMate PHP support, and
- Reduction or elimination of intraprocedural complications such as hypotension.

15.2 Anticipated Potential Adverse Events

Risks associated with the HeartMate PHP and procedure, together with their likely incidence, are described in **Appendix IV**.

Anticipated potential adverse events associated with use of the HeartMate PHP are listed below:

- Aortic Insufficiency
- Aortic Valve Injury
- Bleeding
- Cardiac Arrhythmias
- Cardiogenic Shock
- Cardiac Tamponade
- Cerebrovascular Accident
- Death
- Device Malfunction
- Emergent Surgery
- Endocarditis
- Hemolysis
- Hepatic Dysfunction
- Hypertension
- Hypotension
- Insertion Site Infection
- Left Ventricular Perforation
- Limb Ischemia
- Myocardial Infarction
- Myocardial Ischemia
- Renal Dysfunction or Failure
- Respiratory Dysfunction
- Sepsis
- Thrombocytopenia
- Thromboembolism
- Transient Ischemic Attack
- Vascular Access Site and Access-related Complications and Vascular Injury

Anticipated potential adverse events associated with other procedures in this investigation beyond what is anticipated in high-risk PCI:

- Pulmonary Vasculature Injury (see **Section 15.4**)

There may be risks related to the device that are unknown at present. Likewise, the exact frequency of the risk may be unknown.

15.3 Residual Risks Associated with the Device Under Investigation

The HeartMate PHP Risk Management Report* utilizes the Failure Modes and Effects Analysis (FMEA) tool to systematically identify potential hazards associated with the process, design, components, and use of the HeartMate PHP System. Based upon preclinical, clinical and bench data, all residual risks are appropriate and acceptable. The benefit of treatment from the HeartMate PHP outweighs the potential risks to the patient.

As of January 2017, the HeartMate PHP has been used in more than 290 patients clinically and commercially. Comprehensive analysis of clinical data confirms that any undesirable risks identified are outweighed by the potential clinical benefits of the device[27].

Residual risks are likewise disclosed in the IFU in the form of clear instructions of what actions to take or to avoid, to avoid a hazardous situation of harm from occurring (contra-indications, warnings, and precautions). The anticipated AEs disclosed in the IFU (and CIP Appendix IV) provide further information to enable the user, and potentially the patient, to make an informed decision that weighs the residual risk against the benefit of using the device.

*RISKD, Risk Management Report, HeartMate PHP (High-Risk PCI Indication) # 1012172

15.4 Risks Associated with Participation in this Clinical Investigation

The potential risks associated with HeartMate PHP use are included in **Section 15.2** and **Appendix IV**. The risks are in general consistent with those in procedures such as diagnostic cardiac angiography and PCI. As the HeartMate PHP will be inserted into the left ventricle through the aortic valve, there might be potential risks of aortic valve injury or insufficiency associated with the use. However, the risks of valve injury or insufficiency also exist in cardiac angiography and/or PCI procedures[29-34], albeit at a much lower rate compared to the risk of such during participation in this clinical investigation. The exact rate of valve injury or insufficiency resulting from angiography or PCI is not presently known.

[redacted]

[redacted]

15.5 Steps That will be Taken to Control or Mitigate Risks

In-depth recommendations, special precautions and instructions regarding subject selection, device handling, physician training, device placement and system removal are included in the IFU/IB. Mitigations and treatment for all adverse events will be performed per the current practice standards/standards of care as determined by the Investigator.

Risks associated with the use of the HeartMate PHP during this clinical investigation are minimized through device design, investigator selection and training, pre-specified subject eligibility requirements, study monitoring to ensure adherence to the CIP, and the use of a DSMB. Furthermore, the Sponsor will provide a trained product field specialist for every HeartMate PHP system used in the clinical investigation.

These risk management aspects are detailed below:

Device Design

[redacted]

[redacted]

Investigator Selection and Training:

It is also stated in the IFU that the devices can only be used by physicians who have received appropriate training on how to use the device. This statement is interpreted to mean that the physician users must complete Sponsor-provided device training prior to clinical use and are expected to be aware of the known and foreseeable safety risks associated with the use of the devices including the surgical and/or non-surgical treatment of these conditions.

- Only physicians who are skilled in the manipulation of catheter-based technology in the vasculature and heart, and have a good understanding of the risks associated with these manipulations, will be selected as investigators for this clinical investigation.
- Site investigators will undergo training on the techniques required to optimally place and operate the device in the left ventricle. The physician users are expected to be aware of the known and foreseeable safety risks associated with the use of the devices, including the surgical and/or non-surgical treatment of these conditions.
- Emergency surgical back-up should be available as per the institution's standard procedures.
- Each case would be supported by Abbott field personnel.
- Pre-specified patient eligibility requirements - as stated in **Section 5.3** of the CIP.

Ensuring Strict Adherence to the CIP

The clinical investigation will be carefully monitored by the Sponsor monitor (or designee) to ensure adherence to the CIP. Adverse events and device deficiencies will be reported to the Sponsor/designee and will be monitored internally for safety surveillance purposes. A DSMB will be used for the clinical investigation. Stopping rules will be discussed with the DSMB and applied for subject safety through enrollment.

15.6 Risk to Benefit Rationale

Patients with complex coronary anatomy or depressed left ventricular function undergoing PCI may be at risk of hemodynamic collapse during PCI due to decreases in coronary perfusion during balloon inflations or in the event of complications such as vessel occlusion or dissection. These patients undergoing high-risk PCI may require the use of hemodynamic support devices. The HeartMate PHP is a high-flow, rapid-insertion percutaneous left ventricular assist devices which can provide hemodynamic support during high-risk PCI by increasing output from the left ventricle to the ascending aorta at a rate of over 4.0 liters per minute, which may provide hemodynamic stabilization for the patient. The potential benefits of hemodynamic support using the HeartMate PHP include reduced or eliminated periods of coronary ischemia, more complete revascularization than would be possible without HeartMate PHP support, and reduction or elimination of intraprocedural complications such as hypotension.

While there may be potential risks associated with the use of HeartMate PHP as listed in **Section 15.2** and **Appendix IV**, these risks are in general consistent with those in procedures such as diagnostic cardiac angiography and PCI. Hemodynamic collapse may lead to severe consequences including death. Given the potential reduction in the risk of hemodynamic collapse during high-risk PCI that the HeartMate System can provide, the potential benefits outweigh the potential risks associated with the use of the HeartMate PHP System.

APPENDIX I: ABBREVIATIONS AND ACRONYMS

Acronym or Abbreviation	Complete Phrase or Definition
AE	Adverse event
ACT	Activated clotting time
ALT	Alanine aminotransferase
AMI	Acute myocardial infarction
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AT	As-treated
BARC	Bleeding Academic Research Consortium
BUN	Blood urea nitrogen
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCS	Canadian Cardiovascular Society
CE	Conformité Européene
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CI	Cardiac index
CO	Cardiac output
CPO	Cardiac power output
CPR	Cardiopulmonary resuscitation
FDA	Food and Drug Administration
CK	Creatine kinase
CK-MB	Creatine kinase myocardial-band isoenzyme
CRF	Case report form
CTA	Clinical trial agreement
CVA	Cerebrovascular accident (or stroke)
dL	Deciliter
DSMB	Data Safety Monitoring Board
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture

Acronym or Abbreviation	Complete Phrase or Definition
FDA	Food and Drug Administration (U.S.)
FFR	Fractional flow reserve
FMEA	Failure modes and effects analysis
GCP	Good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
IABP	Intra-aortic balloon pump
IB	Investigator Brochure
ICF	Informed Consent Form
ICU	Intensive care unit
IDE	Investigational Device Exemption
IFU	Instructions for Use
INR	International normalized ratio
IRB	Institution Review Board
ITT	Intent-to-treat
IVRS	Intravascular ultrasound
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MAP	Mean arterial pressure
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Myocardial infarction
mm	Millimeter
NYHA	New York Heart Association
OUS	Outside the United States
PfHgb	Plasma-free hemoglobin
PAP	Pulmonary arterial pressure
PCI	Percutaneous coronary intervention
PCWP	Pulmonary capillary wedge pressure
PP	Per-protocol
PTT	Partial thromboplastin time
RAP	Right atrial pressure
SAE	Serious adverse event

Acronym or Abbreviation	Complete Phrase or Definition
SAP	Statistical Analysis Plan
SAQ	Seattle Angina Questionnaire
SBP	Systolic blood pressure
STEMI	ST elevation myocardial infarction
STS	Society of Thoracic Surgery
TIA	Transient ischemic attack
UADE	Unanticipated adverse device effect
ULN	Upper limit of normal
US	United States
USADE	Unanticipated serious adverse device effect

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