Cover Page

Portico & Navitor India Clinical Trial

Study Protocol (REDACTED)

NCT #: NCT05171712

Ministry of Health Protocol Approval Date: December 28, 2022

Clinical Investigation Plan

CIP Number: [redacted]

Portico & Navitor India Clinical Trial

Version Number	[redacted]
Date	[redacted]
Planned Number of Sites and Region(s)	[redacted]
Clinical Investigation Type	Prospective, two-phase, multi-center, non-randomized, phase IV clinical trial
Abbott Medical Expert	[redacted]
Sponsor	St. Jude Medical India Pvt. Ltd, (Abbott Structural Heart) [redacted]
Electronic Data Capture Software	[redacted]
Core Laboratory	[redacted]
CIP Author of Current Version	[redacted]

Clinical Investigation Plan

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I have read and agree to adhere to the clinical investigation plan and all regulatory requirements applicable in conducting this clinical study.

Site Principal Investigator

Printed name:
Signature:
Date (DD-MM-YYYY):

Clinical Investigation Plan

TABLE OF CONTENTS

Clinical Investigation Plan

COMPLIANCE STATEMENT:

This clinical investigation will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki, ISO 14155:2020 standard and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the clinical investigation will be approved by the appropriate Ethics Committee (EC) of the respective clinical site and as specified by local regulations.

1.0 INTRODUCTION

This document is a clinical investigation plan (CIP) for the Portico & Navitor India Phase IV clinical trial. This phase IV clinical trial is intended to collect data on procedural safety and device performance of the Portico™ device, Navitor™ device, and FlexNav™ delivery system in the Indian population and is required as a condition for the Portico & Navitor India import license. This Phase IV Clinical trial is sponsored by Abbott.

This clinical investigation will be conducted in accordance with this 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.

1.1 Background and Rationale

1.1.1 Background

Aortic stenosis is a clinically important degenerative valvular heart disease that is associated with poor prognosis following the onset of cardiac symptoms. In the elderly patient population, the prevalence of aortic stenosis and severe aortic stenosis is estimated at 12.4%, and 3.4%, respectively.[1] Historically, surgical aortic valve replacement (SAVR) has been the primary treatment option for severe aortic valve stenosis until seminal findings from the Placement of Aortic Transcatheter Valves (PARTNER) Cohort A and B Trials revealed transcatheter aortic valve replacement (TAVR), a less invasive treatment option, to be non-inferior to SAVR[2] and superior to conventional medical therapy[3] with respect to survival rates at 1 year. Several randomized trials have since been published validating the safety and effectiveness of TAVR and the novel therapy is now a class I indication for the treatment of symptomatic patients with severe aortic valve stenosis that are either high-risk or ineligible for surgery.[4]

Abbott's first-generation Portico TAVR system first received CE Mark in 2012 and is indicated for the treatment of symptomatic, severe aortic stenosis in patients that are at high surgical risk for mortality. The Portico IDE study, designed to gain US approval in high or extreme surgical risk patients, has completed enrollment and primary endpoint follow-up. The Portico TAVI system and FlexNav delivery system and loading system received FDA approval in September 2021.

Abbott's latest-generation Navitor TAVI system offers the same valve sizes as the Portico system and uses the FlexNav delivery system, with the Navitor™ loading system. The Navitor TAVI system received CE Mark in May 2021 and is indicated for the treatment of symptomatic, severe aortic stenosis in patients that are high surgical risk for mortality.

[redacted]

[redacted] The FlexNav delivery system and loading system received regulatory and licensing approval in India on 22 Dec 2020. The Portico transcatheter heart valve (THV) received regulatory and licensing approval in India on 28 Jan 2021 [redacted]

The Navitor loading system received regulatory and licensing approval in India on 9 February 2022, followed by the Navitor THV, which received regulatory and licensing approval on 18 May 2022. [redacted]

This Phase IV clinical trial investigating the Portico valve [redacted] the Navitor valve [redacted], the FlexNav delivery system and loading system, and the Navitor loading system aims to characterize the procedural safety and device performance in patients with severe symptomatic aortic stenosis at high or extreme risk for surgical aortic valve replacement in India.

1.1.2 Rationale for Conducting this Clinical Investigation

This phase IV clinical trial is intended to collect data on procedural safety and device performance of the Portico device, Navitor device, FlexNav delivery system and loading system, and the Navitor loading system on the Indian population and is required as a condition of approval for the device licenses issued by the Indian competent authority.

2.0 CLINICAL INVESTIGATION OVERVIEW

2.1 Clinical Investigation Objective

2.1.1 Primary Objective(s)

The objective of this Phase IV clinical trial is to characterize the procedural safety and device performance of the Portico valve, Navitor valve, FlexNav delivery system and loading system, and Navitor loading system to treat patients with severe aortic stenosis.

2.1.2 Name of the Device(s) Under Investigation

This study will include market released Abbott Portico valves, Navitor valves, FlexNav delivery system and loading system, and Navitor loading system in patients with symptomatic severe native aortic stenosis who are considered high (or above) surgical risk as per the Instructions for Use (IFU).

The Portico Valve, Navitor Valve, the FlexNav delivery system and the loading system, and the Navitor loading system are to be used in accordance with the IFU. Please refer to the IFU for further details. This protocol covers the use of all four Portico valve sizes (23mm, 25mm, 27mm and 29mm), Navitor valve sizes (23mm, 25mm, 27mm and 29mm), and the FlexNav delivery system (small and large) and loading system (small and large), and the Navitor loading system (small and large) which are all CE marked (refer to Table 1, Figure 1, Figure 2, Figure 3, and Figure 4).

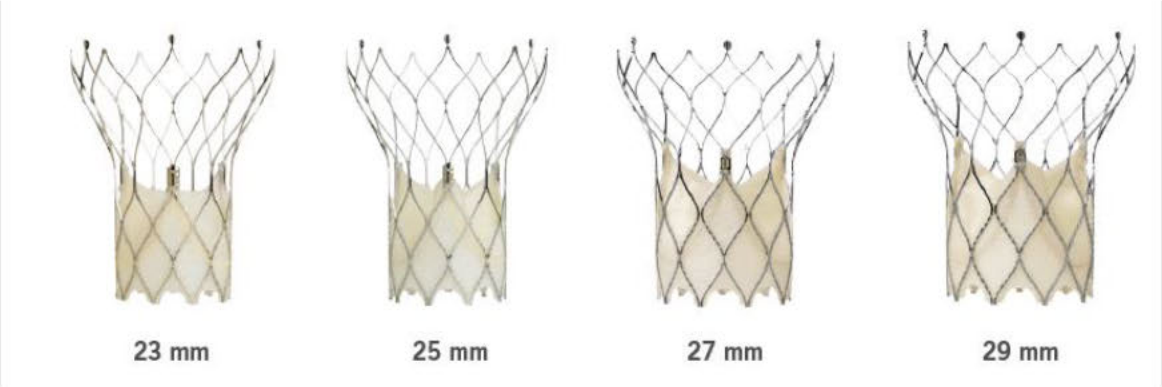
Clinical Investigation Plan

Table 1: Identification of Devices Included in the Study

Device name	Model/Type	Serial/Lot Controlled	Manufacturer	Region/ Country	Regulatory licensing approval for commercialization
Portico™ valve	PRT-23/25/27/29	Serialized	SJM	India	28 Jan 2021
Navitor™ valve	NVTR-23/25/27/29	Serialized	SJM	India	18 May 2022
FlexNav™ Delivery System	FNAV-DS-SM, FNAV-DS-LG	Lot	SJM	India	22 Dec 2020
FlexNav™ Loading System	FNAV-LS-SM, FNAV-LS-LG	Lot	SJM	India	22 Dec 2020
Navitor Loading System	NVTR-LS-SM, NVTR-LS-LG	Lot	SJM	India	9 Feb 2022

Clinical Investigation Plan

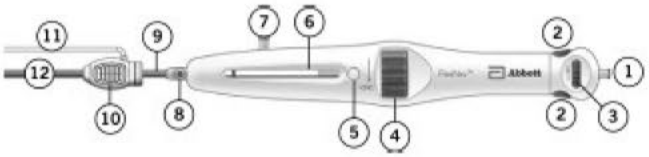
Figure 1: Portico Valve Sizes



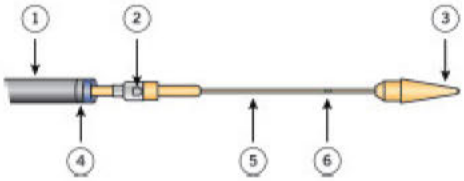
[redacted]

Clinical Investigation Plan

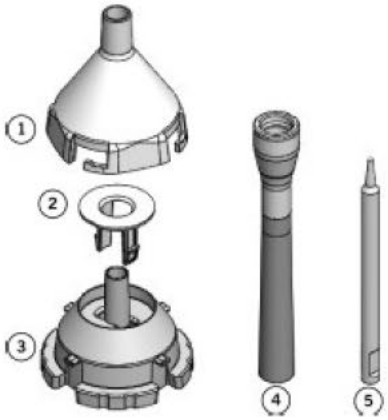
Figure 3: FlexNav Delivery System and Loading System



1. Guidewire lumen flush port
2. Macro slide buttons
3. Micro adjustment wheel
4. Deployment/re-sheath wheel
5. Deployment lock button
6. Deployment indicator
7. Valve capsule flush port
8. Stability layer flush port
9. Stability layer
10. Integrated sheath hub
11. Integrated sheath layer flush port
12. Integrated sheath



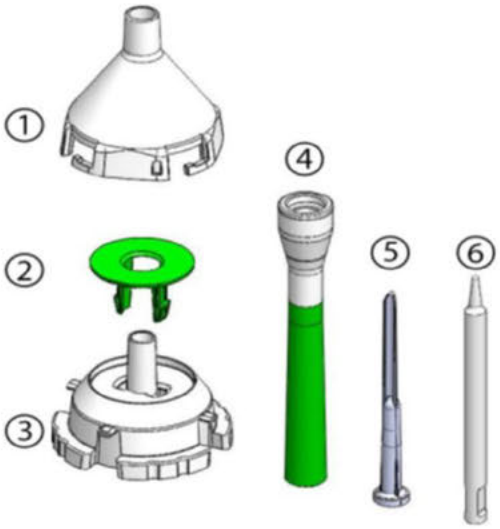
1. Valve capsule
2. Retainer receptacle
3. Radiopaque tip
4. Valve capsule marker band
5. Inner shaft
6. Inner shaft marker band



1. Loading funnel
2. Base insert
3. Loading base
4. Loading tube
5. Leaflet tester

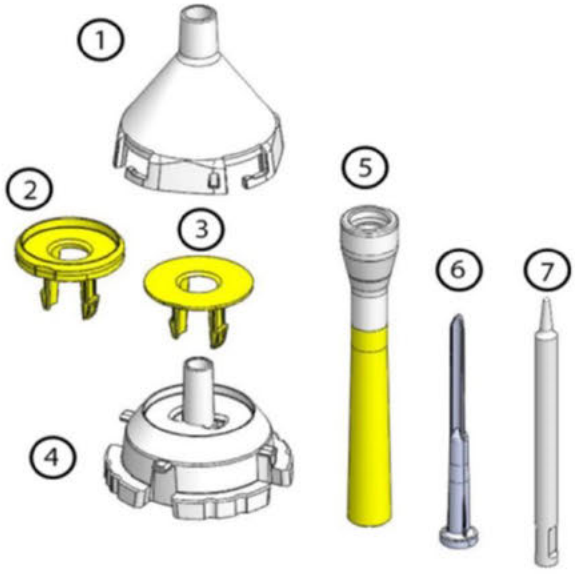
Clinical Investigation Plan

Figure 4: Navitor Loading System (Small and Large)



Navitor LS Small

1. Loading funnel
2. Base insert
3. Loading base
4. Loading tube
5. Stent guide



Navitor LS Large

1. Loading funnel
2. 27 mm base insert
3. 29 mm base insert
4. Loading base
5. Loading tube
6. Stent guide

2.1.3 Indication for Use

The Portico valve and Navitor valves are indicated for transcatheter delivery in patients with symptomatic severe native aortic stenosis who are considered high or extreme surgical risk.

The FlexNav delivery system is indicated for transfemoral or subclavian/axillary delivery of the Portico & Navitor valve. The delivery system is indicated for insertion into the vessel with or without an arterial introducer sheath.

The FlexNav loading system is indicated for loading the Portico valve in the FlexNav delivery system.
The Navitor loading system is indicated for loading the Navitor valve in the FlexNav delivery system.

Please refer to the approved IFU for the Portico TAVI System and Navitor TAVI System for detailed information regarding the indicated indication of the device used in this Phase IV study.

2.1.4 Description of the Devices Under Investigation

The Portico transcatheter aortic heart valve is a tri-leaflet bovine pericardial valve mounted in a self-expanding stent designed for intra-annular placement using minimally invasive techniques. The Portico valve consists of a stent frame manufactured from nitinol, a material that has self-expanding properties and is radiopaque. The valve cuff is made from porcine pericardium and is sutured to the stent frame. The valve cuff provides the sealing area for implantation. The valve is manufactured by suturing three valve leaflets, each made from a single layer of bovine pericardium, into a tri-leaflet configuration on the stent frame. [redacted]

The Navitor transcatheter aortic heart valve is a tri-leaflet bovine pericardial valve sutured to the frame in the frame of a self-expanding nitinol stent. [redacted] New features to the Navitor Valve from the Portico valve include the addition of an outer cuff, and replacement of the inner cuff material (Figure 2). Both the inner and outer cuff are made from [redacted]. These cuffs produce the sealing area to provide paravalvular leak reduction at implantation by filling with blood in voids between the native valve and the stent frame.

Relative to the first-generation Portico valve, the Navitor valve also includes:

- [redacted]
- [redacted]

The valve is sterilized using a multi-component sterilant (i.e., glutaraldehyde, formaldehyde, and ethanol) and provided sterile and non-pyrogenic.

The FlexNav delivery system is an over-the-wire compatible system that includes a hydrophilic-coated, integrated sheath to facilitate gradual, controlled deployment of the Portico or Navitor valve in patients with a minimum vessel diameter of ≥ 5mm. The delivery system allows for transfemoral or subclavian/axillary access methods with the current range of valve sizes. It has a working length of 107 cm and is composed of a handle at the proximal end. The FlexNav delivery system is available in two sizes with equivalent integrated sheath diameters of 14 F (small) or 15 F (large), and outer diameters of 6.0 mm (small) and 6.3 mm (large) at the distal end, respectively.

The Sponsor requires clinical sites to store all investigational products according to the labeling and Instructions for Use in a secure area to prevent unauthorized access or use. Please refer to the IFU for additional information regarding the device used in this phase IV study.

3.0 CLINICAL INVESTIGATION DESIGN

This is a prospective, non-randomized, two-phase, multicenter Phase IV clinical trial for patients clinically indicated for implantation of a Portico or Navitor transcatheter aortic heart valve. [redacted] The clinical trial has broad inclusion criteria (symptomatic degenerative aortic stenosis) and minimal exclusion criteria to ensure the results are generalizable to the broadest TAVR population. A total of [redacted] subjects [redacted] at up to [redacted] sites in India will undergo transcatheter aortic valve replacement (independent of valve size) using either Portico or Navitor valves and the FlexNav delivery system.

Subjects will undergo prospective enrollment with baseline data collection prior to receiving their study valve (up to a maximum of 180 days prior to the study valve implant procedure). The implant procedure will be conducted per standard protocol established at each center. After the procedure, subjects will undergo a pre-discharge visit at the time of hospital discharge or within seven days of the index procedure, whichever occurs first. Subjects will return to the participating institution for a 30-day and 9-month follow-up visit. [redacted]

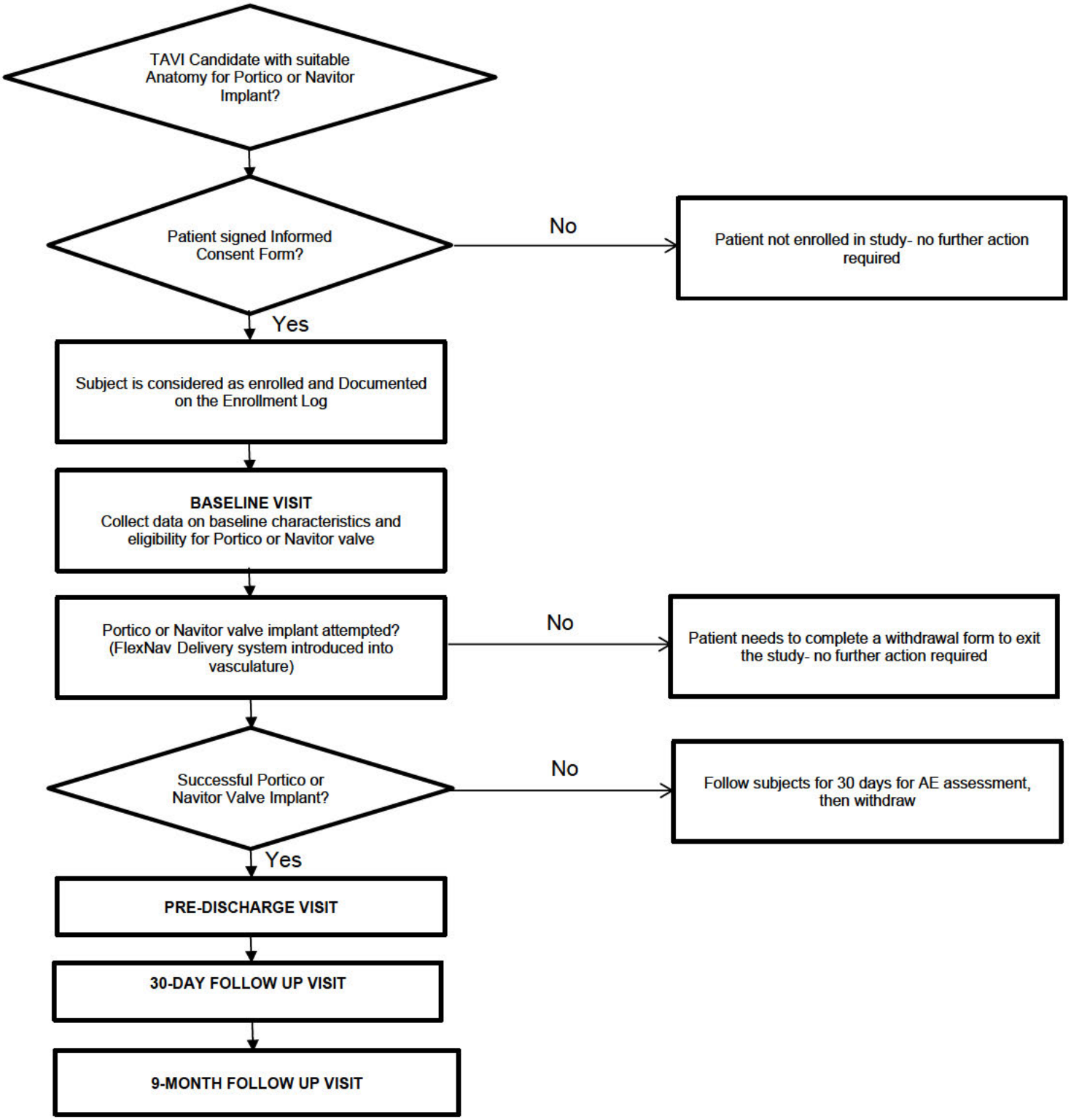
An Echocardiographic Core Laboratory will be utilized to evaluate echo at the 30 day follow up visit. The Echocardiographic Core Laboratory will not be responsible to notify the site of any abnormal findings that are identified in the echo study. Core Laboratory adjudicated echocardiographic measures will be utilized for evaluating valve hemodynamic performance at 30 days. An independent Cardiologist with relevant experience will be utilized as Clinical Event Committee (CEC) to adjudicate key adverse events pertinent to the study's descriptive endpoints. The primary function, responsibilities and membership of the CEC will be described in detail within the CEC charter.

3.1 Clinical Investigation Procedures and Follow-up Schedule

The flowchart (Figure 5) and the follow-up requirements of this clinical investigation are described below.

Clinical Investigation Plan

Figure 5: Clinical Investigation Flowchart



Clinical sites will follow subjects until they complete their 30 days and 9-month visits. Clinical investigation visits will occur at Baseline (confirmation of eligibility), Implant, Pre-discharge,30 days and 9-months.

Measures Taken to Avoid and Minimize Bias

This is a phase IV study for real world use of Portico and Navitor in India. Additional measures used to avoid and minimize bias for this study are mentioned below:

1. Use of Echocardiography Core laboratory; refer section 6.5
2. Use of CEC; refer section 10.8.1

3.2 Suspension or Early Termination of the Phase IV Clinical Trial

While no formal statistical rule for early termination of the Phase IV Clinical Trial for 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 investigator. Possible reason(s) 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
- Further product development is cancelled

Should the Sponsor discontinue the clinical investigation, sites will follow subjects per routine hospital practice with device-related AEs reported to the Sponsor as per vigilance/commercial reporting requirements. The investigator shall return all clinical investigation materials (including devices) to the Sponsor and provide a written statement to the IRB/EC (if applicable). All applicable clinical investigation documents shall be subject to the same retention policy as detailed in [Section 11.5] of the CIP.

If the Sponsor suspends or prematurely terminates the Phase IV trial at an individual site in the interest of safety, the Sponsor will inform all other Principal Investigators.

If suspension or premature termination occurs, the Principal Investigator or authorized designee will promptly inform the enrolled subjects at his/her site, if appropriate, and return patients to their standard medical treatment.

A Principal Investigator, IRB/EC, or regulatory authority may also suspend or prematurely terminate participation in the clinical investigation at the investigational site(s) for which they are responsible. The investigators will follow the requirements specified in the Clinical Trial Agreement.

If a suspended investigation is to be resumed, a prior approval should be obtained from the EC/IRB and a notification should be sent to the regulatory bodies.

4.0 ENDPOINTS

The following descriptive endpoints are reported using summary statistics and no hypothesis tests will be performed.

4.1 Descriptive Endpoint(s)

1. Evaluation of the VARC-2 and VARC-3 defined event rates at 30 days from the index procedure (Implant)
    - All-cause Mortality
    - Cardiovascular Mortality
    - Myocardial Infarction
    - Stroke (including disabling and non-disabling)
    - Bleeding (life-threatening, major, minor)
    - Acute kidney injury
    - Vascular access site and access-related complications (major and minor)
    - Coronary obstruction
    - Permanent pacemaker insertion

2. Delivery profile characteristics such as access vessel diameter, sheath utilization and sheath size

3. Implant success defined as:
    - Absence of procedural mortality
    - Correct positioning of a single Portico or Navitor prosthetic heart valve into the proper anatomical location
    - No conversion to open surgery

4. Echocardiographic assessment of valve performance at 30 days compared to baseline for the subjects with Portico or Navitor valve implanted
    - Mean gradient
    - Effective orifice area
    - Paravalvular leak (PVL) assessed per VARC-2
        - none/trace, mild, moderate or severe

    (Core Lab adjudicated echocardiographic measures will be utilized for evaluating valve hemodynamic performance at 30 days)

5. Evaluation of the VARC-2 and VARC-3 defined event rates beyond 30 days through 9-months from the index procedure (Implant)
    - All-cause Mortality
    - Stroke (including disabling and non-disabling)

6. Clinical improvement from baseline to 30 days and baseline to 9-months for the subjects with Portico & Navitor valve implanted assessed by:

- New York Heart Association (NYHA) functional class
- Quality of Life (QoL) questionnaire (EQ5D-5L)

NOTE: Should new VARC or ESC Guidelines be published during the course of this study, endpoint analysis would be adjusted accordingly and analyzed to the extent that the previously gathered data supports the analyses based on the most current guidelines.

5.0 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This clinical investigation will enroll subjects of all genders who are at or over the age of 60 years, have severe symptomatic (NYHA class ≥ II) aortic stenosis (AS), at high or extreme surgical risk and are considered to be a suitable candidate for TAVI.

5.2 Subject Recruitment/Screening and Informed Consent

5.2.1 Subject Recruitment and Screening

A member of the site's clinical investigation team previously trained to the CIP must evaluate patients for the general clinical investigation eligibility criteria, and if applicable, will enter the patients into a site-specific Enrollment/screening log. A patient who does not satisfy all general eligibility criteria prior to informed consent is considered a recruitment failure and should not be enrolled in the clinical investigation.

Sites will ask patients meeting general inclusion criteria and no general exclusion criteria to sign an Informed Consent form following the established Informed Consent process (described in [Section 5.2.2]) if they wish to participate in the clinical investigation. Sites will enter these patients into the enrollment/screening log. Once a duly dated and signed Informed Consent form is obtained, sites will perform CIP-specific assessments as part of the clinical investigation screening process as mentioned in section 6.1.1.

Subjects who do not meet the clinical investigation screening criteria are considered a screen failure and should be withdrawn from the clinical investigation. The Principal Investigator or the delegated clinical investigation personnel will record the screen failure in the hospital records and on an enrollment/screening log 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 Institutional Review Boards (IRB) or Ethics Committee (EC). This process will include a verbal discussion with the patient on all aspects of the clinical investigation that are relevant to the patient's decision to participate, such as details of clinical investigation

procedures, anticipated benefits, and potential risks of clinical investigation participation. Sites must inform patients 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 patient 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 patient and will respect patient's legal rights. Financial incentives will not be given to patients. Patients may be compensated for time and travel directly related to the participation in the clinical investigation. The site shall provide the patient with the Informed Consent form written in a language that is understandable to the patient and that has been approved by the center's IRB/EC. The patient 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 patient understands the information provided. If the patient agrees to participate, they must sign and date the Informed Consent form, along with the person obtaining the consent prior to any clinical investigation-specific procedures. The site will file the signed original in the patient's hospital or research charts and provide a copy to the patient.

Sites should report any failure to obtain informed consent from a patient to the Sponsor within 5 working days and to the reviewing center's IRB/EC according to the IRB's/EC's reporting requirements.

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 (if applicable) will provide this information to the subject. If relevant, sites will ask the subject to confirm their continuing informed consent in writing.

5.2.2.1 Special Circumstances for Informed Consent

Sites may enroll individuals who are unable to make the decision to participate in a clinical investigation on their own. Sites will obtain informed consent from the patient's legally authorized representative and will inform the patient about the clinical investigation within his/her ability to understand. During the informed consent discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence and make sure there is no manipulation of the patient and patient's legal rights are respected. Enrollment of these patients is important as data of comparable validity cannot be obtained from clinical research involving persons able to give informed consent or by other research methods. Additionally, the clinical investigation directly relates to a medical condition from which the individual suffers, and the clinical investigation is expected to produce a direct benefit to the individual, outweighing the risks and burdens involved.

The legally acceptable representative will represent the individual during the Informed Consent process, which will be performed according to the requirements in [Section 5.2.2]. Sites will respect the explicit wish of the individual to decline participation or withdraw from the clinical investigation at any time. In addition, no incentives or financial inducements will be provided to these patients or their legally authorized representatives for their participation in the clinical investigation.

Sites may enroll individuals unable to read or write in this clinical investigation.

Sites will obtain informed consent through a supervised oral process. An independent witness will be present throughout the Informed Consent process. A member of the site's clinical investigation team previously trained to the CIP will read the written Informed Consent form and any other information aloud and explain to the prospective subject or his/her legally acceptable representative and will sign and personally date the Informed Consent form. The witness will also sign and personally date the Informed Consent form attesting that the information was accurately explained, and that informed consent was freely given. In addition, no incentives or financial inducements will be provided to these patients or their legally authorized representatives for their participation in the clinical investigation.

The clinical investigation excludes pregnant or breastfeeding women.

5.3 Eligibility Criteria

5.3.1 General Eligibility Criteria

Assessment for general eligibility criteria is based on medical records of the site and interview with a candidate patient. Patients must meet ALL general inclusion criteria to participate in the clinical investigation. If ANY general exclusion criteria are met, the patient is excluded from the clinical investigation and cannot be enrolled (recruitment failure).

If any clinical and/or laboratory tests are required for patient screening and are not included in a site's standard tests, they must be completed after written informed consent is obtained.

5.3.2 Inclusion Criteria

5.3.2.1 General Inclusion Criteria

1. Subject must provide written informed consent prior to any clinical investigation-related procedure.
2. Are ≥60 years of age in host country, have severe symptomatic (NYHA class ≥ II) aortic stenosis (AS), at high or extreme surgical risk and have been identified as a candidate for a Portico or Navitor valve implant.
3. Subjects must have a Society of Thoracic Surgeons (STS) score of ≥7% OR documented heart team agreement of high or extreme risk for surgical aortic valve replacement due to frailty or co-morbidities not captured by the STS score.

5.3.3 Exclusion Criteria

5.3.3.1 General Exclusion Criteria

1. Have tested positive for the COVID-19 virus at any time AND currently have residual signs or symptoms associated with the COVID-19 virus (e.g. evidence of thrombosis, damaged/inflamed heart muscle, damaged/inflamed lung tissue, etc.)
2. Have sepsis, including active endocarditis
3. Have any evidence of left ventricular or atrial thrombus
4. Have vascular conditions (i.e. caliber, stenosis, tortuosity, or severe calcification) that make insertion and endovascular access to the aortic valve improbable
5. Have a non-calcified aortic annulus
6. Have congenital bicuspid or unicuspid leaflet configuration
7. Are unable to tolerate antiplatelet/anticoagulant therapy
8. Are pregnant at the time of signing informed consent
9. Are currently participating in a drug or device study that may impact this study (unless prior Sponsor approval for co-enrollment is granted)

5.4 Subject Enrollment

All subjects who meet all inclusion criteria, do not meet any exclusion criteria, and sign an EC approved Informed Consent are considered enrolled. Only those enrolled subjects that also have an attempted implant (defined as the FlexNav delivery system entering the subject's vasculature) will be included in the analysis population for this trial.

All enrolled subjects that undergo an implant attempt should be followed for 30 days regardless of the procedure outcome.

5.5 Subject Withdrawal and Discontinuation

Each subject meeting all general and screening eligibility criteria shall remain in the clinical investigation until completion of the required follow-up period; 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 benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Subject death
- Subject voluntary withdrawal
- Subject lost-to follow-up as described below
- Subject's follow-up is terminated according to [Section 3.2].

Sites must notify the Sponsor of the reason(s) for subject discontinuation. Investigators must also report this to their respective IRB/EC as defined by their institution's procedure(s).

No additional follow-up is required, or data recorded from subjects once withdrawn from the clinical investigation, except for the status (deceased/alive).

However, if a subject withdraws from the investigation due to problems related to the safety or performance of the device under investigation, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical investigation.

Lost-to-Follow-up

If the subject misses two consecutive scheduled follow-up time points 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, at each contact time point:

- A minimum of two telephone calls on different days over the specified follow-up windows 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, the site should send a letter (certified if applicable) to the subject.
- If a subject misses one or more non-consecutive follow-up contact time points, it will be considered a missed visit. The subject may then return for subsequent visits. If the subject misses two consecutive time points and the above-mentioned attempts at communicating with the subject are unsuccessful, the subject will be considered lost-to-follow-up.

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.

5.6 Number of Subjects

The clinical investigation will enroll [redacted] subjects that undergo a study valve implant attempt [redacted].

5.7 Total Expected Duration of the Clinical Investigation

[redacted] The expected duration of each subject's participation is 9-months, including the scheduled visits and data collection for this clinical investigation that will occur at baseline, implant, pre-discharge,30 days and 9-months. Subjects will exit the trial at the end of their 9-month follow-up visit. [redacted]

6.0 TREATMENT AND EVALUATION OF ENDPOINTS

6.1 Baseline

6.1.1 Baseline/Pre-procedure/Pre-treatment Clinical Assessments

For patients indicated for implantation of a study valve (Portico or Navitor), a baseline visit will occur prospectively (before receiving the study Valve) at a maximum of 180 days prior to the implant procedure. Data available in the patient's medical record may be utilized to fulfill screening and baseline requirements and testing does not need to be repeated if performed within 180 days prior to the implant procedure.

The following assessments and information will be collected at the baseline visit:

- Obtain Patient Informed Consent and document the process in the patient's records
- Collection of baseline demographics including patient age and gender
- Collection of medical and cardiovascular history including pre-existing cardiovascular history, previous cardiovascular procedures, and other pertinent medical conditions
- Eligibility assessment for study valve implantation – Implant center may follow the Heart Team approach for patient evaluation recommended by VARC-3 However, eligibility assessment for study valve implantation will be conducted per standard of care guidelines at each center. Data on baseline patient characteristics and comorbidities which contributed to the patient's surgical risk assessment (Appendix V) will be collected on the Baseline CRF
- Frailty assessment – If a frailty factor contributed to the patient's surgical risk designation, this data will be collected on the Baseline CRF (Appendix VII)
- Native aortic valve assessment using either Echo or as per standard of care guidelines at the implant center
- Access site assessment (site, size, tortuosity, calcium burden, etc.)
- Blood work (most recent pre-procedure creatinine, hemoglobin, and troponin)
- Physical assessment including height, weight, and office blood pressure
- Neurologic assessment (eg. National Institutes of Health Stroke Scale (NIHSS), Modified Rankin Score (mRS), or other neurologic evaluation per SOC)
- Echocardiogram (TTE or TEE)
- Electrocardiogram (ECG)
- New York Heart Association (NYHA) functional class assessment
- Completion of the QoL questionnaire (EQ5D – 5L)
- Anti-platelet and anti-coagulation medication assessment
- Adverse events assessment

Implant center may follow the Heart Team approach for patient evaluation recommended by VARC-3. However, eligibility assessment for study valve implantation will be conducted per standard of care guidelines at each center.

For neurologic assessments, NIHSS, mRS, or other SOC neurologic evaluations should be completed at each applicable scheduled and unscheduled visit. For all NIHSS, a Neurologist, Neurology Fellow, or

trained/certified Neurology Specialist must perform the assessment. The results must be documented in the subject's medical record.

6.2 Index Procedure

The heart team performing the TAVR procedure will typically consist of:

- An implanting physician (either an interventional cardiologist or a cardiac surgeon) at the center who will perform the procedure
- A second operator (a cardiac surgeon or a cardiologist) may be present during the procedure as needed
- An anesthesiologist and a perfusionist as needed for their own functions

NOTE: Anticoagulation use is left to the physician's discretion or should be established as with any other biological valve implantation, considering risks and benefits for the patient. The implant procedure will be conducted per standard of care guidelines at each center, and in accordance with the product IFU and Sponsor's training program.

Data collection during the procedure will consist of the following:

- Adverse events assessment
- Document transcatheter aortic valve deployment and performance information
- Procedural characteristics
- Procedural imaging (angiogram, intra-procedural echocardiography assessments) may also be collected if available as part of standard of care
- Medication assessment

During the procedure, the implanting physician may determine the implantation of the study (Portico or Navitor) valve is either not feasible or not in the best interest of the patient. Reasons for procedural exclusion may include, but are not limited to, anatomy that is not suitable for implantation, inability to gain access, ventricular arrhythmia, or any other contraindication.

If the implant procedure was attempted (i.e., the FlexNav delivery system was introduced into subject's vasculature) but the study valve could not be implanted (e.g., Portico or Navitor attempted but other valve ultimately placed in the annulus), the subject will be withdrawn from the study after a 30-day adverse event collection period.

If the subject was consented but the implant procedure was not attempted (i.e. the FlexNav delivery system was never introduced into the subject's vasculature), the subject will be withdrawn from the trial and will not be included in the analysis population Refer to Section 5.4: Subject Enrollment.

Following the procedure, the delivery and loading system should be disposed of per hospital requirements for hazardous materials. If there are any concerns noted with the delivery system, loading system, or valve during the procedure, they should be returned to the Sponsor for evaluation.

6.3 Pre-Discharge Visit

The pre-discharge visit will take place at discharge or seven days post implant, whichever is sooner. Discharge testing may be completed the day after procedure up until discharge or within 7 days after the procedure if the subject is yet to be discharged. The pre-discharge assessment will include:

- Physical assessment
- Neurologic assessment (eg. NIHSS, mRS, or other neurology evaluation per SOC)
- Site performed echocardiography assessment of the Portico or Navitor valve
- Blood work (Blood sample: between day 2 to 4 post-implant, or at discharge, whichever occurs first) to obtain, hemoglobin, creatinine, and troponin values)
- Medication assessment
- Pacemaker dependency assessment (as applicable)
- Adverse events assessment

6.4 Follow-up Assessments

Follow-up visit is scheduled at 30 days and 9-months after implant/index procedure. The scheduled visit windows are calculated from the implant date.

At each visit, the following procedures must be completed:

30 Days Follow Up Visit (30 Days + 60 Days)

- Physical assessment
- Neurologic assessment (eg. NIHSS, mRS, or other neurology evaluation per SOC)
- Blood work (creatinine, hemoglobin, troponin)
- Echocardiogram*
- Electrocardiogram (ECG)
- NYHA functional status classification
- Completion of QoL questionnaire (EQ5D-5L)
- Medication assessment
- Adverse events assessment
- Pacemaker dependency assessment (as applicable)

*Each site will be responsible for performing and interpreting the 30-day follow-up echocardiogram using the VARC-2 and VARC-3 definitions. Echocardiograms will be sent to an Echocardiographic Core Laboratory for further analysis per the Echocardiography Core Laboratory Acquisition Protocol. Exams should be recorded in DICOM format and should be de-identified prior to sending to the Sponsor.

9-Months Follow Up Visit (270 Days ± 60 Days) (In-clinic)

- Physical assessment

- Neurologic assessment (eg. NIHSS, mRS, or other neurology evaluation per SOC)
- NYHA functional status classification
- Completion of QoL questionnaire (EQ5D-5L)
- Medication assessment
- Adverse events assessment
- Pacemaker dependency assessment (as applicable)

Sponsor Representatives may be involved in providing support during the follow-up procedures.

6.4.1 Patient Reported Outcome (PRO) Measures

The EuroQoL 5D-5L questionnaire will be administered by the investigators, the study coordinators or designee to the subject. The questionnaire is a standardized instrument widely used as a measure of health outcome and quality of life. It is important the subject understands the meaning of all words and instructions in the questionnaire. The subject should be instructed to ask any questions about the questionnaires if further explanation is needed. Once the questionnaires are completed, the Study Coordinator or designee will review for completeness to verify that all questions have been answered according to the directions provided.

The EuroQol (EQ) 5D-5L questionnaire is a standardized instrument widely used as a measure of health outcome and quality of life. The self-administered/electronic questionnaire consists of two pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The questionnaire is cognitively simple and takes only a few minutes to complete. The EQ-5D-5L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels: no problems, some problems, extreme problems. An EQ-5D health state may be converted to a single summary index by applying a formula that attaches weights to each of the levels in each dimension.

The questionnaire will be administered to all patients at Baseline, 30 days and 9-month follow-up visit. A copy of this questionnaire can be found under Appendix VI: EQ5D-5L Quality of Life Questionnaire.

6.4.2 Unscheduled Visit Follow Up:

An unscheduled visit is defined as a visit that occurs between Implant and 30-day follow-up visits and between 30 day and 9-month follow up visits where the patient is examined for either a physician requested follow-up or for an adverse event. Any data collected related to the clinical study endpoints should be documented by completing the appropriate section of the Follow-up or Echocardiogram electronic Case Report Form (eCRF) or Adverse Event Form as applicable. Neurologic assessments (eg. NIHSS, mRS, or other SOC neurology evaluation) must be completed for neurologic events and documented in the medical records.

6.4.3 Schedule of Events

The data collection elements required for each study visit are summarized in Table 2 below.

Clinical Investigation Plan

Table 2: Summary of Study Procedures

CIP Activity	Baseline (-180-0 d)	Index Procedure (0 d)	Pre-Discharge (0-7d)	30 days (+60d)	9-Months (±60d)	Unscheduled Visit (0-30d or 31d-9M)
Informed Consent Process	X					
Demographics	X					
Physical assessment	X		X	X	X	(X)
Medical and cardiovascular history	X					
Surgical risk assessment*	X					
Frailty assessment*	X					
Native aortic valve assessment*	X					
Access site assessment*	X					
Blood Work: - hemoglobin, creatinine, and troponin	X		X	X		(X)
NYHA class assessment	X			X	X	(X)
Quality of Life questionnaire (EQ5D-5L)	X			X	X	(X)
Neurologic assessment^	X		X	X	X	X
Implant characteristics		X				
Electrocardiogram (ECG)	X			X		(X)
Echocardiogram	X		X	X		(X)
Medication assessment	X	X	X	X	X	(X)
Adverse events assessment	X	X	X	X	X	(X)
Pacemaker Dependence Assessment			(X)	(X)	(X)	

* Per standard of care testing for a TAVI and should be within 180 days prior to index procedure
() if available or as applicable
^For neurologic assessments, NIHSS, mRS, or other SOC neurologic evaluations should be completed at each applicable scheduled and unscheduled visit. For all NIHSS, a Neurologist, Neurology Fellow, or trained/certified Neurology Specialist must perform the assessment. The results must be documented in the subject's medical record.

6.5 Requirement for Echocardiogram Core Laboratories

An independent Echo Core Laboratory will be utilized for evaluating 30-day echocardiograms. Each site is responsible for performing the echocardiogram according to the core laboratory imaging protocol and submitting de-identified DICOM images to the Core Lab for interpretation.

It is the responsibility of each site to perform the local interpretation of the echocardiogram for clinical assessment. The responsibility of the core laboratory is to assess the data and complete relevant Sponsor data collection forms. Data obtained from the core laboratory readings will be used for study purposes only and not for clinical treatment of the subject. The Sponsor will use only the measurements provided by the core laboratories for analysis. If the core laboratory determines that the data are unreadable, the site may be requested to contact the subject for a repeat assessment.

7.0 ADVERSE EVENTS

To comply with worldwide standards and guidelines on Phase IV clinical trial 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.

The Medical Device Rules, India (2017)[5] and New Drugs and Clinical Trial Rules, India (2019)[6] will be followed for this adverse event reporting during this Phase IV clinical trial as applicable.

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, in the context of a clinical investigation, whether or not related to the investigational medical device.

As part of ISO14155 Section 3.2, the Adverse Event definition has the following notes:

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 the use of investigational medical devices or comparators.

7.1.2 Serious Adverse Event

Serious Adverse Event is an AE that led to any of the following:

a) Death

b) Serious deterioration in the health of the subject, that resulted in any of the following:

1. Life-threatening illness or injury,
2. Permanent impairment of a body structure or a body function,
3. Hospitalization or prolongation of patient hospitalization,
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) Fetal distress, fetal death or a congenital physical or mental impairment or birth defect.

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

7.1.3 Device Deficiency/Device Malfunction

Device deficiency is defined as any inadequacy in the identity, quality, durability, reliability, usability, safety, or performance of an investigational device, including malfunction, use errors or inadequacy in the information supplied by the manufacturer including labeling.

Note 1: The definition includes device deficiencies related to investigational medical device or the comparator.
Note 2: Cyber-security incidents related to the investigational product, shall be reported as device deficiencies

A device malfunction is the failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP, or IB.

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 form. Determination should be based on the 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 (USADE) 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/Device Malfunction Reporting

7.3.1 Adverse Event Reporting

Safety surveillance and reporting starts as soon as the patient is enrolled and approved for the study procedure in the Phase IV clinical trial. Adverse events will not be collected for screen failure subjects. Safety surveillance and reporting will continue until sites perform the last follow-up visit, the subject is deceased, the subject concludes participation in the clinical investigation, or the subject withdraws from the clinical investigation. Sites will collect all adverse event data, including deaths and device deficiency data, throughout the period defined above and will report these events to the Sponsor/CRO (contract research organization) on a CRF. Sites should update additional information regarding an adverse event on the appropriate CRF.

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

An offline form 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. Sites must still enter all information in the EDC system as soon as feasible.

<u>SAE Reporting</u>

The investigator must report all SAEs to the Sponsor/CRO as soon as possible but no later than outlined below.

Clinical Site	Reporting timelines
All Sites	Sites must report SAEs to the Sponsor/CRO no later than 48 hours 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.

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

7.3.2 Unanticipated Serious Adverse Device Effect Reporting to Sponsor and IRB (if applicable)

The Sponsor requires the Investigator to report any USADE to the Sponsor/CRO within 48 hours of the investigator's knowledge of the event, unless local requirements are more stringent, and to the IRB/EC per IRB/EC requirements.

If an unanticipated adverse event (UADE) occurs during a live case, it should be noted as such in the report to the Sponsor and IRB/EC including a discussion on how the nature of a live case could have impacted the adverse event.

7.3.3 Device Deficiency/Malfunction Reporting

The investigator must report all device deficiencies/malfunctions to the Sponsor/CRO as soon as possible but no later than outlined below.

Clinical Sites	Reporting timelines
All Sites	Sites must report device deficiencies/malfunctions to the Sponsor/CRO no later than 48 hours 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.

Sites must report device deficiencies/malfunctions to the IRB/EC per the investigative site's local requirements.

Sites should return the device, if not implanted or not remaining in the subject, to the Sponsor.

7.3.4 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

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

Abbott Structural Heart Product Performance Group (PPG) will complete the Medical Device Adverse Event Reporting Form for Industry and send to DCGI per the guidance of Materiovigilance Programme of India[7].

1. Event allegedly caused by Device (within 15 calendar days):
    - Death of a patient, user, or other person
    - Serious deterioration in state of health of a patient, user, or other person.

A serious deterioration in state of health can include:

- Pacemaker implantation
- Renal Failure
- Access site complications
- Hemorrhage

8.0 STATISTICAL CONSIDERATIONS

The following section describes the statistical methods for the Phase IV Clinical Trial.

8.1 Analysis Populations

The primary analysis population for the study consists of all subjects enrolled in the Phase IV Clinical Trial that had a Portico or Navitor valve implant attempt. Additionally, number of enrolled subjects without a Portico or Navitor valve implant attempt will be summarized.

8.2 Statistical Analyses

No pre-specified hypothesis tests are planned for this Phase IV Trial. Baseline characteristics and follow-up data will be presented using appropriate summary statistics. Continuous data will be summarized using descriptive statistics including mean, standard deviation, median and range. Categorical data will be summarized by the counts and percentages. Subject data related to Portico valve implants will be evaluated separately from Navitor valve implants.

For events of death, the Clinical Event Committee (CEC) will adjudicate deaths and determine if the death was COVID-19 related. A sensitivity analysis will be performed to include all death events in relevant descriptive endpoints.

8.3 Sample Size Calculation

This is a Phase IV Clinical Trial to characterize clinical safety and performance of the Portico and Navitor valves at TAVR centers using the Portico valve, Navitor valve, FlexNav delivery system and loading system, and Navitor loading system to treat patients with severe aortic stenosis. No formal power analysis and sample size calculations are performed. In order to understand procedural characteristics and safety and performance outcomes in a 'standard of care' setting, the study will enroll a total [redacted] subjects [redacted] with a valve implanted from up to [redacted] TAVI centers in India.

8.4 Timing of Analysis

The final analysis will be conducted when the last enrolled subject with a Portico or Navitor valve implant attempted has reached 9-months post procedure.

8.5 Planned Interim Analysis

No interim analyses are planned for this study.

9.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution will permit direct access to source data/documents for performing clinical investigation-related monitoring, audits, IRB/EC 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, the 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 Phase IV clinical trial. 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 Phase IV clinical trial.

10.2 Clinical Investigation Finances and Agreements

Abbott will finance the Phase IV clinical trial and will compensate investigational sites for participation in the clinical investigation per the conditions of agreement between Abbott and the investigational site. Abbott will also provide devices under this Phase IV Clinical trial free of cost to the patients.

10.3 CIP Amendments

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

Sites must document in writing acknowledgement/approval of the CIP amendment by the IRB/EC prior to implementation of the CIP amendment. Sites must also provide copies of this documentation to the Sponsor. The Sponsor will also notify local regulatory body regarding the CIP amendment as per applicable laws.

10.4 Training

10.4.1 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, electronic case report form 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. Prior to signing the training log, Investigators and clinical investigation personnel must not perform any CIP-related activities that are not considered standard of care at the site.

10.5 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 Undertaking (Appendix XIV) and 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.
- Sites must have source documentation (including original medical records) 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 and will maintain a monitoring visit sign-in log 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.

10.6 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 to eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify Sponsor/CRO immediately by phone or in writing.

The Sponsor will not grant any waivers for CIP deviations. Sites must report all deviations to the Sponsor/CRO using the Deviation CRF. The Sponsor will monitor the occurrence of CIP for evaluation of investigator compliance to the CIP and regulatory requirements and handle according to written procedures. Investigators will inform their IRB/EC or equivalent committee of all CIP deviations in accordance with their specific IRB/EC 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 will 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 (email/mail) 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, the Sponsor may terminate the investigator's participation in the clinical investigation.

10.7 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.

If 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 the 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.). The Sponsor may provide any needed assistance in responding to regulatory audits.

10.8 Committees

10.8.1 Clinical Events Committee (CEC)

An independent Cardiologist with relevant experience not participating in the Portico & Navitor India trial will be utilized as Clinical Event Committee (CEC) to adjudicate key adverse events pertinent to the study's descriptive endpoints. The primary function and responsibilities will be described in detail within the CEC charter. For subjects that have tested positive for COVID-19 (prior to or during the study) and die during the study, the CEC will adjudicate deaths to determine the relationship to COVID-19.

11.0 DATA HANDLING AND RECORD KEEPING

Sponsor/CRO 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/CRO.

At the end 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 Informed Consent Forms (ICFs), device accountability records (if applicable), correspondence with the IRB/EC 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/CRO 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/CRO requires the investigational sites to enter only pseudonymous Personal Information (key-coded) necessary to conduct the clinical investigation, such as the patient's medical condition, treatment, dates of treatment, etc., into Sponsor's/CRO's data management systems. 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. All parties will observe confidentiality of Personal Information always throughout the clinical investigation.

All reports and data publications will preserve the privacy of each subject and confidentiality of his/her information.

The Sponsor/CRO 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/CRO 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 Sponsor/CRO may update the DMP throughout the duration of the clinical investigation. The Sponsor/CRO will track, and document control all revisions.

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. To comply with these regulatory requirements/GCP, sites should include the following information 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)
- AEs reported and their resolution, including supporting documents, such as discharge summaries, catheterization laboratory 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
- Patient reported outcome measures may be completed using CRF worksheets. This serves as source documentation.

11.4 Case Report Form Completion

Site research personnel trained on the CIP and electronic Case Report Form (eCRF) completion will perform the primary data collection clearly and accurately based on source-documented hospital and/or clinic chart reviews. The investigator will ensure accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor/Contract Research Organization (CRO) on the CRFs and in all required reports.

Sites will collect data on all subjects who sign an informed consent form, including subjects who may not meet all inclusion/exclusion criteria during screening at the index procedure.

Only authorized site personnel will be permitted to enter the CRF data through the electronic data capture (EDC) system deployed by the Sponsor/CRO. The Sponsor/CRO will use an electronic audit trail to track any subsequent changes of the entered data.

11.5 Record Retention

The Sponsor/CRO 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.

12.0 ETHICAL CONSIDERATION

12.1 Institutional Review Board/Ethics Committee Review and Approval

The Principal Investigator at each investigational site will obtain IRB/EC approval for the CIP and ICF/other written information provided to the patient prior to consenting and enrolling patients in this clinical investigation. The site must receive the approval letter prior to the start of this clinical investigation and provide a copy to the Sponsor.

Sites will submit any amendments to the CIP as well as associated ICF changes to the IRB/EC and written approval obtained prior to implementation, according to each institution's IRB/EC requirements.

No changes will be made to the CIP or ICF or other written information provided to the patient without appropriate approvals, including IRB/EC, 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/EC requirements. Written approval must be obtained from the IRB/EC yearly to continue the clinical investigation, or according to each institution's IRB/EC requirements.

Sites will not perform any investigative procedures, other than those defined in this CIP, on the enrolled subjects without the written agreement of the IRB/EC and the Sponsor.

13.0 PHASE IV CLINICAL TRIAL CONCLUSION

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

15.0 RISK ANALYSIS

15.1 Anticipated Clinical Benefits

The information collected in this clinical investigation will be added to the current knowledge and understanding of treatment options for patients with severe symptomatic aortic stenosis who require a TAVR procedure. It is expected that patients implanted with a Portico valve or Navitor valve will have the same benefits as patients implanted with other commercially available transcatheter valves.

The design features of the FlexNav Delivery System are intended to improve deliverability and deployment accuracy and enhance overall ease of use.

15.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

Adverse events potentially associated with the use of transcatheter valves and their potential complications are documented in the Instructions for Use. Also kindly refer to Appendix IX. for foreseeable adverse events with rates of occurrence.

15.3 Residual Risks Associated with the Device Under Investigation, as Identified in the Risk Management Report / Risk Analysis Report

Risk analyses of the study devices have been performed in accordance with the Risk Analysis Plan, Failure Mode Effect Analysis (FMEA), and Hazard Analysis (HA) to systemically identify potential hazards associated with the design and use of these devices. Based upon bench testing and prior Abbott sponsored clinical study data, all risks have been identified and mitigated as far as possible through application of appropriate controls and inspections and determined to be within acceptable levels.

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 IX) 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.

15.4 Risks Associated with Participation in this Clinical Investigation

Protocol-required assessments are summarized in Table 2. Possible risks and discomforts associated with participation in the study will be similar to those associated with any routine transcatheter aortic valve implantation procedure and related follow-up procedures.

Study-specific assessments that are not considered standard of care include echocardiogram exam during scheduled follow-up visits (excluding at discharge). There are no know clinical risks associated with echocardiogram; however, a subject may experience mild discomfort from the pressure of the transducer during the exam.

15.5 Possible Interactions with Protocol-Required Concomitant Medications

All medications at baseline and post -procedure are administered per the current guidelines and are standard of care. Although there are no protocol-required medications being used as part of this study, post-procedure antiplatelet/anticoagulation therapy and prophylactic antibiotics for endocarditis as per the standard care are highly recommended. The risks associated with these medications are described in the drug summary of product characteristics.

There are no known interactions of the Portico valve or Navitor valve with concomitant medical treatment. Patients experiencing an adverse event shall be treated by their treating physician or per the standard of care at the investigation center.

15.6 Steps Taken to Control or Mitigate Risks

Actions to control or mitigate risks at the clinical investigation center level will include the selection of qualified and experienced investigators and implant center personnel, intensive device training for investigators, and strict adherence to the CIP. Data collected during this clinical study will include, but not be limited to, echocardiography, ECG, and adverse event assessment. In addition, investigators shall be actively involved in the follow-up of patients implanted with a Portico or Navitor or other commercially available transcatheter valve.

Risks shall be minimized by careful assessment of each patient prior to, during, and after implant of the Portico or Navitor Valve.

As the Sponsor, Abbott has taken up study specific insurance in accordance with the requirements of the applicable local laws. An appropriate Abbott country representative will be utilized to understand the requirements for the type of insurance that will be provided for patients, and such information will be incorporated into the center informed consent, as applicable.

15.7 Risk to Benefit Rationale

The risks associated with the use of the Portico valve or Navitor valve, FlexNav transfemoral delivery system and valve loading system are anticipated to be comparable to those associated with the use of other commercially available transcatheter valve and delivery systems. Patients participating in this study are indicated for a TAVI procedure as part of their standard medical management and are subject to the risks associated with these devices.

15.8 References:

1. Osnabrugge RL, Mylotte D, Head SJ, Van Mieghem NM, Nkomo VT, LeReun CM, Bogers AJ, Piazza N, Kappetein AP. Aortic stenosis in the elderly: Disease prevalence and number of candidates for transcatheter aortic valve replacement: A meta-analysis and modeling study. Journal of the American College of Cardiology. 2013;62:1002-1012
2. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T, Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN, Wang D, Pocock SJ, Investigators PT. Transcatheter versus surgical aortic-valve replacement in high-risk patients. The New England journal of medicine. 2011;364:2187-2198
3. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN, Wang D, Pocock S, Investigators PT. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. The New England journal of medicine. 2010;363:1597-1607
4. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, III, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, III, Thomas JD, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Creager MA, Curtis LH, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen W-K, Stevenson WG, Yancy CW. 2014 aha/acc guideline for the management of patients with valvular heart disease. The Journal of Thoracic and Cardiovascular Surgery.148:e1-e132
5. Medical Device Rules, (2017), Government of India, 31st Jan, 2017.
6. New drugs and Clinical trials rules 2019, Government of India, 19th March 2019.
7. Guidance Document Materiovigilance Programme of India (MvPI) (Reporting Medical Device Adverse Event

APPENDIX I: ABBREVIATIONS AND ACRONYMS

Abbreviation	Term
ADE	Adverse Device Effect
AE	Adverse Event
AHA	American Heart Association
AS	Aortic Stenosis
AVA	Aortic Valve Area
AVR	Aortic Valve Replacement
BARC	Bleeding Academic Research Consortium
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CTA	Clinical Trial Agreement
eCRF	Electronic Case Report Form
EC	Ethics Committee
ECG	Electrocardiogram
Echo	Echocardiography
EDC	Electronic Data Capture
EF	Ejection Fraction
EOA	Effective Orifice Area
EU	European Union
GCP	Good Clinical Practice
ICF	Informed Consent Form
IFU	Instructions For Use
IRB	Institutional Review Board
Kg	Kilogram
LBBB	Left Bundle Branch Block
MI	Myocardial Infarction
mRS	Modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PI	Principal Investigator
QoL	Quality of Life
PVL	Paravalvular Leak
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAVR	Surgical Aortic Valve Replacement
STS	Society of Thoracic Surgeons
TAVI	Transcatheter Aortic Valve Implantation
TAVR	Transcatheter Aortic Valve Replacement

TEE	Transesophageal Echocardiogram
TTE	Transthoracic Echocardiogram
UADE	Unanticipated Adverse Device Effect
VARC-2	Valve Academic Research Consortium 2
VARC-3	Valve Academic Research Consortium 3

APPENDIX II: DEFINITIONS

VARC-2 DEFINITIONS:

Cardiovascular Mortality **(VARC-2)**	**Any of the following criteria:** • Death due to proximate cardiac cause (e.g., myocardial infarction, cardiac tamponade, worsening heart failure) • Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease • All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure • All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related adverse events • Sudden or unwitnessed death • Death of unknown cause
Myocardial Infarction **(VARC-2)**	**Periprocedural MI (less than or equal to ≤ 72 h after the index procedure)** New ischemic symptoms (eg, chest pain or shortness of breath), or new ischemic signs (eg, ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, or imaging evidence of new loss of viable myocardium or new wall motion abnormality), ***AND*** Elevated cardiac biomarkers within 72 h after the index procedure consisting of at least 1 sample postprocedure with a peak value exceeding 15x upper reference limit (troponin) or 5x for CK-MB. If cardiac biomarkers are increased at baseline (>99th percentile), a further increase of at least 50% postprocedure is required AND the peak value must exceed the previously stated limit. **Spontaneous MI (greater than 72 h after the index procedure)** Any 1 of the following criteria: • Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least 1 value above the 99th percentile URL, together with evidence of myocardial ischemia with at least 1 of the following: o Symptoms of ischaemia o ECG changes indicative of new ischemia [new ST-T changes or new Left Bundle Branch Block] o New pathological Q waves in at least 2 contiguous leads o Imaging evidence of new loss of viable myocardium or new wall motion abnormality

	• Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST-segment elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/ or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. • Pathological findings of an acute myocardial infarction.
Stroke **(VARC-2)**	a. Stroke: Stroke is an acute episode of focal or global neurological dysfunction cause by the brain, spinal cord or retinal vascular injury as a result of hemorrhage or infarction. *Subclassifications of stroke:* Ischemic Stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Hemorrhagic Stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage. A stroke may be classified as 'undetermined' if there is insufficient information to allow the classification as ischemic or hemorrhagic. *Stroke Disability (consistent with VARC2 Definitions):* Severity i. Disabling: A disabling stroke is one that results (at 90 days after stroke onset) in an mRS score of ≥2 and an increase in ≥1mRS category from an individual's prestroke baseline ii. Nondisabling: A nondisabling stroke is one that results (at 90 days after stroke onset) in an mRS score of <2 or that does not result in an increase in >1 mRS category from an individual's prestroke baseline b. Cerebral Infarction: Evidence of brain cell death from imaging studies or pathological examination. If there are clinical symptoms, then it is a stroke; otherwise, it is an asymptomatic cerebral infarction. c. Transient Ischemic Attack (TIA): A transient episode of focal neurological dysfunction caused by the brain, spinal cord, or retinal ischemia, without acute infarction. The difference between TIA and ischemic stroke is the presence of tissue damage on neuro-imaging studies or new sensory-motor deficit persisting > 24 hours. d. Encephalopathy: Altered mental state (e.g., seizures, delirium, confusion, hallucinations, dementia, coma, psychiatric episode). e. Intracranial Hemorrhage: Collection of blood between the brain and skull. Subcategorized as epidural, subdural, and subarachnoid bleeds.
Bleeding **(VARC-2)**	**Life-threatening or disabling bleeding** • Fatal bleeding (BARC type 5) **OR** • Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) **OR**

Clinical Investigation Plan

	• Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) **OR** • Overt source of bleeding with drop in hemoglobin of greater than or equal to 5 g/dl or whole blood or packed red blood cells (RBCs) transfusion greater than or equal to 4 U (BARC type 3b). *Given 1 U of packed RBC typically will raise blood hemoglobin concentration by 1 g/dL, an estimated decrease in hemoglobin will be calculated.* **Major bleeding (BARC type 3a)** • Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery **AND** • Does not meet criteria of life-threatening or disabling bleeding **Minor bleeding (BARC type 2 or 3a, depending on the severity)** • Any bleeding worthy of clinical mention (eg, access site hematoma) that does not qualify as life-threatening, disabling, or major
Acute Kidney Injury *(AKIN Classification)* **(VARC-2)**	The increase in creatinine must occur within 48 hours **Stage 1** Increase in serum creatinine to 150% to 199% (1.5 to 1.99 X increase compared with baseline) or increase of greater than or equal to 0.3 mg/dL (26.4 mmol/L) or Urine output <0.5 mL/kg per hour for >6 but <12 hours **Stage 2** Increase in serum creatinine to 200% to 299% (2.0 to 2.99 X increase compared with baseline) or Urine output <0.5 mL/kg per hour for >12 but <24 hours **Stage 3** Increase in serum creatinine to greater than or equal to 300% (3 X increase compared with baseline) or serum creatinine of ≥ 4.0 mg/dL (354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L)or Urine output <0.3 mL/kg per hour for ≥24 hours or anuria for ≥12 hours. *Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.*
Vascular Access Site and Access-Related Complications (VARC-2)	**Major vascular complications** • Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm or • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) ***leading to*** death, life-threatening or major bleeding*, visceral ischaemia or neurological impairment or • Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage or • The use of unplanned endovascular or surgical intervention ***associated*** with death, major bleeding, visceral ischaemia or neurological impairment or

Clinical Investigation Plan

	• Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram or • Surgery for access site-related nerve injury or • Permanent access site-related nerve injury **Minor vascular complications** • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula, pseudoaneuysms, hematomas, percutaneous closure device failure) ***not leading to*** death, life-threatening or major bleeding*, visceral ischaemia or neurological impairment or • Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage or • Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication or • Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft) or **Percutaneous closure device failure** Failure of a closure device to achieve haemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)
Device Success	The composite endpoint of device success is defined by VARC as: • Absence of procedural mortality • Correct positioning of a single prosthetic heart valve into the proper anatomical location AND • Intended performance of the prosthetic heart valve (no prosthesis-patient mismatch and mean aortic valve gradient <20 mm Hg or peak velocity <3 m/s, AND no moderate or severe prosthetic valve regurgitation For the descriptive endpoint of this study, implant success will be defined as: • Absence of procedural mortality • Correct positioning of a single Portico or Navitor prosthetic heart valve into the proper anatomical location
Valve malpositioning	**Valve migration** • After initial correct positioning, the valve prosthesis moves upwards or downwards, within the aortic annulus from its initial position, with or without consequences **Valve embolization** • The valve prosthesis moves during or after deployment such that it loses contact with the aortic annulus

Clinical Investigation Plan

Conversion to open surgery	Conversion to open sternotomy during the TAVI procedure secondary to any procedure-related complications			
Coronary Obstruction	Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary ostium, either by the valve prosthesis itself, the native leaflets, calcifications, or dissection, occurring during or after the TAVI procedure			
TAV-in-TAV deployment	An additional valve prosthesis is implanted within a previously implanted prosthesis because of suboptimal device position and/or function, during or after the index procedure			
Prosthetic Valve Stenosis Criteria ***In conditions of normal or near normal stroke volume (50–70 ml).*** **(VARC-2)**	**Parameter**	**Normal**	**Mild Stenosis**	**Moderate/severe Stenosis**
	Peak velocity (m/s)	less than 3	3–4	greater than 4
	Mean gradient (mm Hg)	less than 20	20–40	greater than 40
	Doppler velocity index	greater than 0.35	0.35–0.25	less than 0.25
	Effective orifice area (cm^2) §	greater than 1.1*	1.1–0.8	less than 0.80
	Effective orifice area (cm^2) β	greater than 0.9*	0.9 – 0.6	Less than 0.60
Prosthetic Valve Regurgitation Criteria (Central and Paravalvular) **(VARC-2)**	**Parameter**	**Mild**	**Moderate**	**Severe**
	Valve structure and motion	Usually normal	Usually abnormal	Usually abnormal
	Left ventricular size	Normal	Normal/mildly dilated	Dilated
	Doppler parameters ***(qualitative or semiquantitative)***			
	Jet width in central jets (% LVO diameter): color	Narrow (less than or equal to 25%)	Intermediate (26%–64%)	Large (greater than or equal to 65%)
	Jet density: CW Doppler	Incomplete or faint	Dense	Dense

* Effective orifice area (EOA) used in this protocol is 1.0 cm^2 for Portico valve of 23 mm diameter.
§ BSA ≥ 1.6 cm^2
β BSA < 1.6 cm^2

	Jet deceleration rate (PHT, ms): CW Doppler	Slow (greater than 500)	Variable (200–500)	Steep (less than 200)
	LV outflow vs. pulmonary flow: PW Doppler	Slightly increased	Intermediate	Greatly increased
	Diastolic flow reversal in the descending aorta (semi-quantitative parameters)			
	PW Doppler	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic
	Circumferential extent of paraprosthetic AR	less than 10%	10–29%	greater than or equal 30%
	Doppler parameters *(quantitative)*			
	Regurgitant volume (ml/beat)	less than 30%	30–59%	greater than or equal 60%
	Regurgitant fraction	less than 30%	30–49%	greater than or equal 50%

VARC-3 Definitions:

Acute Kidney Injury (AKI) VARC-3	Stage 1: At least one of the following: • Increase in serum creatinine ≥150-200% (≥1.5-2.0x increase) within 7 days compared with baseline • Increase of ≥0.3mg/dl (≥26.4 µmol/L) within 48 h of the index procedure Stage 2: • Increase in serum creatinine >200-300% (>2.0-3.0x increase) within 7 days compared with baseline Stage 3: At least one of the following: • Increase in serum creatinine > 300% (> 3.0x increase) within 7 days compared with baseline • Serum creatinine ≥4.0 mg/dl (≥354 µmol/L) with an acute in-crease of ≥0.5 mg/dl (≥44 µmol/L) Stage 4: • AKI requiring new temporary or permanent renal replacement therapy Given practical challenges with the use of urine output criteria in daily practice, AKI should be solely defined based on serum creatinine values. Acute kidney

	in-jury defined by urine output using the following criteria might be used in the con-text of a dedicated AKI study: AKI Stage 1: Urine output <0.5 mUkg/h for >:6 but <12 h; AKI stage 2: Urine output <0.5 mUkg/h for >:12 but <24 h; AKI stage 3: Urine output <0.3 mUkg/h for >:24 h or anuria for >: 12 h.
Bleeding and Transfusions[a] (VARC-3)	Overt bleeding that fulfills one of the following criteria: Type 1: • Overt bleeding that does not require surgical or percutaneous intervention, but does require medical intervention by a health care professional, leading to hospitalization, an increased level of care, or medical evaluation (BARC 2) • Overt bleeding that requires a transfusion of 1 unit of whole blood/red blood cells< (BARC 3a). Type 2: • Overt bleeding that requires a transfusion of 2-4 units of whole blood/red blood cells< (BARC 3a) • Overt bleeding associated with a haemoglobin drop of >3 g/dl (>1.86 mmoVL) but <5 g/d (<3.1 mmoVL) (BARC 3a). Type 3: • Overt bleeding in a critical organ, such as intracranial, intraspinal, intraocular, pericardia! (associated with haemodynamic compromise/tamponade and necessitating intervention), or intramuscular with compartment syndrome (BARC 3b, BARC 3c) • Overt bleeding causing hypovolemic shock or severe hypotension (systolic blood pressure <90 mmHg lasting > 30 min and not responding to volume resuscitation) or requiring vasopressors or surgery (BARC 3b) • Overt bleeding requiring reoperation, surgical exploration, or re-intervention for the purpose of controlling bleeding (BARC 3b, BARC 4) • Post-thoracotomy chest tube output ≥2 L within a 24-h period (BARC 4) • Overt bleeding requiring a transfusion of ≥5 units of whole blood/red blood cells (BARC 3a)[c] • Overt bleeding associated with a haemoglobin drop ≥5 g/dl (≥3.1 mmol/L) (BARC 3b). Type 4: • Overt bleeding leading to death. Should be classified as: • Probable: Clinical suspicion (BARC 5a) • Definite: Confirmed by autopsy or imaging (BARC 5b)

Clinical Investigation Plan

	[a]The timing, indication, and number of transfused blood products should be collected and reported specifically during the index procedure, during the entire index hospitaliza-tion, and during follow-up after discharge, whether or not overt bleeding is identified. [b]Overt bleeding is defined as any clinically obvious source of bleeding or bleeding source identified after appropriate investigation and diagnostic testing (e.g. imaging). Any procedural blood loss should be considered overt bleeding. [c]Total number of transfusions should be reported separately for (i) within 48 h of the index procedure, (ii) the total duration of the index procedure hospitalization, and (iii) during any subsequent repeat hospitalization.
Mortality VARC-3 ➢ All-cause mortality	
➢ Cardiovascular	Death meeting one of the following criteria: • Related to heart failure, cardiogenic shock, bioprosthetic valve dysfunction, myocardial infarction, stroke, thromboembolism, bleeding, tamponade, vascular complication, arrhythmia or conduction system disturbances, cardiovascular infection (e.g. mediastinitis, endocarditis), or other clear cardiovascular cause • Intra-procedural death • Sudden death • Death of unknown cause
➢ Non-cardiovascular	Death clearly related to a non-cardiovascular cause: such as re-spiratory failure not related to heart failure (e.g. pneumonia), renal failure, liver failure, infection (e.g. urosepsis), cancer, trauma, and suicide.
Myocardial Infarction (VARC-3)	Type 1: • Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL with at least one of the following: ➢ Symptoms of acute ischaemia ➢ New ischaemic ECG changes (new ST-segment or T-wave changes or new LBBB) ➢ New pathologic Q-waves in 2 contiguous leads ➢ Imaging evidence of a new loss of viable myocardium or new wall motion abnormality in a pattern consistent with an ischaemic etiology 0 Identification of a coronary thrombus by angiography or autopsy • Post-mortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large circumscribed area of

	necrosis with or without intramyocardial haemorrhage, meets the type 1 MI criteria regardless of cTn values Type 2: • Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following: ➢ Symptoms of ischaemia ➢ ECG changes indicative of new ischaemia (new ST-segment or T-wave changes or new LBBB) ➢ New pathologic Q-waves in ≥2 contiguous leads ➢ Imaging evidence of a new loss of viable myocardium or new wall motion abnormality Type 3: • Patients who suffer cardiac death, with symptoms suggestive of myocardial ischaemia accompanied by presumed new ischaemic ECG changes or ventricular fibrillation but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination. Type 4A: • In patients with normal baseline CK-MB: The peak CK-MB measured within 48 h of the procedure ≥10x the local laboratory ULN or CK- MB ≥5 x ULN with one or more of the following: ➢ New pathologic Q-waves in ≥2 contiguous leads ➢ New persistent LBBB[c] ➢ Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch ➢ Substantial new loss of viable myocardium on imaging related to the procedure • In the absence of CK-MB measurements and a normal baseline c T n, a c T n (I or T) level measured within 48 h of the procedure rises to ≥70x the local laboratory ULN or ≥35 x ULN with one or more of the following: ➢ New pathologic Q-waves in ≥2 contiguous leads ➢ New persistent LBBB[c] ➢ Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch ➢ Substantial new loss of viable myocardium on imaging related to the procedure • In patients with elevated baseline CK.MB (or cTn): The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above

	from the most recent pre-procedure level plus new ECG changes as described. Type 4B: • Stent thrombosis as documented by angiography or autopsy using the same criteria utilized for type 1 MI. • Acute: 0 to 24 h • Subacute: >24 h to 30 days • Late: > 30 days to 1 year • Very late: >1 year after stent implantation Type 5: • In patients with normal baseline CK-MB: The peak CK-MB measured within 48 h of the procedure ≥10x the local laboratory ULN or CK-MB ≥5 x ULN with one or more of the following: ➢ New pathologic Q-waves in ≥2 contiguous leads ➢ New persistent LBBB ➢ Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch ➢ Substantial new loss of viable myocardium on imaging related to the procedure • In the absence of CK-MB measurements and a normal baseline c T n, a c T n (I or T) level measured within 48 h of the procedure rises to ≥70x the local laboratory ULN or ≥35 x ULN with one or more of the following: • New pathologic Q-waves in c2 contiguous leads • New persistent LBBB' • Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch • Substantial new loss of viable myocardium on imaging related to the procedure • In patients with elevated baseline CK-MB (or cTn): The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level plus new ECG changes described. The use of high-sensitivity (hs}-troponins is recommended for diagnosis of spontaneous MI, but has not been studied for assessment of periprocedural MI. Standard troponin assays are therefore recommended for evaluation of periprocedural MI. Periprocedural biomarker elevation >ULN not meeting the criteria for MI should be categorized as 'myocardial injury not meeting MI criteria'. CK-MB, creatine kinase-MB; cTn, cardiac troponin; ECG, electrocardiogram; LBBB, left bundle branch block; MI, myocardial infarction;

	SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; ULN, upper limit of normal; URL, upper reference limit.
Neurologic Events (VARC-3)	Ischemic Stroke: • Acute onset of focal neurological signs or symptoms conforming to a focal or multifocal vascular territory within the brain, spinal cord, or retina (NeuroARC Type 1a or 1aH) and fulfilling one of the following criteria: ➢ -Signs or symptoms lasting ≥24 h or until death, with pathology or neuroimaging evidence of CNS infarction, or absence of other apparent causes ➢ -Symptoms lasting <24 h, with pathology or neuroimaging confirmation of CNS infarction in the corresponding vascular territory.[c] Haemorrhagic Stroke: • Acute onset of neurological signs or symptoms due to intracranial bleeding from intracerebral or subarachnoid haemorrhage not due to trauma (NeuroARC Types 1b or 1c). Stroke, not otherwise specified: • Acute onset of neurological signs or symptoms persisting ≥24 h or until death but without sufficient neuroimaging or pathology evidence to be classified (NeuroARC Type 1 d). **Covert CNS infarction[c] or haemorrhage** • Neuroimaging or pathological evidence of CNS focal or multifocal ischaemia (NeuroARC Type 2a or 2aH) or haemorrhage (NeuroARC 2b) without acute neurological symptoms consistent with the lesion or bleeding location. **Neurologic dysfunction (acutely symptomatic) without CNS injury (NeuroARC Type 3):** • **TIA:** Transient focal neurological signs or symptoms lasting <24 h presumed to be due to focal brain, spinal cord, or retinal ischaemia, but without evidence of acute infarction by neuroimaging or pathology, or with no imaging performed (NeuroARC Type 3a or Type 3aH). • **Delirium without CNS injury:** Transient non-focal neurological signs or symptoms, typically of variable duration, without evidence of infarction on neuroimaging or pathology, or with no imaging performed (NeuroARC Type 3b). Acute Stroke Severity[d]: • Mild neurological dysfunction: NIHSS 0-5 • Moderate neurological dysfunction: NIHSS 6-14

	• Severe neurological dysfunction: NIHSS ≥15 Stroke Disability[e]: • Fatal Stroke: death resulting from a stroke • Stroke with disability: mRS score of ≥2 at 90 days[e] and increase of ≥1 from pre-stroke baseline • Stroke without disability: mRS score of 0 (no symptoms) or 1 (able to carry out all usual duties and activities) at 90 days• or no increase in mRS category from pre-stroke baseline. CNS, central nervous system; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; TIA, transient ischaemic attack. [a]in general, all studies should report at a minimum all stroke and stroke disability. [b]Includes haemorrhagic conversions when ischaemic infarction is the primary mechanism. [c]When CNS infarction location does not match transient (<24h) symptoms, the event should be classified as covert CNS infarction (NeuroARC Type 2a) and TIA (NeuroARC Type 3a), not as an ischaemic stroke. [d]Severity assessment should be performed at the time of stroke diagnosis using the NIHSS. [e]Disability assessment using the mRS should be performed between 30 and 90 days with 90 days being optimal.
Vascular and Access-Related Complications (VARC-3)	Major Vascular Complications One of the following: • Aortic dissection or aortic rupture Vascular (arterial or venous) injury (perforation, rupture, dissection, stenosis, ischaemia, arterial or venous thrombosis including pulmonary em-bolism, arteriovenous fistula, pseudoaneurysm, haematoma, retroperitoneal haematoma, infection) or compartment syndrome resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment • Distal embolization (non-cerebral) from a vascular source resulting in death, amputation, limb or visceral ischaemia, or irreversible end-organ damage • Unplanned endovascular or surgical intervention resulting in death, VARC type ≥2 bleeding. limb or visceral ischaemia, or irreversible neurologic impairment • Closure device failure[c] resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment Minor Vascular Complications

	One of the following: • Vascular (arterial or venous) injury (perforation, rupture, dissection, stenosis, ischaemia, arterial or venous thrombosis including pulmonary em-bolism, arteriovenous fistula, pseudoaneurysm, haematoma, retroperitoneal haematoma, infection) not resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment • Distal embolization treated with embolectomy and/or thrombectomy, not resulting in death, amputation, limb or visceral ischaemia, or irreversible end-organ damage • Any unplanned endovascular or surgical intervention, ultra-sound guided compression, or thrombin injection, not resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment • Closure device failure[c] not resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment Major Access-Related Non-Vascular Complications One of the following: • Non-vascular structure, non-cardiac structured perforation, injury, or infection resulting in death, VARC type ≥2 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention • Non-vascular access site (e.g. trans-apical left ventricular) perforation, injury, or infection resulting in death, VARC type ≥2 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention Minor Access-Related Non-Vascular Complications One of the following: • Non-vascular structure, non-cardiac structured perforation, injury, or infection not resulting in death, VARC type ≥2, irreversible nerve injury, or requiring unplanned surgery or percutaneous intervention • Non-vascular access site (e.g. trans-apical left ventricular) perforation, injury, or infection not resulting in death, VARC type ≥2 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention [a]Any complication related to the device insertion. delivery, and complete removal of all its components (delivery catheter, sheath, guide wire). excluding the actual implantation in the heart. [b]Any device-related vascular access site and any other accessory access sites (venous or arterial) used during procedure.

Clinical Investigation Plan

	[c]A failure to achieve haemostasis at the access site, resulting in alternative treatment (other than manual compression or planned adjunctive endovascular balloon inflation). [d]Including, but not limited to, the lung (e.g. pneumothorax), direct nerve injury, access site or wound infection, mediastinitis, sternal instability, wound dehiscence, and inability to close the chest.

NEW YORK HEART ASSOCIATION CLASSIFICATION (NYHA CLASS)

Class I	Patients with cardiac disease but without resulting limitations of physical activity.
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. Patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnoea, or anginal pain.
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. Patients are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation dyspnoea, or anginal pain.
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

APPENDIX III: CLINICAL INVESTIGATIONAL PLAN SUMMARY

CIP Name and Number	[redacted]
Title	Portico & Navitor India Clinical Trial
Objective(s)	To characterize the procedural safety and device performance of the Portico valve, Navitor valve and FlexNav delivery system and loading system, and Navitor loading system to treat patients with severe aortic stenosis.
Device Under Investigation	Portico Valve, Navitor Valve, FlexNav delivery system and loading system, and Navitor loading system
Study Design and Number of Subjects Required for Inclusion in CIP	Prospective, multi-center phase IV clinical trial of [redacted] patients [redacted] Portico valve and [redacted] determined to be eligible to receive study devices per the current indications for use.
Clinical Endpoint(s)	The following descriptive endpoints are reported using summary statistics and no hypothesis tests will be performed. Descriptive Endpoint(s) or Additional Data 1. Evaluation of the VARC-2 and VARC-3 defined event rates at 30 days from the index procedure (Implant) • All-cause Mortality • Cardiovascular Mortality • Myocardial Infarction • Stroke (including disabling and non-disabling) • Bleeding (life-threatening, major, minor) • Acute kidney injury • Vascular access site and access-related complications (major and minor) • Coronary obstruction • Permanent pacemaker insertion 2. Delivery profile characteristics such as access vessel diameter, sheath utilization and sheath size 3. Implant success defined as: • Absence of procedural mortality • Correct positioning of a single Portico or Navitor prosthetic heart valve into the proper anatomical location

Clinical Investigation Plan

	• No conversion to open surgery 4. Echocardiographic assessment of valve performance at 30 days compared to baseline for the subjects with Portico or Navitor valve implanted • Mean gradient • Effective orifice area (EOA) • Paravalvular leak (PVL) assessed per VARC-2 ▪ Three-class grading scheme: none/trace, mild, moderate or severe (Core Lab adjudicated echocardiographic measures will be utilized for evaluating valve hemodynamic performance at 30 days) 5. Evaluation of the VARC-2 and VARC-3 defined event rates beyond 30 days through 9-months from the index procedure (implant) • All-cause Mortality • Stroke (including disabling and non-disabling) 6. Clinical improvement from baseline to 30 days and baseline to 9-months for the subjects with Portico or Navitor valve implanted assessed by: • New York Heart Association (NYHA) functional class • Quality of Life (QoL) questionnaire (EQ5D-5L)
Subject Follow-up	Subjects will undergo prospective enrollment with baseline data collection prior to receiving their Portico or Navitor valve (up to a maximum of 180 days prior to the valve implant procedure). The implant procedure will be conducted per standard protocol established at each center. After the procedure, subjects will undergo a pre-discharge visit at the time of hospital discharge or within seven days of the index procedure, whichever occurs first. Subjects will return to the participating institution for a 30-day and 9-month follow-up visit.
Inclusion Criteria	1. Subject must provide written informed consent prior to any clinical investigation-related procedure. 2. Are ≥60 years of age in host country and have been identified as a candidate for a Portico or Navitor valve implant 3. Subjects must have a Society of Thoracic Surgeons (STS) score of ≥7% OR documented heart team agreement of high

	risk for surgical aortic valve replacement due to frailty or co-morbidities not captured by the STS score
Exclusion Criteria	1. Have tested positive for the COVID-19 virus at any time AND currently have residual signs or symptoms associated with the COVID-19 virus (eg. evidence of thrombosis, damaged/inflamed heart muscle, damaged/inflamed lung tissue, etc.) 2. Have sepsis, including active endocarditis 3. Have any evidence of left ventricular or atrial thrombus 4. Have vascular conditions (i.e. caliber, stenosis, tortuosity, or severe calcification) that make insertion and endovascular access to the aortic valve improbable 5. Have a non-calcified aortic annulus 6. Have congenital bicuspid or unicuspid leaflet configuration 7. Are unable to tolerate antiplatelet/anticoagulant therapy 8. Are pregnant at the time of signing informed consent 9. Are currently participating in a drug or device study that may impact this study (unless prior sponsor approval for co-enrollment is granted)

APPENDIX IV: SITE CONTACT INFORMATION

Contact information for each participating clinical site is available under separate cover by contacting the Sponsor at:

St. Jude Medical India Pvt. Ltd, (Abbott Structural Heart)

[redacted]

APPENDIX V: SURGICAL RISK ASSESSMENT TOOLS

Risk calculations conducted as part of standard of care while determining that the patient is a high surgical risk for conventional open-heart surgery, will be noted on the applicable CRF.

1. The Society of Thoracic Surgeons' (STS) risk calculation tool (short-term risk calculator as of Nov. 15, 2018)
   https://www.sts.org/resources/risk-calculator

APPENDIX VI: EQ5D-5L QUALITY OF LIFE QUESTIONNAIRE

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about ❑
- I have slight problems in walking about ❑
- I have moderate problems in walking about ❑
- I have severe problems in walking about ❑
- I am unable to walk about ❑

SELF-CARE

- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT

- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑

I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

ANXIETY / DEPRESSION

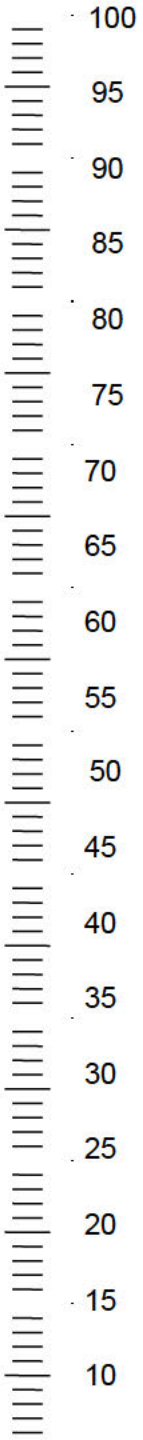
I am not anxious or depressed	❑
I am slightly anxious or depressed	❑
I am moderately anxious or depressed	❑
I am severely anxious or depressed	❑
I am extremely anxious or depressed	❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

Clinical Investigation Plan

The best healthyou can imagine

YOUR HEALTH TODAY = [ ]



Clinical Investigation Plan

The worst healthyou can imagine

APPENDIX VII: FRAILTY ASSESSMENT

The Frailty Index Data Collection Form will be used as an assessment tool to determine if frailty is a risk factor for subjects prior to enrollment. This assessment will be performed after the informed consent has been obtained and prior to procedure. The assessment can be administered by either an investigator or research coordinator.
The frailty assessment consists of three evaluations:

1. Katz Index of Independence in Activities of Daily Living
2. Grip Strength
3. 5 Meter walk test

1. Katz Index of Independence in Activities of Daily Living Activities

Points (1 or 0)	Independence (1 Point) NO supervision, direction or personal assistance	Dependence (0 Points) WITH supervision, direction, personal assistance or total care
BATHING Points: _____	(1 POINT) Bathes self completely or needs help in bathing only a single part of the body such as the back, genital area or disabled extremity	(0 POINTS) Need help with bathing more than one part of the body, getting in or out of the tub or shower. Requires total bathing
DRESSING Points: _____	(1 POINT) Get clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes.	(0 POINTS) Needs help with dressing self or needs to be completely dressed.
TOILETING Points: _____	(1 POINT) Goes to toilet, gets on and off, arranges clothes, cleans genital area without help.	(0 POINTS) Needs help transferring to the toilet, cleaning self or uses bedpan or commode.
TRANSFERRING Points: _____	(1 POINT) Moves in and out of bed or chair unassisted. Mechanical transfer aids are acceptable.	(0 POINTS)Needs help in moving from bed to chair or requires a complete transfer.
CONTINENCE Points: _____	(1 POINT) Exercises complete self control over urination and defecation.	(0 POINTS) Is partially or totally incontinent of bowel or bladder.
FEEDING Points: _____	(1 POINT) Gets food from plate into mouth without help. Preparation of food may be done by another person.	(0 POINTS) Needs partial or total help with feeding or requires parenteral feeding.
TOTAL Points:_____		

2. Grip strength

Subjects elbow should be at a 90 degree angle without arm supported or resting on table or against chest wall. Each grasp should be completed with the dynamometer in the dominant hand.

Grasp 1_____ Grasp 2_____Grasp 3_____ Average_____

Grip Strength, stratified by gender and body mass index (BMI) quartiles

Gender	BMI	Cutoff for grip strength (Kg) criterion for frailty
Male		
	≤24	**≤29**
	24.1–26	**≤30**
	26.1–28	**≤31**
	>28	**≤32**
Female		
	≤ 23	**≤17**
	23.1–26	**≤17.3**
	26.1–29	**≤18**
	>29	**≤21**

3. 5 Meter Walk Time

This examination should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The walking course must be 5 meters in length (15 feet). The time to walk this distance is to be recorded.

_____seconds

Walk Time, stratified by gender and height

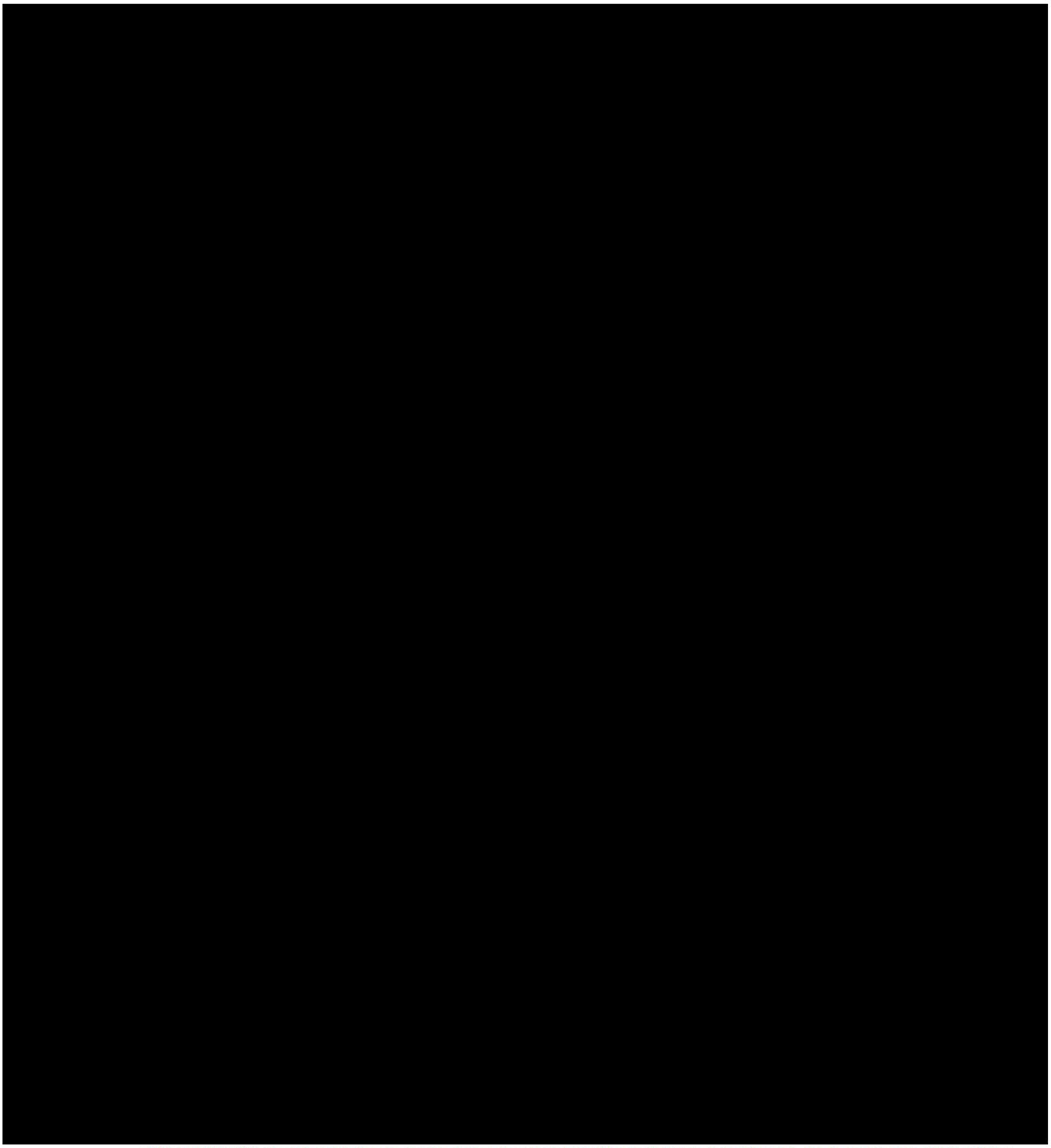
Gender	Height	Cutoff values for Time to Walk 5 meters criterion for frailty
Male		
	≤ 173 cm	**≥ 7sec**
	> 173 cm	**≥ 6sec**
Female		
	≤159 cm	**≥ 7sec**
	> 159 cm	**≥ 6sec**

APPENDIX VIII: LITERATURE REVIEW

Please refer to the Portico Valve or Navitor Valve Instructions for Use (IFU) for a relevant overview of the device.

APPENDIX IX: RATES OF FORSEEABLE ADVERSE EVENTS

[redacted]



Clinical Investigation Plan

APPENDIX X: LABELS

Refer to the Instructions for Use (IFU) for labels used for the Portico device, Navitor device and FlexNav systems and Navitor loading system.

APPENDIX XI: CASE REPORT FORMS

Final draft of Electronic Case Report Forms (CRFs) will be sent under a separate cover.

APPENDIX XII: INFORMED CONSENT FORM

A template informed consent form (ICF) will be provided under a separate cover.

APPENDIX XIII: MONITORING PLAN

A copy of the Monitoring Plan can be obtained upon request from the Sponsor Clinical Project Manager for the clinical investigation.

APPENDIX XIV: UNDERTAKING BY THE INVESTIGATOR

Clinical Investigation Plan

[redacted]

Clinical Investigation Plan

[redacted]

Clinical Investigation Plan

APPENDIX XV: REVISION HISTORY

This CIP may be amended as appropriate by the Sponsor. Rationale will be included with each amended version in the revision history table below. The version number and date of amendments will be documented.

IRB/EC and relevant Regulatory Authorities, if applicable, will be notified of amendments to the CIP.

Amendment Number	Version	Date	Details	Rationale
[redacted]				

Clinical Investigation Plan

Amendment Number	Version	Date	Details	Rationale
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Clinical Investigation Plan

Amendment Number	Version	Date	Details	Rationale
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

APPENDIX XVI: EXCEPTIONS FROM ISO 14155 COMPLIANCE

Minimal exceptions to ISO 14155:2020 compliance are expected according to Annex I of the standard. These exceptions do not affect the safety and protection of the clinical investigation subjects and do not compromise data quality and security.

- This clinical investigation provides market approved devices, which will be used within their intended purpose, thus clinical investigation labelling will not be applied, a separate investigator Brochure will not be created, and clinical device accountability will not be set up.
- The study will not be submitted for review to the Competent Authority, only standard vigilance reporting will be observed. Local and/or regional requirements might be still applicable and will be tracked in a study specific Safety Plan.
- Financial disclosures will not be collected from the Investigators.