NCT Number: NCT03752866
The **CONFIDENCE** Registry **CON**trolled delivery **F**or **I**mprove**D** outcom**E**s with cli**N**i**C**al **E**vidence
CRD_909
Study Document No: SJM-CIP-CL1003491
Version B – Amendment 1
Date: 08-Nov-19
Clinical Investigation Plan (CIP)

Sponsor

Abbott
5050 Nathan Lane
Plymouth, MN 55442
USA

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1 Introduction

This document is a clinical investigation plan (CIP) for the CONFIDENCE (**CON**trolled delivery **F**or **I**mprove**D** outcom**E**s with cli**N**i**C**al **E**vidence) Registry. This registry is intended to characterize clinical safety and device performance from experienced TAVI centers in Europe that use the Portico™ valve, delivery system and loading system to treat patients with severe aortic stenosis. This registry is sponsored by Abbott.

This registry will be conducted in accordance with this CIP. All parties involved in the conduct of the clinical study will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

2 Background and Justification for Registry

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 (formerly St. Jude Medical's) self-expanding Portico™ TAVI system has been in commercial use in Europe since 2012 when the 23mm Portico valve and transfemoral delivery system first received CE Mark. Since this time, approximately 5000 commercial procedures have been performed across 34 countries using the full family of Portico TAVI system sizes (23, 25, 27 and 29mm). Despite growing acceptance of the Portico™ TAVI system in Europe, the totality of published clinical evidence remains limited. Thus far, the only prospective, multi-center study publication is the 30-day outcomes from the pivotal Pre-CE Mark Study (Portico TF EU) with 222 subjects.[5] The 1-year data from the same cohort has been accepted for publication with an anticipated publication date of February 2018.

A longer-term follow-up study of the Portico™ valve was required as a condition of CE Mark. The Portico I study was initiated to fulfill this requirement. Portico I represents early user experience. The study began shortly after CE mark of the 23mm Portico valve and gained momentum as additional sizes were commercialized. There were only 12 participating sites in the TF EU study while the Portico I study spanned 61 sites and 14 countries. As result, many of the Portico I patients represent the participating center's initial experience with the valve. The Portico I study also allows Pre-CE Mark TF EU study participants to roll-over to the longer-term follow-up which continues for all patients to 5 years. This study completed enrollment in 2017 and the will eventually contribute to

the pool of published literature on the performance of the Portico valve, however the first publication isn't anticipated until the latter half of 2018.

As TAVR becomes part of routine care it is important to characterize the utilization and impact of these devices on all patients receiving them. Indeed, it has been projected that 27,000 new TAVR candidates at high or prohibitive surgical risk will each year require treatment in Europe and North America.[1] A recent meta-analysis of 7 European national TAVR-registries (Belgium, France, Germany, Italy, Spain, Swiss, UK) that includes data on 9786 patients provides important insight into the real-world practice of TAVR in the western world.[6] Unfortunately, Portico was not among the valves utilized in these registries. Portico is also absent from another informative weighted meta-analysis of 16 TAVR trials.[7]

Overall, all-cause mortality at 30 days in clinical practice ranged from 1.6% to 8.5% across the nine registries.[8-17] As expected, newer-generation THVs were associated with lower mortality rates at 30 days compared to their predicate devices. For example, the third – generation SAPIEN 3 valve was associated with a substantially lower 30 day all-cause mortality rate compared to first-generation SAPIEN valve (2.2% vs 8.5%).[12-14]

A majority of Portico I study enrollment comprised users' initial commercial experience, and inclusion and exclusion criteria were similar to the Portico TF EU Study. Furthermore, during the first years following the commercial availability of all Portico valve sizes, much was learned about optimal implant techniques and the value of consistent, informed industry and proctor case support. Abbott has recently retrained Portico operators to achieve more predictable, consistent and durable results. This registry is being conducted to characterize outcomes in experienced operators under these recently introduced guardrails.

The design of this registry allows the inclusion of next generation Abbott TAVI products (including the sheathless indication and the next generation delivery system) and expanded indications when approved. [redacted] enrollment in the Confidence Registry with 1st generation product will be limited to 500 subjects. Enrollments will resume when next generation product is commercially available with up to 1000 total subjects enrolled.

3 Device(s) Used in the Registry

3.1 Identification and Description of the Devices Used

3.1.1 Identification

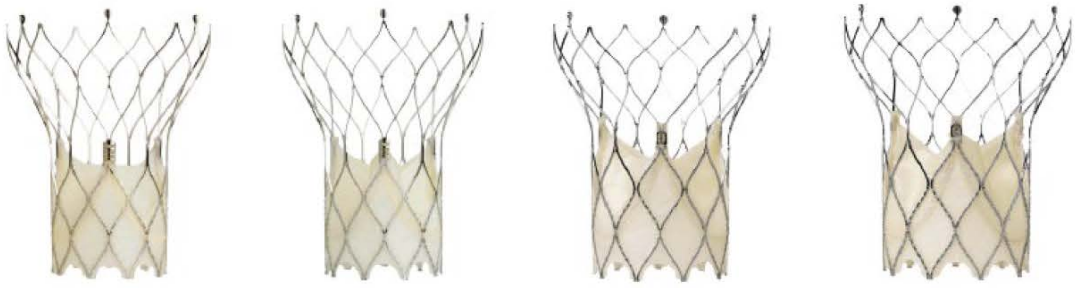
This registry will include market released St. Jude Medical (SJM) Portico™ valves, delivery systems and loading systems. Future generations of the system components or expanded indications will also be included in the registry as they become commercially available.

[redacted]

Table 1 below identifies the devices that will be included in the study.

Table 1: Identification of Devices Included in the Study

Device name	Model/Type	Manufacturer	Region/ Country	Regulatory Status
Heart Valve	PRT-23/25/27/29	SJM	Europe	Market Released
Delivery System	PRT-DS-TF-18F/19F	SJM	Europe	Market Released
Loading System	PRT-LS-TF/ALT-18F/19F	SJM	Europe	Market Released



3.1.2 Device Description and Intended Purpose

The Portico™ Valve, the Delivery System and the Loading System are to be used in accordance with the Instructions for Use (IFU). Please refer to the Instructions for Use for further details. This protocol covers the use of all four Portico™ valve sizes (23mm, 25mm, 27mm and 29mm) and the Portico™ Delivery System(s) (18 F and 19 F) and loading system, which are all CE marked.

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. **Table 2** specifies the available Portico™ valve sizes. The valve is designed to be implanted in the native aortic heart valve without open heart surgery and without concomitant surgical removal of the failed native valve.

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.

The cuff and leaflet pericardial tissue is preserved and cross-linked in glutaraldehyde. Glutaraldehyde, formaldehyde and ethanol are used in the valve sterilization process. The valve and valve cuff are processed using Linx™ anti-calcification technology. The valve is supplied sterile and non-pyrogenic.

Table 2: Portico™ Transcatheter Aortic Heart Valve Sizes

Model Number	Intended to Treat Aortic Annulus Diameter (Range in mm)
PRT-23	19-21
PRT-25	21-23
PRT-27	23-25
PRT-29	25-27

The Portico™ Transfemoral Delivery System is an over-the-wire, 0.035"compatible system. **Table 3** describes delivery systems specifications. The distal (deployment) end of the delivery system features a radiopaque inner member marker band, and an atraumatic, radiopaque tip. The inner member marker band provides a reference point with which to align the valve in the native annulus.

Table 3: Portico™ Transfemoral Delivery System Specifications

Model Number	Associated Portico Valve	Outer Diameter		Vessel Diameter
		Distal	Proximal	
PRT-DS-TF-18F	23mm	18 Fr	13 Fr	≥ 6mm
PRT-DS-TF-18F	25mm	18 Fr	13 Fr	≥ 6mm
PRT-DS-TF-19F	27mm	19 Fr	13 Fr	≥ 6.5mm
PRT-DS-TF-19F	29mm	19 Fr	13 Fr	≥ 6.5mm

A protective sheath covers and maintains the valve in a collapsed position. The protective sheath features a radiopaque distal marker band that provides a reference point that is used to determine the extent of valve deployment.

The handle is located on the proximal end of the delivery system and is used to load and deploy the valve. The delivery system handle includes a deployment

and re-sheath knob, and a post re-sheath adjuster to facilitate precise placement of the valve. The handle also includes a sliding system.

The delivery system deployment and re-sheath knob is turned to the user's right to retract the protective sheath, deploying the valve. The delivery system will deploy the annulus end of the valve first and allow gradual deployment of the valve. The position of a partially deployed valve can be evaluated, and if needed, the valve can be re-sheathed and re-deployed, provided the valve has not been fully deployed (beyond 80%) from the delivery system. The partially deployed valve may be re-sheathed up to two times at the implantation site by reversing the deployment procedure by turning the deployment and re-sheath knob to the user's left.

The Portico™ Loading System compresses the valve onto the delivery system. The loading system includes the following elements: loading base, loading funnel, and loading tube.

The loading system for use with the 18F delivery system is model TAVI-LS-TF. The loading system for use with the 19F delivery system is model PRT-LS-TF/ALT-19F.

The registry will also allow future iterations of the Portico valve and delivery system along with expanded indications to be included as they receive approval for commercial use in the country where the subject is enrolled.

3.1.3 Device Handling and Storage

All study devices must be stored according to the labeling and Instructions for Use as per standard practice at the center.

4 Registry Design

4.1 Design

This is a prospective, non-randomized, observational, single-arm, multicenter registry of patients clinically indicated for implantation of a Portico™ transcatheter aortic heart valve. The registry has broad inclusion criteria (symptomatic degenerative aortic stenosis) and minimal exclusion criteria to ensure the results are generalizable to the broadest TAVI population. Approximately 1000 subjects will undergo transcatheter aortic valve replacement (independent of valve size) using a commercially available Portico™ valve and transfemoral delivery system.

[redacted] total enrollment in the Confidence Registry will consist of 500 subjects treated with first generation product and 500 with the next generation product.

[redacted]

The registry will collect 'standard of care' clinical and device performance data from up to 50 experienced, high volume TAVI implant centers to ensure consistency with other published post-market TAVI registries. Experienced implanters, defined as those that have completed the commercial Portico implant training program and undertaken at least 20 Portico implants within the last 12 months, will be invited to participate in the registry. No center may enroll more than 10% of total subjects (100) and maximum 50 subjects in each half of the study.

Subjects will undergo prospective enrollment with baseline data collection prior to receiving their Portico Valve (up to a maximum of 180 days prior to the Portico 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 follow-up visit followed by a 12-month vital status/survival status check. The 12-month vital status/survival status check may be conducted via a phone call if an in-office visit is not feasible. The expected duration of enrollment is 18 months. The total duration of the clinical investigation is expected to be approximately 30 months depending on the rate of enrollment.

4.2 Objectives

The objective of this registry is to characterize the procedural safety and device performance of the Portico™ valve from experienced TAVI centers that commercially use the Portico™ valve, delivery system and loading system to treat patients with severe aortic stenosis.

4.3 Endpoints

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

1. Evaluation of the VARC-2 event rates at 30 days from the index procedure
   - 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)
   - Annular rupture
   - Conversion to open surgery
   - Coronary obstruction
   - Valve embolization
   - Transcatheter valve-in-valve deployment
   - 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 prosthetic heart valve into the proper anatomical location

4. Echocardiographic assessment of valve performance at 30 days compared to baseline for the subjects with Portico valve implanted
   - Mean gradient
   - Effective orifice area
   - Paravalvular leak (PVL)

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

5. Clinical improvement from baseline to 30 days for the subjects with Portico valve implanted assessed by:
   - New York Heart Association (NYHA) functional class
   - Quality of Life (QoL) questionnaire (EQ5D-3L)

6. All-cause mortality at 30 days and 12-months

NOTE: Should new VARC or ESC Guidelines be published during the course of the registry, 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.

4.4 Study Population

The intended population for this registry comprises of patients who are over the legal age of consent in the host country, have severe symptomatic (NYHA class $\geq$ II) aortic stenosis (AS), and are considered to be a suitable candidate for TAVI.

4.4.1 Inclusion Criteria

Eligible patients will meet **all** of the following:

1. Are $\geq$18 years of age or legal age in host country and have been identified as a candidate for a Portico™ valve implant

2. Have been informed of the nature of the study, agree to its provisions and have provided written informed consent as approved by the Ethics Committee (EC) of the respective clinical center

4.4.2 Exclusion Criteria

Patients will be excluded if they meet **any** of the following:

1. Have sepsis, including active endocarditis
2. Have any evidence of left ventricular or atrial thrombus
3. Have vascular conditions (i.e. caliber, stenosis, tortuosity, or severe calcification) that make insertion and endovascular access to the aortic valve improbable
4. Have a non-calcified aortic annulus
5. Have congenital bicuspid or unicuspid leaflet configuration
6. Are unable to tolerate antiplatelet/anticoagulant therapy
7. Are pregnant at the time of signing informed consent
8. Are currently participating in a drug or device study that may impact the registry (unless prior sponsor approval for co-enrollment is granted)

5 Procedures

Approval from the Sponsor and Ethics Committee must be received prior to initiating study procedures.

The following sections provide a detailed description of procedures required by this CIP.

5.1 Patient Recruitment

All patients being considered for a commercial Portico™ valve implant at participating implant centers should be considered for inclusion in this registry.

5.2 Informed Consent Process

The Principal Investigator or his/her authorized designee will conduct the informed consent process, as required by applicable regulations and the center's Ethics Committee (EC). This process will include a verbal discussion with the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate, such as details of clinical investigation procedures, anticipated benefits, and potential risks of clinical investigation participation. During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the subject and will respect subject's legal rights. The subject shall be provided with the informed consent form written in a language that is understandable to the subject and has been approved by the center's EC. The subject shall have adequate time to review, ask questions and consider participation in the study.

If the subject agrees to participate, the Informed Consent Form must be signed and dated by the subject and by the person obtaining the consent. The signed original form will be filed in the subject's hospital or research charts, and a copy will be provided to the subject.

The Principal Investigator or his/her authorized designee will document the informed consent process in the subject's hospital and/or research charts. The date of signature will be entered on an applicable Case Report Form (CRF).

Failure to obtain informed consent from a subject prior to clinical investigation enrollment should be reported to the Sponsor within five working days and to the reviewing center's EC according to the 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 will provide this information to the subject. If relevant, the subject will be asked to confirm their continuing informed consent in writing.

5.3 Point of Enrollment

All subjects who meet all inclusion criteria, do not meet any exclusion criteria, sign an EC approved Informed Consent and have an attempted implant (defined as the Portico delivery system entering the subject's vasculature) will be considered enrolled in the registry.

The Principal Investigator or delegated study personnel will record enrollment information (name of the clinical investigation, date of consent and Inclusion/exclusion information) in the hospital records and complete and submit all applicable CRFs in a timely manner.

Notification of enrollment to the Sponsor is considered to have occurred when the Sponsor has received the applicable CRF (Procedure Form).

All enrolled subjects should be followed for 30 days regardless of the procedure outcome.

5.4 Scheduled Procedures

The Principal Investigator is responsible for ensuring all clinical data is collected as required per CIP scheduled procedures. The data collection elements required for each study visit are summarized in Table 4 below.

Table 4: Summary of study procedures

Study activities and visits	Baseline	Index procedure	Pre-Dis	30 days	12-months**
Visit window	-180d-0	0	0-7d	30-120d	358-410d
Informed consent	X				
Demographics	X				
Medical and cardiovascular history	X				
Surgical risk assessment*	X				
Frailty assessment*	X				
Native aortic valve assessment*	X				
Access site assessment*	X				
Physical assessment	X		X	X	
Blood Work: § - Hemoglobin, Creatinine and Troponin	X		X	X	
NYHA class assessment	X			X	
Quality of Life questionnaire (EQ5D-3L)	X			X	
Implant characteristics		X			
Electrocardiogram (ECG) §	X			X	
Echocardiogram	X			X	
Anti-platelet and anti-coagulation medication assessment	X	X	X	X	
Assessment of resource utilization		X	X		
Adverse events assessment	X	X	X	X	
Vital status/mortality check					X

** Per standard of care testing for a TAVI and should be within 180 days prior to index procedure*

***This visit may be completed via a phone call*

§ If available

5.4.1 Baseline Visit

For patients indicated for implantation of a Portico™ valve, a baseline visit will occur prospectively (before receiving the Portico 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 Baseline visit consists of the following activities:

- 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 Portico valve implantation – Implant center may follow the Heart Team approach for patient evaluation recommended by VARC-2. However, eligibility assessment for Portico 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 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
- Native aortic valve assessment using either Echo or Multi-Slice Computer Tomography (MSCT) 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, if available as part of standard of care)
- Physical assessment including height, weight and office blood pressure
- Echocardiogram (TTE or TEE)
- New York Heart Association (NYHA) functional class assessment
- Completion of the QoL questionnaire (EQ5D – 3L)
- Heart rate and rhythm assessment
- Anti-platelet and anti-coagulation medication assessment
- Adverse events assessment

Each implanting center will be responsible for performing and interpreting the baseline echocardiogram [Trans-Thoracic Echocardiogram (TTE) or Trans-Esophageal Echocardiogram (TEE)] using VARC-2 definitions.

5.4.2 Portico Valve Implant or Index Procedure

The medical team performing the TAVI 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

[redacted]

- 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. The procedure will consist of the following activities:

1. Adverse events assessment
2. Document transcatheter aortic valve deployment information
3. Procedural characteristics
4. Procedural imaging (angiogram, intra-procedural echocardiography assessments) if available as part of standard of care
5. Resource utilization assessment

It is recommended to follow the peri-procedural instructions for the assessment of aortic regurgitation and implant depth as mentioned in Appendix E: Peri-procedural Guidelines. However, an implant center may follow their own standard of care practices and failure to follow these instructions will not be considered a protocol deviation.

During the procedure, the implanting physician may determine the implantation of the Portico 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 not attempted (i.e. the Portico delivery system was never introduced into the subject's vasculature), the subject will not be considered enrolled. Refer to Section 5.3: Point of Enrollment.

If the implant procedure was attempted (i.e. the Portico delivery system was introduced into subject's vasculature) but the Portico valve could not be implanted (e.g. Portico 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.

Following the procedure, the delivery and loading systems should be securely disposed as 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.

5.4.3 Pre-discharge Visit

The pre-discharge visit will take place at the time of hospital discharge or within seven days after the index procedure, whichever occurs first. If the patient is expected to be discharged over the weekend, the discharge tests may be completed on the last weekday prior to discharge. The assessment will include:

- Physical assessment
- Blood sample (Creatinine, Hemoglobin, Troponin, if available, as part of standard of care)
- Anti-platelet and anti-coagulation medication assessment
- Adverse events assessment
- Pacemaker dependency assessment (as applicable)
- Data on resource utilization will be collected to determine the costs associated with hospitalization for a Portico implant procedure

5.4.4 30 Day Follow-up Visit

Each patient will return to the participating institution for a follow-up visit at 30 days (30+90 days) post index procedure. The scheduled visit window is calculated from the date of implant procedure.

The following procedures must be completed at the 30-day follow-up visit:

- Physical assessment
- Blood sample (Creatinine, Hemoglobin, troponin) if available as part of standard of care
- Echocardiogram*
- NYHA functional status classification
- Completion of QoL questionnaire (EQ5D-3L)
- Heart rate and rhythm assessment
- Anti-platelet and anti-coagulation medication assessment
- Adverse events assessment
- Pacemaker dependency assessment (as applicable)

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

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

5.4.5 12 Months Vital Status/Survival Status

Each patient will have a survival status check at 12 months (-7 days, +45 days) post index procedure. The scheduled visit window is calculated from the date of implant procedure. The vital status check will be performed to determine patient survival at 12 months only and may be conducted via an in-office visit or by telephone call with the patient during the visit window.

Every effort should be made to contact the subject for the 12 month vital status/mortality check. The subject should not be considered 'lost to follow-up' until:

- A minimum of two phone calls from a physician or delegate at the implanting center have been attempted to reach the patient. These two phone calls must be documented in the patient's hospital records

AND

- A letter has been sent to the patient's last known address or general practitioner (GP). A copy of this letter should be maintained in the patient's hospital records.

5.5 Patient Reported Outcome (PRO) Measures

The EuroQoL 5D-3L questionnaire will be administered by the investigators, the study coordinators or designee to the subject. 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-3L 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-3L 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 and at the 30 day follow-up visit. A copy of this questionnaire can be found under Appendix D: EQ5D-3L Quality of Life Questionnaire.

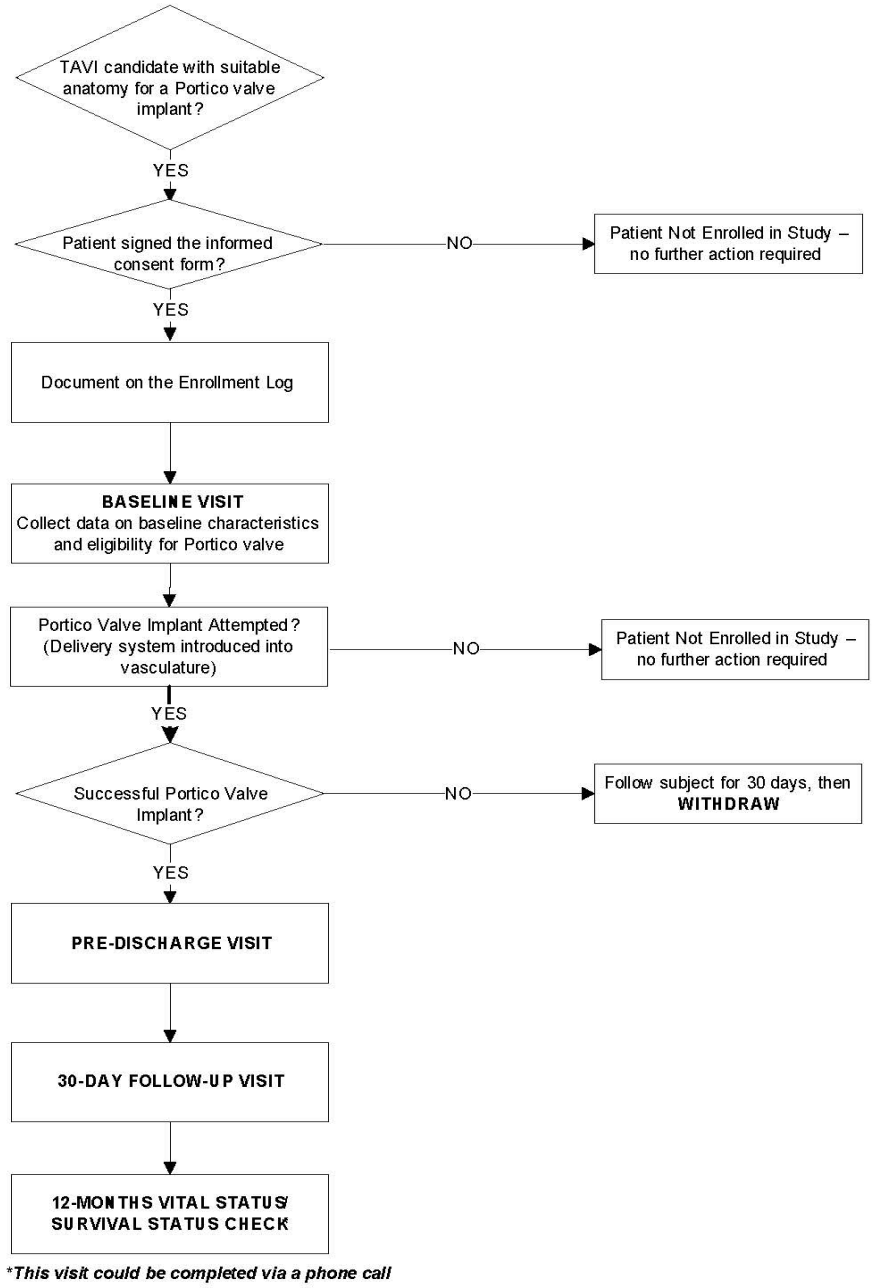
5.6 Unscheduled Visits

An unscheduled visit is defined as a visit that occurs between Implant and 30 day 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.

5.7 Study Flow Chart

The Study Flow Chart and Figure 1 below summarize subject flow and requirements of the study.

Figure 1: Flow Chart



**This visit could be completed via a phone call*

5.8 Health Care Economic Data Collection

Resource utilization will be collected during the index procedure and hospital admission to characterize intensity of the medical care and acuity of the health care delivery setting.

5.9 Description of Activities Performed by Sponsor Representatives, if applicable

Trained sponsor personnel will provide technical expertise and technical guidance on the implant of the Portico valve as needed.

While sponsor representatives may perform these activities, the Principal Investigator remains responsible for ensuring all required data is collected as required per CIP.

5.10 Subject Study Completion

Subject participation in the clinical investigation will conclude upon completion of the 12 month vital status check. Upon completion of subject participation in the clinical investigation, the subject will return to standard of care.

5.11 Subject Withdrawal

Each patient should remain in the investigation until completion of the required follow up period; however, a patient's participation in the investigation may be discontinued. Should this occur, the reason for discontinuation must be documented in the source documents.

Patients must be informed about their right to withdraw from the clinical investigation at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled. Withdrawal from the clinical investigation will not jeopardize their future medical care or relationship with the investigator. Patients will be requested to specify the reason for the request to withdraw. The investigator must make all reasonable efforts to retain the subject in the clinical investigation until completion of the clinical investigation.

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

For this registry, a patient will be considered 'lost to follow up' after

- A minimum of two phone calls from a physician or delegate at the implanting center have been attempted to reach the patient. These two phone calls must be documented in the patient's hospital records

AND

- A letter has been sent to the patient's last known address or general practitioner (GP). A copy of this letter should be maintained in the patient's hospital records.

When subject withdrawal from the clinical investigation is due to an unsuccessful valve implant attempt, the subject will be followed for 30 days, until resolution of that adverse event, or determination that the subject's condition is stable. The status of the subject's condition should be documented at the time of withdrawal.

In case of subject withdrawal, the center should make attempts to schedule the subject for a final study visit.

5.12 Requirements for Clinical Laboratories

5.12.1 Echo Core Lab

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.

5.13 Study Committees

5.13.1 Steering Committee (SC)

The Coordinating Investigator/National Investigator will provide oversight and act as the main contact for all investigators in case of medical questions related to the conduct of the registry. A Steering Committee (SC) may be established to guide study execution and publications. A SC charter will define membership of the committee and outline the roles and responsibilities of the committee.

5.13.2 Clinical Events Committee (CEC)

An independent CEC will be utilized 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.

6 Statistical Considerations

Baseline 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 frequencies and percentages.

6.1 Sample Size Determination

[redacted] In order to understand procedural characteristics and safety and performance outcomes in a 'standard of care' setting, the study will enroll approximately 1000 subjects with attempted valve implant from up to 50 experienced TAVI centers worldwide.

6.2 Analysis Population

The analysis population will include patients who undergo an attempted implant with the Portico valve. A subject is defined as having undergone an "attempted implant" if the Portico delivery system enters the subject's body. Patients who do not undergo an attempted implant of the Portico device will be excluded from analyses.

6.3 Descriptive Endpoints

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

1. Evaluation of the VARC-2 event rates at 30 days from the index procedure
   - Cardiovascular Mortality
   - Myocardial Infarction
   - Stroke (including disabling and non-disabling)
   - Bleeding (life-threatening and/or disabling, major, minor)
   - Acute kidney injury
   - Vascular access site and access-related complications (major and minor)
   - Annular rupture
   - Conversion to open surgery
   - Coronary obstruction
   - Valve embolization
   - Transcatheter valve-in-valve deployment
   - 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 at 30 days
   - Correct positioning of a single Portico prosthetic heart valve into the proper anatomical location

4. Echocardiographic assessment of hemodynamic valve performance at 30 days compared to baseline for the subjects with Portico valve implanted
   - Mean gradient
   - Effective Orifice Area
   - Paravalvular leak (PVL)

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

5. Clinical improvement from baseline to 30 days for the subjects with Portico valve successfully implanted (implant success is defined in descriptive endpoint 3) by assessment of:
   - New York Heart Association functional class
   - Quality of Life (QoL) questionnaire (EQ5D-3L)

6. All-cause mortality at 30-days and 12-months

Valve hemodynamic performance, vessel size, implant depth and other continuous variables will be summarized using descriptive statistics including mean, standard deviation, median, and range. The remaining categorical variables will be summarized by frequency and percentage. Additional analysis of predictors of VARC-2 events (e.g. PVL or new permanent pacemaker) may be conducted.

6.4 Justification of Clinical Investigation Design

This is a prospective, non-randomized, observational, single-arm, multicenter registry of patients planned to be implanted with a Portico transcatheter aortic heart valve. The registry has broad inclusion criteria (symptomatic senile degenerative aortic stenosis) and minimal exclusion criteria to ensure the results are generalizable. The registry will also allow future iterations of the Portico TAVI system, delivery system and expanded indications to be included in the registry as they become commercially available in Europe.

It is acknowledged that in-hospital complications are more common in centers during the start-up phase and that a large number (≥50) of TAVI procedures (equivalent to 2 years of activity in most European countries) is generally required to become proficient in the procedure and achieve acceptable clinical outcomes [18]. Therefore, this registry includes experienced, high volume implant centers to characterize outcomes in the hands of experienced implanters.

[redacted]

To ensure consist evaluation of adverse events and echocardiograms, an independent Clinical Events Committee will review any potential VARC 2 events and an independent echocardiographic core laboratory will assess 30 day echocardiograms. Both entities will classify the data according to respective VARC 2 definitions.

6.5 Overall Sample Size

There will be approximately 1000 subjects enrolled in the study. The first half of the study sample size (n=500) will enroll subjects treated with first generation products and the second half of the study (n=500) will enroll subjects treated with the next generation of products.

6.6 Timing of Analysis

The final analysis will be conducted when the last enrolled patient has reached one year post procedure.

6.7 Interim Report

Interim reporting of endpoints will be performed before the study's conclusion, upon recommendation of the Coordinating Investigator.

Interim reporting of relevant data will also be performed for reimbursement purposes upon request of sponsor Health Economics and Reimbursement (HE&R) department.

6.8 Statistical Criteria for Termination

There are no pre-specified criteria for terminating the clinical investigation on statistical grounds.

6.9 Deviations from Statistical Plan

If any deviations from the original statistical plan occur, such deviations will be documented in the clinical study report or statistical report containing the analysis results.

7 Risks and Benefits

The risks associated with the Portico™ transcatheter heart valve, the delivery and loading systems can be found in the Instructions for Use. The study does not require any additional procedures or assessments over the standard of care other than the EQ5D-3L Quality of Life Questionnaire. There are no additional risks introduced to patients enrolled in the study.

7.1 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. Instructions for Use are available upon request.

7.2 Risk Control Measures

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 other commercially available transcatheter valve.

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

7.3 Possible Interactions with Concomitant Treatments

There are no known interactions of the Portico™ 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.

7.4 Anticipated 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 TAVI procedure. It is expected that patients implanted with a Portico™ valve will have the same benefits as patients implanted with other commercially available transcatheter valves.

7.5 Risk-to-Benefit Rationale

The risks associated with the use of the Portico™ valve, 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 registry are indicated for a TAVI procedure as part of their standard medical management and are subject to the risks associated with these devices.

8 Requirements for Investigator Records and Reports

8.1 Deviations from CIP

A deviation is defined as an instance(s) of failure to follow, intentionally or unintentionally, the requirements of the CIP. The investigator should not deviate from the CIP.

In some cases, failure to comply with the CIP may be considered failure to protect the rights, safety and well-being of patients; such non-compliance exposes patients to unreasonable risks. Examples: failure to adhere to the inclusion/exclusion criteria, failure to perform safety assessments intended to detect adverse events. Investigators should seek to minimize such risks by adhering to the CIP.

The PI must maintain accurate, complete, and current records, including documents showing the date of and reason for each deviation from the CIP. Relevant information for each deviation will be documented as soon as possible on the applicable CRF. The center will submit the CRF to the Sponsor.

The PI is required to adhere to local regulatory requirements for reporting deviations to the EC.

Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of patients may proceed without prior approval of the Sponsor and the EC. Such deviations shall be documented and reported to the Sponsor and the EC as soon as possible.

8.2 Safety Reporting

Safety surveillance within this study and the safety reporting performed both by the Investigator (per local country requirements) and Sponsor commences at the time of procedure.

The safety surveillance and the safety reporting will continue until the final study visit has been performed, the subject is deceased, the subject/Investigator concludes their participation into the clinical investigation or the subject withdraws from the clinical investigation.

All adverse event data will be collected through the 30 day visit and will be reported to the Sponsor through the electronic data capture system (EDC). All deaths will be collected throughout the clinical study and will be reported to the Sponsor through the EDC using the applicable CRF. The Investigator will record all reportable adverse events and deaths on the appropriate case report forms.

Records relating to the subject's subsequent medical course must be maintained and submitted (as applicable) to the Sponsor until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained. Adverse events will be monitored until they are adequately resolved, the subject is withdrawn, or completes the study. At the 1 year vital status check, only mortality status will be collected.

For the purposes of this clinical investigation, the following events will be reported through the 30 day follow up visit with deaths reported through one year. All adverse events will be reported as soon as possible. Serious Adverse Events will be reported no later than 3 calendar days after becoming aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined (see Appendix B: Definitions).

1. VARC-2 Adverse Events
    - Death

- Myocardial infarction
- Vascular access site and access-related complications
- Stroke/TIA
- Bleeding events
- Acute kidney injury
- Coronary Obstruction
- Pacemaker

2. All Adverse Device Effects

3. All Serious Adverse Events (whether or not the event is considered device or procedure related)

Non-serious adverse events documentation and reporting are limited to cardiovascular and neurovascular events only; all events must be reported regardless of their relationship with the device or the procedure.

The implant centers should notify the Sponsor of reportable adverse events by creating and saving the applicable CRF as complete within the EDC. Additional information may be requested by the Sponsor in order to support the reporting of adverse events to regulatory authorities. The Investigator must notify the EC, if appropriate, in accordance with national and local laws and regulations, of the adverse events reported to the Sponsor. All adverse events will be reported as per applicable regulatory requirements.

8.2.1 Subject Death

Subject deaths will be documented and reported to the Sponsor as soon as possible but no later than 3 calendar days after becoming aware of the event. All deaths should be reported via an Adverse Event, a Withdrawal form and a Product Out of Service form.
Source documentation (including any hospital records, autopsy reports and death certificates) is required and should be provided to the sponsor for Adjudication purposes.

In the event of a subject death, an autopsy should be performed whenever possible and the Portico valve explanted and returned to the Sponsor for evaluation.

8.2.2 Complaints

During the study, the Investigator will be responsible for reporting all complaints. A complaint is defined as any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a device after it is released for distribution.

If the complaint does not involve an adverse event, the Investigator must notify the Abbott Post Market Surveillance Department by submitting the information on the device via email to [redacted] as soon as possible after becoming aware of the complaint. This information will not be collected on a CRF for the study.

8.3 Source records

Source documents will be created and maintained by the investigational center team throughout the clinical investigation. The data reported on the CRFs will be derived from, and be consistent with, these source documents, and any discrepancies will be explained in writing.

8.4 Records Retention

The Sponsor and the Principal Investigators will maintain the clinical investigation documents as required. Measures will be taken to prevent accidental or premature destruction of these documents. The Principal Investigator or the Sponsor may transfer custody of records to another person/party and document the transfer at the investigational center or the Sponsor's facility, as appropriate.

These documents must be retained by the investigational center for a period of two years after the conclusion of the clinical investigation and made available for monitoring or auditing by the Sponsor's representative or representatives of the applicable regulatory agencies.

All original source documents must be stored for the maximum time required by the regulations at the hospital, research institute, or practice in question. If original source documents can no longer be maintained at the center, the Investigator will notify the Sponsor.

9 Clinical Data Handling

The Sponsor will be responsible for handling of study data. The Sponsor and/or its affiliates will be responsible for compiling and submitting all required reports to government agencies. Data will be analyzed by the Sponsor and may be transferred to the Sponsor's locations worldwide and/or any other worldwide regulatory authority in support of a market-approval application.

9.1 Protection of Personally Identifiable Information

The Sponsor respects and protects personally identifiable information collected or maintained for this clinical investigation. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data. Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data will be secured against unauthorized access.

9.2 Data Management Plan

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

Subject data will be captured in a validated electronic data capture (EDC) system hosted by the Sponsor.

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

9.3 Document and Data Control

9.3.1 Traceability of Documents and Data

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

9.3.2 Recording Data

The CRF will be reviewed by the authorized site personnel. An appropriate comment will be provided to explain changes to data reported on the CRF.

10 Monitoring

It is the responsibility of the Sponsor to ensure the clinical investigation is conducted, recorded and reported according to the approved CIP, subsequent amendment(s), applicable regulations and guidance documents.

Centralized monitoring will occur through routine internal data review. This monitoring is designed to identify missing and inconsistent data, data outliers, and potential CIP deviations that may be indicative of center non-compliance. On-site monitoring may occur at the discretion of the Sponsor.

11 Compliance Statement

11.1 Statement of Compliance

This registry will be conducted in compliance with the most current regional and local laws and regulations. Principles of Good Clinical Practice will be followed as based on the most current version of the World Medical Association (WMA) Declaration of Helsinki.

The Investigator will sign a Clinical Trial Agreement and agrees to be compliant with the agreement. The Investigator will not start enrolling patients or requesting

informed consent from any subject prior to obtaining EC approval and relevant regulatory authority approval, if applicable, and authorization from the Sponsor in writing for the clinical investigation. If additional requirements are imposed by the EC or relevant regulatory authority, those requirements will be followed. If any action is taken by an EC or a relevant regulatory authority with respect to the clinical study, that information will be forwarded to the Sponsor.

As the Sponsor, Abbott has taken up general liability 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. If required, additional subject coverage or a clinical study specific insurance will be provided by the Sponsor.

11.2 Quality Assurance Audits and Regulatory Inspections

The Investigator and/or delegate should contact the Sponsor immediately upon notification of a regulatory authority inspection at the implant center. A monitor or designee will assist the Investigator and/or delegate in preparing for the audit. The Sponsor may perform quality assurance audits, as required.

The Principal Investigator or institution will provide direct access to source data during and after the clinical study for monitoring, audits, EC review and regulatory authority inspections, as required. The Principal Investigator or institution will obtain permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical study.

11.3 Repeated and Serious Non-Compliance

In the event of repeated non-compliance or a one-time serious non-compliance, as determined by the Sponsor, a monitor or designee will attempt to secure compliance by one or more of the following actions:

- Visiting the Investigator,
- Contacting the Investigator by telephone,
- Contacting the Investigator in writing,
- Retraining of the Investigator.

If an Investigator is found to be repeatedly non-compliant with the signed agreement, the CIP or any other conditions of the clinical study, the Sponsor will either secure compliance or, at its sole discretion, terminate the Investigator's participation in the clinical study. In case of termination, the Sponsor will inform the responsible regulatory authority, as required, and ensure that the EC is notified, either by the Principal Investigator or by the Sponsor.

12 Suspension or Premature Termination of the Clinical Investigation

The Sponsor reserves the right to terminate the clinical study at any stage, with appropriate written notice to the Investigators, ECs and relevant regulatory authorities, if required.

A Principal Investigator, EC or regulatory authority may suspend or prematurely terminate participation in a clinical study at the study centers for which they are responsible. The investigators will follow the requirements specified in the Clinical Trial Agreement.

If suspicion of an unacceptable risk to patients arises during the clinical study or when so instructed by the EC or regulatory authority, the Sponsor may suspend the clinical study while the risk is assessed. The Sponsor will terminate the clinical study if an unacceptable risk is confirmed. If the Sponsor completes an analysis of the reasons for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, the Sponsor will inform the Principal Investigators, EC, or regulatory authority, where appropriate, of the rationale, providing them with the relevant data supporting this decision. Approval from the EC or regulatory authority, where appropriate, will be obtained before the clinical study resumes. If patients have been informed of the suspension, the Principal Investigator or authorized designee will inform them of the reasons for resumption.

If the Sponsor suspends or prematurely terminates the clinical study at an individual investigational center in the interest of safety, the Sponsor will inform all other Principal Investigators.

If suspension or premature termination occurs, the Sponsor will remain responsible for providing resources to fulfill the obligations from the CIP and existing agreements for following up the patients enrolled in the clinical study, and the Principal Investigator or authorized designee will promptly inform the enrolled patients at his/her investigational center, if appropriate.

The clinical investigation will be concluded when:

- All centers are closed AND
- The final report has been provided to Investigators or the Sponsor has provided formal documentation of clinical investigation closure.

13 Publication Policy

Publications or presentations of clinical study methods or results will adhere to Abbott's publication policy [redacted]. A copy of the policy will be provided upon request of the Investigator.

Publication planning and authorship determinations will be overseen by the Steering Committee (see section 5.13), and investigators will be notified via email about the dissemination of study data and opportunities for involvement as authors on publications/presentations.

[redacted]

14 Reporting Results on ClincalTrials.gov Website

This clinical investigation will be registered on ClinicalTrials.gov. A full report of the pre-specified outcomes, regardless of the results, will be made public through the ClinicalTrials.gov website no later than 12 months after clinical investigation completion, as required by section 801 of the FDA Amendments Act. If this clinical investigation is terminated early, the Sponsor will make every effort to hasten the release of the pre-specified outcomes through the ClinicalTrials.gov website.

Appendix B: Definitions

Adverse Event (AE)
Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in patients, users or other persons, whether or not related to the medical device.

This definition includes events related to the medical device or the comparator.
This definition includes events related to the procedures involved.

Serious Adverse Event (SAE)
An adverse event that led to:

- Death
- A serious deterioration in the health of the subject, that either resulted in:
  - A life-threatening illness or injury OR
  - A permanent impairment to a body structure or a body function OR
  - An in-patient or prolonged hospitalization OR
  - A medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function OR
  - Chronic disease
- Fetal distress, fetal death or a congenital abnormality or birth defect

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

Adverse Device Effect (ADE)
An adverse event related to the use of a medical device.

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the medical device.

This definition includes any event resulting from the use error or from intentional misuse of the medical device.

Serious Adverse Device Effect (SADE)
Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

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: ○ Symptoms of ischaemia ○ ECG changes indicative of new ischemia [new ST-T changes or new Left Bundle Branch Block] ○ New pathological Q waves in at least 2 contiguous leads ○ 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** • 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 • 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 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
Conversion to open surgery	Conversion to open sternotomy during the TAVI procedure secondary to any procedure-related complications

[redacted]

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
	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

* 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

[redacted]

	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%

Appendix C: 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. Logistic EuroSCORE (www.euroscore.org/calcold/html)
2. Euro SCORE II (http://euroscore.org/calc.html), and
3. The Society of Thoracic Surgeons' (STS) risk calculation tools, Version 2.73 (http://riskcalc.sts.org/STSWebRiskCalc273/de.aspx)

Appendix D: EQ5D-3L Quality of Life Questionnaire

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some 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 with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

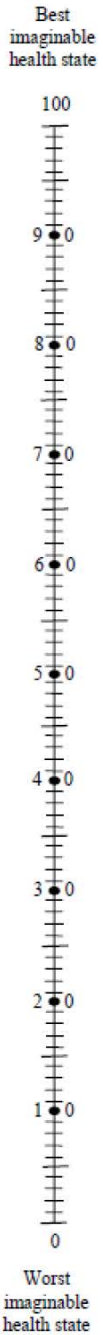
Anxiety/Depression

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

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix E: Peri-procedural Guidelines

Assessment of aortic regurgitation

Angiography will be performed >5 minutes after valve deployment. Use projection where the valve frame is aligned / in-plane - often shallow LAO or RAO and some cranial tilt. Left ventricular (LV) apex must be included in the imaging field. The pigtail catheter should be located in the upper third part of the frame, give 20-30 mL non-diluted contrast at 10 mL/sec, 15 frames/sec and at least 5 heart cycles.

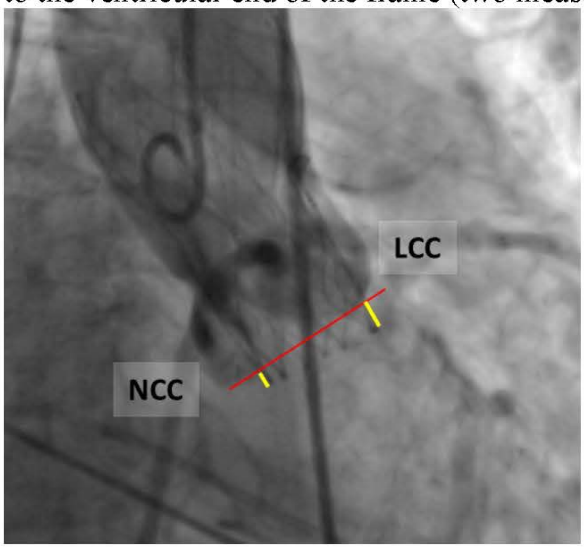
Echocardiography: Use color-Doppler in the short-axis view of the ventricular part of the valve frame. The circumferential extent of the regurgitant jet determine the degree of PVL; <10% = mild (I), 10-29% = moderate (II), >30% = severe (III-IV).

The pressure in the left ventricle and in the ascending aorta should be determined simultaneously after the procedure (within 5 to 10 min after valve deployment). The gradient between diastolic blood pressure (DBP) in the aorta and left ventricular end diastolic pressure (LVEDP) should be calculated over several cardiac cycles to evaluate the severity of periAR.

To adjust the gradient for the respective systolic blood pressure (SBP) of the patient, the dimensionless AR index should be calculated according to the following formula: [(DBP - LVEDP)/SBP] x100.

Assessment of implant depth

For implantation depth, use the angiography with the valve frame aligned with the imaging plane and measure both the distance from the non-coronary cusp (NCC) and left coronary cusp (LCC) to the ventricular end of the frame (two measurements).



Appendix F: NYHA Class Assessment guidelines

Class I	Patient has cardiac disease but without resulting limitations of ordinary physical activity. Ordinary physical activity (eg, walking several blocks or climbing stairs) does not cause undue fatigue, palpitation, dyspnea, or anginal pain. Limiting symptoms may occur with marked exertion.
Class II	Patient has cardiac disease resulting in slight limitation of ordinary physical activity. Patient is comfortable at rest. Ordinary physical activity such as walking more than 2 blocks or climbing more than 1 flight of stairs results in limiting symptoms (eg, fatigue, palpitation, dyspnea, or anginal pain).
Class III	Patient has cardiac disease resulting in marked limitation of physical activity. Patient is comfortable at rest. Less than ordinary physical activity (eg, walking 1 to 2 level blocks or climbing 1 flight of stairs) causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patient has dyspnea at rest that increases with any physical activity. Patient has cardiac disease resulting in inability to perform any physical activity without discomfort. Symptoms may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Appendix G: Data Collection Method

Sponsor/Investigators are required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each subject 1:1. Source documents include all original records from which eCRF's derive their data.

Worksheet might be provided. The purpose of these worksheets is to aid investigators in the capture of clinical investigational data and ensure all protocol required data, which is not captured in medical records, is recorded to support data for the investigation. These worksheets will not be a copy of the eCRF's, but will contain entry blanks for clinical investigation required data not routinely collected by the investigators.

All documentation pertaining to clinical assessments and medical evaluations should be signed and dated by the appropriate clinical personnel.

Electronic Data Capture (EDC) will be used for this registry, therefore, please find below instructions on how to access and use the eCRF application.

Access to eCRF application
The eCRF application is accessed through the internet and requires the use of a personal user account and password.

The following documents and information are required prior to receipt of personnel user account and password:

- Current signed and dated CV (as applicable for role)
- Completed Delegation of Authority Log
- Documented training
- Email address and telephone

Personal user account and password are provided via email. User account and password are confidential and personal. They are not to be shared with other people.
The first time the application is accessed, the password will need to be changed.
If the password is forgotten and/or lost, a new password can be provided via email by following the instructions on the webpage.

Each center must be authorized to start enrolling patients in the investigation before access privileges to the application is made available.
Access privileges are based on the tasks assigned on the Signature and Delegation List and will be either:

- Data entry and review
- Data entry, review and sign off

All eCRF's have to completed, saved ('save complete') and approved by an investigator (as applicable) in a timely manner.

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