CPRB Code : CV-12-054-EU-PV
Project Acronym : PORTICO I
Project Version : 5.0
Version Date : 14JUL2016

PORTICO I STUDY

International Long-term Follow-up Study of Patients Implanted with a PORTICO™ Valve

Clinical Investigation Plan (CIP)

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Date _____ _____

Portico™ Valve will be referred as Portico Valve in the rest of the document.

Coordinating Investigator

SIGNATURE PAGE

CIP PORTICO I

International Long-term Follow-up Study of Patients Implanted with a PORTICO™ Valve

Version 5.0

14JUL2016

Reference #:

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

Coordinating Investigator

Printed name: _____

Signature: _____

Date: _____

Revision History				
Amendment N°	Project Version	Date	Rationale	Details
NAP	V1.0	28JAN2013	First release of the CIP	
1	V2.0	29APR2013	Global modification of the CIP : • To allow collection of any other data acquired as part of patient's native aortic valve assessment not captured by default in the case report forms (CRF). • To address comments received from l'Agence nationale de sécurité du médicament et des produits de santé (ANSM) in France regarding device deficiencies.	See summary of changes (in CIP V2.0)
2	V3.0	25JUN2013	Global Modification of the CIP: • To include two additional countries (Canada and Australia) to participate into the clinical investigation and to adjust subsequently the approximate number of sites. To include an additional exclusion criterion.	See summary of changes (in CIP V3.0)
3	V4.0	17DEC2013	Global modification of the CIP: • To include additional assessments and recommendations strongly advised by Steering Committee members. • To clarify 1 exclusion criterion and certain study activities required by the protocol in order to avoid misinterpretation and to ensure all required examinations are performed.	See summary of changes (in CIP V4.0)
4	V5.0	22JUN2016	Global modification of the CIP: • To integrate all local revisions (Australia, Canada, France and Other EU version) into one Global version. • To update the protocol to match routine practice for TAVI patient follow-up.	See summary of changes (in CIP V5.0)

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List of Appendicies

1 Summary of changes

1.1 Rationale for revision

The primary purpose of this revision is to create a single global Portico I Clinical Investigation Plan (CIP), compiling the EMEA, French, Australian and Canadian CIP versions into a single global version. Minor geographical differences will be outlined as necessary in the appropriate sections. A detailed Summary of Changes comparing each of the previous CIP versions is separately available. Additional modifications have been made to align the study assessments and data collection with current practice.

Modification 1
Local CIP versions (EMEA Revision 4.0 17DEC2013 France Revision 3.1 27JAN2014, Australian Revision 4.1 28JAN2014, and Canadian Revision 4.1 22JAN2014) are consolidated into one global CIP version. For this reason both Clinical Coordinating Investigators, Prof L.Søndergaard (EU), Prof F. Maisano (EU), and both National Principal Investigators, Prof S. Worthley (AU) and Dr. Rhodes (CA), are listed with their respective addresses including their signatures. Specific local requirements are provided in the global protocol in their respective sections.

Modification 2
The 6 Month visit was removed throughout the CIP because a visit at this interval is not done in routine practice. This includes the removal of all separate assessments at 6 months and their corresponding eCRFs.

Modification 3
The Secondary Endpoints have been modified to align with VARC 2 defined events. The rate of all-cause mortality, cardiovascular mortality, myocardial infarction, stroke (disabling and non-disabling), bleeding (life-threatening, major and minor), acute kidney injury, vascular access complications (major and minor) through 30 days following index procedure, new or worsened conduction disturbances and cardiac arrhythmias will be evaluated at 30 days and annually through 5 years post implant. Prosthetic valve function and clinical benefit endpoints will be evaluated at 30 days and annually through 5 years post implant.

Modification 4
The Secondary Endpoint “Evaluation of the TAVI-related resource utilization up to 5-years post-implant” has been changed to “Evaluation of the TAVI-related resource utilization until discharge”. This includes a simplified hospital resources utilization section on the case report form.

Modification 5
The Secondary Endpoint “Evaluation of the device implantability characteristics” (deliverability, retrievability, and repositionability, placement accuracy and deployment) is removed. Separate characteristics on deliverability, retrievability, and repositionability, placement accuracy will still be collected.

Modification 6
The Secondary Endpoint “Reporting of the VARC 2 event rates for a sub-population comprising the non-proctored cases only” has been removed.

Modification 7

The Secondary Endpoint “Impact of annulus sizing method (MSCT versus Echocardiography or other imaging modalities) on patient’s outcomes” has been removed.

Modification 8
The data collection for the Secondary Endpoint “Evaluation of impact of anesthesia on patient’s outcome” has been reduced. The type of anesthesia will still be collected.

Modification 9
The time points for reporting on the Secondary Endpoint "Interim reporting of all-cause mortality on a subset of patients compared with an appropriate external comparator" has been changed from 6 months and 1year to 30 days and 1 year.

Modification 10
The window for the echo Baseline measurement has been changed from within 45 days of index procedure to within 6 months of index procedure.

Modification 11
The Inclusion Criterion has underlined verbiage in addition:
"Subject has senile degenerative aortic valve stenosis confirmed by echocardiographically derived criteria:

- An initial aortic valve area (AVA) of less than or equal to (≤) 1.0 cm^2 (or indexed EOA less than or equal to (≤) 0.6 cm^2/m^2)
  AND
- A mean gradient greater than (>)40 mmHg or jet velocity greater than (>)4.0 m/s or Doppler Velocity Index less than (<)0.25.

If the mean gradient is <40 mmHg and left ventricular ejection fraction (LVEF) <55%, then the site may as well perform a dobutamine stress echo to see if the mean gradient increases to >40 mmHg."
(Baseline measurement taken by echo within 6 months of index procedure.)

Modification 12
The Exclusion Criterion **"**Patient needs an embolic protection device" was removed.

Modification 13
The time point requirements for the frailty assessments (e.g. 5 meters walking time, grip strength with hand-held dynamometer, wasting and malnutrition assessment (including blood sample to obtain serum albumin value)) and cognitive impairment or dementia assessment (via the mini-mental state examination (MMSE)) have been reduced. These tests will be assessed at Enrollment/Baseline, 30d and 1Year only.

Modification 14
The time point requirements for the Modified Rankin Scale (mRS) have been reduced. The mRS will be conducted Enrollment/Baseline, Pre-Discharge, 30 days, 1Year and (if possible) 90 days after any neurological event (stroke, TIA, encephalopathy).

Modification 15
The requirement to assess a 12 Lead ECG beyond the 1 year follow-up has been removed. In addition the uploading of the required 12 Lead ECG at Enrollment/Baseline, Pre-discharge, 30 days and 1 year has been removed. An ECG may still be requested in the case of potential cardiac related AE.

Modification 16
The requirement to provide Baseline CT Scan (if routinely performed), angiography and echocardiography exams at the predefined visits to Sponsor has been removed. These recording will only be provided to Sponsor upon Sponsor request . Echocardiography will be routinely provided to the Core Laboratory for analysis.

Modification 17
The requirement to complete and sign a record of the heart team's recommendation for each patient enrolled in the study has been removed. The Heart team recommendation, including the presence of physicians, can be documented according to the sites standard procedure and available for periodic site monitoring.

Modification 18
The Steering Committee will consist of 4 members: Prof. L. Søndergaard (EU), Prof. F. Maisano (EU), Prof. S. Worthley (AU) and Dr. Rhodes (CA).

Modification 19

The protocol section on the Internal Safety Committee is removed because an external committee will be used.

Modification 20
The 6 month Echo requirement has been removed.
The requirement to use a separate echocardiographic guideline has been removed. Routine echocardiograms can be used to complete the reduced datafields on the echocardiogram study Case Report Forms (CRFs).

Modification 21
Patients that undergo an implant attempt but did not receive a Portico Valve Implant will be followed for resolution of any procedure or Portico system related AEs. The patient should then be withdrawn from the clinical investigation.

Modification 22
Annual follow-up visits beginning at year 2 may be conducted at outside hospitals and reported to the study site provided the study site follows local laws and appropriately obtains the necessary source documents to complete the study Case Report Forms (CRFs).

Modification 23
Appendix J title has been changed from Instruction towards Recommendation for paced rhythm assessment in patients with a TAVI related implantation of permanent pacemaker.

Other modifications
Minor corrections of typos and grammatical errors having no impact on the content of the protocol have also been made.

2 Synopsis

Title:	International long-term follow-up study of patients implanted with a PORTICO valve.
Acronym:	PORTICO I
Purpose:	The purpose of this clinical investigation is to further assess the performance and safety profile of the Portico™ TAVI System in patients with severe symptomatic aortic stenosis.
Objectives:	The primary objective of this clinical investigation is to assess the 1 year all-cause mortality of patients with severe symptomatic aortic stenosis, implanted with a Portico Valve as per current guidelines.[1] The secondary objective of this clinical investigation is to assess the 30 day and long-term performance and safety profile of the Portico valve in patients with severe symptomatic aortic stenosis.

Endpoints:	The primary endpoint is all-cause mortality at 1 year post implant
	
	The secondary Endpoints are:
	• Evaluation of the VARC-2[19] defined event* rates at 30 days, 1 year, 2 years, 3 years, 4 years and 5 years post implant.
	  ○ All-Cause Mortality
	  ○ Cardiovascular Mortality
	  ○ Myocardial Infarction
	  ○ Stroke (disabling and non-disabling)
	• Evaluation of the VARC-2[19] defined event* rates at 30 days from the index procedure
	  ○ Vascular access site complication (major and minor)
	  ○ Bleeding (life-threatening, major and minor)
	  ○ Acute kidney injury
	• New or worsened conduction disturbances and cardiac arrhythmias (including pacemaker implantation rate at 30 days and new-onset atrial fibrillation (AF))
	• Prosthetic valve function at 30 days, 1 year, 2 years, 3 years, 4 years and 5 years post implant. (Prosthetic valve stenosis and prosthetic valve regurgitation).
	• Clinical benefit endpoints as measured with NYHA classification and 6MWT, at 30 days, 1 year, 2 years, 3 years, 4 years and 5 years post implant, and QOL (EQ-5D questionnaire) until 1 year post implant.
	
	• Evaluation of the TAVI-related resource utilization through hospital discharge (e.g. index procedural hospital/physician resources).
	
	• Interim reporting at 30 days and 1-year all-cause mortality data may be performed on a subset of patients and compared with an appropriate external comparator. The results will be presented to appropriate agencies in France and in other countries where it will be deemed necessary for reimbursement purposes.
	
	*Events will be adjudicated as specified in the CEC charter.

Design:	This is an international multicenter, prospective, non-randomized clinical investigation without concurrent or matched control, designed to assess the 1 year all-cause mortality rate of patients implanted with a Portico Valve. In addition, performance and safety profile data of the Portico Valve will be evaluated at 30 days, 1 year, 2 years, 3 years, 4 years and 5 years.

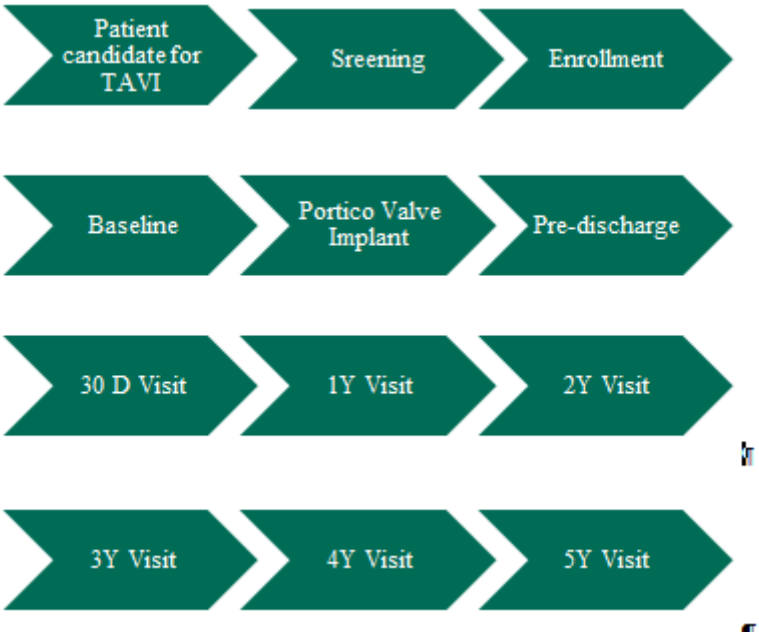
Devices used:	For EU sites: Any commercially available Portico Valve, delivery system, loading system or other accessory may be used according to its labeling. For Australian and Canadian sites: Any investigational Portico devices approved for inclusion in the trial by the respective governing regulatory authorities may be utilized in Canada and Australia. As these products are approved commercially in these countries, they may continue to be utilized in the trial. Future iterations of Portico devices and expanded indications may be included in this clinical study as they become either commercially available or approved for inclusion as an investigational device by the respective governing regulatory body for each geography.
Patient Population:	The population to be enrolled in this clinical investigation comprises both male and female patients with severe symptomatic aortic stenosis (AS) who meet specific eligibility criteria defined within this document. The total population to be enrolled in the clinical investigation is at least 866 for COHORT A, added up with any additional patient enrolled in COHORT B, to a maximum of 1046 patients in total. Cohort A: Patients enrolled directly into the Portico I study. Cohort B: Patients implanted in previous SJM sponsored regulated (pre-market) investigations and first-in-human trials whom consent for ongoing follow-up in the Portico I study after the completion of their participation in the initial study. This population has the same underlying disease as the target population of this clinical investigation; that is severe symptomatic aortic stenosis. The expected duration of participation in this clinical investigation of patients in Cohort A will be 5 years from the date of implant. For Cohort B, the expected duration of participation in this clinical investigation will be a maximum of 4 years, depending on their inclusion time post-implant.
Inclusion Criteria:	1. Patient has signed the Patient Informed Consent prior to participating in the clinical investigation. 2. Patient has been referred for a Portico Valve implant as per heart team decision. Or, patient has received a Portico Valve as participant in an SJM sponsored regulated (pre-market or first-in-human) trial. 3. Patient has senile degenerative aortic valve stenosis confirmed by echocardiographically derived criteria*: • An initial aortic valve area (AVA) of less than or equal to (≤) 1.0 cm^2 (or indexed EOA less than or equal to (≤) 0.6 cm^2/m^2) AND • A mean gradient greater than (>)40 mmHg or jet velocity greater than (>)4.0 m/s or Doppler Velocity Index less than (<)0.25. If the mean gradient is <40 mmHg and left ventricular ejection fraction (LVEF) <55%, then the site may as well perform a dobutamine stress echo to see if the mean gradient increases to >40 mmHg." (Baseline measurement taken by echo within 6 months of index procedure.) 4. Patient has a life expectancy of more than (>) 12 months.* *Note*: This criteria is not applicable for a patient who has received a Portico Valve as a participant in a SJM sponsored regulated (pre-market or first-in-*

	human) trial. Additional criteria for patients enrolled at a French site: 5. Patient is at high risk for surgery as demonstrated by a Logistic EuroSCORE equal or more than (≥) 20 and/or a Society of Thoracic Surgeon (STS) mortality risk score of more than (>) 10% and/or by clinical judgment of the Heart Team based on the individual risk profile (comorbidities).
Exclusion criteria:	1. Any case in which the Portico Valve would not be indicated for the patient as per current IFU (i.e. any "off-label" use). 2. Patient has a non-tricuspid aortic valve. 3. Patient has a prosthetic valve or ring in the aortic position. 4. Patient needs a concomitant structural heart procedure. 5. Patient is unwilling or unable to comply with all clinical investigation-required follow-up evaluations. 6. Patient is pregnant.

2.1 Clinical investigation flow charts

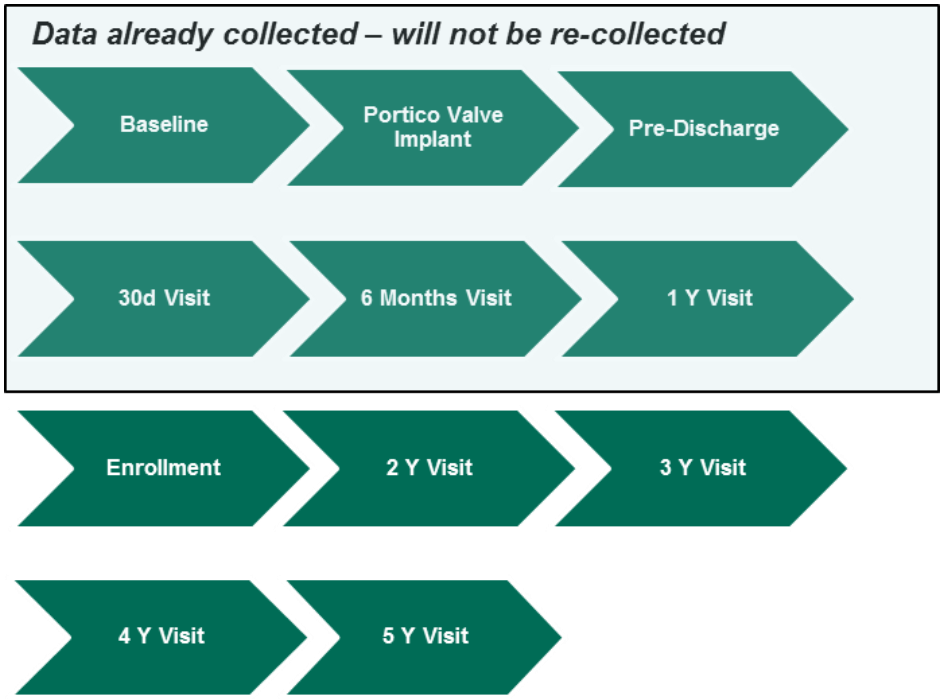
All the patients enrolled prospectively will follow the below clinical investigation flow. This group of patients is in Cohort A.

Figure 1: Clinical investigation flow chart (Cohort A)



All the patients, who participated in a SJM sponsored regulated (pre-market or first-in-human) trial and who consented to participate in this extended follow-up clinical investigation will follow the below clinical investigation flow. This group of patients will constitute Cohort B.

Figure 2: Clinical investigation flow chart (Cohort B)



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4 Background

Calcific aortic valve stenosis is a common cardiovascular disease with an increasing incidence in an aging population.[2] In cases of severe aortic stenosis, patients develop symptoms and functional limitation unavoidably followed by physical deterioration, heart failure and poor prognosis.

For many decades, surgical aortic valve replacement has been an effective treatment improving symptoms and survival[3] but more than one-third of patients with symptomatic severe aortic stenosis do not undergo surgery because of a high surgical risk; these patients are not referred, are refused or are declined surgery.[4]

Transcatheter aortic valve implantation (TAVI), first performed in 2002, has permitted the treatment of patients with excessive surgical risk.[5] Since the first TAVI case in 2002, 50.000 transcatheter aortic valve procedures have been performed worldwide comparing favorably with surgery in selected cohorts of patients; TAVI being the only intervention for inoperable aortic stenosis that demonstrated to prolong life in a randomized study.[6] Several studies have also reported symptomatic improvement in the short term[7,8,9,10] and midterm[11,12,14] after TAVI. However, nearly 20% of patients experienced no symptomatic improvement[10,13] highlighting Aortic Regurgitation (AR) as the most frequent complication and one of the main factors affecting symptoms and survival. Although significant transvalvular AR is rare after TAVI, paravalvular regurgitation or leak (PVL) is more common, mainly due to incomplete annular sealing. Paravalvular leaks may occur due to device undersizing, a mismatch between the prosthesis size and the annulus or incomplete expansion also depending on the anatomical characteristics of the patient's annulus and ascending aorta. PVL can be caused also by a non-optimal implantation site where the device is positioned too high or too low within the valve annulus. While severe PVL may result in severe hemodynamic consequences, some studies have shown moderate and even mild leaks are associated with less favorable late survival rates than no regurgitation [14,15] however the data is inconclusive on less severe PVL. Although moderate and severe AR after surgical aortic valve replacement or balloon valvuloplasty has only been reported anecdotally, the prevalence of moderate and severe PVL after TAVI has ranged from 6% to 21%. Recently, the impact of moderate and severe PVL on survival and symptoms after TAVI has been highlighted. Significant PVL is a main contributor to in-hospital death and an independent predictor of 1-year mortality and poor treatment response. In the absence of approved therapies, strategies for the prevention of significant PVL seem to be warranted. Prevention and treatment of AR are of particular importance because there is an increase in the use of TAVI.[15]

Regarding valve durability, mid-term reports of commercially available devices up to 5 years are showing a rare occurrence of leaflet failure and in vitro accelerated wear testing is comparable with surgical prostheses[13,14,16] However, more studies and more time will be needed to demonstrate whether transcatheter bioprosthesis durability will equal that of surgical bioprosthesis.

Another risk of TAVI is related to rhythm disturbances such as partial or complete heart block due to the position of the atrioventricular conduction system that passes superficially through the interventricular septum immediately below the aortic valve. Risk factors are demonstrated to be advanced age, right bundle branch block, atrioventricular delay, prosthesis oversizing and ventricular positioning. Published studies report a different number of new pacemaker implants according to the device used ranging from 4.5% at 1 year[6] to 3-fold increase with other devices.[17, 18]

The Portico transcatheter aortic valve is indicated for transcatheter delivery in patients with symptomatic severe native aortic stenosis who are considered high surgical risk. It has been designed to minimize the incidence of paravalvular leakage and damage to the conduction system. Durability is aimed to be comparable to that of currently available TAVI bioprostheses. The self-expanding stent is designed to be fully resheathable and repositionable at the implant site and retrievable if needed. Additionally the low leaflet/cuff within the stent design allows for sealing without the valve extending deep into the LVOT, potentially reducing the risk of damage to the AV node or His bundle and subsequent need for permanent pacemaker implantation. Large stent cells in the annulus section of the stent allows for tissue to conform around calcific nodules potentially minimizing paravalvular leaks. Bovine leaflets and porcine cuff are treated with Linx™ Anti-calcification Technology.

The aim of this study is to evaluate the Portico transcatheter aortic Valve up to five years, according to the VARC 2 criteria.[19]

5 Clinical study design

This is an international multicenter, prospective, non-randomized clinical investigation without concurrent or matched control, designed to assess the mid-term safety and performance of the Portico valve in patients with severe symptomatic aortic stenosis whom are high risk for surgical valve replacement. The primary endpoint is 1 year all-cause mortality. In addition, the performance and safety profile of the Portico valve will be further evaluated at 30 days, 1 year, and annually through 5 years post-implant.

The investigation will be conducted at approximately 65 centers in approximately 15 countries in Europe, Middle-East, Africa, Canada, Australia and New Zealand.

The clinical investigation is expected to last approximately 9 years; it includes the enrollment period (3 years), the follow up period (5 years) and the close-out and termination period (1 year).

5.1 Purpose

The purpose of this clinical investigation is to further assess the performance and safety profile of the Portico Valve implanted using the Portico Delivery System and the Portico Loading System in patients with severe symptomatic aortic stenosis.

5.2 Objectives

5.2.1 Primary Objective

The primary objective of this clinical investigation is to assess the 1 year all-cause mortality of patients, with severe symptomatic aortic stenosis, implanted with a Portico Valve as per current guidelines[1].

5.2.2 Secondary Objective

The secondary objectives of this clinical investigation are to assess the peri-procedural and long-term performance and safety profile of the Portico Valve implanted, using the Delivery System and the Loading System, in patients with severe symptomatic aortic stenosis.

5.3 Endpoints

5.3.1 Primary Endpoint

- The primary endpoint is all-cause mortality at 1 year post implant (according to VARC-2[19]).

5.3.2 Secondary Endpoints

- Evaluation of the VARC-2[19] defined event rates at 30 days, 1 year and annually through 5 years post implant. Definitions are detailed in Appendix D: VARC 2 Endpoints Definitions.
  - All-Cause Mortality
  - Cardiovascular Mortality
  - Myocardial Infarction
  - Stroke (disabling and non-disabling)
  - New or worsened conduction disturbances and cardiac arrhythmias (including pacemaker implantation rate at 30 days and new-onset atrial fibrillation (AF)

- Evaluation of the VARC-2[19] defined event rates at 30 days from the index procedure.
  - Vascular access site complication (major and minor)
  - Bleeding (life-threatening, major and minor)
  - Acute kidney injury

- Prosthetic valve function at 30 days, 1 year and annually through 5 years post implant. (Includes prosthetic valve stenosis and prosthetic valve regurgitation).

- Clinical benefit endpoints at 30 days, 1 year and annually through 5 years post implant (if available)
  - NYHA functional classification
  - 6 Minute Walk Test (6MWT)
  - Quality of life measured with EQ-5D questionnaire through 1 year post-implant

- Evaluation of the TAVI-related resource utilization through hospital discharge (e.g. index procedural hospital/physician resources)

- Interim reporting at 30 days and 1-year all-cause mortality data may be performed on a subset of patients and compared with an appropriate external comparator. The results will be presented to appropriate agencies in France and in other countries where it will be deemed necessary for reimbursement purposes.

NOTE: Should new VARC or ESC Guidelines be published, 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.

5.4 Population

The population to be enrolled in this clinical investigation comprises both male and female patients with severe symptomatic aortic stenosis (AS) who meet specific eligibility criteria defined within this document. The total population to be enrolled in the clinical investigation is at least 866 for COHORT A, added up with any additional patient enrolled in COHORT B, to a maximum of 1046 patients in total.

Cohort A: Patients enrolled directly into the Portico I study.

Cohort B: Patients implanted in previous SJM-sponsored regulatory (pre-market) investigations and first-in-human trials whom consent for ongoing follow-up in the Portico I study after the completion of their participation in the initial study. This population has the same underlying disease as the target population of this clinical investigation; that is severe symptomatic aortic stenosis.

The expected duration of participation in this clinical investigation of patients in Cohort A will be 5 years from the date of implant. For Cohort B, the expected duration of participation in this clinical investigation will be a maximum of 4 years, depending on their inclusion time post-implant.

5.5 Device description

The Portico Valve is a catheter-delivered aortic prosthetic valve that combines a bioprosthetic valve mounted on a self-expandable stent. The Portico Valve, the Delivery System and the Loading System are indicated for use in high risk patients with severe aortic stenosis who require aortic valve replacement (AVR). 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 and the Investigator Brochure for further details. The Instruction for Use of the devices used in this investigation can be obtained upon request.

The legal manufacturer of the Portico Valve, the Delivery System and the Loading System is St. Jude Medical, Cardiovascular Division, located at 177 E. County Road B, St. Paul, MN 55117, USA which has various sites for its manufacturing activities.

Future iterations of Portico devices and expanded indications may be included in this clinical study as they become either commercially available or approved for inclusion as an investigational device by the respective governing regulatory body for each geography.

Table 11 contains terminology that will be employed throughout this document. The terminology defined in Table 1 will accommodate any new device size and access type. The only device that is implanted in the study patient is the Portico valve.

Table 1: Devices glossary

Item	Prosthetic valve	Delivery system	Loading system
Definition	Aortic prosthetic valve (device under evaluation).	Manual system that allows the aortic prosthetic valve to be implanted in the patient.	Manual system that allows the operator to load the prosthetic valve into the delivery system.
Commercial name	Portico™ Transcatheter Aortic Valve	Portico™ Delivery System	Portico™ Loading System
Terminology used in this CIP	Portico Valve	Delivery System	Loading System

5.6 Geographical device considerations

5.6.1 **For EU sites:**

In Europe, any commercially available (CE Marked) Portico valve, delivery system, loading system or other accessory may be used in this trial according to its labeling (IFU). It is the responsibility of the investigator to ensure that the devices:

- Will be used according to the IFUs
- Will be accounted for together with the patient's contact details in the Patient Identification Log (PIL)

5.6.2 **For Australian and Canadian sites:**

Portico devices utilized in this trial in Canada and Australia may be investigational and used according to their respective regulatory submission documents. These products may continue to be used in the trial upon commercial release in each country. It is the responsibility of the investigator to ensure that the devices:

- Will be used according to the IFUs/IB
- Will be accounted for together with the patient's contact details in the Patient Identification Log (PIL)
- Will be traced using the appropriate traceability documentation (Note: this requirement applies to investigational devices only)

5.6.3 **Investigational device accountability for Australian and Canadian sites:**

Access to devices which haven't received regulatory approval shall be controlled and these devices shall be used only in the clinical investigation and according to the CIP and IFU/IB.

The sponsor shall keep records to document the physical location from shipment of these devices to the investigation sites until use, return or disposal. The Principal Investigator or authorized designee shall keep records documenting the date of receipt, the unique identification or lot number of each investigational device, the patient identification, the date of use, the expiry date, the date on which the investigational device was returned/explanted from the patient (if applicable) and the date of return of unused, expired or malfunctioning investigational devices (if applicable).

5.7 Hospital heart team

The "Heart Team" is a multi-disciplinary team involving at least (but not limited to):

- Two physicians of which one should be a cardiologist or an interventional cardiologist and a cardiac surgeon
- Any other relevant function such as an imaging specialist or a TAVI nurse.

The objective of the Heart Team is to review and interpret patient's clinical data in order to obtain a consensus on the optimal treatment strategy for each patient. The heart team will be responsible for ensuring and documenting patient's eligibility to receive a Portico Valve.

Investigational sites will use their standard documentation to report the heart team's recommendations, including the members of the heart team, for each patient prospectively or retrospectively enrolled in the study. This instruction only applies to Cohort A.

In certain circumstances, it might be decided to send relevant clinical data (such as echocardiogram, CT/MRI or Angiogram) out of the hospital for further analysis to determine if patient's valve anatomy is suitable for participation in the clinical investigation. If required, an authorization form to release medical information outside the hospital is available for sign-off by the patient.

5.8 Patient screening

Patient candidates for a TAVI procedure or who already received a Portico Valve as part of a SJM-sponsored regulatory or first-in-human trial can be screened by any member of the investigational team trained on the CIP and delegated to do so. Patients who do not meet the inclusion/exclusion criteria will not be eligible to participate in this clinical investigation. Patients meeting the inclusion/exclusion criteria will be fully informed about the clinical investigation and asked to participate. In case a patient agrees to participate, a duly signed and dated Patient Informed Consent (PIC) will be obtained.

All patient candidates for a TAVI procedure should be accounted for and documented on the screening and enrollment log in an anonymous fashion. This log should be kept up to date throughout the clinical investigation by the principal investigator or his/her authorized designee.

The investigational sites involved in previous SJM-sponsored regulatory or first-in-human trials involving the Portico Valve will also be asked to contact the patients who participated and invite them to participate in this extended follow-up clinical investigation. These patients shall be accounted for in a separate screening and enrollment log.

5.9 Point of enrollment

Patients will be considered enrolled in the clinical investigation once they have provided signed and dated written Informed Consent (refer to section 7.2 for the Informed Consent Process).

Once enrolled, a patient is expected to comply with the required clinical investigation visits and assessments. All patients enrolled in the clinical investigation (including those withdrawn or lost to follow-up) shall be accounted for and documented on the Patient Identification Log, assigning an identification code linked to their names, alternative identification or contact information. This log shall be kept up to date throughout the clinical investigation by the principal investigator or his/her authorized designee. Since patient privacy and confidentiality of data must be maintained throughout the clinical investigation, this log will remain on site.

5.10 Inclusion and Exclusion Criteria

The following inclusion and exclusion criteria will be used to determine a patient's enrollment eligibility in the clinical investigation. Candidates for this clinical investigation must meet all the inclusion criteria and none of the exclusion criteria.

5.10.1 Inclusion Criteria

All candidates will meet the following inclusion criteria:

1. Patient has signed the Patient Informed Consent prior to participating in the clinical investigation.
2. Patient has been referred for a Portico Valve implant as per Heart Team decision **or** patient has received a Portico Valve as per participation in an SJM sponsored regulatory or first-in-human trial.
3. Patient has senile degenerative aortic valve stenosis confirmed by echocardiographically derived criteria*:
   - An initial aortic valve area (AVA) of less than or equal to (≤) 1.0 cm^2 (or indexed EOA less than or equal to (≤) 0.6 cm^2/m^2)
     AND
   - A mean gradient greater than (>)40 mmHg or jet velocity greater than (>)4.0 m/s or Doppler Velocity Index less than (<)0.25.

   If the mean gradient is <40 mmHg and left ventricular ejection fraction (LVEF) <55%, then the site may as well perform a dobutamine stress echo to see if the mean gradient increases to >40 mmHg."
   (Baseline measurement taken by echo within 6 months of index procedure.)
4. Patient has a life expectancy more than (>) 12 months.*

For patients enrolled in a French site:

5. Patient is at high risk for surgery as demonstrated by a Logistic EuroSCORE equal or more than (≥) 20 and/or a Society of Thoracic Surgeon (STS) mortality risk score of more than (>) 10% and/or by clinical judgment of the Heart Team based on the individual risk profile (comorbidities).

**Not applicable for a patient who has received a Portico Valve as per participation in an SJM sponsored Regulatory or First-In-Human trial.*

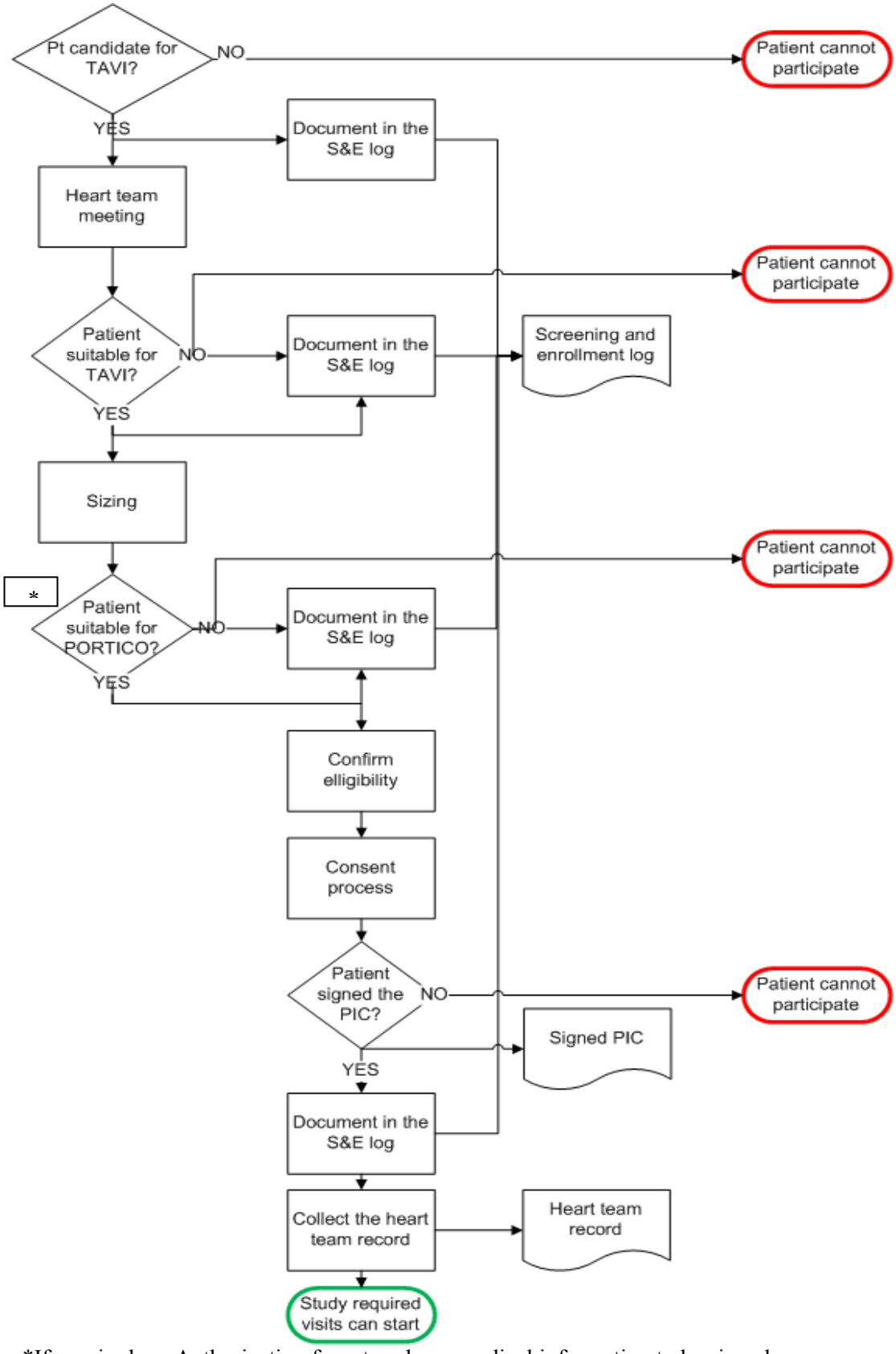
5.10.2 Exclusion Criteria

Candidates will be excluded from the clinical investigation if any of the following criteria is present:

1. Any case in which the Portico Valve would not be indicated for the patient as per current IFUs (i.e. any "off-label" use).
2. Patient has any other aortic valve than tricuspid one.
3. Patient has a prosthetic valve or ring in the aortic position.
4. Patient needs a concomitant structural heart procedure.
5. Patient is unwilling or unable to comply with all clinical investigation-required follow-up evaluations.
6. Patient is pregnant.

The figure below summarizes the screening, enrollment and eligibility assessment scheme for Cohort A.

Figure 3: Patient's eligibility assessment scheme (Cohort A)



*If required, an Authorization form to release medical information to be signed

5.10.3 **Additional considerations**

In case of patient's death and/or occurrence of adverse events (serious or not) prior to the Portico valve implant, these events will be reported separately and will not be taken into account in the study endpoints reporting.

In case a patient signed the PIC but would not receive a Portico Valve, reasons for patient not receiving a Portico Valve will be reported separately and will not be taken into account in the study endpoints reporting. Patient will then be withdrawn from the study. However, if the Portico valve or delivery system entered the patient's body but was not successfully implanted, the patient should continue in follow-up until 30 days or until all adverse events associated with the Portico device or procedure are resolved (whichever occurs first). Possible reasons for patient not receiving a Portico Valve are listed below but are not limited to:

- Screening failure (patient did not meet all inclusion criteria or/and meet one exclusion criteria) before the index procedure
- Investigator's decision to withdraw the patient before the procedure
- Adverse event affecting patient's eligibility to TAVI
- Procedural exclusion
- Unsuccessful implant attempt
- Consent withdrawn, lost to follow-up or death before the procedure

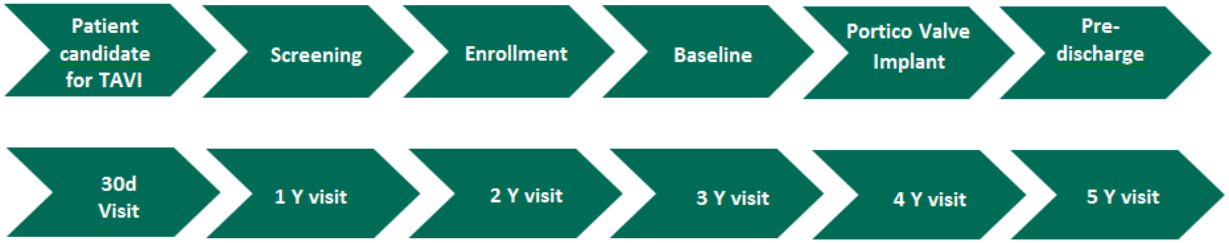
6 Procedures

6.1 Clinical investigation flow chart

6.1.1 Cohort A (Prospective)

All the patients enrolled prospectively will follow the below clinical investigation flow. This group of patients is in Cohort A.

Figure 4: Clinical investigation flow chart (Cohort A-prospective)

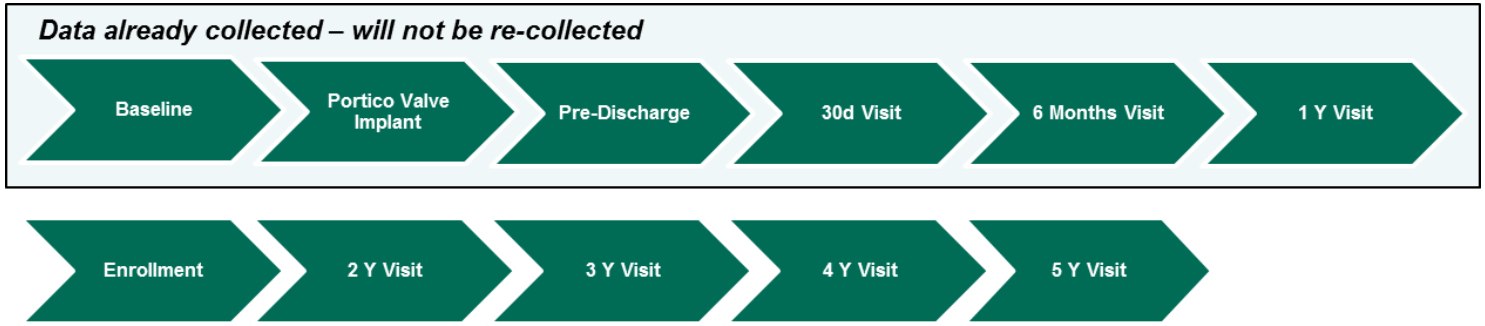


6.1.2 Cohort B

All the patients, who participated in a SJM sponsored regulatory or first-in-human trial and who consented to participate in this extended follow-up clinical investigation will follow the below clinical investigation flow. This group of patients will constitute Cohort B.

- For these patients, the data collection will start after consent is obtained and will include any study related event (AE, unscheduled visit, etc.) documented after the patient has exited the SJM sponsored regulatory or first-in-human trial.
- For these patients, the data collected up to the 1 year follow-up visit will not need to be re-collected.

Figure 5: Clinical investigation flow chart (Cohort B)



6.2 Clinical investigation activities and visits

Table 2 : List of clinical investigation activities and visits

Study activities and visits	En/Bas*	Imp*	P-Dis*	30 d*	1 Y*	2 Y	3 Y	4 Y	5 Y
Visit window	-6m-0**	0	0-7d	-7d+14d	±90d	±90d	±90d	±90d	±90d
Informed Consent	X								
Patient's eligibility assessment	X								
Angiography	X								
Demographics	X								
Medical and Cardiovascular History	X								
Native aortic valve assessment	X								
Access site assessment	X								
Surgical risk assessment	X								
Frailty assessment: - 5 meters walking time - Grip strength - Wasting and malnutrition parameters - Cognitive impairment or dementia (MMSE)	 X X X X			 X X X X	 X X X X				
Blood sample: - Serum Albumin (Frailty assessment) - Hemoglobin, Creatinine (if available) - Troponin	 X X X		 X X[a]	 X X X	 X X X				
Physical assessment	X		X	X	X	X	X	X	X
12 lead ECG	X		X[b]	X	X				
Paced rhythm assessment[f]				(X)					
Medication assessment	X	X	X	X	X	X	X	X	X

Echocardiography	X	X[c]	X	X	X	X	X	X	X
NYHA Classification	X		X	X	X	X	X	X	X
QoL questionnaire (EQ-5D)	X[d]		X	X	X				
The six-minute walking test	X			X	X	X	X	X	X
Modified Rankin Scale[e]	X		X	X	X				
Adverse Events Assessment	X	X	X	X	X	X	X	X	X
Device Deficiency Assessment	X	X	X	X	X	X	X	X	X
Resources utilization		X	X						

(X) as applicable

* For Cohort B, the informed consent and eligibility assessment will be conducted but all the other above mentioned data up to 1 year will not be re-collected (equivalent to grey background). Depending on time point of informed consent signed, the patient will enter the Portico I study at 1Y or later.

** For Cohort A, tests to confirm baseline measurements (e.g. Angio, CT, echocardiogram) should be within 6 months of index procedure.

[a] Blood Sample for Troponin to be obtained between day 2 and 4 post-implant or at discharge whatever occurs first.

[b] ECG within 24 hrs Post-implant AND at discharge but no later than 7 days Post-implant-whatever occurs first.

[c] Assess aortic regurgitation with TEE if available or via fluoroscopy/angiography

[d] The QoL questionnaire should be completed by the patient the closest possible to the implant date

[e] The Modified Rankin scale should be completed additionally (if possible) 90 days after any neurological event (stroke, TIA, encephalopathy).

[f] The permanent paced rhythm assessment is performed only if applicable

Table 3: Clinical investigation activity definition

Study activities	Definitions
Informed Consent	An Ethics Committee (EC) and Sponsor approved Informed Consent must be obtained in accordance to section 7.2 (Informed Consent Process) of this Clinical Investigation Plan.
Patient's eligibility assessment	Refer to the patient's eligibility assessment process as illustrated in **Figure 3**.
Demographics (NAP for Cohort B)	Patient's Age and Gender
Medical and Cardiovascular History (NAP for Cohort B)	Medical and Cardiovascular history of the patient: • Cardiovascular and neurovascular history • Previous cardiovascular procedures • Other medical conditions (e.g., diabetes, kidney disease, lung disease, etc.) • Baseline status and risk factors
Native aortic valve assessment (NAP for Cohort B)	Native aortic valve information such as annulus size or valve morphology will be collected based on examinations conducted at the investigational site as standard of care. We recommend the use of Multi Slice Computed Tomography (MSCT) in particular for annulus sizing; however other imaging modalities, such as Trans Esophageal Echocardiography (TEE) are also acceptable. It is recommended to perform both non-contrast and contrast MSCT, if routinely performed. It is also recommended to perform both thoracic and abdominal CT, if routinely performed. MSCT exams (if routinely performed) and any other data acquired as part of patient's native aortic valve assessment (such as additional (pre-) sizing information), should be sent to Sponsor on request only. If requested, MSCT should be recorded in Dicom format and all material should be de-identified and sent to the sponsor.
Access site assessment (NAP for Cohort B)	Patient's recommended TAVI access site characteristics (Transfemoral, transapical, etc.)
Surgical Risk Assessment (NAP for Cohort B)	Three Surgical Risk Assessment tools will be used: Logistic EuroSCORE I, Logistic EuroSCORE II and the STS Risk Score. Refer to Appendix E: Surgical Risk Assessment Tools, for links to the on-line score calculators.
Frailty assessment (NAP for Cohort B)	Patient Frailty index will be assessed at baseline, at 30 days and at 1 Year. Frailty is a risk factor not included in the current surgical risk assessment tools. Frailty Index assessment will include: - 5 meters walking time - Grip strength - Wasting and malnutrition parameters (including weight loss, BMI and Serum albumin value to be obtained via blood sample)

Study activities	Definitions
	- Cognitive impairment or dementia as measured with the mini–mental state examination (MMSE). For further details/instructions, please refer to Appendix F: Frailty Assessment.
Blood sample (NAP for Cohort B)	• Albumin: see frailty assessment • Hemoglobin, Creatinine (if available) • Troponin: at Enrollment/Baseline and between day 2 and 4 Post-implant or at discharge whatever occurs first.
Physical assessment (From 2Y visit onward for Cohort B)	At the baseline visit the following measurement must be assessed: • Height • Weight • Systolic/Diastolic blood pressure The following measurements must be assessed at all visits: • Weight • Systolic/Diastolic blood pressure
12 Leads ECG (NAP for Cohort B)	Assessment of dominant rhythm, heart rate, PR interval, QRS duration, bundle branch block, fascicular block etc. The ECG is to be performed at baseline, within 24 hours Post-implant, at hospital discharge but no later than 7 days Post-implant, whatever occurs first and at 30days and 1 Year.
Medication assessment (From 2Y visit onward for Cohort B)	The following information on medication will be collected at each visit: • Beta Blockers • Calcium Channel Blockers • Anticoagulants • Antiplatelet agents including Aspirin • Diuretics • Ace-Inhibitors • Angiotensin Receptor Blocker (ARBs) • Statins At the implant visit the prophylactic antibiotics regimen will also be collected
Echocardiogram (From 2Y visit onward for Cohort B)	Each site will be responsible for performing and interpreting the baseline & post-implant and follow-up echocardiograms using the VARC 2 definitions. For further details on echocardiographic variables, please refer to Appendix D: VARC 2 Endpoints Definitions.

Study activities	Definitions
	Echocardiograms can be requested to be sent to an echo Core Laboratory. If requested, exams should be recorded in Dicom format and should be de-identified prior to sending. Routine echocardiograms can be used to complete the echocardiogram study Case Report Forms (CRFs).
NYHA Classification (From 2Y visit onward for Cohort B)	The New York Heart Association (NYHA) Functional Classification provides a simple way of classifying the extent of heart failure.
QoL questionnaire (EQ-5D) (NAP for Cohort B)	The EQ-5D questionnaire will be used. It is a standardized instrument for use as a measure of health outcomes.
The six-minute walking test (From 2Y visit onward for Cohort B)	The six-minute walking test (6MWT) is a commonly used objective measure of functional exercise capacity in individuals with moderately severe impairment. For further details/instructions, please refer to Appendix G: ATS Guidelines25 for the Six Minute Walk Test instructions.
Modified Rankin scale (mRS)	The modified Rankin Scale (mRS) is a functional measurement to assess the degree of disability or dependence in the daily activities of people who have suffered a stroke. mRS at Enrollment/Baseline, 30days, 1year and is to be completed additionally (if possible) 90days after any neurological event (stroke, TIA, encephalopathy) ***This assessment must be completed by a rater who has a current certificate that demonstrates completion of an accredited training program for this stroke scale, using the structured interview found in*** Appendix H: Structured Interview for the Modified Rankin Scale (mRS)**.**
Portico Valve Implant (NAP for Cohort B)	Procedural information must be collected including: • Pre-implant information (such as access type, use of balloon valvuloplasty, etc.) • Implant information (such as prosthetic valve information, use of rapid pacing, etc.) • Aortic regurgitation • Implant depth and prosthesis-patient mismatch • Post-implant information including hemodynamics The **assessment of aortic regurgitation** must be performed with a combination of echocardiography, angiography and hemodynamic approach, preferably according to the instructions provided in Appendix I: Peri-procedural instructions. **Implant depth measurement** should be assessed via aortic root angiography and further instructions are also provided in Appendix I: Peri-procedural instructions. **Prosthesis-patient mismatch** will be measured by means of echocardiography according to the VARC 2 guidelines.

Study activities	Definitions
	Any other data acquired as part of the patient's implant procedure (such as routinely performed aortography) can be collected by the Sponsor as well to obtain additional procedural information regarding the implant.
Adverse Events Assessment **(From 1Y visit onward for Cohort B)**	All adverse events will be documented according to Section 7.3 (Adverse Events, Adverse Device Effect, and Device Deficiency).
Device Deficiency Assessment	All device deficiencies will be documented according to Section 7.3 (Adverse Events, Adverse Device Effect, and Device Deficiency).
Paced Rhythm Assessment (NAP for Cohort B)	If the patient received a new permanent pacemaker, due to an AV-block, within 30 days after their TAVI procedure, then the patient's dependence to pacemaker will be checked according to the recommendations provided in Appendix J: Recommendation for paced rhythm assessment in patients with a TAVI related implantation of permanent pacemaker.
Resource utilization Assessment (until discharge for COHORT A) (NAP for Cohort B)	Procedural resources: Material resources such as devices used during the procedure (valve, guiding catheters, valvuloplasty balloons, etc.), operators' resources and procedure duration will be collected at procedure time. Hospital resources: length of stay in different wards (ICU, non ICU, etc.); will be collected at discharge.

Table 4: Data Collection Forms for COHORT A and COHORT B (identical to Cohort A with exception of grey background boxes)

Study activities	En/Bas	Imp	P-Dis	30 d	1 Y	2 Y	3 Y	4 Y	5 Y
Enrollment Form	X								
Baseline Form	X								
Portico Valve Implant Form		X							
Echocardiogram Form	X		X	X	X	X	X	X	X
EQ-5D Form	X		X	X	X				
Follow-Up Visit Form			X	X	X	X	X	X	X
Adverse Events Form	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Device Deficiency Form	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Deviation Form	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Termination Form	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X
Death Form	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Exams	All exams (ECG, Echo, angio, MSCT and any other exam) should be provided to Sponsor on request. In addition, Echocardiograms can be requested to be sent to an echo core laboratory. If requested, exams should be recorded in Dicom format and should be de-identified prior to sending.								

6.2.1. Enrollment Visit

For the patients who participated in a SJM-sponsored regulatory or first-in-human trial, the enrollment will occur retrospectively (after the date they received their Portico Valve). The historical data collected through 1 year in those trials will not need to be re-collected for this clinical investigation.

For patients indicated for implantation of a new Portico Valve, the enrollment will occur prospectively (before the date they will receive their Portico Valve) at a maximum of 45 days prior to the date of the Portico Valve implant and no later than the date of the Portico Valve implant but before the implant takes place.

The following enrollment activities are performed after the patient has been screened and must occur before any investigational procedure/visit.

- The principal or delegated site personnel is responsible for screening all potential patients to determine patient eligibility for the investigation
- If a patient meets all pre-procedural inclusion criteria and does not meet any of the pre-procedural exclusion criteria, he/she is eligible for the investigation.
  - Inform the eligible patient verbally about the investigation and provide the information sheet and consent to the patient.
  - Provide ample time for the patient to read and understand the information sheet and consent and to consider participation in the clinical investigation. Invite the patient to ask questions if needed.
  - Obtain the signature and date hand-written from the eligible patient on the EC approved informed consent (If an eligible patient does not sign and date the informed consent, he cannot participate in the investigation. No further protocol required activities are performed)
  - Obtain the signature and date from the principal or delegated investigator who obtained consent on the EC approved consent
  - Provide one copy of the signed and dated version of the informed consent to the patient (signed by both patient and investigator)
  - File the original signed and dated version of the informed consent in the Investigator Site Binder (ISB).
- Record enrollment information (name of the investigation, date of consent and Inclusion/exclusion information) in the hospital records and complete the Enrollment form preferably within 5 days after enrollment (failure to meet this timeline will not be considered a protocol deviation)
- Notify the sponsor by submitting the enrollment form.

NOTE: As soon as the patient signs the PIC, adverse events and device deficiencies need to be reported according to the guidelines mentioned in section 7.3. For Cohort B, patients, adverse event and device deficiency reporting includes events having occurred after their last documented follow-up visit.

In case the patient was consented to participate in the investigation, but does not meet inclusion/exclusion criteria (i.e. screen failure before the index procedure), the following actions shall be taken:

- Document enrollment information (consent and inclusion/exclusion) in the hospital records; complete the Enrollment, deviation and Termination forms. The form must be authorized / approved by the principal or delegated investigator.
  - Refer to Appendix C: Data Collection Method.
  - Inform the patient about his/her withdrawal.

- The EC/IRB and NCA/NRA should be notified appropriately about any deviations with regards to obtaining the informed consent.

6.2.2. Baseline Visit (Cohort A only)

This visit can take place the same day as the enrollment visit. The data from previously conducted diagnostic tests/procedures, as indicated with an " (X) as applicable
, performed as standard of care will be collected during this visit. It is not necessary to repeat these tests if they were collected within the clinical investigation visit window. All other data must be collected after obtaining clinical investigation specific consent and within 45 days prior to the TAVI procedure. The baseline visit consists of the following activities:

- Demographics
- Medical and Cardiovascular History
- Native aortic valve assessment
- Access site assessment (Trans-femoral, trans-apical, etc.)
- Surgical Risk Assessment
- Frailty Assessment (including assessment of 5 meters walking time, grip strength, wasting and malnutrition and cognitive impairment or dementia via MMSE)
- Blood sample (Serum Albumin value as part of frailty assessment. Creatinine, Hemoglobin if available (SOC) and Troponin values)
- Physical Assessment
- 12 lead ECG
- Medication assessment
- Echocardiogram
- NYHA Classification
- QoL questionnaire (EQ-5D)
- 6MWT
- Modified Rankin Scale
- Adverse events assessment
- Device Deficiency assessment

6.2.3. Portico Valve Implant visit - Index procedure (Cohort A only)

The medical team performing the TAVI procedure will typically consist of:

- An interventional cardiologist or a cardiac surgeon at the site will perform the procedure according to local guidelines.
- A second operator (a cardiac surgeon or a cardiologist) may be present during the procedure as needed.
- An anesthesiologist and/or a perfusionist as needed.

The implanting physician should be trained according to SJM Portico training program prior to implant of the Portico Valve.

NOTE: The above medical team members do not need to be trained on the protocol if they only perform the Portico Valve implant and no other study related tasks.

NOTE: Anticoagulation 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.

At least one device may be deployed in every patient who has signed the PIC and is not procedurally excluded. Although not recommended, if a physician determines it is in the best interest of the patient to have a second device placed, a patient may receive an additional device.

The procedure visit will consist of the following steps:

- Pre-implant (access preparation)
- Implant (valve deployment)
- Aortic regurgitation assessment combining angiography, echocardiography and hemodynamic approach
- Implant depth and prosthesis-patient mismatch assessment
- Post-implant (access closure)
- Medication assessment
- Device implantability assessment
- Adverse events assessment
- Device Deficiency assessment
- Resource utilization assessment

It is strongly recommended to follow the peri-procedural instructions for the assessment of aortic regurgitation and implant depth as mentioned in Appendix I. However, failure to follow these instructions will not be considered a protocol deviation.

Procedural Exclusion

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. Any patient that does not have a delivery system enter his or her body will be considered "procedurally excluded."
Data will be collected on these subjects from the Baseline through the 30-day follow-up, including reason for exclusion and collection of possible adverse events.

The patient should then be withdrawn from the clinical investigation.

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 SJM per instructions provided in Appendix K: Explant, Return, and Analysis of Valve and Appendix L: Instructions for device return - Large and Small Kits.

6.2.4. Pre-Discharge visit (Cohort A only)

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 week day prior to discharge. The assessment will include:

- Physical assessment
- Blood sample (between day 2 to 4 Post-implant or at discharge whatever occurs first) to obtain Hemoglobin, Creatinine and Troponin values
- 12 lead ECG (within 24hrs Post-implant and at hospital discharge but no later than 7 days Post-implant, whatever occurs first).
- Medication assessment
- Echocardiography (if a post-procedure echo has been done within 24 hours prior to discharge, an additional discharge echo is not required)
- NYHA functional classification
- QoL questionnaire (EQ-5D)
- Modified Rankin Scale
- Adverse events assessment
- Device Deficiency assessment
- Resource utilization assessment

6.2.5. 30 Day follow-up visit (Cohort A only)

The 30 Day visit will take place at 30days (-7 days, +14days) after the index procedure, and will include:

- Frailty Assessment by means of the following components: 5 meters walking time, grip strength, wasting and malnutrition (including blood sample to obtain Serum Albumin value) and cognitive impairment or dementia (via MMSE)
- Physical assessment
- 12 lead ECG
- Medication assessment
- Echocardiography
- NYHA functional classification
- QoL questionnaire (EQ-5D)

- 6MWT
- Modified Rankin Scale
- Adverse events assessment
- Device Deficiency assessment
- Permanent Pacemaker Control (if applicable)
- Resource utilization assessment

6.2.6. 1 Year follow-up visit (Cohort A only)

The 1 Year visit will take place at 365 days (± 90days) after the index procedure, and will include:

- Frailty Assessment by means of the following components: 5 meters walking time, grip strength, wasting and malnutrition (including blood sample to obtain Serum Albumin value) and cognitive impairment or dementia (via MMSE)
- Physical assessment
- 12 lead ECG
- Medication assessment
- Echocardiography
- NYHA functional classification
- QoL questionnaire (EQ-5D)
- 6MWT
- Modified Rankin Scale
- Adverse events assessment
- Device Deficiency assessment
- Resource utilization assessment

6.2.7. 2 Year follow-up visit

To accommodate subject referrals from distant hospitals, the referring physician may conduct the 2 Y follow-up visit. In such cases, the investigator may contact the referring physician's office and/or obtain the appropriate source documents to complete Case Report Forms (CRFs).

The 2 Year visit will take place at 730 days (± 90 days) after the index procedure, and will include:

- Physical assessment
- Medication assessment
- Echocardiography

- NYHA functional classification
- 6MWT
- Adverse events assessment
- Device Deficiency assessment

6.2.8. 3 Year follow-up visit

To accommodate subject referrals from distant hospitals, the referring physician may conduct the 3 Y follow-up visit. In such cases, the investigator may contact the referring physician's office and/or obtain the appropriate source documents to complete Case Report Forms (CRFs).

The 3 Year visit will take place at 1095days (± 90days) after the index procedure, and will include:

- Physical assessment
- Medication assessment
- Echocardiography
- NYHA functional classification
- 6MWT
- Adverse events assessment
- Device Deficiency assessment

6.2.9. 4 Year follow-up visit

To accommodate subject referrals from distant hospitals, the referring physician may conduct the 4 Y follow-up visit. In such cases, the investigator may contact the referring physician's office and/or obtain the appropriate source documents to complete Case Report Forms (CRFs).

The 4 Year visit will take place at 1460days (± 90days) after the index procedure, and will include:

- Physical assessment
- Medication assessment
- Echocardiography
- NYHA functional classification
- 6MWT
- Adverse events assessment
- Device Deficiency assessment

6.2.10. 5 Year follow-up visit

To accommodate subject referrals from distant hospitals, the referring physician may conduct the 5 Y follow-up visit. In such cases, the investigator may contact the referring physician's office and/or obtain the appropriate source documents to complete Case Report Forms (CRFs).

The 5 Year visit will take place at 1825days (± 90days) after the index procedure, and will include:

- Physical assessment
- Medication assessment
- Echocardiography
- NYHA functional classification
- 6MWT
- Adverse events assessment
- Device Deficiency assessment

6.2.11. Unscheduled Visit

An unscheduled visit is defined as a visit that occurs between two scheduled investigational 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 investigation endpoints needs to be documented such as Echocardiography, ECG or modified Rankin Stroke Scale by completing the appropriate section of the Follow-up or Echocardiogram electronic Case Report Form (eCRF).

NOTE: The Modified Rankin scale should be completed at every visit and additionally (if possible) 90 days after any neurological event (stroke, TIA, encephalopathy). Use the unscheduled visit to record the Modified Rankin scale score. This score can be obtained over a telephonic interview. Failure to obtain the Modified Rankin scale score 90 days after the onset of a neurological event will not be considered a protocol deviation.

NOTE: For cohort B patients, in the event of an unscheduled visit occurring after the patient 1 year follow-up, this visit is to be documented as part of this clinical investigation.

6.2.12. Description of activities performed by Sponsor Representatives

A physician proctor and SJM Field clinical Specialist (FCS) will attend all proctored procedures to answer device and procedural questions, until the implanting investigator is deemed trained and he and his team are ready for independence. Physician training and proctoring will be documented appropriately.

It is permissible that a FCS will periodically attend procedures throughout the investigational study to observe the implanting investigator and his team. This will afford the opportunity for continued training if required and allow the investigator continued product support from the sponsor.

Sponsor personnel will not:

- Perform the informed consent process
- Practice medicine or participate directly in the procedure
- Provide medical diagnosis or treatment to patients
- Discuss a patient's condition or treatment with a patient
- Independently collect clinical investigational data or complete study documentation

6.2.13. Description of post-investigational provision of medical care

When the patient's participation in the clinical investigation has been completed the patient will return to medical care as per physician's recommendation.

7 Clinical Investigation Conduct

7.1 Statements of Compliance

The investigation will be performed in accordance with the most current versions of the World Medical Association (WMA) Declaration of Helsinki and any regional and/or national regulations as appropriate.
ISO14155 2011 shall be used as a guideline with following exceptions: limited adverse event reporting and device accountability.

The investigator shall not start enrolling patients or requesting informed consent prior to obtaining EC approval and national competent authority/national regulatory authority approval, if applicable, and authorization from the sponsor in writing for the investigation. In case additional requirements will be imposed by the EC or national competent authority/national regulatory authority they shall be followed, if appropriate.

As sponsor, SJM has taken up general liability insurance in accordance with the requirements of the applicable local laws. If required, additional patient coverage or an investigation specific insurance shall be provided by the Sponsor as well.

7.1.1. Adherence to the Clinical Investigation Plan

The principal investigator and delegates are required to adhere to the CIP in order to prevent patients from being exposed to unreasonable risks. In addition, the principal investigator and delegates are required to be compliant with the signed clinical investigation agreement, applicable national or local laws and regulations, and any conditions required by the appropriate EC or applicable regulatory authorities are expected as well. Instances of failure, intentionally or unintentionally, to adhere to the requirements of the CIP are considered a deviation.

In some cases failure to comply with the protocol may be considered failure to protect the rights, safety and well-being of patients, since the non-compliance exposes patients to unreasonable risks. For example, failure to adhere to the inclusion/exclusion criteria: these criteria are specifically defined by the sponsor to exclude patients for whom the investigational device is not beneficial and the use involves unreasonable risks. This may be considered failure to protect the rights, safety and well-being of the enrolled patient. Similarly, failure to perform safety assessments intended to detect adverse events may be considered failure to protect the rights, safety and well-being of the enrolled patient. Investigators should seek minimization of such risks by adhering to the protocol.

Simultaneously, in the event that adhering to the protocol might expose the patient to unreasonable risks, the investigator is also required to protect the rights, safety and well-being of the patient by intentionally deviating from the requirements of the CIP, so that patients are not exposed to unreasonable risks.
It is the responsibility of the investigator to provide adequate medical care to a patient enrolled in an investigation.

The PI shall promptly report to the sponsor any deviations from the CIP that affect the rights, safety or well-being of the patient or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances. The reporting of these deviations should be done as soon as

possible but no later than 72 hours after the investigator becomes aware. The investigator shall also notify promptly the EC, as per their requirements. Any corrective and preventive actions required by the EC must be complied with by the site.

The sponsor will notify the national competent authorities/national regulatory authorities and EC as per their requirements.

7.1.2. Repeated non-compliance

In the event of repeated non-compliance or a serious non-compliance, as determined by the sponsor, a clinical research associate or a clinical representative will attempt to secure compliance by one or more of the following actions:

- Contacting the investigator by telephone
- Contacting the investigator in writing
- Visiting the investigator
- Retraining of the investigator
- Site "for-cause" audit
- Implementation of corrective action preventive action (CAPA) plan

If an investigator is found to be repeatedly non-compliant with the signed clinical investigation agreement, the CIP or any other conditions of the clinical investigation, the sponsor will either secure compliance or, at its sole discretion, terminate the investigator's participation in the clinical investigation.

7.2 Informed Consent Process

7.2.1. General Process

Provision of the informed consent is mandatory. Informed consent is required from all patients (or their legal representatives) prior to participation in the clinical investigation. The process of obtaining informed consent shall comply with the most recent version of the declaration of Helsinki, ISO 14155 2011 and all applicable regulations.

The principal investigator or his/her authorized designee will conduct the informed consent process. 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 in the clinical investigation. It is crucial that this discussion is documented in the source documents (records of the patient).
The patient will be provided with the informed consent form that is written in native non-technical language, understandable for the patient, and has been approved by EC. The patient is given ample time to consider participation and ask questions if necessary.
In order to avoid any possible coercion or undue improper influence on, or inducement of the patient to participate, the sponsor requests the investigator to only sign the informed consent form once the patient has signed and dated the document and therefore decided to participate in the investigation.
Informed consent of a patient shall always be indicated by personally dated signature of the patient and by the investigator responsible for conducting the informed consent process. It is crucial that the signature of the informed consent is documented in the source documents (records of the patient).

One original signed consent document must be retained on file by the investigator and a copy of the signed and dated consent is provided to the patient (investigator's responsibility).
The patient's legal rights will not be waived nor the appearance that these will be waived. Important new information that becomes available throughout the clinical investigation will have to be provided in writing to new and existing patients. If relevant, all affected patients shall be asked to confirm their continuing informed consent in writing.

NOTE: In certain circumstances, it might be decided during screening to send relevant clinical data (such as echocardiogram, CT/MRI or Angiogram) out of the hospital for further analysis to determine if patient's valve anatomy is suitable for participation in the clinical investigation. If required, an authorization form to release medical information outside the hospital is available for sign-off by the patient. In case this authorization form is signed by the patient, the patient is not yet considered enrolled.

7.2.2. Patient unable to read or write

Informed consent shall be obtained through a supervised oral process if a patient or legally authorized representative is unable to read or write. An independent witness shall be present throughout the process. The written informed consent form and any other information shall be read aloud and explained to the prospective patient or his/her legally authorized representative and, whenever possible, either shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent form attesting that the information was accurately explained and that informed consent was freely given.

7.3 Adverse Event, Adverse Device Effect, Device Deficiency

7.3.1. Definitions (ISO 14155:2011)

Medical device

Any instrument, apparatus, implement, machine, appliance, implant, software, material or other similar or related article

- Intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of
  - Diagnosis, prevention, monitoring, treatments or alleviation of disease,
  - Diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury,
  - Investigation, replacement, modification, or support of the anatomy or of a physiological process,
  - Supporting or sustaining life,
  - Control of conception,
  - Disinfection of medical devices and
- Which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means

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 patient, 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 OR
  - A malignant tumor
- 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 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.

Unanticipated Serious Adverse Device Effect (USADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Anticipated Serious Adverse Device Effect (ASADE)

A serious adverse device effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

Device Deficiency (DD)
An inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.
Device Deficiencies include malfunctions, use errors and inadequate labeling.

7.3.2. Procedure for assessing, recording and reporting adverse events, adverse device effects, serious adverse events, serious adverse device effects and device deficiencies

Safety surveillance and reporting will be done for all patients enrolled in this investigation.

Safety surveillance within this clinical investigation and safety reporting, both performed by the investigator, starts as soon as the patient is enrolled in this clinical investigation (date of signature of the informed consent). The safety surveillance and the safety reporting will continue until the last investigational visit has been performed or the patient is deceased or the patient/investigator concludes his participation into the clinical investigation.
NOTE: If an adverse event is documented at the patient's last follow up visit, both the notification and follow-up information on the AE eCRF are to be provided to the sponsor.

- All Serious Adverse Events (regardless of their relationship with the device or the procedure) and all Adverse Device Effects (serious or non-serious) are to be documented and reported to the sponsor maximum 3 calendar days after becoming aware of the event.
- All Device Deficiencies, that could have led to a Serious Adverse Device Effect,
  - if either suitable action had not been taken;
  - if intervention had not been made or
  - if circumstances had been less fortunate,

  are to be documented and reported to the sponsor maximum 3 calendar days after becoming aware of the event.
- Non-serious adverse events documentation and reporting are limited to cardiovascular and neurovascular events; they all have to be reported regardless of their relationship with the device or the procedure.

7.3.3. Should an AE or DD occur, record AE or DD information in the hospital records, document the information into the adverse event form or device deficiency form as soon as possible. By completing the form, the sponsor will be notified. Refer to

and Appendix C: Data Collection Method. In case of EDC failure, notify Sponsor via Fax or via AdverseEvent@sjm.com.

The Sponsor safety department will be responsible for ensuring the assessment of immediate AE and DD 'reportability' or 'non-reportability' to the national competent authorities/national regulatory authorities. All the AEs and DDs will be documented and reported in periodic report(s) as per local requirements.

Additional information may be requested, when required, by the sponsor in order to support the reporting of AEs or DDs to regulatory authorities and to support AE or DD analysis. The investigator must notify the EC, if appropriate, in accordance with national and local laws and regulations, of the AEs and DDs reported to the sponsor.

In case of disagreement between sponsor and investigator in the AE or DD assessment, then both assessments will be reported.

7.4 Patient Death

7.4.1. Procedure for recording and reporting Patient Death

7.4.2. All patient deaths are to be documented and reported to the sponsor maximum 3 calendar days after becoming aware of the event. Should death occur, the investigator is requested to record death information in the hospital records and immediately document the information on the Death Form. By completing the form the sponsor will be notified. Refer to

and Appendix C: Data Collection Method. In case of EDC failure, notify Sponsor via Fax or via AdverseEvent@sjm.com.

All efforts (including use of national death registries) should be made to identify, precisely characterize, and appropriately classify any death.

Patient death is an outcome of a serious adverse event (SAE). All efforts to get SAE details should be made and the Adverse Event eCRF must be completed.

If available, the explanted Portico valve should be returned to SJM per instructions provided in Appendix K: Explant, Return, and Analysis of Valve and Appendix L: Instructions for device return - Large and Small Kits.

The patient's death is an early conclusion of the patient's participation in the investigation. Therefore, the investigator is requested to complete the termination form. The investigator must notify the EC/IRB, if appropriate, in accordance with national and local laws and regulations.

7.5 Criteria and procedures for patient withdrawal or discontinuation

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 investigation at any time and for any reason without sanction, penalty or loss of benefits to which the patient is otherwise entitled and withdrawal from the investigation will not jeopardize their future medical care or relationship with the investigator. Patients will be asked to specify the reason for the termination, but have the right not to answer.
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.

Reasons for patient's withdrawal include, but are not limited to:

- Patient refuses to continue participating in the investigation (refuse all subsequent testing/follow up)
- Patient does not meet the inclusion/exclusion criteria prior to baseline procedure
- Patient is deceased (cause must be documented)
- Patient's non-compliance
- Patient's participation is terminated by the PI or investigator, although the patient consented, since participation is no longer medically justified
- Patient is 'lost to follow up': Patient does not adhere to the scheduled follow up visits but has not explicitly requested to be withdrawn from the clinical investigation. (This does not apply to missed visits). Site personnel should at all times make all reasonable efforts to locate and communicate with the patient in order to achieve patient compliance to the scheduled follow up visits. A patient will be considered 'lost to follow up' after
    - A minimum of 2 phone calls from a physician or delegate at the investigational site have been attempted to reach the patient. These 2 phone calls need to be documented in the patient's hospital records.
    - And a certified 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. If these attempts are unsuccessful,

Note: If a patient misses one or more of the scheduled follow up visits, this will be considered as a missed visit. The patient may therefore still return for subsequent visits and will not be excluded from the investigation. The missed visits will be considered a protocol deviation.

If the patient misses two consecutive scheduled follow up visits and the above mentioned attempts to contact the patient or/and GP were unsuccessful, the patient will be considered 'lost to follow up' and patient's termination form should be completed. The investigator ensures that all attempts are documented in the patient's hospital records.

7.6 Document and data control

7.6.1. Traceability of documents and data

The investigator shall ensure accuracy, completeness, legibility and timeliness of the data reported to the sponsor on the eCRF's and in all required reports. Where copies of the original source document as well as print outs of original electronic source documents are retained, these shall be signed and dated by a member of the investigation site team with a statement that it is a true reproduction of the original source document.

7.6.2. Definition of source data

Investigators shall ensure that all source documents are accurate, complete, legible, up to date, original, attributable and capable of being audited. They shall not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Photocopies of eCRF's are not considered acceptable source documents. Source documents are original records in which raw data are first recorded. These include, but are not limited to hospital/clinic/general practitioner records, charts, diaries, X-rays, laboratory results, printouts, pharmacy records, care records, ECG. Source documents should be kept in a secure, limited access area.

7.6.3. Recording of data

Source documents shall be created and maintained by the investigation site team throughout the clinical investigation. The data reported on the eCRF's shall be derived from, and be consistent with, these source documents. Attempts to clarify any conflicting information (discrepancy) shall be documented using the appropriate option in the Electronic Data Capture (EDC) system. The eCRF's shall be validated by the principal investigator or delegated investigator. Any change or correction to data reported on an eCRF shall be tracked.

7.6.4. Review of data (source data verification)

The clinical investigation will be monitored by reviewing the electronic eCRF's approved by the investigators. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source data (Source Data Verification). All data reported on the eCRF's should be supported by source data.

The following activities will occur:

- eCRFs will be reviewed for completeness and accuracy by sponsor.
- The investigator, co-investigator and/or delegate will be notified regarding any missing or unclear/inconsistent data.
- The investigator (co-investigator) and/or delegate will be requested to clarify or correct the inconsistency.

7.7 Monitoring

On site-monitoring will be performed during the clinical investigation in order to guarantee adherence to all applicable regulations, the clinical investigation plan and the signed clinical investigation agreement. By monitoring, the sponsor can also verify the accuracy of data collected on the accompanying eCRF's throughout the duration of the clinical investigation.

Monitoring is necessary to ensure adequate protection of the rights and safety of human patients involved in the clinical investigation and the quality and integrity of the data obtained during the clinical investigation. The sponsor will at the same time assess the investigational site and clinical investigation team on staffing and facilities to ensure the clinical investigation can continue in a safe and effective fashion.

During the monitoring visits, data reported on the eCRF shall be reviewed as specified in the monitoring plan. (Refer to section 7.7.2).

7.7.1. Designated Monitors

Only monitors qualified by education, training and experience, which have been trained on the CIP, device and its indication for use, eCRF content, use of eCRF guidelines, Monitoring Plan, relevant requirements and informed consent process will be allowed to perform monitoring activities during this clinical investigation. The monitor's qualifications and training will be documented by the sponsor. A list of monitors is available upon request.

7.7.2. Monitoring Plan

Prior to the start of the site monitoring activities for this clinical investigation, a project specific Monitoring Plan (MP) will be created and will be available upon request.
At a minimum, the Monitoring Plan will include the following:

- Frequency of monitoring visits
- % of source data verification
- Monitoring visit requirements
- Action to be taken in case of serious site non-compliance
- Monitoring report content and timelines
- Close-out visit procedures

The monitoring plan may be updated as appropriate. All revisions will be tracked.

7.7.3. National Competent Authority (NCA)/ National Regulatory Authority (NRA) Inspections

The investigator and/or delegate should contact SJM immediately upon notification of a NCA/NRA inspection at the site. A clinical monitor will assist the investigator and/or delegate preparing for the audit.

An investigator who has authority to grant access shall permit authorized NCA/NRA employees, at reasonable times and in reasonable manner, to enter and inspect any establishment where devices are held (including any establishment where devices are used or where records or results are kept).

An investigator, or any person acting on behalf of such a person with respect to the investigation, shall permit authorized NCA/NRA employees, at reasonable times and in reasonable manner, to inspect and copy all records relating to the investigation.

An investigator shall permit authorized NCA/NRA employees to inspect and copy records that identify patients, upon notice that NCA/NRA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator, to the Sponsor or EC/IRB have not been submitted or are incomplete, inaccurate, false or misleading.

7.8 Investigation Termination

The Sponsor reserves the right to stop the investigation at any stage, with appropriate written notice to the investigator. Possible reasons for early termination of the investigation by the sponsor, either at local, national or international level, may include, but are not limited to:

- The device fails to perform as intended

- Occurrence of USADE which cannot be prevented in future cases
- Sponsor's decision
- Request from regulatory bodies
- Request of EC(s)

The investigation will then be terminated according to applicable regulations.

The investigator may also discontinue participation in the clinical investigation with appropriate written notice to the Sponsor.

7.8.1. Investigation Conclusion

The investigation will be concluded when:

- A close-out visit has been performed at each participating site
- The final report has been provided by sponsor

8 Risks and Benefits of the clinical investigation

8.1 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 TAVI procedure. It is expected that patients implanted with a Portico Valve will have the same benefits as patients implanted with other transcatheter valves.

8.2 Anticipated Adverse Events and 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.

8.3 Possible interactions with concomitant medical 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 site.

8.4 Steps that will be taken to control or mitigate the risks

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

Risks shall be minimized by careful assessment of each patient prior to, during and after implant of the Portico Valve. After implantation, patients in this clinical investigation shall be followed at regular intervals to monitor their condition.

8.5 Risk-to-Benefit Rationale

The risks associated with the use of Portico Valve and transcatheter delivery system and valve loading system are anticipated to be comparable to those associated with the use of other currently available transcatheter valve and delivery systems. Patients participating in this clinical investigation are indicated for a TAVI procedure as part of their standard medical management and are subject to the risks associated with these devices.

9 Statistical considerations

9.1 Analysis population

All patients who have signed a PIC will be considered enrolled in the clinical investigation (refer to Section 4: Clinical investigation design). However, it is anticipated that there will be patients who are enrolled in the clinical investigation but will not be included in the analysis dataset.

These patients are described as follow:

- Patients who gave consent to participate in the clinical investigation but did not satisfy the inclusion and/or exclusion criteria before the index procedure (screen failure), or have been excluded from the study by the investigator before the index procedure.
- Patients who have enrolled in the clinical investigation and started the procedure, but did not have the Portico Valve implanted and are procedural exclusions due to their anatomy, circumstances related to the procedure, or physician judgment.
- Patient who died, were lost to follow-up or withdraw consent before the index procedure.

Patients enrolled in the clinical investigation and implanted with a PORTICO valve for whom a deviation related to inclusion and/or exclusion criteria is identified, should be followed throughout the study. The statistical analysis plan, will further describe how the data of these patients will be handled.

9.2 Sample size estimation

9.2.1 Cohort A

The sample size estimation is based on the primary endpoint of this study, all-cause mortality at 1 year post implant for patients having received a Portico Valve.

It is assumed that the expected mortality rate at 1 year post implant will be 22.1% [20]), and the total recruitment period will be 2 years; at least 608 patients are required to be at risk at 1 year post implant, in order to establish a two sided 95% confidence limit (18.8%, 25.4%) using non-parametric survival analysis with Peto's variance[21]. With a dropout rate of 10%, at least 866 patients need to be recruited.

9.2.2 Cohort B

The anticipated number of patients who participated to a SJM-sponsored Regulatory or First-In-Human trial conducted in Europe and who will participate to the clinical investigation will be approximately 180.

The total population to be enrolled in the clinical investigation is at least 866 for COHORT A, added up with any additional patients enrolled in Cohort B, to a maximum of 1046 patients in total.

9.3 Primary endpoint analysis

The primary endpoint analysis will only include patients from Cohort A.

Non-parametric survival analysis will be used to calculate the mortality rate at 1 year post index procedure and build its 95% confidence limit. The corresponding variance will be computed using Peto's formula for survival analysis. The survival time will be calculated as the number of days between the implant date and the death date for the patients who die at 1 year (365 days) post implant. And for the patients who are considered as censored (loss to follow up, explanted, etc.), the survival times will be calculated as the number of days between the implant date and the last known adverse event or the last documented contact date before 1 year follow up. A Kaplan-Meier curve with the cumulative survival rate will also be presented.

A Cox regression model can be used for further explanatory analysis of the relationship of the prognostic factors and the mortality. These factors will include baseline factors such as age, gender, NYHA class etc., and other factors defined by steering committee can also be analyzed.

9.4 Secondary endpoint analysis

The secondary endpoint analysis will include both cohorts but results will be presented separately.

All safety secondary endpoints will be estimated using non-parametric survival analysis, and the data will be presented with the aid of Kaplan-Meier curve. The time to event will be defined as from the implant date to the first occurrence of the event for the patients who experienced the event, or to the last documented contact date for the patients without the event.

All safety secondary endpoints will be reported at 30 days, 1 year, 2 years, 3 years, 4 years and 5 years post implant, as recommended by VARC 2.
Note: Safety events which occurred prior to the index procedure will be reported separately and will not be included in the safety secondary endpoints reporting.

All continuous secondary endpoints will be summarized with the number of non-missing data, mean ± standard deviation, median and range (minimum – maximum).

All categorical secondary endpoints will be tabulated with number of occurrence, and the percentage.

Generalized linear mixed model will be used to assess the evolution of the NYHA class at baseline, 30 days, 1 year, 2 years, 3 years, 4 years and 5 years post implant.

General linear mixed model will be used to evaluate the improvement for the QOL at baseline, 30 days, 1 year, 2 years, 3 years, 4 years and 5 years post implant.

Other secondary endpoints analysis will be described in a separate statistical analysis plan. This document will be available upon request.

9.5 Interim reporting

Interim reporting of primary and secondary endpoints will be performed, before the study's conclusion, upon recommendation of the steering committee.
Interim reporting of relevant data will also be performed for reimbursement purposes upon request of sponsor Health Economics and Reimbursement (HE&R) department.

10 Data Management

Overall, the sponsor will be responsible for the data handling. The sponsor and/or its affiliates will be responsible for compiling and submitting all required reports to governmental agencies. Investigational data will be analyzed by the sponsor and may be transferred to the sponsor's locations outside of Europe and/or any other worldwide regulatory authority in support of a market-approval application.

St. Jude Medical respects and protects personally identifiable information that we collect or maintain. As part of our commitment, SJM is certified to the U.S. - European Union Framework and U.S. – Swiss Safe Harbor Framework Agreements regarding human resources and patient clinical trial personal information.

10.1 Data Management Plan

eCRF data will be entered in a validated electronic database using Oracle Clinical. The investigator or designee is required to enter the data through an electronic data capture system (EDC) system.

The Data Validation Procedure (DVP), which is part of the Data Management Plan (DMP), describes all the computerized data cleaning checks (validation rules) as programmed at the time of database set-up. However, these validation rules may change and be updated throughout the course of the investigation.
Manual review and Data Cleaning Convention (DCC) will be used in addition to computerized data cleaning checks, to check for discrepancies and to ensure consistency of the data.
More information will be provided in the DMP which may be updated as appropriate. All revisions will be tracked and include an effective date. The DMP will be available upon request.

11 Document Retention

The principal investigator (PI) shall maintain all essential clinical investigation documents from prior, during and (as specified) after the clinical investigation on file at the site for a minimum of 15 years after the termination of this investigation, or longer as per local laws, or when it is no longer needed to support a marketing application, whichever is later.

The PI must contact the sponsor prior to destroying or archiving off-site any records and reports pertaining to this investigation to ensure that they no longer need to be retained on-site.

All original patient files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the site, the investigator will notify the sponsor.

All data and documents shall be made available on request of the relevant authorities in case of an audit.

The sponsor will archive and retain all essential clinical investigation documents from prior, during and (as specified) after the clinical investigation as per requirements.

12 Amendments to Clinical Investigation Plan

The CIP, CRFs, informed consent form and other patient information, or other clinical investigation documents shall be amended as needed throughout the clinical investigation, and a justification statement shall be included with each amended section of a document. Proposed amendments to the CIP shall be agreed upon between the sponsor and principal investigator, or the coordinating investigator. The amendments to the CIP and the patient's informed consent shall be notified to, or approved by, the EC and regulatory authorities, if required. The version number and date of amendments shall be documented.

The amendment will identify the changes made, the reason for the changes and if it is mandatory or optional to implement the amendment.

Any amendment affecting the patient requires that the patient be informed of the changes and a new consent be signed and dated by the investigator and patient prior to the patient's next follow up.

Changes to, or formal clarifications of, the CIP will be documented in writing and provided to the investigators. This information will be incorporated when an amendment occurs.

13 Publication Policy

The results of the clinical investigation will be submitted, whether positive or negative for publication.

A publication agreement will be signed between the principal investigator of each participating site and the sponsor.

If such a publication agreement is not signed by both parties as a separate agreement it may be part of the overall clinical investigation agreement. A publication committee may also be selected and a study specific charter may be developed.

For more information on publication guidelines, please refer to the International Committee of Medical Journal Editors (ICMJE) on www.icmje.org.

14 Investigation Organization

14.1 Investigation Management/Sponsor

The organization which takes responsibility for the initiation, implementation and coordination of the clinical investigation is SJM International, Inc., with offices located at:

St. Jude Medical Coordination Center BVBA
Corporate Village
Da Vincilaan 11, Box F1
B-1935 Zaventem
Belgium
Tel: +32 2 774 69 37
Fax: +32 2 774 69 46

The SJM safety department can be reached at:

SJM International, Inc.
Clinical Safety Department
Corporate Village
Da Vincilaan 11, Box F1
B-1935 Zaventem
Belgium
Fax: +800 2546 2546
Email: AdverseEvent@sjm.com

14.1.1 Sponsor Responsibilities

Sponsor's responsibilities are in accordance with applicable guidelines. This includes but is not limited to the following activities:

- Sign off the clinical investigational plan before the start of the investigation or after modifications to the protocol.
- Develop the database.
- Select the clinical investigators.
- Train the clinical investigational sites.
- Activate the sites after receipt of the required documentation.
- Monitor the participating centers by reviewing collected data and investigation documentation for completeness and accuracy.
- Perform the data analysis.
- Ensure that all adverse events, adverse device effects and device deficiencies are reported and reviewed with the clinical investigator(s) and where appropriate that all serious adverse events, serious adverse device effects and device deficiencies that could have led to a serious adverse device effect are reported to the relevant authorities and EC(s) and/or safety monitoring committee(s).
- Maintain an updated list of principal investigators, investigational sites and institutions. This list will be available upon request.

SJM retains the right to terminate the participation of an investigator for any of, but not limited to, the following reasons:

- Concern for patient safety and welfare.
- Failure to secure PIC prior to any investigational activity.
- Failure to report unanticipated adverse device effects within 72 hours to SJM.

- Failure to report unanticipated adverse device effects to the EC
- Repeated non-compliance with this CIP or the clinical investigation agreement.
- Inability to successfully implement this CIP.
- Violation of the Declaration of Helsinki 2008 (refer to Appendix B).
- Violation of applicable national or local laws and regulations.
- Falsification of data, or any other breach of ethics or scientific principles.

14.2 Clinical Investigators

This clinical investigation will be conducted by qualified investigators who have experience with:

- TAVI procedures.
- Management of patients with severe aortic stenosis and associated co-morbidities.
- Conduct of clinical investigations.

14.2.1 Investigator's responsibilities

By agreeing to this CIP, the investigators accept to allow monitoring, audits (internal or external), EC review, and regulatory inspections that are related to the clinical investigation. They also agree to provide authorized individuals with direct access to source data and documentation as well as the right to copy records, provided such activities do not violate patient consent and patient data confidentiality.

A principal investigator should have experience in and/or will be responsible for:

- Providing signed clinical investigation agreement and appropriate appendices.
- Providing the sponsor with copies of any clinical-investigation-related communications between the Principal Investigator and the EC.
- Screening and selecting appropriate patients.
- Providing appropriate EC approved informed consent.
- Collecting and archiving of source data obtained prior to implant, during implant, at follow-up examinations and after the investigation has been completed.
- Strict adherence to the CIP investigational requirements to provide for optimal safety and efficacious use of the device under clinical investigation.
- Adequate safety reporting.
- Maximizing the quality of data entered in the eCRF's.
- Supporting the monitor, and auditor, if applicable, in their activities to verify compliance with the CIP, to perform source data verification and to correct the eCRF where inconsistencies or missing values are identified.

It is acceptable for the principal investigator to delegate one or more functions to an associate or co-investigator, however, the principal investigator remains responsible for the proper conduct of the clinical investigation, complying with the investigational plan and collecting all required data. This delegation of specific functions shall be documented on the signature and delegation list (provided by Sponsor). The investigation is not transferable to other implant centers attended by the investigator unless prior approval is obtained from SJM.

14.2.2 **Clinical Coordinating Investigators**

In addition to the responsibilities of the investigators, the Clinical Coordinating Investigators and National will:

- Sign off the final version of the investigational protocol and any amendment to the protocol;
- Act as main contact for all investigators in case of medical questions related to the conduct of the investigation.
- Be a member of the study steering committee (SC).

The following investigators have been appointed by the Sponsor as Clinical Coordinating Investigators:

Prof L. Søndergaard	Prof F. Maisano	Prof S. Worthley	Dr. J. Rodes
Rigshospitalet Copenhagen University Hospital	University Hospital Zurich	St Andrews Hospital	Institut Universitaire De Cardiologie Et De Pneumologie de Québec (ICUPQ)
Kardiologisk Klinik B	Cardiac Surgery	Dept Cardiology	
Blegdamsvej 9	Ramisstrasse 100	350 South Terrace Adelaide	2725 ch Sainte-Foy,
2100 Copenhagen	Zurich CH-8091	SA, 5000	Québec, QC G1V 4G5
Denmark	Switzerland	Australia	Canada
Tel: +45 35452018	Tel: +41 (0)44 255 33 81 Fax: +41 (0)44 255 44 67	Tel: +61 8 8223 4288	Tel: +1 418 656 8711 Fax: +1 418 656 4544

14.2.3 **Source Data and Patient Files**

The investigator has to keep a written or electronic patient files for every patient participating in the clinical investigation including the screening failures. In this hospital file, the available demographic and medical information of a patient has to be documented, in particular the following:

- Name
- Patient identification code
- Age on consent date
- Gender
- Height
- Weight

- Medical history
- Concomitant diseases
- Concomitant medication (including changes during the course of the clinical investigation)
- Clinical investigation identification
- Date of informed consent
- All clinical investigation visit dates including the unscheduled visits
- Predefined performed examinations and clinical findings
- Heart team recommendations
- Observed AEs, and DDs that led to an AE
- Reason for withdrawal from the clinical investigation, if applicable.

All data recorded on the eCRF must also be part of the patient's source data.

It should be possible to verify the inclusion and exclusion criteria for the investigation from the available data in this file. It must be possible to identify each patient by using this patient file. Additionally, any other documents with source data have to bear at least the patient identification and the printing date printed by the recording device to indicate to which patient and to which investigational procedure the document belongs. The medical evaluation of such records should be documented as necessary and signed/dated by the investigator.

14.3 Boards

14.3.1 Steering Committee

The SC will be championed by the clinical coordinating investigators (CCI) Prof L. Søndergaard and Prof F. Maisano. The National Principal Investigators Prof. Worthley and Dr. Rodes will be part as well.

This committee will be actively involved in the clinical investigation, and review its progress at regular intervals. At any time, this committee may request that the investigation is being put on hold or even terminated for safety, ethical or other reasons.
A specific charter will be established for the steering committee member's activities and will be available upon request.

14.3.2 Clinical Event Committee

An independent clinical events committee will be established for this clinical investigation. The CEC will include, at a minimum, an interventional cardiologist or a cardiologist, and a cardiothoracic surgeon whose main objective is to review and adjudicate specific adverse events which will occur throughout the duration of this trial, as specified in a separate CEC charter. The CEC will adjudicate these safety related events according to the VARC 2 criteria.
The CEC charter will be established for the CEC member's activities and will be available upon request.

14.4 Outsourcing of duties and functions

The sponsor may transfer any or all of the duties and functions related to the clinical investigation, including monitoring, to an external organization (such as a CRO or individual contractor), but the ultimate responsibility for the quality and integrity of the clinical investigation shall reside with the sponsor. All requirements applying to the sponsor shall also apply to the external organization inasmuch as this organization assumes the clinical-investigation-related duties and functions of the sponsor.

14.4.1 Power of Attorney

The POA delegates sponsor's responsibility for specified tasks to the country entities involved in the clinical project. The POA is signed and dated by appropriate parties. The POA can consist of, but is not limited to:

- Ensure that the clinical investigation agreements are prepared appropriately, comply with legal obligations and are signed/dated by all parties.
- Ensure that essential documents to activate the center are collected and maintained in the ISB.
- Activate the centers and manage the centers throughout the duration and close of the investigation.
- Report Adverse Events to relevant authorities.
- Ensure that patient data relevant to the investigation is referenced in the hospital records, collected and provided to Sponsor

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Appendix A: Abbreviations

Abbreviation	Term
6MWT	6 Minute Walk Test
ACS	Acute Coronary Syndrome
ADE	Adverse Device Effect
AE	Adverse Event
AS	Aortic Stenosis
ASADE	Anticipated Serious Adverse Device Effect
AVR	Aortic Valve Replacement
BARC	Bleeding Academic Research Consortium
BMI	Body Mass Index
CAD	Coronary Artery Disease
CATD	Cardiovascular and Ablation Technologies Division
CCI	Clinical Coordinating Investigator
CEC	Clinical Event Committee
CHF	Congestive Heart Failure
CIP	Clinical Investigational Plan
CBP	Cardio Pulmonary Bypass
CRF	Case Report Form
DCC	Data Cleaning Convention
DD	Device Deficiency
DMP	Data Management Plan
DVP	Data Validation Procedure
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EROA	Effective Regurgitant Orifice Area
HE&R	Health Economic and Reimbursement
FCS	Field Clinical Specialist
GP	General Practitioner
ICMJE	International Committee of Medical Journal Editors
IFU	Instructions For Use
IRB	Institutional Review Board
ISB	Investigator Site Binder
ISO	International Organization for Standardization
LBBB	Left Bundle Branch Block
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction
MP	Monitoring Plan
MSCT	Multi Slice Computed Tomography
NAP	Not Applicable
NCA	National Competent Authority
NRA	National Regulatory Authority
NYHA	New York Heart Association
PI	Principal Investigator
PIC	Patient Informed Consent
POA	Power of Attorney
PIL	Patient Identification Log
QoL	Quality of Life
RBC	Red Blood Cell
RDC	Remote Data Capture

RIFLE	Risk Injury Failure Loss End-Stage Kidney Disease
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SC	Steering Committee
SJM	St. Jude Medical
TAVI	Transcatheter Aortic Valve Implantation
TEE	Trans-Esophageal Echocardiography
TIA	Transient Ischemic Attack
USADE	Unanticipated Serious Adverse Device Effect
VARC	Valve Academic Research Consortium
WMA	World Medical Association

Appendix B: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects
Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.
The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.
2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.
9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or

eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation. Meas
ures to minimize the risks must be implemented. The risks must be continuously monitored, assessed and documented by the
researcher. 18. Physicians may not be
involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.
When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional
harm. All vulnerable groups and individuals
should receive specifically considered protection. 20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research
protocol. The protocol should contain a
statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding,

sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.
26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.
After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed. All medical research subjects should be given the option of being informed about the general outcome and results of the study.
27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.
28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed

with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorized representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:
Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or
Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention
and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven
intervention. Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be

declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

Appendix C: Data Collection Method

Sponsor/Investigators are required to prepare and maintain adequate an 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 investigation, 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
- Completed Signature and Delegation List
- 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 in a timely manner.

Summary of Casebook Status Icons – Home Page

	No Data Entry is started.
	At least some Data Entry is saved. No Open Discrepancies.
	At least some Data Entry is saved. Active Discrepancy present on at least one CRF requiring current user's attention. May also include Other Discrepancies.
	At least some Data Entry is saved. Other Discrepancy present on at least one CRF requiring current user's attention. No Active Discrepancies present.

Summary of CRF Status Icons – Casebook Page

	CRF not started. Data entry is expected.
	Save Incomplete CRF – The CRF was started and only the Visit Header Date was completed.
	Save Incomplete CRF – Data Entry is incomplete. User is not done inputting all the data, and will finish at a later time.
	Save Complete CRF – Data Entry is complete. User has met all the requirements for the form, and the responses are considered complete. Automated Discrepancy Edit Checks are activated. CRF has no open issues.
	Save Complete CRF – Data Entry is complete. CRF contains Other Discrepancies that another user group must address.
	Save Complete CRF – Data Entry is complete. CRF contains Active Discrepancies that the current user group must address.
	*Approved CRF – CRF Data responses have been approved by an investigator. CRFs must at least be at "Save Complete" status. No Open Discrepancies. (If Open Discrepancies are present, the icon would also be red or yellow.)
	*CRF requires Re-Approval – Looped arrow next to signature indicates Data, an Investigator Comment, and/or Discrepancy was updated since the CRF was Approved. (If Open Discrepancies are present, the icon would also be red or yellow.)
	Verified CRF – CRF Data responses are verified against source documents. CRFs must at least be at "Save Complete" status. No Open Discrepancies. (If Open Discrepancies are present, the icon would also be red or yellow.)
	CRF requires Re-Verification – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified. No Open Discrepancies. (If Open Discrepancies are present, the icon would also be red or yellow.)
	CRF requires Re-Verification – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified. Active Discrepancies present.
	CRF requires Re-Verification – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified. Other Discrepancies present.
	*CRF is Verified and Approved – CRF Data responses are verified against source documents by the FCRA / CRA, and the Data responses approved by the Principal Investigator.
	CRF requires Re-Verification and Re-Approval – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified and Approved. Active Discrepancies present.
	*CRF requires Re-Verification and Re-Approval – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified and Approved. Other Discrepancies present.
	*CRF requires Re-Verification and Re-Approval – Looped arrow indicates Data, an Investigator Comment, and/or a Discrepancy was updated since the CRF was Verified and Approved. No Open Discrepancies. (If Open Discrepancies are present, the icon would also be red or yellow.)
	CRF at Pass 2 Complete. This icon indicates Data Entry was completed by the sponsor in-house using data submitted on paper CRFs.

*APPROVAL FEATURE CURRENTLY AVAILABLE TO INVESTIGATORS FOR THE DEATH CRF ONLY.

Summary of Discrepancy Status Icons – Data Entry Window (DEW) Navigator Pane

	Active Discrepancy that the current user group must address.
	Other Discrepancy that another user group must address.
	Resolved Discrepancy requiring no further action by any user group.

NOTE: Obsolete Discrepancies due to Data updates or Validation Procedure / Automated Edit Check updates will be removed from the List sub-pane.

Summary of Data Entry Window (DEW) Toolbar Icons

	Add Discrepancy		Delete Row		Approval History		*Print		First/Previous Page		Close
	Investigator Comment		Verification History		Approval		Save		Next/Last Page		

*DO NOT USE THESE TOOLBAR FUNCTIONS

Helpful Hints:

1. **CRF Deletions** – If a CRF with saved data requires deletion notify your SJM contact, providing information about the form.
2. **Refresh** – Press the "Refresh" button to refresh RDC OnSite with current information (statuses, etc.)
3. **Printing a Subject Casebook / CRF** – Go to the RDC OnSite Report Page to print a Patient Data Report. Report types include casebooks with saved Subject data and blank Subject casebooks.
4. **Logout** – Use the web browser close icon "X" to exit. To re-enter, navigate through the SJM Portal.

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Appendix D: VARC 2 Endpoints Definitions [19]

Mortality **(VARC 2)**	**<u>Cardiovascular Mortality:</u>** Any one 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 non-structural valve dysfunction or other valve-related adverse event. • Sudden or witnessed death. • Death of unknown cause. **Non-Cardiovascular mortality:** • Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide)
Myocardial Infarction **(VARC 2)**	**<u>Peri-procedural MI (≤ 72 h after the index procedure)</u>** New ischemic symptoms (e.g., chest pain or shortness of breath), or new ischemic signs (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q-waves in at least two contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality), Elevated cardiac biomarkers (preferably CK-MB) within 72 h after the index procedure **AND** consisting of at least one sample post-procedure with a peak value exceeding 15× as the upper reference limit for troponin or 5× for CK-MB. If cardiac biomarkers are increased at baseline (>99th percentile), a further increase in at least 50% post-procedure is required **AND** the peak value must exceed the previously stated limit. **<u>Spontaneous MI (>72 h after the index procedure)</u>** Any one of the following criteria: • Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with evidence of myocardial ischemia with at least one of the following: o Symptoms of ischemia o ECG changes indicative of new ischemia [new ST-T changes or new Left Bundle Branch Block (LBBB)] o New pathological Q waves in at least two 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 and TIA
 	
(VARC 2)
	<u>Diagnostic criteria</u>
	• Acute episode of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, haemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke.
	• Stroke: duration of a focal or global neurological deficit ≥24h; OR <24h, if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death.
	• TIA: duration of a focal or global neurological deficit <24h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct.
	• No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycaemia, peripheral lesion, pharmacological influences) to be determined by or in conjunction with the designated neurologist[a].
	• Confirmation of the diagnosis by at least one of the following:
	  o Neurologist or neurosurgical specialist
	  o Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone.
	
	<u>Stroke classification</u>
	• Ischaemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue.
	• Haemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid haemorrhage.
	• A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischaemic or haemorrhagic.
	
	<u>Stroke definitions</u>[b]
	• Disabling stroke: an mRS score of 2 or more at 90 days and an increase in at least one mRS category from an individual's pre-stroke baseline.
	• Non-disabling stroke: an mRS score of <2 at 90 days or one that does not result in an increase in at least one mRS category from an individual's pre-stroke baseline
	
	[a] Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies (CT scan or Brain MRI)
	[b]Modified Rankin Score assessments should be made by qualified individuals according to a certification process.

Bleeding **(VARC 2)**	**<u>Life-threatening or disabling bleeding</u>** • Fatal bleeding (BARC(22) type 5) **OR** • Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) **OR** • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) **OR** • Overt source of bleeding with drop in hemoglobin ≥ 5 g/dl or whole blood or packed red blood cells (RBCs) transfusion ≥ 4 Units[a] (BARC type 3b). [a]Given 1 U of packed RBC typically will raise blood hemoglobin concentration by 1 g/dl, an estimated decrease in hemoglobin will be calculated. **<u>Major bleeding (BARC type 3a)</u>** • Overt bleeding either associated with a drop in the hemoglobin level of at least

	3.0 g/dl or requiring transfusion of two or three 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 **<u>Minor bleeding (BARC type 2 or 3a, depending on the severity)</u>** • Any bleeding worthy of clinical mention (e.g., access site hematoma) that does not qualify as life-threatening, disabling or major.
Acute Kidney Injury ***AKIN classification*** **(VARC 2)**	**<u>Stage 1</u>** Increase in serum creatinine to 150% - 199% (1.5 to 1.99 X increase compared with baseline) **OR** increase of ≥ 0.3 mg/dl (≥26.4 mmol/l) **OR** Urine output <0.5 mL/kg/h for >6h but <12h **<u>Stage 2</u>** Increase in serum creatinine to 200% -299% (2.0 to 2.99 X increase compared with baseline) **OR** Urine output <0.5 mL/kg/h for >12h but <24h **<u>Stage 3</u>** Increase in serum e 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/h for ≥24h **OR** Anuria for ≥12h 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, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) leading to death, life-threatening or major bleeding[a], visceral ischemia 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 ischaemia 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, arterio-venous fistula, pseudoaneuysms, hematomas , percutaneous closure device failure) not leading to death, life-threatening or major bleeding[a], 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)
-

Percutaneous close 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)

[a]Refers to VARC 2 bleeding definitions

Other TAVI-related complications **(VARC 2)**	**Conversion to open surgery** • Conversion to open sternotomy during the TAVI procedure secondary to any procedure-related complications **Unplanned use of cardiopulmonary bypass (CPB)** • Unplanned use of CPB for haemodynamic support at any time during the TAVI procedure **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 **Ventricular septal perforation** • Angiographic or echocardiographic evidence of a new septal perforation during or after the TAVI procedure **Mitral valve apparatus damage or dysfunction** • Angiographic or echocardiographic evidence of new damage (chordae papillary muscle, or to the leaflet) to the mitral valve apparatus or dysfunction (e.g. restrictions due to the THV) of the mitral valve during or after the TAVI procedure **Cardiac tamponade** • Evidence of a new pericardial effusion associated with haemodynamic instability and clearly related to the TAVI procedure **Endocarditis** Any one of the following • Fulfilment of the Duke endocarditis criteria (23) • Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during a re-operation • Findings of abscess, pus, or vegetation involving a repaired or replaced valve during an autopsy **Valve thrombosis** • Any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Note that valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve-related should not be reported as valve thrombosis **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 • Ectopic valve deployment : Permanent deployment of the valve prosthesis in a location other than the aortic root **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
Potential failure modes of prosthetic valve Dysfunction **(VARC)**	**Aortic stenosis** • Stent creep • Pannus • Calcification • Support structure deformation (out-of-round configuration), under-expansion,

	fracture, or trauma (cardio-pulmonary resuscitation, blunt chest trauma) • Mal-sizing (prosthesis-patient mismatch) • Endocarditis • Prosthetic valve thrombosis • Native leaflet prolapse impeding prosthetic leaflet motion **Aortic regurgitation** • Pannus • Calcification • Support structure deformation (out-of-round configuration), recoil, under-expansion, fracture, insufficient radial strength, or trauma (cardio-pulmonary resuscitation, blunt chest trauma) • Endocarditis • Prosthetic valve thrombosis • Malposition (too high, too low) • Acute mal-coaptation • Leaflet wear, tear/perforation, prolapse, or retraction • Suture breakage or disruption • Native leaflet prolapse impeding prosthetic leaflet motion

Prosthetic Valve Stenosis ***In conditions of normal or near normal stroke volume (50–70 ml).*** **(VARC 2)**	**Parameter**	**Normal**	**Mild Stenosis**	**Moderate/Severe Stenosis**
	Quantitative parameters (flow-dependent)			
	Peak velocity (m/s)	< 3m/s	3–4m/s	> 4m/s
	Mean gradient (mm Hg)	< 20mmHg	20–40 mmHg	> 40 mmHg
	Doppler velocity index For LVOT >2.5 cm, significant stenosis criteria is <0.20.	> 0.35	0.35–0.25	< 0.25
	Quantitative parameters (flow-independent)			
	Effective orifice area (cm^2) Use in setting of BSA ≥1.6 cm2	> 1.1cm^2	1.1–0.8 cm^2	< 0.80 cm^2
	Effective orifice area (cm^2) Use in setting of BSA <1.6 cm2.	> 0.9 cm^2	0.9 – 0.6 cm^2	< 0.6 cm^2
Prosthesis–patient mismatch (PPM) **(VARC 2)**	**Parameter**	**Insignificant**	**Moderate**	**Severe**
	Indexed effective orifice area (cm^2/m^2) Use in setting of BMI <30 kg/ cm^2.	>0.85 cm^2/m^2	0.85–0.65 cm^2/m^2	< 0.65 cm^2/m^2
	Indexed effective orifice area (cm^2/m^2) Use in setting of BMI ≥30 kg/ cm^2.	>0.90 cm^2/m^2	0.90–0.60 cm^2/m^2	< 0.60 cm^2/m^2
Prosthetic	**Parameter**	**Mild**	**Moderate**	**Severe**

Valve Regurgitation **(VARC 2)**	**Semi quantitative parameters**			
	Diastolic flow reversal in the descending aorta—PW	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic
	Circumferential extent of prosthetic valve paravalvular regurgitation (%) Not well-validated and may overestimate the severity compared with the quantitative Doppler.	<10%	10–29%	≥30%
	Quantitative parameters			
	Regurgitant volume (mL/beat)	<30 mL	30–59 mL	≥60 mL
	Regurgitant fraction (%)	<30%	30–49%	≥50%
	EROA (cm^2)	0.10 cm^2	0.10–0.29 cm^2	≥0.30 cm^2
Device Success **(VARC 2)**	• Absence of procedural mortality AND • 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[a] and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, AND no moderate or severe prosthetic valve regurgitation[a])			
Early Safety (at 30 days) **(VARC 2)**	• All-cause mortality • All stroke (disabling and non-disabling) • Life-threatening bleeding • Acute kidney injury—Stage 2 or 3 (including renal replacement therapy) • Coronary artery obstruction requiring intervention • Major vascular complication • Valve-related dysfunction requiring repeat procedure (BAV, TAVI, or SAVR)			
Clinical efficacy (after 30 days) **(VARC 2)**	• All-cause mortality • All stroke (disabling and non-disabling) • Requiring hospitalizations for valve-related symptoms or worsening congestive heart failure[b] • NYHA class III or IV • Valve-related dysfunction (mean aortic valve gradient ≥20 mmHg, EOA ≤0.9–1.1 cm2(c) and/or DVI <0. 35 m/s, AND/OR moderate or severe prosthetic valve regurgitation[a]			
Time-related valve safety **(VARC 2)**	• Structural valve deterioration • Valve-related dysfunction (mean aortic valve gradient • ≥20 mmHg, EOA ≤0.9–1.1 cm^2[c]and/or DVI <0.35 m/s, AND/OR moderate or severe prosthetic valve regurgitation[a]) • Requiring repeat procedure (TAVI or SAVR) • Prosthetic valve endocarditis • Prosthetic valve thrombosis • Thrombo-embolic events (e.g. stroke)			

	• VARC bleeding, unless clearly unrelated to valve therapy (e.g. trauma)
	[a]refers to VARC definitions [b]As a basis for calculation of 'days alive outside the hospital' endpoint. Supplementary appendix of Leon et al. Includes heart failure, angina, or syncope due to aortic valve disease requiring intervention or intensified medical management; clinical symptoms of CHF with objective signs including pulmonary oedema, hypoperfusion, or documented volume overload AND administration of IV diuresis or inotropic therapy, performance of aortic valvuloplasty, institution of mechanical support (IABP or ventilation for pulmonary oedema) or haemodialysis for volume overload; clear documentation of anginal symptoms AND no clinical evidence that angina was related to CAD or ACS; documented loss of consciousness not related to seizure or tachyarrhythmia. [c]Depending on the body surface area.

Appendix E: Surgical Risk Assessment Tools

This clinical investigation requires the use of three (3) surgical risk assessment tools which are available online:

- Logistic Euro SCORE I
  - http://euroscore.org/calcold.html
- Logistic Euro SCORE II
  - http://euroscore.org/calc.html
- The Society of Thoracic Surgeons' (STS) risk calculation tools, Version 2.73
  - http://riskcalc.sts.org/STSWebRiskCalc273/de.aspx

Appendix F: Frailty Assessment

Frailty assessment will be performed according to the VARC 2 guidelines. Frailty components have to be assessed concomitantly.

5 meters walking time: Patients will be requested to walk for 5 meters. The time the patient takes to walk this distance, with or without a walking aid will be measured.

Walk Time, stratified by gender and height (24).

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

Grip strength: Patients will be requested to squeeze a hand-held dynamometer. Patients 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. The best of three attempts will be used.

Grip Strength, stratified by gender and body mass index (BMI) quartiles (24)

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

Wasting and malnutrition: The following parameters will be determined for each patient

Parameters	Cutoff values for criterion for frailty
Weight Loss (unintentional)	>5Kgs/year
BMI	<20kg/m^2
Serum albumin	< 3.5g/dL

Cognitive impairment or dementia: The mini–mental state examination (MMSE) will be performed.

Appendix G: ATS Guidelines[25] for the Six Minute Walk Test

This Six Minute Walk (6MWT) Test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. It evaluates the global and integrated responses of all the systems involved during exercise, including the pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units, and muscle metabolism. It does not provide specific information on the function of each of the different organs and systems involved in exercise or the mechanism of exercise limitation, as is possible with maximal cardiopulmonary exercise testing.

SAFETY ISSUES

- Testing should be performed in a location where a rapid, appropriate response to an emergency is possible. The appropriate location of a crash cart should be determined by the physician supervising the facility.
- Supplies that must be available include oxygen, sublingual nitroglycerine, aspirin, and albuterol (metered dose inhaler or nebulizer). A telephone or other means should be in place to enable a call for help.
- The technician should be certified in cardiopulmonary resuscitation with a minimum of Basic Life Support by an American Health Association–approved cardiopulmonary resuscitation course. Advanced cardiac life support certification is desirable. Training, experience, and certification in related health care fields (registered nurse, registered respiratory therapist, certified pulmonary function technician, etc.) are also desirable. A certified individual should be readily available to respond if needed.
- Physicians are not required to be present during all tests. The physician ordering the test or a supervising laboratory physician may decide whether physician attendance at a specific test is required.
- If a patient is on chronic oxygen therapy, oxygen should be given at their standard rate or as directed by a physician or a protocol.

Reasons for immediately stopping a 6MWT include the following: (1) chest pain, (2) intolerable dyspnea, (3) leg cramps, (4) staggering, (5) diaphoresis, and (6) pale or ashen appearance.

Technicians must be trained to recognize these problems and the appropriate responses. If a test is stopped for any of these reasons, the patient should sit or lie supine as appropriate depending on the severity or the event and the technician's assessment of the severity of the event and the risk of syncope. The following should be obtained based on the judgment of the technician: blood pressure, pulse rate, oxygen saturation, and a physician evaluation. Oxygen should be administered as appropriate.

CONTRAINDICATIONS

Absolute contraindications for the 6MWT include the following: unstable angina during the previous month and myocardial infarction during the previous month. Relative contraindications include a resting heart rate of more than 120, a systolic blood pressure of more than 180 mm Hg, and a diastolic blood pressure of more than 100 mm Hg.

Patients with any of these findings should be referred to the physician ordering or supervising the test for individual clinical assessment and a decision about the conduct of the test. The results from a resting electrocardiogram done during the previous 6 months should also be reviewed before testing. Stable exertional angina is not an absolute contraindication for a 6MWT, but patients with these symptoms should perform the test after using their antiangina medication, and rescue nitrate medication should be readily available. A deviation from the Clinical Investigation Plan will need to be collected if the patient is unable to complete this test.

LOCATION

The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. If the weather is comfortable, the test may be performed outdoors. The walking course must be 30 m in length. A 100-ft hallway is, therefore, required. The length of the corridor should be marked every 3 m. The turnaround points should be marked with a cone (such as an orange traffic cone). A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor using brightly colored tape.

PROCEDURE

Required Equipment

- Countdown timer (or stopwatch)
- Mechanical lap counter
- Two small cones to mark the turnaround points
- A chair that can be easily moved along the walking course
- Worksheets on a clipboard
- A source of oxygen
- Sphygmomanometer
- Telephone
- Automated electronic defibrillator

Patient Preparation

- Comfortable clothing should be worn.
- Appropriate shoes for walking should be worn.
- Patients should use their usual walking aids during the test (cane, walker, etc.).
- The patient's usual medical regimen should be continued.
- A light meal is acceptable before early morning or early afternoon tests.
- Patients should not have exercised vigorously within 2 hours of beginning the test.
- This test should be performed about the same time of day for each interval to minimize intraday variability.
- A "warm-up" period before the test should not be performed.
- The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Complete the first portion of the worksheet.

Baseline Measurements

1. Have the patient stand and rate their baseline dyspnea and overall fatigue using the Borg scale.
2. Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment (lap counter, timer, clipboard, Borg Scale, worksheet) and move to the starting point.

Instruct the patient as follows:

"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

Start now, or whenever you are ready."

Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.

Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

After the first minute, tell the patient the following (in even tones):
"You are doing well. You have 5 minutes to go."

When the timer shows 4 minutes remaining, tell the patient the following:
"Keep up the good work. You have 4 minutes to go."

When the timer shows 3 minutes remaining, tell the patient the following:
"You are doing well. You are halfway done."

When the timer shows 2 minutes remaining, tell the patient the following:
"Keep up the good work. You have only 2 minutes left."

When the timer shows only 1 minute remaining, tell the patient:
"You are doing well. You have only 1 minute to go."

Do not use other words of encouragement (or body language to speed up).

If the patient stops walking during the test and needs a rest, say this:
"You can lean against the wall if you would like; then continue walking whenever you feel able."

Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

When the timer is 15 seconds from completion, say this:
"In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."

When the timer rings (or buzzes), say this: *"Stop!"*

Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped.

Post-test
Record the postwalk Borg dyspnea and fatigue levels and ask this:
"What, if anything, kept you from walking farther?"

1. Record the number of laps from the counter (or tick marks on the worksheet).

2. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.
3. Congratulate the patient on good effort and offer a drink of water.

Appendix H: Structured Interview for the Modified Rankin Scale (mRS)

The modified Rankin Scale (mRS) score is to be determined and graded by a certified rater.

The determination of the scale should be made from 5 to 0, i.e., the order presented.

The purpose of the mRS is to record whether the patient is dead, severely, moderately, or slightly disabled and if not dead or disabled, whether the patient is performing all usual activities without symptoms or not.

Because patients and family members may understate the severity of disability, it is important for the rating clinician to understand that the mRS is a clinical scale and not a patient-reported outcome. The rater may ask questions but must assess the disability whether or not in agreement with the patient or family (26).

5: Severe disability; someone needs to be available at all times; care may be provided by either a trained or an untrained caregiver.

Question: Does the person require constant care?

4: Moderately severe disability; need for assistance with some basic activities of daily living (ADL), but not requiring constant care.

Question: Is assistance essential for eating, using the toilet, daily hygiene, or walking?

3: Moderate disability; need for assistance with some instrumental ADL but not basic ADL.

Question: Is assistance essential for preparing a simple meal, doing household chores, looking after money, shopping, or traveling locally?

2: Slight disability; limitations in participation in usual social roles, but independent for ADL.

Questions: Has there been a change in the person's ability to work or look after others if these were roles before stroke? Has there been a change in the person's ability to participate in previous social and leisure activities? Has the person had problems with relationships or become isolated?

1: No significant disability; symptoms present but no other limitations.

Question: Does the person have difficulty reading or writing, difficulty speaking or finding the right word, problems with balance or coordination, visual problems, numbness (face, arms, legs, hands, feet), loss of movement (face, arms, legs, hands, feet), difficulty with swallowing, or other symptom resulting from stroke?

0: No symptoms at all; no limitations and no symptoms.

Appendix I: Peri-procedural instructions

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).

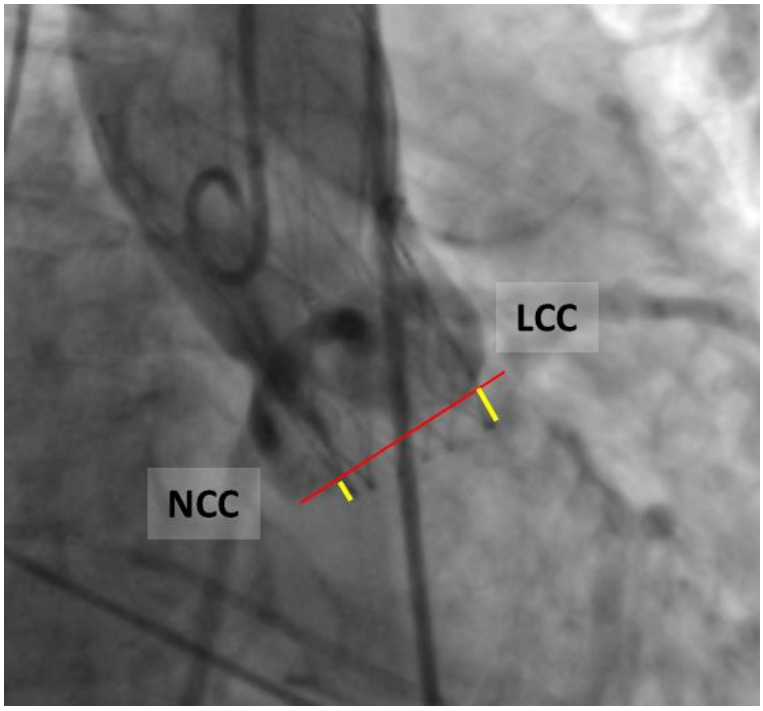
Hemodynamic assessment: the AR index will be calculated as described by Sinning et al (27).

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 J: Recommendation for paced rhythm assessment in patients with a TAVI related implantation of permanent pacemaker

This recommendation will apply for patients who received a new pacemaker, due to any degree of AV-block, within 30 days after their TAVI procedure.

This testing is aimed to determine whether the patient is pacemaker dependent; it will be performed twice, at the 30 days visit and further following routine control.

The patient will have a 12-lead ECG, if the latter shows a “pace rhythm”, then the pacemaker will be set to 30 bpm (VVI or DDD) for and another 12-lead ECG will be performed to see if there is still a “pace rhythm”.

Afterwards the pacemaker will be programmed back to its normal setting.

Appendix K: Explant, Return, and Analysis of Valve

The disposition of explanted valves warrants special consideration, as their proper return will allow for analyses providing valuable information.

Clinical Study Sites' Responsibilities for Explant and Return of Device: SJM requests that all valves that are explanted or recovered be returned to SJM as follows:

- Contact the SJM Clinical Manager(s) for this study as soon as it is learned that a valve will be explanted, or recovered during an autopsy. The Clinical Representative(s) will obtain a RA# (used for returning products to SJM), and then send a St. Jude Medical Product Return Kit to the site for return of the explanted valve.
- When possible, take in situ photographs of the valve.
- Remove the valve from the patient and immediately place it in the inner jar of the product return kit. (If the explant kit is not available, place the valve in any specimen jar until the product return kit arrives.)
- Cover the valve with a formalin solution (usual lab concentration 3-8%). If an alternate solution is used [i.e., alkaline glutaraldehyde (Cidex) at 0.5-1% concentration], please indicate the solution type and concentration on the specimen container.
- Secure the cap.
- Complete the round white label with device, patient, and surgeon information.
- Place the completed label on the cap of the inner jar and fold tape edges down over jar.
- Place the small labeled jar in the absorbent wrapping provided, and place inside the larger jar.
- Secure the cap.
- Place the outer jar into the shipping box. Tape the box closed.
- Write the RA#, and the name and phone number of the person responsible for shipping the valve on the return shipping label.
- For infectious specimens, complete the highlighted portions of the Shipper's Declaration for Dangerous Goods form, and keep this form with the product return kit.
- Send the packaged valve, in situ photographs, and operative/autopsy notes via courier to the following address:

Attn: FER Lab
177 East County Road B
St. Paul, MN 55117 USA

St. Jude Medical's Responsibilities for the Analysis of an Explanted and Returned Device:

Portico Valve that are explanted or recovered at autopsy and returned will, upon receipt at St. Jude Medical, Inc., be evaluated according to documented SJM procedures.

Appendix L: Instructions for device return - Large and Small Kits

Instructions for Packaging and Returning Products to St. Jude Medical from US and Outside of US Locations

St. Jude Medical provides instructions and a Device Return Kit (DRK) for components being returned for analysis. Please follow these instructions when returning products.

1- Email the completed product Complaint and Event Form or Field Experience Report. Please submit event within 2 calendar days of becoming aware of the event.

(NOTE: ONLY ONE DEVICE PER RGA NUMBER AND DEVICE RETURN KIT)

2- Clearly print the RGA number in the designated space on the event report form.

3- Package device to be returned in DRK as follows:
   a. Insert hands into rubber gloves as provided in the DRK
   b. With gloved hands, place device to be retuned into zip lock bag and seal shut.
   c. Carefully position the sealed zip lock bag and device into the bio-hazard bag without damaging returned components.
   d. Place absorbent strip into bio-hazard bag.
   e. Follow instructions on the front facing bag to seal biohazard bag.
   f. Place plastic biohazard bag inside the tyvek envelope (follow instructions on the outside of the tyvek envelope).
   g. Assemble the box provided in the DRK following the directions on the box.
   h. Place the tyvek envelope with the sealed biohazard pouch into box, again being careful not to damage
   i. Close box using the instructions provided on the panel of the box and seal with Chem-Tran Box Sealing.
   j. Affix UN3373 Label to the area as shown on the outer shipping box.

4- Clearly print the RGA number on the outer portion of the DRK box.

5- Affix the address label provided to the outside of the box and return DRK to:

St. Jude Medical
ATTN: Reliability Analysis Laboratory
14901 DeVeau Place
Minnetonka, MN 55345
USA