Clinical Investigation Plan

Detailed information regarding the investigational FlexNav™ Delivery System and FlexNav™ Loading System can be found in the Investigator Brochure.

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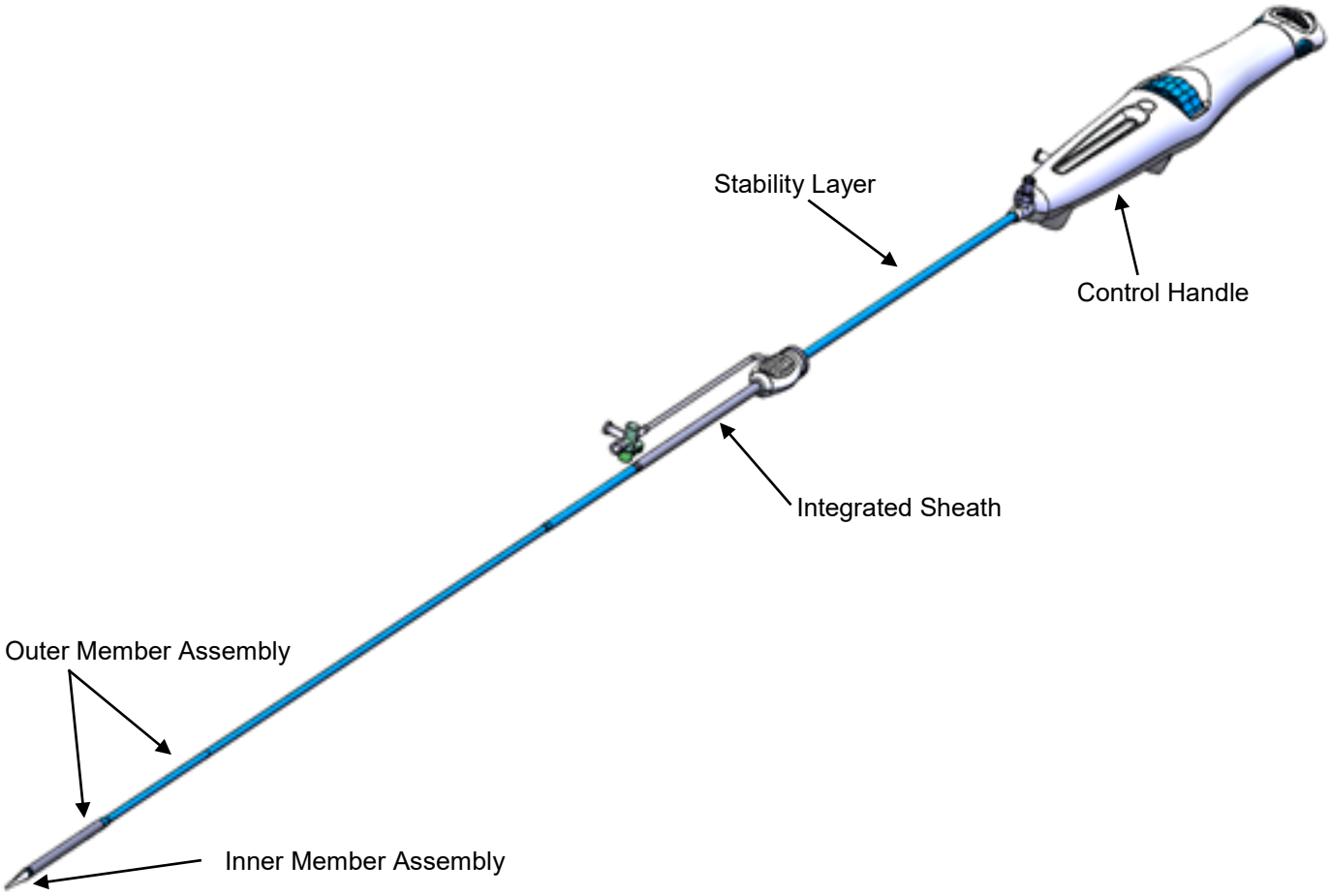

Figure 1:Second-Generation FlexNav™ Delivery System

[redacted]

Clinical Investigation Plan

[redacted] Subject case report forms (CRFs) will be collected for screening, baseline, procedure, at discharge, and at 30 days, 6 months and 12-months post-index procedure. Assessments required at each visit in the FlexNav EU study are outlined in section 3.3.

3.3 Clinical Investigation Procedures and Follow-up Schedule

The Flow Chart and the Follow-up requirements of this clinical investigation are described below.

Subjects will be screened for study eligibility by the Investigator as well as the local Heart Team per the inclusion and exclusion criteria. Subjects will then be reviewed by an independent Subject Selection Committee to confirm anatomical suitability and appropriateness of surgical risk classification assigned by the local Heart Team.

If the Subject Selection Committee determine the subject's anatomy precludes transfemoral implantation of the Portico™ valve using the FlexNav™ Delivery System the subject will be exited from the study as a screen failure. Additionally, if the Subject Selection Committee assign a surgical risk classification that the local Heart Team does not agree with, the subject will be exited from the study as a screen failure.

For subjects approved by the Subject Selection Committee, clinical investigation visits will occur at baseline, implant procedure, discharge, 30 days, 6 months and 12 months post-implantation (Figure 6).

It is strongly recommended the baseline visit be scheduled within 14 days of receiving Subject Selection Committee approval.

Follow-up visits will be conducted in-person at the investigational site and will include a combination of standard of care and study-specific testing. If an in-office visit is not possible for a patient, medical records from another care facility and a phone visit may be conducted. All enrolled subjects will be followed to their 12-month visit.

At the conclusion of the 12-month follow-up visit, participation in the clinical investigation will end and subjects will be followed as part of standard of care.

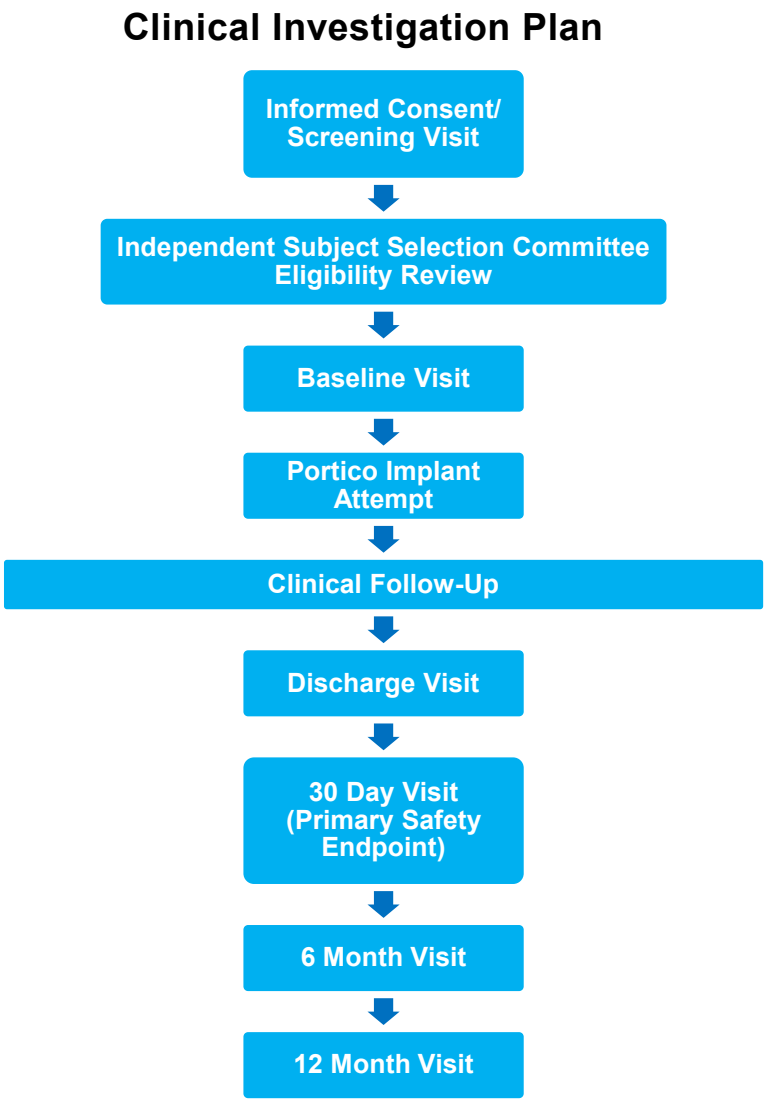

Figure 6: Clinical Investigation Flow Chart

3.4 Measures Taken to Avoid and Minimize Bias

The study will include the following measures to minimize bias in the conduct of the study and analysis of clinical data:

- Screening by an inter-disciplinary local Heart Team
- Assessment of Anatomical Suitability by a Computed Tomography (CT) sizing Core Laboratory
- Use of an Independent Subject Selection Committee
- Adjudication of Adverse Events by an Independent Clinical Events Committee
- Review of Echocardiographic Images by an Independent Echocardiographic Core Laboratory
- Monitoring Follow-Up Compliance
- Standardized Administration of Patient-Reported Outcomes Assessments

[redacted]

3.4.1 Screening by an inter-disciplinary local Heart Team

At each investigational site, a local heart team consisting of at least of one cardiac surgeon and one interventional cardiologist will be responsible for screening patients for anatomical suitability and surgical risk classification for participation in the clinical investigation. The Primary Investigator may serve the role of the cardiac surgeon or interventional cardiologist on the local heart team.

3.4.2 Assessment of Anatomical Suitability by a Computed Tomography (CT) sizing Core Laboratory

An independent Computed Tomography (CT) Core Laboratory will be used for anatomical assessments of each patient prior to enrollment in the study (Refer to section 5.4 for definition of Subject Enrollment). Assessment results will be provided to the Subject Selection Committee for consideration of a subject's eligibility to participate in the study, primary arterial access side (left or right) and valve size selection.

Each investigational site is responsible for performing the CT scan according to the core laboratory imaging protocol. If the CT Core Laboratory determines that the data is unreadable, the site will be responsible for having the subject return for another assessment.

3.4.3 Use of an Independent Subject Selection Committee

An independent Subject Selection Committee (SSC), consisting of cardiologists and surgeons considered experts in the field of aortic valve replacement with a focus on TAVR will be responsible for ensuring all subjects' clinical eligibility (i.e. risk classification) and technical suitability (i.e. anatomical criteria) for implant in conjunction to the protocol and sizing recommendations provided in the IFU. SSC review and approval is required prior to scheduling a subject for a baseline visit.

The same independent SSC responsible for reviewing patients in the Portico US IDE trial will be utilized for the current clinical investigation.

The composition, guiding policies and operating procedures governing the SSC in this clinical investigation is further defined in a separate SSC Charter.

3.4.4 Adjudication of Adverse Events by an Independent Clinical Events Committee

An independent Clinical Events Committee (CEC), consisting of, at a minimum, an interventional cardiologist, cardiologist, cardiothoracic surgeon, and a neurologist will review and adjudicate pre-specified events reported by investigators or identified by Safety personnel in the clinical investigation as defined in the CEC Manual of Operations Charter. Events related to primary and descriptive endpoint criteria will be adjudicated according to the Valve Academic Research Consortium (VARC-2) definitions. The CEC will have final adjudication responsibilities for subject outcomes related to primary and descriptive outcome measures.

The same CEC used in the Portico US IDE pivotal trial will be utilized for this clinical investigation.

3.4.5 Review of Echocardiographic Images by an Independent Echocardiographic Core Laboratory

An independent Echocardiographic Core Laboratory will be utilized for the analysis of the screening and all study visit echocardiograms according to the echocardiographic protocol.

[redacted]

[redacted]

3.4.6 Monitoring Follow-Up Compliance

The Sponsor will work with investigational sites to maintain a high follow-up compliance as follows:

1. Sponsor will emphasize to the site the importance of subject follow-up during site initiation visits and subsequent communications. Site should communicate the importance of follow-up visits to each subject.
2. Sites will be informed to promptly reschedule any missed subject visits, and to reinforce the necessity of a follow-up visit to the subject.
3. Site is advised to involve Sponsor when needed. Example: Arrange alternate transportation if a scheduled visit is missed due transportation/travel issues, or due to subject illness
4. Sites should document reasons for any subject withdrawals from the trial, and request agreement for a follow-up call from the investigator when the last subject has completed the 12-month visit.
5. Sites should monitor follow-up rates closely to promptly identify and address any issues.

Additionally, investigational sites will be educated on the importance of maintaining low rates of withdrawals, and will be expected to make all effort to maintain low withdrawals during trial conduct. Withdrawals from the trial will require discussion between Investigator and the Sponsor.

3.4.7 Standardized Administration of Patient-Reported Outcome Measures and Stroke Assessment Scales (mRS and NIHSS)

A standardized script will be used when administering patient-reported outcome (PRO) measures to minimize bias and undue influence. All PRO measures must be completed by the subject or his/her legal representative (where allowed per local regulations). In the latter case, a note to file must be completed to document the inability of the subject to complete the measures(s).

The Modified Rankin Scale (mRS) and National Institute of Heath Stroke Scale(NIHSS) must be completed by an assessor who has a current certificate that demonstrates completion of an accredited training program for these stroke scales.

3.5 Suspension or Early Termination of the Clinical Investigation

[redacted]

The Sponsor reserves the right to discontinue the clinical investigation at any stage or reduce the follow-up period with suitable written notice to the investigator. Possible reason(s) may include, but are not limited to:

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

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

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

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

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

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

4 ENDPOINTS

4.1 Primary Endpoint and Rationale

The primary safety endpoint of the FlexNav EU study is VARC-2 defined major vascular complications at 30 days post index procedure.

According to VARC-2 criteria, a major vascular complication is defined as:

- 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*, 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 ischemia or neurological impairment or

- Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram or
- Surgery for access site-related nerve injury or
- Permanent access site-related nerve injury

[redacted]

4.2 Descriptive Endpoint(s)

A selection of descriptive endpoints including valve performance parameters, clinical function assessments and adverse events defined according to VARC 2 criteria will be assessed at 30 days and at 12 months as defined below. All descriptive endpoints will be summarized separately using descriptive statistics.

Descriptive endpoints to be assessed at 30 days and included in the CE Mark submission:

- Non-hierarchical composite of all-cause mortality, disabling stroke, life threatening bleeding requiring blood transfusion, acute kidney injury requiring dialysis, or major vascular complications at 30 days from the index procedure.
- All-cause mortality at 30 days from the index procedure.
- Disabling stroke at 30 days from the index procedure.
- Non-disabling stroke at 30 days from the index procedure.
- Life threatening bleeding requiring blood transfusion at 30 days from the index procedure.
- Major bleeding at 30 days from the index procedure.
- Acute kidney injury at 30 days from the index procedure.
- Minor vascular complication rates at 30 days from the index procedure.
- Permanent pacemaker insertion at 30 days from the index procedure.
- Paravalvular Leak (PVL) at 30 days from the index procedure.
- NYHA functional classification at 30 days from the index procedure.
- KCCQ Quality of Life (QOL) score from baseline to 30 days from the index procedure.
- Technical device success defined as successful vascular access, delivery and deployment of the Portico Valve; retrieval with the delivery system and correct positioning of a single valve in the proper anatomical location.

Additional descriptive endpoints to be assessed at one year but not included in the CE Mark submission:

- Composite of all-cause mortality or disabling stroke at one year from the index procedure.
- All-cause mortality at one year from the index procedure.
- Disabling stroke at one year from the index procedure.

[redacted]

- Non-disabling stroke at one year from the index procedure.
- Paravalvular Leak (PVL) at one year from the index procedure.
- KCCQ Quality of Life (QOL) score from baseline and one year from the index procedure.
- NYHA functional classification at one year from the index procedure.

5 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This clinical investigation will enroll male and female subjects from a valvular disease population who have symptomatic, severe AS and are determined to be at high or extreme operative risk for SAVR.

Subjects must sign and date the informed consent prior to conducting any study-specific procedures not considered standard of care. Any patient data transmitted to the independent CT and Echocardiographic core laboratories, SSC or Sponsor for screening purposes must have prior signed and dated Informed Consent.

The operative risk determination of study candidates will be based on the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Risk Calculator score and the EuroSCORE II score.

Subject case review will be conducted by the SSC to determine the patient's anatomical eligibility to receive a Portico valve using the FlexNav™ Delivery System and final risk classification. Refer to the SSC charter for a full description of the review process. Subjects will be assigned as high or extreme risk according to criteria below:

5.1.1 High Risk Classification:

High risk classification will be assigned to subjects with severe aortic stenosis symptoms for whom conventional aortic valve replacement surgery is associated with high risk equivalent to an STS risk score that is ≥8%.

Patients with an STS risk score that is <8% will be assigned high risk if frailty indices and/or existing co-morbidities not captured by STS are also present. Specifically, assessments of patient's physical performance including a 15-foot (5m) gait speed test, grip strength testing and Katz Index of Independence in Activities of Daily Living will be considered along with surgical comorbidities not addressed in the STS score (including porcelain aorta, pulmonary hypertension, severe mitral regurgitation, moderate-severe tricuspid regurgitation, diabetes, chronic kidney disease, chronic and oxygen dependent lung disease).

5.1.2 Extreme risk classification

Extreme risk classification will be assigned to subjects with severe aortic stenosis symptoms who are deemed unsuitable for conventional aortic valve replacement because of predicted probability of ≥50% mortality, or at risk for a serious irreversible complication by 30 days.

Subjects with an STS risk score that is >8%, aged >90 years and with a frailty index≥2 will automatically qualify for extreme risk classification.

6.1.2 Pre-procedure Antiplatelet/Anticoagulation Medications

Antiplatelet/Anticoagulation and other medications should be administered pre-procedure per the standard of care at the investigational site.

6.1.3 Pre-Procedure Blood Test

The following blood tests will be performed at the investigational site within 72 hours prior to the index procedure:

1. Cardiac enzymes (Troponin or CK/CK-MB)
2. BUN and Creatinine

6.2 Index Procedure

6.2.1 Procedure Involved in the Use of the Investigational Devices

Please refer to IFU for instructions on handling and preparation of the FlexNav™ Delivery System, FlexNav™ Loading System and Portico™ valve. All Investigators must read and understand the IFU and Investigator Brochure.

6.2.2 Anticoagulation Therapy

Anticoagulation use during the procedure is left to the physician's discretion or should be established as with any other biological valve implantation, considering risks and benefits for the patient. The activated clotting time (ACT) should be monitored and recorded on source documentation during the procedure and medications should be adjusted to attempt to keep the subject's ACT>250 seconds.

6.2.3 Treatment Procedures

The local heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of the TAVR procedure.

It is strongly encouraged that the index procedure occur within 14 calendar days following SSC approval.

At least one transcatheter aortic valve may be implanted in a subject who has signed the Informed Consent Form, and Data Protection Form (if applicable). Although not recommended, if a physician determines it is in the best interest of the subject to have a second transcatheter aortic valve placed, a subject may receive an additional transcatheter aortic valve (Valve-in-Valve).

Standardized imaging techniques will be used during the index procedure to implant the valve and to assess valve performance and coronary patency.

The following data will be collected during the implant procedure:

1. Device access, deployment and final valve placement data collection
2. Aortic systolic/diastolic pressure, mean aortic pressure, mean aortic valve gradient, peak aortic valve gradient and aortic regurgitation (post-implant only) immediately pre- and post implant,
3. If performed, right atrial pressure, pulmonary artery systolic/diastolic pressure, mean pulmonary artery pressure, pulmonary wedge pressure (PCWP) immediately pre- and post implant
4. Cardiac Rhythm Monitoring

   Rhythm changes will be monitored and recorded at the following time points:

[redacted]

4. NIH Stroke Scale (NIHSS)
5. Barthel Index
6. Echocardiography
7. 12 lead ECG (for subjects receiving a new permanent pacemaker, ECG should be completed showing the underlying rhythm as well as the current pacing programming)
8. Lab Measurements (including CBC and Platelet count, BUN and creatinine, BNP or ProBNP, INR if subject is on coumadin, warfarin or other anticoagulants/vitamin K antagonists in lieu of warfarin, Troponin or CK/CK-MB and Albumin)
9. NYHA Functional Classification
10. Frailty Index Assessment (Katz Index of Activities of Daily Living, Grip Strength, 5 meter walk test)
11. Quality of Life Measures (SF-36, EQ-5D and KCCQ)
12. MMSE-2:SV
13. Six Minute Walk Test (6MWT)
14. Cardiovascular medications documentation
15. Adverse events assessment

6.5.2.2 6 Month Follow-Up

The 6-month follow-up visit will take place at 6 months (±30 days) post-index procedure, and will include the following assessments:

1. Physical exam
2. Canadian Cardiovascular Society (CCS) Angina Scale Assessment
3. Modified Rankin Scale (mRS)
5. NIH Stroke Scale (NIHSS)
6. Barthel Index
7. Echocardiography
8. 12 lead ECG (for subjects receiving a new permanent pacemaker, ECG should be completed showing the underlying rhythm as well as the current pacing programming)
9. Lab Measurements (including CBC and Platelet count, BUN and creatinine, BNP or ProBNP, INR if subject is on coumadin, warfarin or other anticoagulants/vitamin K antagonists in lieu of warfarin, Troponin or CK/CK-MB and Albumin)
10. NYHA Functional Classification
11. Frailty Index Assessment (Katz Index of Activities of Daily Living, Grip Strength, 5 meter walk test)
12. Quality of Life Measures (SF-36, EQ-5D and KCCQ)
13. MMSE-2:SV

Refer to APPENDIX XV for a copy of the Modified Rank Score and APPENDIX XVI for a copy of the NIH Stroke Scale.

6.5.4 Patient Reported Outcome (PRO) Measures

The following PRO measures will be collected according to the CIP requirements to assess whether the health of subjects has improved since enrollment in the clinical investigation:

- EuroQoL (EQ) 5D-3L Questionnaire
- SF-36
- KCCQ
- Mini-Mental State Examination (MMSE-2)
- Canadian Cardiovascular Society (CCS) Angina Scale Assessment
- New York Heart Association Functional Classification
- Barthel Index

Refer to APPENDIX VIII-XIV for copies of the exact format and version of PRO measures that will be administered as part of the clinical investigation

The Principal Investigator, research coordinator or study designee will administer the patient-reported outcome (PRO) measures. It is important the subject understands the meaning of all words and instructions in the measures. The subject should be instructed to ask any questions about the measures if further explanation is needed. Once the PRO measures are completed, the research coordinator or study designee will review for completeness to verify that all questions have been answered according to the directions provided.

6.5.4.1 EQ-5D-3L questionnaire

The EuroQol 5D 3 level version (EQ-5D-3L) questionnaire is a standardized instrument used as a measure of health outcome and quality of life. The self-administered questionnaire consists of two pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The questionnaire is cognitively simple and takes only a few minutes to complete. The EQ-5D-3L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels: no problems, some problems, extreme problems. The EQ VAS records the respondent's self-rated health on a 20cm vertical, visual analogue scale where the endpoints are labelled '100 =Best imaginable health state' and '0=Worst imaginable health state'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents. An EQ-5D health state may be converted to a single summary index by applying a formula that attaches weights to each of the levels in each dimension. Refer to APPENDIX X for the sample questionnaire.

6.5.4.2 SF-36

The Medical Outcomes Study Questionnaire Short Form 36 Health Survey version 2 (SF-36 v2) is a widely used, validated questionnaire that provides an indicator of overall health status. The self-administered questionnaire consists of 10 items across eight separate domains (Vitality, Physical functioning, Bodily pain, General health perceptions, Physical role functioning, Emotional role functioning, Social role functioning, Mental health). The questionnaire takes approximately five to 10 minutes to complete; elderly subjects may require 15 minutes.

Two sets of scores are derived from the SF-36; eight individual domain scores, and two summary scores, one for the physical component (PCS) and one for the mental component (MCS) summary scores. For each set of scores, two alternative approaches may be used in calculating scores: a normal, additive approach that produces 0-to-100 scores for the eight scales (with a lower score indicating more disability and higher scores less disability), and a norm-based approach that adjusts these raw scores to have a mean of 50 and a standard deviation of 10. Refer to APPENDIX XI for the sample questionnaire.

6.5.4.3 Kanas City Cardiomyopathy Questionnaire (KCCQ)

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item, validated, self-administered instrument that quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life in patients with congestive heart failure or weakened heart muscle due to prior heart attacks, heart valve problems, viral infections, or other causes.

The KCCQ evaluates eight (8) clinically relevant domains including: physical limitations, symptoms (frequency and severity), change over time, self-efficacy and knowledge, social function and quality of life. The questionnaire requires, on average, 4–6 minutes to complete. The KCCQ is scored by assigning each response an ordinal value, beginning with 1 for the response that implies the lowest level of functioning and summing items within each domain. Missing values within each domain are assigned the average of the answered items within that same domain. Scale scores are transformed to a 0 to 100 range by subtracting the lowest possible scale score, dividing by the range of the scale and multiplying by 100. To facilitate interpretability, two summary scores were developed; functional status score and a clinical summary score where higher scores reflect better health status. Refer to APPENDIX XII for the sample questionnaire.

6.5.4.4 Mini-Mental State Examination

The Mini Mental State Examination (MMSE) is a validated, 11-question tool used to assess mental status. The MMSE tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. It takes 5-10 minutes to complete and must be administered using a script to the study subject.

The MMSE begins with a graded assessment of orientation to place and time, followed by testing two aspects of memory (immediate recall for three objects presented orally, followed by a serial sevens task which is interposed to assess attention, concentration, calculation, and to prevent the individual from rehearsing the three objects previously learned). The third and final section surveys aphasia by testing functions of naming, repetition, understanding a three-stage command, reading, writing and copying a drawing. A maximum score of 30 is possible with a score of 23 or lower indicative of cognitive impairment. Refer to APPENDIX XIII for the sample questionnaire.

6.5.4.5 Canadian Cardiovascular Society (CCS) Angina Scale Assessment

The Canadian Cardiovascular Society angina grading scale (CCS Angina Scale) is a widely used, self-administered four-point ordinal scale that classifies angina pectoris from mild (class I: angina occurring only during strenuous or prolonged physical activity) to severe (class IV: inability to perform any activity without angina, or angina at rest) and includes the full spectrum of angina from chronic stable to unstable. The assessment takes approximately 1-2 minutes to complete. Refer to APPENDIX IX for the sample questionnaire.

6.5.4.6 New York Heart Association Functional Classification

The New York Heart Association (NYHA) Functional Classification is a validated tool used to classify the extent of heart failure in patients. It places patients in one of four categories based on how much they are

limited during physical activity; the limitations/symptoms are in regard to normal breathing and varying degrees in shortness of breath and/or angina. The NHYA function classification remains the most important prognostic marker for heart failure in routine clinical use. The current version includes two sections: functional capacity NYHA Classification based on patient symptoms and an objective assessment based on physical exam and diagnostic tools. Refer to APPENDIX VIII for the sample questionnaire.

6.5.4.7 Barthel Index

The Barthel Index for Activities of Daily Living (Barthel Index) is used to measure functional independence in activities of daily living (ADL). The validated tool takes 5 minutes to complete and assesses 10 performance items describing ADL and mobility including: feeding, bathing, grooming, dressing, bowel control, bladder control, toilet use, transfers (bed to chair to back), mobility on level surfaces, stair use). Each performance item is rated on a scale with a given number of points assigned to each level or ranking with a higher number associated with a greater likelihood of being able to live at home with a degree of independence following discharge from the hospital. Total possible scores range from 0 – 100, with lower scores indicating increased disability. If used to measure improvement after treatment, changes of more than two points in the total score reflect a probable genuine change, and change on one item from fully dependent to independent is also likely to be reliable. Refer to APPENDIX XIV for the sample questionnaire.

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[redacted]

4. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
5. chronic disease

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

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

7.1.3 Device Deficiency

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

Note: Performance specifications include all claims made in the labeling of the device.

7.2 Device Relationship

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

7.2.1 Unanticipated Serious Adverse Device Effect (USADE)

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

7.3 Adverse Event and Device Deficiency Reporting

7.3.1 Adverse Event Reporting

Safety surveillance and reporting starts as soon as the patient is consented into the clinical investigation. Safety surveillance and reporting will continue until the last 12-month follow-up visit has been performed, the subject is deceased, the subject concludes participation in the clinical investigation or the subject withdraws from the clinical investigation. All adverse event data, including deaths and device deficiency data, will be collected throughout the time period defined above and will be reported to the Sponsor on a CRF. Additional information with regard to an adverse event should be updated within the appropriate CRF.

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

Adverse event reporting will include:

1. All Adverse Events
2. All Adverse Device Effects
3. All Serious Adverse Events (whether or not the event is considered device or procedure related)
4. Unanticipated Serious Adverse Device Effects
5. 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

7.3.1.1 SAE Reporting

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

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

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

7.3.2 Unanticipated Serious Adverse Device Effect Reporting to Sponsor and EC

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

7.3.3 Device Deficiency

All device deficiencies should be reported on the appropriate CRF form. The investigator should report all device deficiencies to the Sponsor as soon as possible but no later than outlined below.

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

The device, if not implanted or not remaining in the subject, should be returned to the Sponsor.

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

8.3 Sample Size Calculation and Assumptions

[redacted]

8.4 Timing of Analysis

[redacted]

8.5 Subgroup Analysis

[redacted]

8.6 Multiplicity

[redacted]

8.7 Pooling Strategy

[redacted]

[redacted]

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

11.1 Protection of Personally Identifiable Information

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

11.2 Data Management Plan

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

11.3 Source Documentation

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

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

11.4 Case Report Form Completion

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

with use of the FlexNav™ Delivery System will be similar to those associated with any routine TAVI procedure and related follow-up.

As outlined in the IFU, potential anticipated adverse events associated with the use of transcatheter bioprosthetic heart valves include but are not limited to, the following:

1. access site complications (e.g., pain, bleeding, infection, hematoma, pseudoaneurysm, etc.)
2. acute coronary obstruction
3. acute myocardial infarction
4. allergic reaction to antiplatelet agents, contrast medium, or valve components
5. aortic rupture
6. ascending aorta trauma
7. atrio-ventricular node block
8. cardiac arrhythmias
9. embolism
10. endocarditis
11. heart failure
12. hemodynamic compromise
13. hemolysis
14. hemolytic anemia
15. hemorrhage
16. hypotension or hypertension
17. infection
18. myocardial ischemia
19. mitral valve insufficiency
20. multi-organ failure
21. non-structural dysfunction (i.e., entrapment by pannus, paravalvular leak, inappropriate sizing or positioning)
22. pericardial effusion
23. perforation of the myocardium or a blood vessel
24. pannus
25. renal insufficiency or renal failure
26. sepsis
27. stroke
28. structural deterioration (i.e., calcification, leaflet tear)
29. thrombosis
30. tamponade
31. valve migration
32. vessel dissection or spasm.

It is possible these complications could lead to:

1. transfusion
2. conversion to open surgical procedure
3. reoperation
4. emergent balloon valvuloplasty
5. emergent percutaneous coronary intervention (PCI)
6. emergent surgery (i.e., coronary artery bypass, heart valve replacement)
7. explantation
8. permanent disability

[redacted]

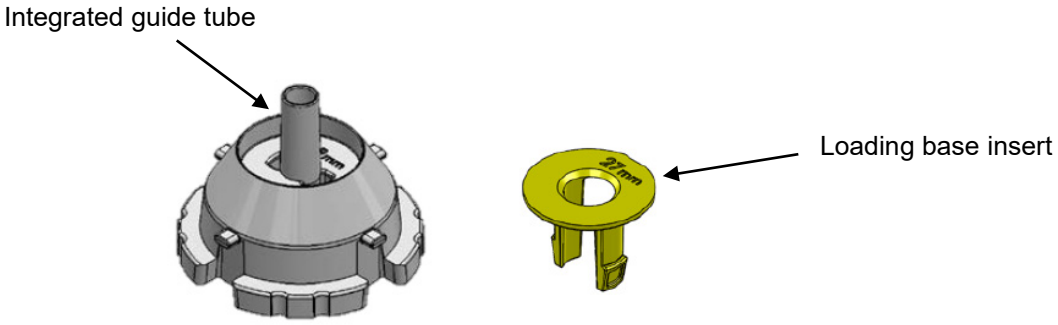


Figure 2: Second-Generation FlexNav™ Loading System Base and Insert

2.2.2 Intended Indication for Use

The FlexNav™ Delivery System is indicated for transcatheter delivery of the Portico™ valve. The delivery system is indicated for insertion into the vessel with or without an arterial introducer sheath.

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

The Portico™ Transcatheter Heart Valve is indicated for transcatheter delivery in patients with symptomatic severe native aortic stenosis who are considered high or extreme surgical risk.

The Portico™ Valve, FlexNav™ Delivery System and the FlexNav™ Loading System will be used in accordance with the Instructions for Use (IFU). Please refer to the SJM FlexNav™ Portico Transcatheter Aortic Valve Implantation System IFU (Number 600035013) for further details.

2.2.3 Description of the Device(s) Under Investigation

Devices under investigational use in this clinical investigation include the FlexNav™ Delivery System(s) and the FlexNav™ Loading System(s).

2.2.3.1 Second-Generation FlexNav™ Delivery System

The second-generation FlexNav™ Delivery System (“FlexNav Delivery System”) is an over-the-wire, 0.035”- compatible system that includes a hydrophilic-coated, integrated sheath to facilitate gradual, controlled deployment of the Portico™ valve in patients with a minimum vessel diameter of ≥5mm.

[redacted]

Clinical Investigation Plan

5.2 Subject Screening and Informed Consent

5.2.1 Subject Screening

Potential patients presenting at the study sites will be fully informed about the clinical investigation, following the established Informed Consent process (described in Section 5.2.2). Once a duly dated and signed Informed Consent form is obtained, the clinical investigation-specific screening procedures may begin. All cardiac medications and all medications given for cardiovascular effect may be continued at their prescribed dosages for the screening assessments.

The following assessments are performed as part of the screening process:

1. Demographics (age on consent date, gender, height)
2. Medical History (including previous cardiovascular operations and events, coexisting cardiovascular diseases, clinically significant peripheral vascular disease, previous peripheral vascular operations, other coexisting medical conditions e.g., diabetes, hypertension, kidney and lung disease, endocarditis)
3. Canadian Cardiovascular Society (CCS) Angina Scale Assessment
4. Surgical Risk Assessment tools (STS Risk Score and EuroSCORE II)
5. Forced Expiratory Volume (FEV1) Test, if clinically indicated
6. Physical Exam (including weight, heart rate, blood pressure)
7. Echocardiography to include comprehensive transthoracic or transesophageal 2D echocardiogram, including assessment of aortic valve gradients (mean and peak), areas, indices, degree of regurgitation, cardiac output and cardiac index, left ventricle systolic function (global and segmental)
8. Lab Measurements (including CBC and Platelet count, BUN and creatinine, BNP or ProBNP, and Albumin)
9. 12 Lead Electrocardiogram (ECG)
10. Computed Tomography Scan with Angiography for chest, abdomen and pelvis: aortic root and valve annulus sizing, assessment of suitability of iliofemoral access, and determination of appropriate coaxial angles for optimizing the valve implantation procedure. CT scan performed up to 12 months prior to consent will be acceptable.
11. 3D Transesophageal Echocardiogram (TEE) if CT is contraindicated
12. New York Heart Association (NYHA) Functional Classification
13. Frailty Index Assessment (Katz index of Activates of Daily Living, Grip Strength, 5 meter walk test)
14. Coronary and aortic angiogram (arteriograms of the lower abdominal aorta to the femoral arteries), with runoff if clinically indicated. Coronary and aortic angiogram performed up to 12 months prior to consent will be acceptable.
15. Adverse Event Assessment

Subjects must be screened for clinical investigation eligibility by a member of the study site's clinical investigation team (Principal Investigator and/or Research Coordinator) previously trained to the CIP, and if applicable will be entered into a site-specific screening log.

a) Upon crossing native valve with the guidewire
b) Upon positioning of the guidewire
c) Prior to valvuloplasty (if performed)
d) Immediately post valvuloplasty (if performed)
e) Before valve crosses the AV valve
f) After valve crosses the annulus
g) After valve is deployed in final position

5. Procedural information and imaging (angiogram, cine, intra-procedure echocardiography to be available to the Sponsor and provided upon request by the site)

Investigational sites should follow study-specific guidelines for the assessment of aortic regurgitation and implant depth. Refer to APPENDIX XVIII for a description of standardized methods for measuring aortic regurgitation according to VARC II criteria and instructions for assessing implant depth in the LVOT.

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

If the implant procedure was not attempted (i.e. the FlexNav™ Delivery System was never introduced into the subject's vasculature), the subject will not be considered enrolled. Refer to Section 5.4 Subject Enrollment.

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

All the required information must be recorded on the applicable CRF.

Sponsor Representatives will be involved in providing support during the implant procedure.

Following the procedure, the FlexNav™ Delivery and Loading Systems should be securely disposed as per hospital requirements for hazardous materials. If there are any concerns noted with the FlexNav™ Delivery System, FlexNav™ Loading System, or Portico™ valve during the procedure, they should be returned to the Sponsor for evaluation per the instructions provided in

14. Six Minute Walk Test (6MWT)
15. Cardiovascular medications documentation
16. Adverse events assessment

6.5.2.3 12-Month Follow-Up

The 12-month follow-up visit will take place at 12 months (-30 days, +45 days) post-index procedure, and will include the following assessments:

1. Physical exam (weight, heart rate, blood pressure)
2. Canadian Cardiovascular Society (CCS) Angina Scale Assessment
3. Modified Rankin Scale (mRS)
4. NIH Stroke Scale (NIHSS)
5. Barthel Index
6. Echocardiography
7. 12 lead ECG (for subjects receiving a new permanent pacemaker, ECG should be completed showing the underlying rhythm as well as the current pacing programming)
8. Lab Measurements (including CBC and Platelet count, BUN and creatinine, BNP or ProBNP, INR if subject is on coumadin, warfarin or other anticoagulants/vitamin K antagonists in lieu of warfarin, Troponin or CK/CK-MB and Albumin)
9. NYHA Functional Classification
10. Frailty Index Assessment (Katz Index of Activities of Daily Living, Grip Strength, 5 meter walk test)
11. Quality of Life Measures (SF-36, EQ-5D and KCCQ)
12. MMSE-2:SV
13. Six Minute Walk Test (6MWT)
14. Cardiovascular medications documentation
15. Adverse events assessment

6.5.3 Unscheduled Follow-up

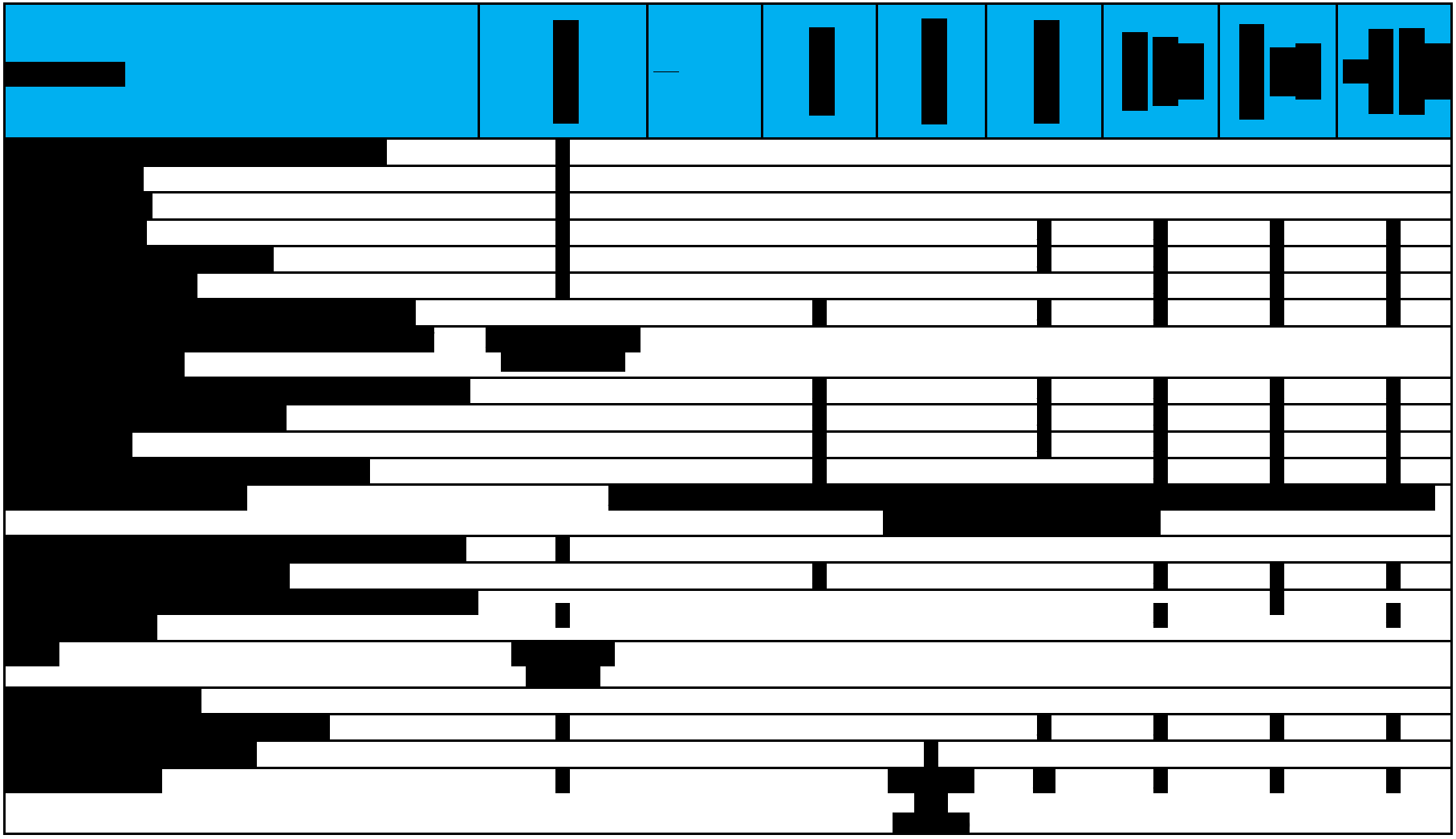
6.5.3.1 Unscheduled Follow-Up Visits for Evaluation of Suspected Neurological Event

If the subject experiences a neurological event (trans-ischemic attack (TIA), stroke, or encephalopathy), the event should be documented on an adverse event form and further evaluation should be performed at an unscheduled visit 90 days (±14 days) from the date of the neurological event. The unscheduled visit will include the following assessments:

- Neurological Assessment conducted by a neurologist or a neurology fellow
- Modified Rankin Score (mRS)
- NIH Stroke Scale

6.5.5 Schedule of Events

[redacted]



6.6 Requirement for Core Laboratories

Independent core laboratories used in the Portico US IDE pivotal trial will be utilized for evaluating CT images and echocardiograms in the clinical investigation. Contact details for the CT and echocardiographic core laboratories are included in APPENDIX XXII.

CT scan and echo exams will be forwarded to the respective core laboratories for interpretation by each investigational site. The core laboratories will not be responsible for notifying the site of any abnormal findings that are identified in the study.

The core laboratories will provide the study required interpretation and documentation of each data submission according to Standard Operating Procedures. Data obtained from the core laboratory readings will be used for study purposes only and not for clinical treatment of the subject. The Sponsor will use only the measurements provided by the core laboratories in data analyses. If the core laboratory determines that the data are unreadable, the site will be responsible for having the subject return for another assessment.

7 ADVERSE EVENTS

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

7.1 Definitions

7.1.1 Adverse Event

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

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

Note 2: This definition includes events related to the procedures involved.

Note 3: For users or other persons, this definition is restricted to events related to medical devices under investigation.

7.1.2 Serious Adverse Event

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

a) Led to a death
b) Led to a serious deterioration in health of the subject, that either resulted in
    1. a life-threatening illness or injury, or
    2. a permanent impairment of a body structure or a body function, or
    3. in-patient hospitalization or prolongation of existing hospitalization, or

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

In case a device deficiency occurred before the patient ID and/or randomization number has been assigned, the device deficiency should be reported to the Sponsor via the offline reporting form.

7.3.4 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

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

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

For investigational sites in Germany, clinical investigation SAEs and device deficiencies reportable per MedDEV 2.7/3 regulations will be submitted to European Competent Authorities by the Sponsor's Clinical Safety Group. Contact details are provided in APPENDIX XVII].

8 STATISTICAL CONSIDERATIONS

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

8.1 Analysis Populations

[redacted]

8.2 Statistical Analyses

8.2.1 Primary Safety Endpoint Analyses

The primary safety endpoint of the FlexNav EU study is VARC II defined major vascular complications at 30 days post index procedure.

8.2.1.1 Analysis Methodology

[redacted]

8.2.1.2 Analysis Population for Primary Safety Endpoint

[redacted]

8.8 Procedures for Accounting for Missing Data

[redacted]

8.9 Planned Interim Analysis

[redacted]

8.10 Statistical Criteria for Termination

[redacted]

8.11 Success Criteria

[redacted]

8.12 Deviations from Statistical Plan

[redacted]

9 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

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

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

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Selection of Clinical Sites and Investigators

[redacted]

10.2 Clinical Investigation Finances and Agreements

[redacted]

Data on CRFs will be collected for all subjects who sign an informed consent form, including subjects who may not meet all inclusion/exclusion criteria during screening at the index procedure.

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

11.5 Record Retention

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

11.6 Investigational Devices Accountability

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

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

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

Inventory Accountability Log supplied by the Sponsor will be used. The Inventory Accountability Log must document the disposition of all investigational devices including those that have been returned to Sponsor.

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

12 ETHICAL CONSIDERATION

12.1 Medical Ethics Committee Review and Approval

Ethics Committee (EC) approval for the CIP and ICF/other written information provided to the patient will be obtained by the Principal Investigator at each investigational site prior to consenting and enrolling patients in this clinical investigation. The approval letter must be received prior to the start of this clinical investigation and a copy must be provided to the Sponsor.

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

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

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

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

9. death
10. permanent pacemaker

Subjects experiencing an adverse event shall be treated per the standard of care at the investigation site.

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

[redacted]

15.4 Risks Associated with Participation in this Clinical Investigation

Protocol-required assessments are summarized in [redacted] of Section 6.5.5. Possible risks and discomforts associated with participation in the study will be similar to those associated with any routine transcatheter aortic valve implantation procedure (and related follow-up).

Study-specific assessments that are not considered standard of care and are associated with additional risk include the six-minute walk test, blood collection for laboratory tests and echocardiogram exam during scheduled follow-up visits (excluding at discharge). Table 6 summarizes known risks associated with these study-specific assessments and measures taken in the clinical investigation to mitigate risk to subjects.

Table 6: Known Risks Associated with Study-Specific Assessments and Mitigation Measures

Study Assessment	Known risks	Mitigation measures
Six-minute walk test	Experience of fatigue, shortness of breath, chest pain and/or leg cramps.	This test will be performed under the supervision of a trained professional in a testing area where medical care is immediately available. The test will be immediately stopped if subjects experience chest pain, intolerable shortness of breath, leg cramps or pale appearance.
Blood sample	The risk of inserting a needle into a vein in the arm may include temporary discomfort from the needle stick. There is also a small risk of infection, bruising, swelling, bleeding or fainting.	These risks are minimized by cleansing the site carefully prior to obtaining the blood sample and applying pressure to the site after the blood sample is obtained.
Echocardiogram	For a Transthoracic Echocardiogram (TTE), a lubricant (gel) is used on the skin to improve picture quality and this may feel	The procedure will be explained to subjects by a trained professional prior to starting to the procedure. There are no known risks associated with receiving a TTE echocardiogram.