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FlexNav EU CE Mark Study
Assessment of the Abbott FlexNav™ Delivery System for Portico Transcatheter Aortic Valve Implantation in High and Extreme Risk Patients with Symptomatic Severe Aortic Stenosis
Study Document No: [redacted]
Version [redacted]
Date: 23-Oct-2018

Sponsor Abbott

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[redacted]

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[redacted]

FlexNav EU CE Mark Study

Assessment of the Abbott FlexNav™ Delivery System for Portico Transcatheter Aortic Valve Implantation in High and Extreme Risk Patients with Symptomatic Severe Aortic Stenosis

Version Number	[redacted]
Date	[redacted]
Coordinating Clinical Investigator/Study Principal Investigator:	[redacted]
Planned Number of Sites and Region(s)	Up to eight (8) sites in Europe including: Switzerland, Denmark, Germany, Italy, United Kingdom
Clinical Investigation Type	Prospective, single-arm, non-randomized, multi-center, CE Mark investigational study
Abbott Medical Expert	[redacted]
Sponsor	Abbott [redacted]
Electronic Data Capture Software	[redacted]
Core Laboratories	[redacted]
Clinical Events Committee Administration	[redacted]
CIP Author of Current Version	[redacted]

[redacted]

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SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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

Site Principal Investigator

Printed name:
Signature:
Date:

Clinical Investigation Plan

STUDY PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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

[Study Principal Investigator]

Printed name:
Signature:
Date:

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COMPLIANCE STATEMENT:

This clinical investigation will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki, ISO 14155:2011 standards and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the clinical investigation will be approved by the appropriate Ethics Committee (EC) of the respective clinical site and as specified by local regulations.

Clinical Investigation Plan

1 INTRODUCTION

This document is a clinical investigational plan (CIP) for a prospective, multi-center, single-arm investigational study intended to support CE Mark of the latest design iteration of the St Jude Medical Portico Delivery System ("second-generation FlexNav™ Delivery System"). The investigational device is intended for use with the CE Marked Portico™ Transcatheter Aortic Heart Valve (Portico™ valve) for the treatment of symptomatic, severe aortic stenosis in high and extreme surgical risk patients.

The primary focus of the clinical investigation is to characterize the safety profile of the FlexNav™ Delivery System with respect to rate of major vascular complications, [redacted] This clinical study is sponsored by Abbott.

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

1.1 Background and Rationale

1.1.1 Background

1.1.1.1 TAVR in the Treatment of Aortic Stenosis

Aortic stenosis (AS) is a clinically important degenerative valvular heart disease that is associated with poor prognosis following the onset of cardiac symptoms. In the elderly patient population, the prevalence of AS and severe AS is estimated at 12.4%, and 3.4%, respectively.[1] Historically, surgical aortic valve replacement (SAVR) has been the primary treatment option for severe AS until seminal findings from the Placement of Aortic Transcatheter Valves (PARTNER) Cohort A and B Trials revealed transcatheter aortic valve replacement (TAVR), a less invasive treatment option, to be non-inferior to SAVR[2] and superior to conventional medical therapy[3] with respect to survival rates at 1 year.

Investment in the TAVR platform has seen the technology emerge as the new standard of care for symptomatic patients with advanced disease at extreme surgical risk for whom no effective definitive therapy is available. In 2017, the AHA/ACC revised their guidelines in a focused update to make TAVR a class I indication (previously a class IIa indication) for the treatment of AS in patients at both high and prohibitive surgical risk.[4] Most recently, TAVR has been shown to be a safe alternative to SAVR in patients in whom surgery is feasible but who are considered to be intermediate risk[5] with new trials in low surgical risk patients currently underway.

[1] Osnabrugge RLJ, Mylotte D, Head SJ et al. Disease Prevalence and Number of Candidates for Transcatheter Aortic Valve Replacement: A Meta-Analysis and Modeling Study. Journal of the American College of Cardiology 2013;62:1002-1012
[2] Smith C, Leon M, Mack M et al. Transcatheter versus Surgial Aortic-Valve Replacement in High-Risk Patients. N Engl J Med 2011;364:2187-2198.
[3] Leon M, Smith C, Mack M et al. Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery. N Engl J Med 2010;363:1597-1607.
[4] Nishimura RA, Otto CM, Bonow RO et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. 2017;70:252-289.
[5] Leon M, Smith C, Mack M et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med 2016;374:1609-20.

1.1.1.2 TAVR and Major Vascular Complications

Transfemoral access is recognized as the safest and thus preferred approach for TAVR with proven superiority over a transapical approach and conventional surgery in high and intermediate risk patients.[6,7] Vascular access (defined by vessel calcification, tortuosity and vessel narrowing) continues to be the main limiting factor for transfemoral TAVR with a minimum vessel access diameter of ≥ 6mm required. As the use of TAVR expands to lower risk populations, minimizing vascular complications which are amongst the most frequent and serious complications of transfemoral TAVR is of paramount importance as studies show vascular and bleeding complications during the procedure are associated with increased morbidity and mortality risk.[8,3]

The incidence of major vascular complications via transfemoral access has reduced with the introduction of next-generation TAVR systems. In a meta-analysis of 1,232 match-controlled patients, the rate of major vascular complications was shown to decline from 7.2% with early-generation TAVR systems to 2.5% with next-generation TAVR systems.[9] Studies show arterial sheath size is an important determinant of major vascular complications and life-threatening/disabling bleeding during TAVR.[10] Vascular complications occur when the minimal artery diameter is smaller than the sheath external diameter.[i] Specifically, a sheath to femoral artery ratio (SFAR) > 1.05 is shown to be associated with increased risk of major vascular complications and mortality at 30 days.[11]

1.1.1.3 Competitor TAVR Delivery Systems

Edwards LifeSciences and Medtronic are the current TAVR market leaders accounting for 95% of the global TAVI market share. Two key design elements of the latest-generation, commercially-available balloon-expandable Edwards Sapien 3™ valve and self-expanding Medtronic CoreValve™ Evolut™ PRO valve systems that help mitigate the frequency of vascular and bleeding complications are: 1) a low insertion profile due to the use of a custom expandable sheath (Sapien 3™) and integrated sheath (Evolut™ PRO™); and 2) the ability to achieve precise valve placement without repositioning or with minimal need to re-sheath and reposition.

The Medtronic Evolut™ PRO transcatheter heart valve is delivered through the EnVeo™ R Delivery Catheter System without the use of a separate arterial sheath and is indicated for vessels down to 5.0 mm. The EnVeo R system features a dedicated InLine Sheath that retains the outer diameter size as the system enters the vessel and advances to the annulus. The addition of the InLine sheath makes the EnVeo™ R Delivery Catheter System the lowest delivery platform currently on the market and provides a greater opportunity to treat patients with smaller vessels through the preferred transfemoral access route.

The Edwards Commander™ Delivery System is used for transfemoral delivery of the Edwards Sapien 3™ transcatheter heart valve. The delivery system uses a low-profile 14F expandable sheath (eSheath) that is intended to reduce the potential for arterial injury during introduction of the delivery system and valve. The expandable sheath transiently expands to accommodate safe passage of the compressed valve and

[6] Arnold SV, Reynolds MR, Lei Y et al. Predictors of Poor Outcomes After Transcatheter Aortic Valve Replacement: Results From the PARTNER (Placement of Aortic Transcatheter Valve) Trial. Circulation. 2014;129:2682-2690.
[7] Thourani VH, Kodali S, Makkar RR, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. The Lancet. 387:2218-2225.
[8] Généreux P, Webb JG, Svensson LG,et al. Vascular Complications After Transcatheter Aortic Valve Replacement: Insights From the PARTNER (Placement of AoRTic TraNscathetER Valve) Trial. J Am Coll Cardiol. 2012;60:1043-1052.
[9] Ando T, Takagi H, Telila T and Afonso L. Comparison of outcomes in new-generation versus early-generation heart valve in transcatheter aortic valve implantation: A systematic review and meta-analysis. Cardiovascular Revascularization Medicine. 2018; 19: 186-191
[10] Mieghem N, Tchetche D, Chieffo A, et al. Incidence, Predictors, and Implications of Access Site Complications With Transfemoral Transcatheter Aortic Valve Implantation. Am J Cardiol 2012;110:1361–1367
[11] Hayashida K, Lefèvre T, Chevalier B, et al. Transfemoral Aortic Valve Implantation: New Criteria to Predict Vascular Complications. *J Am Coll Cardiol Intv*. 2011;4:851-858.

subsequently recoils to its lower profile diameter as the Sapien 3™ valve passes. The transient expansion of the eSheath minimizes the force required to insert and pass the delivery system and valve through the sheath, while maintaining a reduced profile compared to other standard arterial sheaths.

The reduced profile of these next-generation devices has increased the proportion of patients who are now eligible for transfemoral TAVR in Europe without compromising the risk of vascular injuries and access site complications.

1.1.1.4 Commercial Portico Experience in Europe

[redacted]

1.1.1.5 Customer Need for Second-Generation Portico Delivery System

[redacted]

1.1.2 Rationale for Conducting this Clinical Investigation

The rationale for conducting the FlexNav EU study is to collect safety data in a high or extreme surgical risk patient population to support CE Mark of the second-generation FlexNav™ Delivery System and Loading System in Europe.

[redacted]

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2 CLINICAL INVESTIGATION OVERVIEW

2.1 Clinical Investigation Objective

2.1.1 Primary objective

The primary objective of the FlexNav EU study is to characterize the safety of the second-generation Portico FlexNav Delivery System (referred herein as the FlexNav™ Delivery System).

The FlexNav EU study will be conducted as a prospective, multi-center, European, single-arm investigational study and will include up to 200 high or extreme risk patients with symptomatic, severe native aortic stenosis who meet eligibility criteria for Portico™ Transcatheter Aortic Heart Valve implantation via a transfemoral access approach. [redacted].

2.2 Device(s) To Be Used in the Clinical Investigation

2.2.1 Name of the Device(s) Under Investigation

Devices under investigation in this clinical investigation include the FlexNav™ Delivery System(s) (18 F and 19 F) and FlexNav™ Loading System(s) (Small and Large), which are both approved for investigational use only. Other devices to be used in the clinical investigation include all four (4) market-released St. Jude Medical (SJM) Portico™ valve sizes (23mm, 25mm, 27mm and 29mm)

Model numbers for the FlexNav™ Delivery Systems, FlexNav™ Loading Systems and Portico™ valves are provided in Table 1.

Table 1: Identification of Devices Included in the Study

Device name	Model/Type	Serial/Lot Controlled	Manufacturer	Region/ Country	Investigational or Market Released
FlexNav™ Small Delivery System	[redacted]	Serial numbered	St. Jude Medical	Europe	Investigational
FlexNav™ Large Delivery System	[redacted]	Serial numbered	St. Jude Medical	Europe	Investigational
FlexNav™ Small Loading System	[redacted]	Serial numbered	St. Jude Medical	Europe	Investigational
FlexNav™ Large Loading System	[redacted]	Serial numbered	St. Jude Medical	Europe	Investigational
Portico™ 23mm Valve	[redacted]	Serial numbered	St. Jude Medical	Europe	Market Released
Portico™ 25mm Valve	[redacted]	Serial numbered	St. Jude Medical	Europe	Market Released
Portico™ 27mm Valve	[redacted]	Serial numbered	St. Jude Medical	Europe	Market Released
Portico™ 29mm Valve	[redacted]	Serial numbered	St. Jude Medical	Europe	Market Released

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

[redacted]

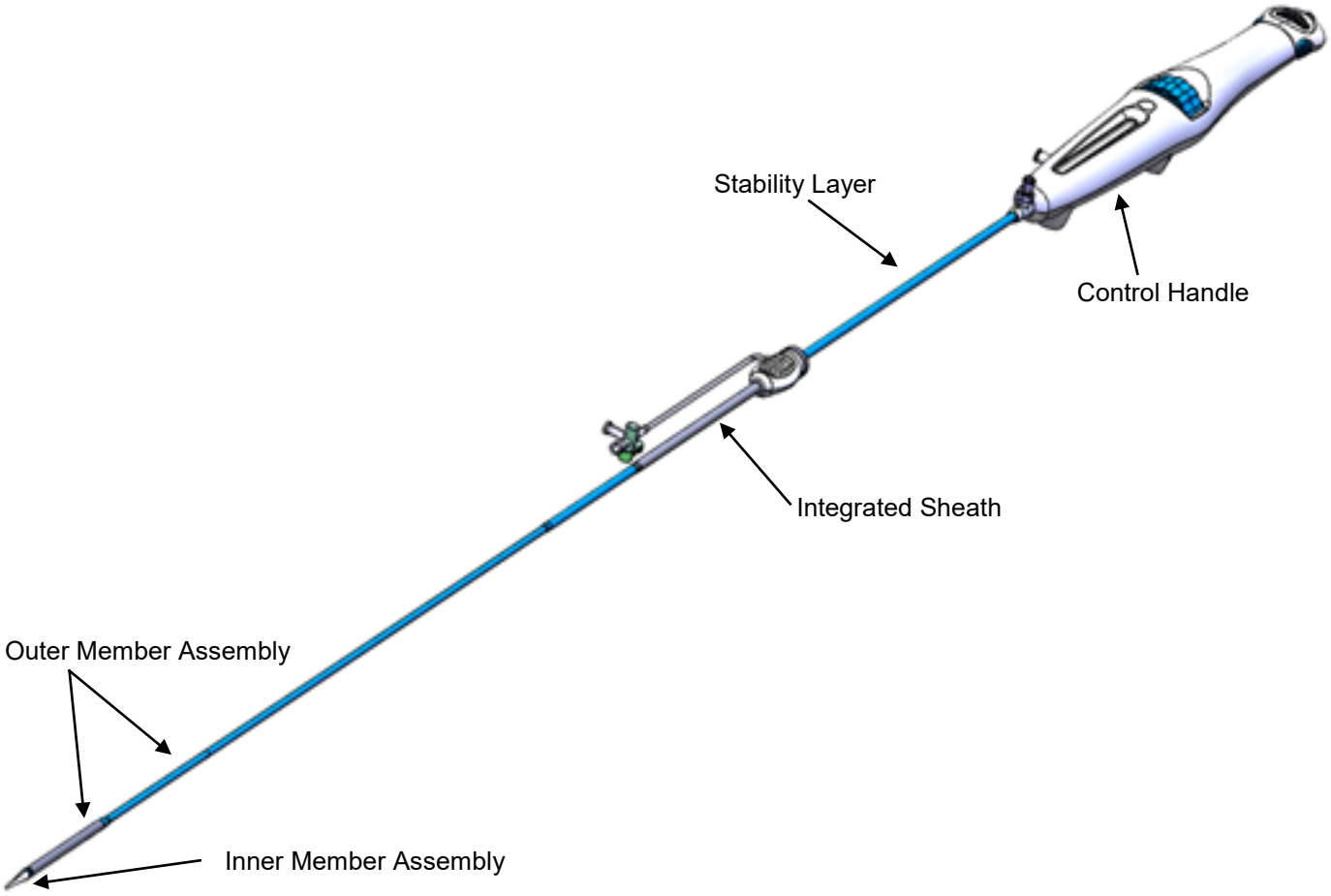


Figure 1:Second-Generation FlexNav™ Delivery System

[redacted]

[redacted]

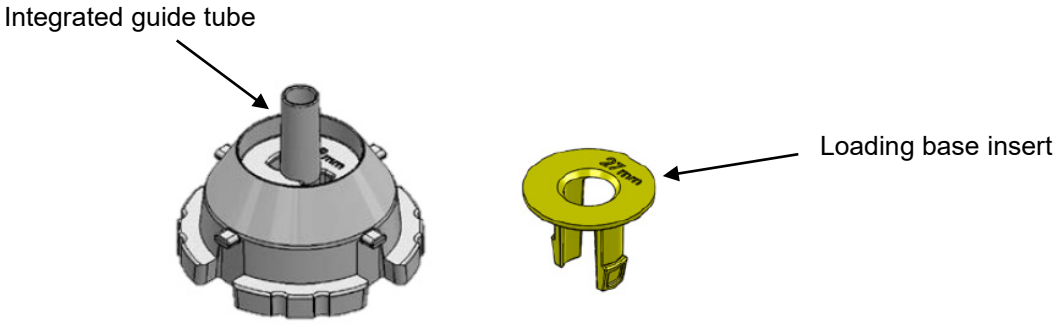


Figure 2: Second-Generation FlexNav™ Loading System Base and Insert

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

Table 2: FlexNav™ Delivery System Models and Compatibility with Portico™ Transcatheter Aortic Valve Sizes

FlexNav Models	Description	Functional Length (CM)	Minimum access vessel size	French Size	Compatible Portico Valve Size
FN-DS-SM-IDE	18 F Portico FlexNav Delivery System	110 cm	5mm	18 F	23mm - 25mm
FN-DS-LG-IDE	19 F Portico FlexNav Delivery System	110 cm	5.5mm	19 F	27mm - 29mm

[redacted]

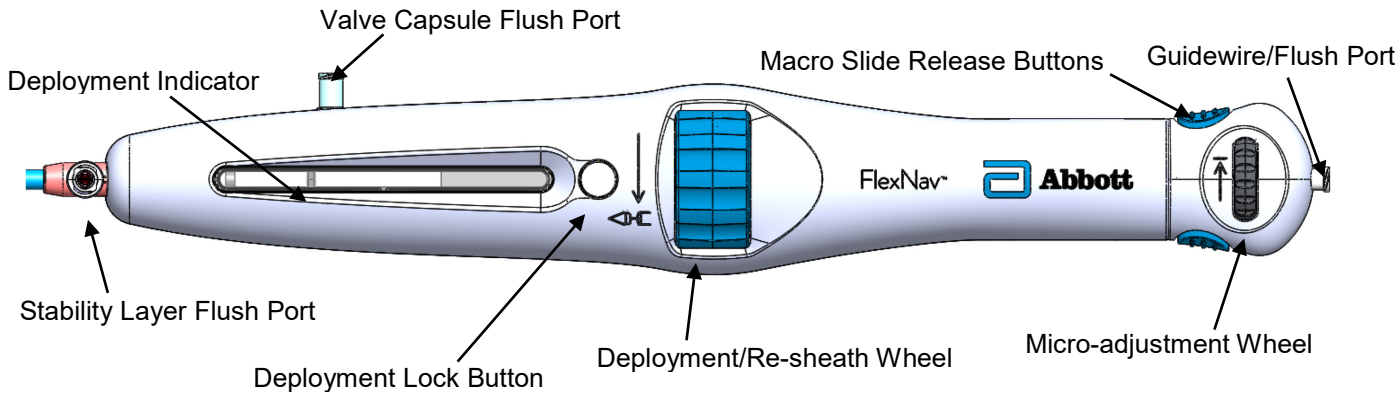


Figure 3: Second-Generation FlexNav™ Delivery System Handle Detail

[redacted]

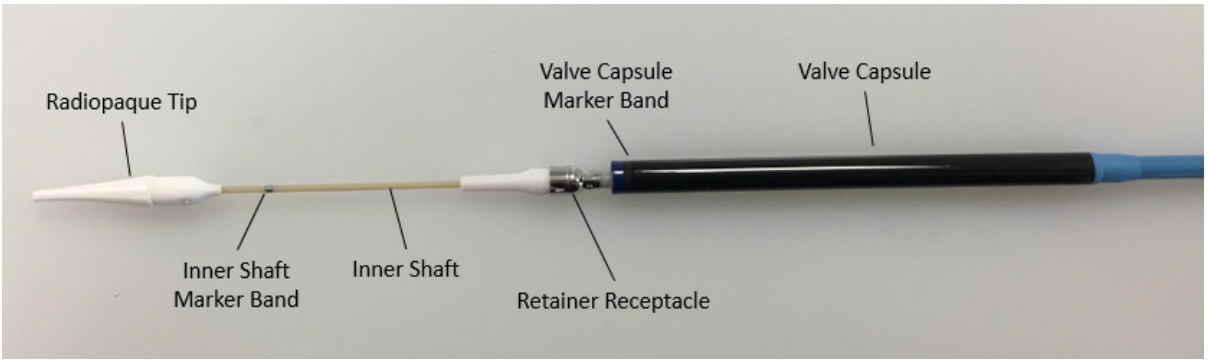


Figure 4: Second-Generation FlexNav™ Delivery System (Proximal End)

[redacted]

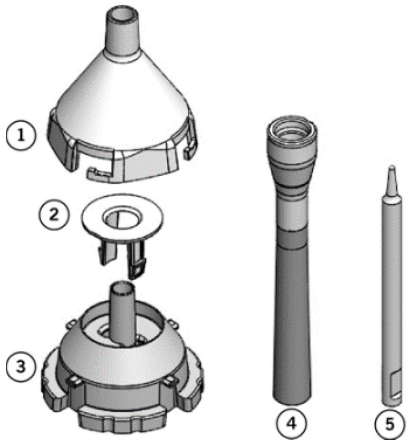
[redacted]

2.2.3.2 FlexNav Loading System

The Portico FlexNav™ Loading System, like the current (first-generation) Portico™ Loading System is an accessory used to compress and load the Portico™ valve onto the FlexNav™ Delivery System.

[redacted]

The 18F FlexNav™ Loading System is used for loading the 23 or 25mm Portico™ valves on the 18F FlexNav™ Delivery System; the 19F FlexNav™ loading system is used for loading the 27 or 29mm Portico™ valves on the 19F FlexNav™ Delivery System.



1. Loading Funnel
2. Base Insert
3. Loading Base
4. Loading Tube
5. Leaflet Tester

Figure 5: FlexNav™ Loading System

[redacted]

2.2.4 Summary of Preclinical Studies

Refer to the Preclinical Studies section of the Investigational Brochure (IB) for summary of results.

2.2.5 Device Handling

The Sponsor requires all investigational products to be stored according to the labeling and Instructions for Use (IFU) in a secure area to prevent unauthorized access or use.

3 CLINICAL INVESTIGATION DESIGN

3.1 Purpose

The purpose of this clinical investigation is to characterize the safety of the FlexNav™ Delivery System for transfemoral implantation of the Portico™ Transcatheter Aortic Heart Valve. Safety data collected as part of the study will be used to support CE Mark of the FlexNav™ Delivery System and Loading System in Europe.

3.2 Design Overview

This CE Mark study is a prospective, multi-center, single-arm investigational study to support commercialization of the FlexNav™ Delivery System and Loading System in Europe.

The design of this clinical investigation is in compliance to ISO standards 14155:2011 and 5840-3:2013.

A maximum of 200 patients with symptomatic, severe AS considered by both a local Heart Team and independent Subject Selection Committee to be high or extreme risk for surgical aortic valve implantation will be enrolled from up to eight (8) experienced, high-volume TAVI implant centers in Europe. [redacted]

To support CE Mark of the FlexNav™ Delivery System and Loading System, data from a minimum of 73 subjects who undergo a Portico™ valve implant attempt will be included in a pre-specified primary safety endpoint analysis at 30 days. To achieve the minimum required sample size, prospective data from subjects enrolled in the FlexNav study of the Portico US IDE pivotal trial (“US IDE FlexNav study”) may be combined with FlexNav EU study subjects.

Subject selection and key data collection in the FlexNav EU study will follow the US IDE FlexNav study to facilitate pooling of safety outcomes data at 30 days. An independent Subject Selection Committee will be responsible for final approval of the subject’s eligibility and risk classification. Upon provision of informed consent, subjects will undergo Portico™ valve implantation via a transfemoral access approach according to the site’s anesthesia protocol for TAVR procedures (conscious sedation or general anesthesia).

[redacted]

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[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.

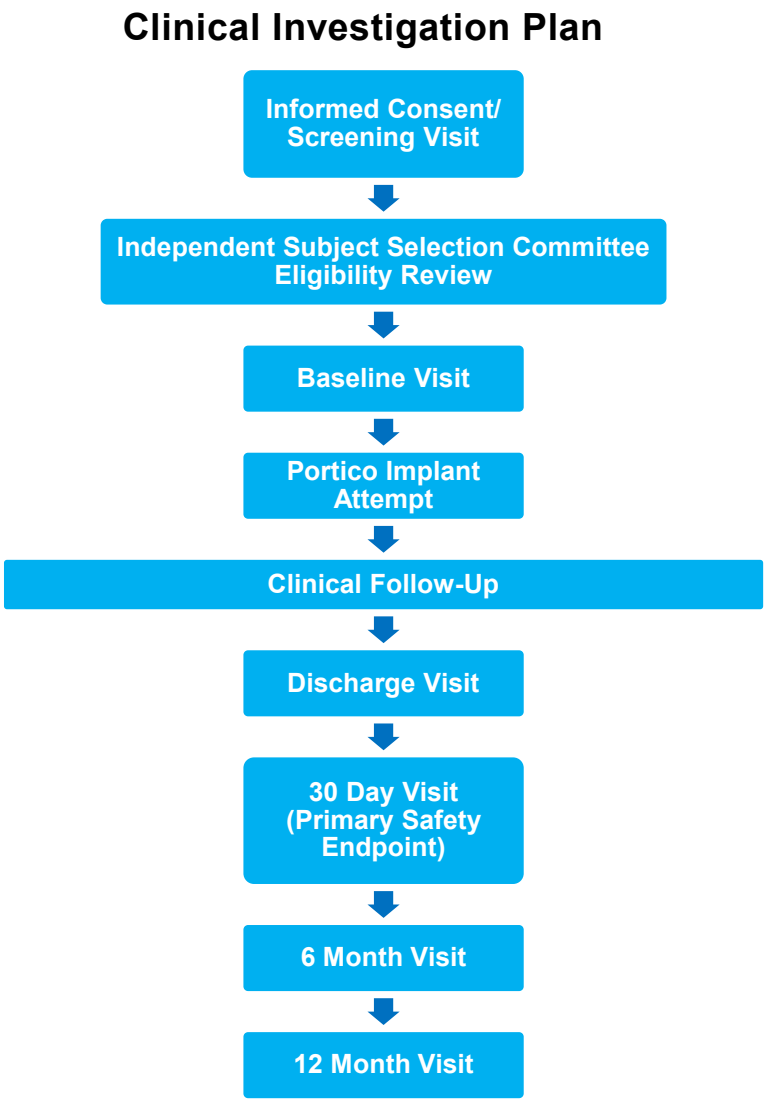

Figure 6: Clinical Investigation Flow Chart

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.

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.

In case the subject does not meet all inclusion criteria or meets any of the exclusion criteria, the subject will be considered a screening failure. The Principal Investigator or the delegated clinical investigation personnel will record the screening failure in the hospital records and on a screening log as applicable.

Patients meeting general inclusion criteria and no exclusion criteria will be asked to sign an Informed Consent form if they wish to participate in the clinical investigation. These patients will also be entered into the screening log.

Providing Informed Consent is the first step in the enrollment process however the subject is not fully enrolled in the study until all enrollment steps are complete per protocol (see section 5.4). However, once the patient has provided Informed Consent, study-specific subject data will be collected in the clinical investigation. Screening tests that are specifically study-related and would generally not be considered standard of care in Europe include:

- Frailty Index Assessment (Katz index of Activates of Daily Living, Grip Strength, 5 meter walk test)
- Forced Expiratory Volume Test (if clinically required)
- New York Heart Association (NYHA) Functional Classification
- Canadian Cardiovascular Society (CCS) Angina Scale Assessment

Refer to APPENDIX VII for a description of the tests involved in the Frailty Index Assessment.

Data available in the patient's medical record may be utilized to fulfill screening requirements and testing does not need to be repeated if performed within 60 days prior to Informed Consent. Computed Tomography (CT) scan with angiography and coronary and aortic angiogram (with runoff if clinically indicated) may be performed within 12 months prior to Informed Consent.

Upon initial screening of eligibility of patients by the local Heart Team, subject case reviews will be conducted by an independent SSC to confirm a patient's eligibility to transfemorally receive a Portico™ valve. The SSC will also provide final determination of a subject's risk classification for the study. If a site disagrees with the committee's final decision regarding risk classification the subject will not be eligible for enrollment in the study. If the SSC does not approve the patient, they will be exited from the study as a screen failure.

5.2.2 Informed Consent

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

During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the subject and will respect subject's legal rights. The subject shall be provided with the Informed Consent form written in a language that is understandable to the subject and has been approved by the center's EC. The subject shall have adequate time to review, ask questions and consider participation. The Principal Investigator or his/her authorized designee will make efforts to ensure that the

subject understands the information provided. If the subject agrees to participate, the Informed Consent form must be signed and dated by the subject and thereafter by the person obtaining the consent prior to any clinical investigation-specific procedures. The signed original will be filed in the subject's hospital or research charts, and a copy will be provided to the subject.

Failure to obtain informed consent from a subject prior to clinical investigation enrollment should be reported to Sponsor within 5 working days and to the reviewing center's EC according to the EC's reporting requirements.

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

5.2.2.1 Vulnerable Populations

Vulnerable patients are defined as patients whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples of populations which may contain vulnerable patients include: Individuals with lack of or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable patients include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention.

This clinical investigation will not permit enrollment of patients from vulnerable populations identified in ISO Standards 14155.

5.3 Eligibility Criteria

5.3.1 General Eligibility Criteria

Assessment for general eligibility criteria is based on medical records of the site and interview with a candidate patient. If some of the clinical and laboratory tests are not included in site standard tests, they must be done but after written Informed Consent is obtained. Patients must meet ALL of the inclusion criteria to be considered for the clinical investigation. If ANY of the exclusion criteria are met, the patient is excluded from the clinical investigation and cannot be enrolled.

5.3.2 Inclusion Criteria

5.3.2.1 Inclusion Criteria - High Risk Cohort

Candidates for High Risk classification must meet all the following inclusion criteria:

1. Subjects must have co-morbidities such that the local heart team concur the predicted risk of operative mortality is ≥15% or a minimum STS score of 8%.

A candidate who does not meet the STS score criteria of ≥ 8% may be included in the study if at least one surgeon in the local heart team concludes and documents the patient's predicted risk of operative mortality is ≥15%. The surgeon's assessment of operative comorbidities (including frailty indices) not captured by the STS score must be documented in the study case report form as well as in the patient medical record.

2. Subject is of legal age or older for consent in the host country.
3. Subject has senile degenerative aortic valve stenosis with echo-derived criteria: mean gradient >40 mmHg or jet velocity greater than 4.0 m/s or doppler velocity index (DVI) <0.25 and an initial aortic valve area (AVA) of ≤ 1.0 cm2 (indexed EOA ≤ 0.6 cm2/m2). (Qualifying AVA baseline measurement must be within 60 days prior to informed consent).
4. Subject has symptomatic aortic stenosis as demonstrated by NYHA Functional Classification of II, III, or IV.
5. The subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Ethics Committee (EC) of the respective clinical site.
6. The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits.
7. Subject's aortic annulus is 19-27mm diameter as measured by CT conducted within 12 months prior to informed consent. If a CT is contraindicated and/or not possible to be obtained for certain subjects, a 3D echo and non-contrast CT of chest and abdomen/pelvis may be accepted.

5.3.2.2 Inclusion Criteria - Extreme Risk Cohort:

All candidates for Extreme Risk classification must meet # 2, 3, 4, 5, 6, 7 of the above criteria, and

1. After formal consultation with the local heart team (including at least one surgeon) it is agreed that medical factors preclude the subject from undergoing operation, based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. Specifically, the probability of death or serious, irreversible morbidity should exceed 50%. The local heart teams' consult notes shall specify the medical or anatomic factors leading to that conclusion and include a printout of the calculation of the STS score to additionally identify the risks in these patients.

5.3.3 Exclusion Criteria - High and Extreme Risk Cohort

Candidates will be excluded if any of the following conditions are present:

1. Evidence of an acute myocardial infarction (defined as: ST Segment Elevation as evidenced on 12 Lead ECG) within 30 days prior to index procedure.
2. Aortic valve is a congenital unicuspid or congenital bicuspid valve, or is non-calcified as verified by echocardiography.
3. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation 3-4+).

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4. Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to index procedure.
5. Pre-existing prosthetic heart valve or other implant in any valve position, prosthetic ring, severe circumferential mitral annular calcification (MAC) which is continuous with calcium in the LVOT, severe (greater than 3+) mitral insufficiency, or severe mitral stenosis with pulmonary compromise.
6. Blood dyscrasias as defined: leukopenia (WBC<3000 mm3), acute anemia (Hb < 9 g/dL), thrombocytopenia (platelet count <50,000 cells/mm³).
7. History of bleeding diathesis or coagulopathy.
8. Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support.
9. Untreated clinically significant coronary artery disease requiring revascularization.
10. Hemodynamic instability requiring inotropic support or mechanical heart assistance.
11. Need for emergency surgery for any reason.
12. Hypertrophic cardiomyopathy with or without obstruction (HOCM).
13. Severe ventricular dysfunction with LVEF <20% as measured by resting echocardiogram.
14. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
15. Active peptic ulcer or upper GI bleeding within 3 months prior to index procedure.
16. A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media which cannot be adequately premedicated.
17. Recent (within 6 months prior to index procedure date) cerebrovascular accident (CVA) or a transient ischemic attack (TIA).
18. Renal insufficiency (creatinine > 3.0 mg/dL) and/or end stage renal disease requiring chronic dialysis.
19. Life expectancy < 12 months from the time of informed consent due to non-cardiac co-morbid conditions.
20. Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5cm or greater; marked tortuosity (hyper acute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding or ulcerated) or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe “unfolding” and tortuosity of the thoracic aorta.
21. Native aortic annulus size < 19 mm or > 27 mm per the baseline diagnostic imaging.
22. Aortic root angulation > 70°.
23. Currently participating in an investigational drug or device study.
24. Active bacterial endocarditis within 6 months prior to the index procedure.
25. Bulky calcified aortic valve leaflets in close proximity to coronary ostia.
26. Non-calcified aortic annulus.

27. Iliofemoral vessel characteristics that would preclude safe insertion of the FlexNav™ delivery system with or without an arterial introducer sheath such as severe obstructive calcification, or severe tortuosity.
28. In the judgment of the investigator, a condition that could limit a patient's ability or willingness to participate in the study, comply with study required testing and/or follow-up visits or that could impact scientific integrity of the study

5.4 Subject Enrollment

A patient will be considered enrolled in the study after completion of all of the following steps:

1. Signed informed consent is obtained.
2. Based on the screening assessments, it is determined that the subject meets all of the inclusion and none of the exclusion criteria.
3. Subject is approved by the Subject Selection Committee.
4. Portico implant attempt defined as insertion of the FlexNav™ Delivery System into the subject's vasculature.

The following terms will be used to describe potential study subjects:

- **Screen Failure:** Consented subjects who undergo study-specific testing and are found to have met exclusion criteria or not all inclusion criteria. Additionally, if a site disagrees with the Subject Selection Committee's final decision regarding risk classification the subject will not be eligible for enrollment in the study and will be considered a screen failure.
- **Pre-procedural Exclusion:** Consented subjects who undergo study-specific testing and meet study criteria but do not undergo a Portico implant attempt will not be considered enrolled and will be exited from the study without further follow up.
- **Enrolled:** These subjects will be considered enrolled in the study and will fall into one of the following categories:
    - **Attempted-to-Treat:** Subjects who undergo a Portico implant attempt but do not have a Portico valve implanted will be followed for 30 days post procedure for adverse events and then formally withdrawn from the study
    - **Implanted:** Subjects who have a Portico valve implanted will be followed according to the clinical investigation and will be included in the analysis population.
    - **CIP Deviations:** Subjects who have a Portico valve implanted and are later found to have met exclusion criteria or not all inclusion criteria. These subjects will be followed according to the clinical investigation and will be included in the analysis population.

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

To ensure enrollment balance across study sites, no investigational site will be permitted to enroll more than 20% of the analysis population.

5.5 Subject Withdrawal

Each enrolled study subject shall remain in the clinical investigation until completion of the required follow-up period; however, a subject's participation in any clinical investigation is voluntary and the subject has

the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Subject death
- Subject voluntary withdrawal
- Subject lost-to follow-up as described below
- Subject's follow-up is terminated according to [Section 3.5].

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

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

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

5.5.1 Lost-to-Follow-up

If the subject misses two consecutive scheduled follow-up time points and the attempts at contacting the subject detailed below are unsuccessful, then the subject is considered lost-to-follow-up. Site personnel shall make all reasonable efforts to locate and communicate with the subject (and document these efforts in the source documents), including the following, at each contact time point:

- A minimum of two telephone calls on different days over the specified follow-up windows to contact the subject should be recorded in the source documentation, including date, time and initials of site personnel trying to make contact.
- If these attempts are unsuccessful, a certified or registered letter should be sent to the subject.
- If a subject misses one or more non-consecutive follow-up contact time points, it will be considered a missed visit. The subject may then return for subsequent visits. If the subject misses two consecutive time points and the above-mentioned attempts at communicating with the subject are unsuccessful, the subject will be considered lost-to-follow-up.

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

5.6 Total Expected Duration of the Clinical Investigation

[redacted]

5.7 Expected Duration of Each Subject's Participation

The expected duration of each subject's participation in the clinical investigation is 12 months.

[redacted]

5.8 Number of Subjects

Up to 200 subjects will be enrolled in the clinical investigation, with a predefined minimum of 73 subjects required to analyze the primary safety endpoint. No site may enroll more than 20% of the maximum number of enrolled subjects (n=40).

5.9 Estimated Time Needed to Select Required Number of Subjects

[redacted]

6 TREATMENT AND EVALUATION OF ENDPOINTS

For patients that have successfully completed screening and been approved by the SSC, scheduled visits will be performed in the following order: Baseline, Index Procedure, Discharge, 30-day, 6 months and 12 months. A description of study-specific assessments to be performed at the scheduled visits is provided in APPENDIX IV.

6.1 Baseline Assessments

6.1.1 Baseline Laboratory and Clinical Tests

Patients who are deemed eligible for transfemoral implantation of a Portico™ valve using the FlexNav™ Delivery System will undergo a baseline visit within 14 days of the scheduled implant procedure (may occur on the day of, but prior to the implant procedure).

The following baseline data will be collected for all subjects prior to the index procedure.

1. Chest X-ray
2. Cardiovascular medications documentation (including dosage)
3. Modified Rankin Scale (mRS)
4. NIH Stroke Scale (NIHSS)
5. Barthel Index
6. Quality of Life Measures (SF-36, EQ-5D and KCCQ)
7. Mini Mental State Exam (MMSE-2:SV)
8. Six Minute Walk Test (6MWT)
9. Lab Measurements (Troponin or CK/CK-MB, INR if subject is on Coumadin or Warfarin or other anticoagulants/vitamin K antagonists in lieu of warfarin)
10. Adverse events assessment

Excluding the chest X-ray scan which is standard of care and will be conducted per hospital guidelines, all baseline assessments are considered study-related assessments.

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]

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

APPENDIX ***XIX*** and APPENDIX XX.

6.2.4 Final (Post-procedure) Imaging

Subjects implanted with a transcatheter aortic valve (Portico™ valve or other commercially- available valve) will be required to undergo an echocardiogram within 48 hours of the procedure.

6.3 Post–procedure (In-hospital)

6.3.1 Post-procedure Laboratory and Clinical Tests

The following laboratory tests should be performed in-hospital post-implant procedure:

1. Troponin, or CK / CK-MB should be collected within approximately 12-24 hours after procedure, approximately 24 hours thereafter, and at approximately 72 hours after the procedure (or at discharge, if patient is discharged prior to 72 hours post procedure).
2. BUN and Creatinine to be collected within 72 hours after index procedure

6.4 Discharge Plan

The discharge visit will take place at the time of hospital discharge or up to 7 days after the procedure, whichever occurs first. If the subject is expected to be discharged over the weekend, the discharge tests may be completed on the last week day prior to discharge.

The discharge assessment will include:

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. Echocardiogram (if not performed during the post procedure testing within 48 hours after procedure)
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. Cardiovascular medications documentation
9. Adverse events assessment
10. Lab Measurements (CBC and Platelet count, BUN and Creatinine, and Troponin or CK/CK-MB if patient is discharged prior to 72 hours post-procedure)

6.5 Follow Up Visits

6.5.1 Follow-up Medications

Medications administered to subjects during the follow-up period will at the physician's discretion and should be prescribed according to current guidelines and standard of care.

6.5.2 Follow-up for All Enrolled Subjects

Required clinical follow-up will be performed at the following intervals for all subjects who underwent a Portico implant attempt and were implanted with a Portico™ valve:

- 30 days (-7 days/ +21 days) follow-up site visit (visit must be conducted even if subject is in hospital)
- 6 months (180 days ± 30 days) follow up site visit
- 12 months (365 days -30 days, +45 days) follow up site visit

Subjects with a Portico implant attempt that did not have a Portico™ valve implanted will only be required to complete the 30 day follow up visit.

Follow-up visits will be calculated from the date of the implant procedure. Follow-up assessments can be performed at any point within the pre-specified follow-up visit window, and should be conducted, whenever possible, by the same individual who performed the baseline tests.

Every effort should be made by the study site to have the subject return to the investigational site for all follow-up visits. If, despite all efforts, the subject is unable to return to the study site during a follow-up window, subjects may undergo a remote follow-up assessment to collect applicable data. Remote assessments should include telephone contact with the subject and/or a visit to a medical facility with all data that can be reasonably and legally collected remotely on the study subject. Follow-up visits occurring at non-study sites will be limited to standard of care data collection only. Authorization for the release of medical records from non-study facility is the responsibility of the investigational site. Protocol deviations will be required for all missed testing.

An enrolled subject may only be followed at another investigational site with prior agreement from that site's Investigator and from the Sponsor.

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

6.5.2.1 30 Day Follow-Up

The 30-day follow-up visit will take place 30 days (-7/+21 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

6.5.2.2 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

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

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

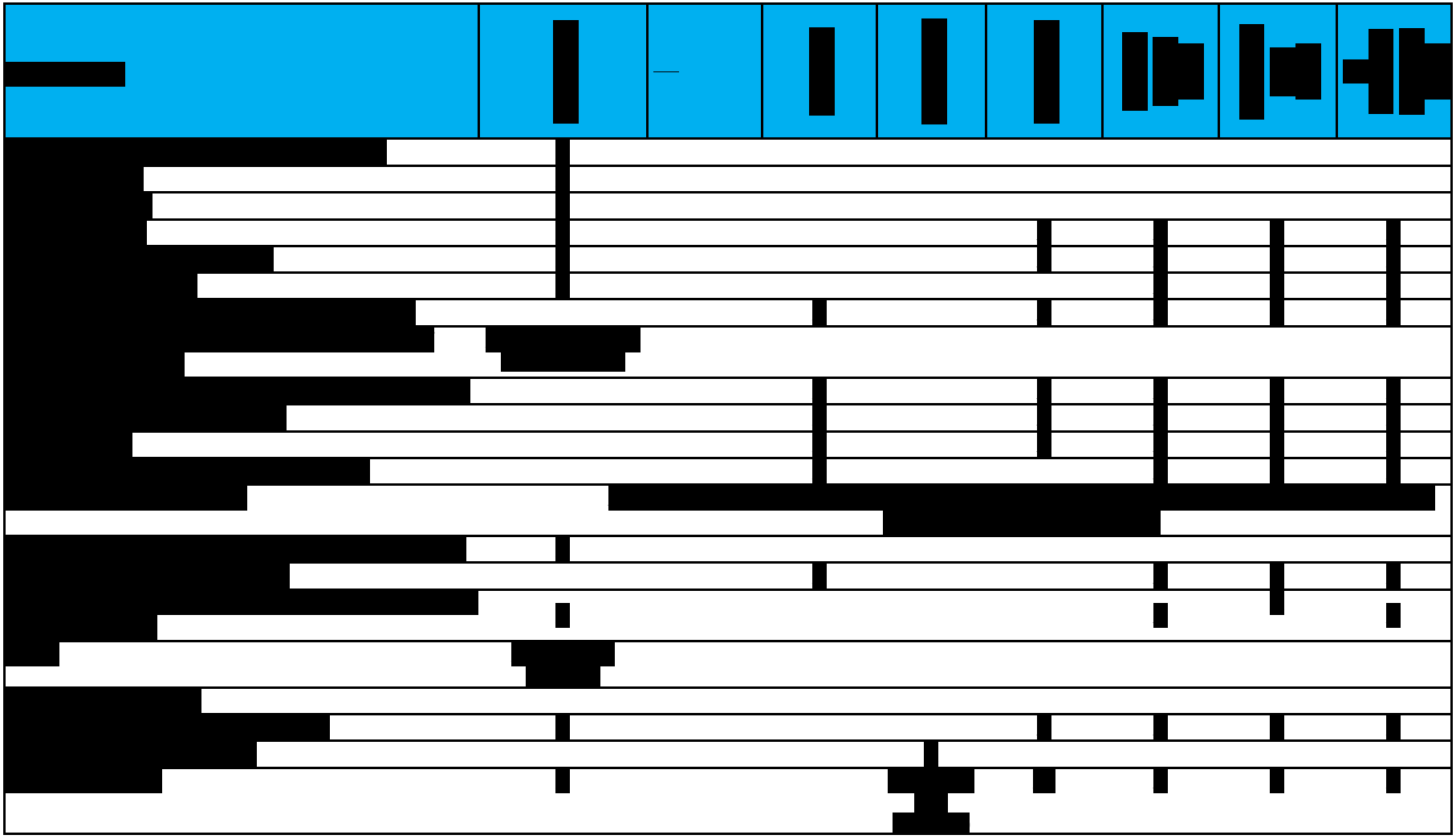
limited during physical activity; the limitations/symptoms are in regard to normal breathing and varying degrees in shortness of breath and/or angina. The NHYA function classification remains the most important prognostic marker for heart failure in routine clinical use. The current version includes 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.

6.5.5 Schedule of Events

[redacted]



Clinical Investigation Plan

[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

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.

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]

8.3 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]

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]

Clinical Investigation Plan

10.3 CIP Amendments

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

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

10.4 Training

10.4.1 Site Training

[redacted]

10.4.2 Training Required for the Use of the FlexNav™ Delivery System

[redacted]

10.5 Monitoring

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

[redacted]

[redacted]

10.6 Deviations from CIP

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

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

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

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

Repeated non-compliance with the signed agreement, the CIP or any other conditions of the clinical investigation may result in further escalation in accordance with the Sponsor's written procedures, including securing compliance or, at its sole discretion, Sponsor may terminate the investigator's participation in the clinical investigation. Table 4 describes potential study protocol deviations in the clinical investigation.

Table 4: Examples of Potential Study Protocol Deviations

Type of Protocol Deviation	Classification
Informed Consent Not Obtained	Major Deviation
Other Informed Consent Deviation	Minor Deviation
Inclusion/Exclusion Criteria Not Met	Major Deviation
Visit Not Done	Minor Deviation
Required Testing/Assessment Not Done or Not Done Per Protocol	Minor Deviation
Missing Study Procedure	Minor Deviation
Visit Outside of Window	Minor Deviation
Required Reporting Timeline Not Followed Per Protocol	Minor Deviation

10.7 Quality Assurance Audit

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

In the event that an investigator is contacted by a Regulatory Agency in relation to this clinical investigation, the Investigator will notify Sponsor immediately. The Investigator and Research Coordinator must be available to respond to reasonable requests and audit queries made during the audit process. The Investigator must provide Sponsor with copies of all correspondence that may affect the review of the current clinical investigation (e.g., Form FDA 483, Inspectional Observations, Warning Letters, Inspection Reports, etc.). Sponsor may provide any needed assistance in responding to regulatory audits.

10.8 Sponsor Auditing

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

10.9 Committees

The clinical investigation will utilize three separate committees:

- Subject Selection Committee (SSC)
- Clinical Events Committee (CEC)
- Steering and Publication Committee

10.9.1 Subject Selection Committee

The Subject Selection Committee (SSC) will consist of cardiac surgeons, cardiac interventionalists, and a neurologist who will be responsible for ensuring subject eligibility in the clinical investigation according to

the study protocol. After Subject Informed Consent is obtained and study eligibility is confirmed by the local Heart Team, subject data will be reviewed by the SSC prior to scheduling a baseline visit to confirm anatomic suitability for the Portico implant procedure based on echocardiographic and pre-implant CT measurements and appropriate risk classification of the patient as defined in the SSC Charter.

The Committee's decision on whether to include the subject in the study must be documented and communicated to the enrolling investigational site by the Sponsor. If the SSC considers the subject ineligible for participation in the study, the subject will be exited from the study and the reason for exclusion will be documented in the reviewers' feedback form. If a site disagrees with the Committee's final decision regarding risk classification the subject will not be eligible for enrollment in the study.

The same SSC membership and process used in the Portico US IDE pivotal trial will be utilized for this clinical investigation. Refer to APPENDIX XXII for a full list of SSC members.

10.9.2 Clinical Events Committee

The Clinical Events Committee (CEC) is an independent adjudication body comprised of qualified physicians (at a minimum, an interventional cardiologist, cardiothoracic surgeon, and a neurologist) who are not participants in the clinical investigation or the Portico US Pivotal IDE trial. The CEC will review and have final adjudication responsibilities for the studies primary safety endpoint and pre-specified descriptive adverse events reported by investigators or identified by Safety personnel for the clinical investigation as defined in the CEC Standards of Operation Charter and according to definitions provided in this CIP.

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

10.9.3 Steering and Publications Committee

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

11 DATA HANDLING AND RECORD KEEPING

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

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

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

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

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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.

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.

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13 CLINICAL INVESTIGATION CONCLUSION

The clinical investigation will be concluded when:

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

14 PUBLICATION POLICY

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

The Sponsor will be responsible for determining whether to register the clinical investigation on www.clinicaltrials.gov or any other clinical trials, in accordance with the International Committee of Medical Journal Editors guidelines, or any other applicable guidelines. In the event Sponsor determines that the clinical investigation should be registered, Sponsor shall be responsible for any such registration and results posting as required by the ClinicalTrials.gov website. Institution and/or Principal Investigator(s) shall not take any action to register the clinical investigation.

15 RISK ANALYSIS

15.1 Anticipated Clinical Benefits

[redacted]

[redacted]

Table 5 [redacted]

[redacted]

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Table 5: Anticipated Clinical Impact of Design Modifications to FlexNav™ Delivery System

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

15.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

[redacted]

15.2.1 Potential Anticipated Adverse Events

The FlexNav™ Delivery System and Loading System are not intended or anticipated to introduce any new risks beyond that observed for the current (first-generation) Portico™ Delivery System and Loading System when implanting the Portico™ valve. For that reason, the potential anticipated adverse events associated

[redacted]

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

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.

	cold. There may be discomfort from the pressure of the transducer as the images are taken.	

15.5 Steps Taken to Control or Mitigate Risks

[redacted]

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[redacted]

Ensuring Strict Adherence to the Clinical Investigational Protocol: The clinical investigation will be monitored by the Sponsor to ensure adherence to the CIP. Subjects will be carefully selected through rigorous screening by both a local Heart Team and independent SSC using pre-specified inclusion and exclusion criteria as stated in section 5.3. Adverse events and device deficiencies will be reported to Abbott and will be monitored internally for safety surveillance purposes and reported to regulatory authorities as applicable.

15.6 Risk to Benefit Rationale

[redacted]

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[redacted]

[20] Maisano F, Worthley S, Rodés-Cabau J, et al. Early commercial experience from transcatheter aortic valve implantation using the Portico™ bioprosthetic valve: 30-day outcomes in the multicenter PORTICO I study. EuroIntervention. 2018. 14- online publish ahead of print August 2018

[redacted]

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16 APPENDICES

APPENDIX I: ABBREVIATIONS AND ACRONYMS

Abbreviation	Term
6MWT	Six Minute Walk Test
ACT	Activated Clotting Time
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AHA	American Heart Association
AS	Aortic Stenosis
AVA	Aortic Valve Area
AVR	Aortic Valve Replacement
BARC	Bleeding Academic Research Consortium
BNP	B-type Natriuretic Peptide
CAD	Coronary Artery Disease
CBC	Complete Blood Count
CE	Conformité Européene (European Conformity)
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CPB	Cardiopulmonary Bypass
eCRF	Electronic Case Report Form
CT	Computed Tomography
CVA	Cerebral Vascular Accident
EC	Ethics Committee
ECG	Electrocardiogram
Echo	Echocardiography
EDC	Electronic Data Capture
EEA	European Economic Area
EF	Ejection Fraction
EOA	Effective Orifice Area
EU	European Union
GI	Gastro Intestinal
HOCM	Hypertrophic cardiomyopathy with or without obstruction
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IFU	Instructions For Use
INR	International Normalized Ratio
KCCQ	Kansas City Cardiomyopathy Questionnaire
Kg	Kilogram
LBBB	Left Bundle Branch Block
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MAC	Mitral Annular Calcification
MI	Myocardial Infarction
MMSE	Mini-mental state examination

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MR	Mitral Regurgitation
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NIHSS	NIH Stroke Scale
NYHA	New York Heart Association
PA	Pulmonary Artery
PCI	Percutaneous Coronary Intervention
PCWP	Pulmonary Capillary Wedge Pressure
PI	Principal Investigator
QoL	Quality of Life
PVD	Peripheral Vascular Disease
PVL	Paravalvular Leak
RA	Right Atrium
RV	Right Ventricular
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAVR	Surgical Aortic Valve Replacement
SJM	St. Jude Medical, Cardiovascular Division
SSC	Subject Selection Committee
STS	Society of Thoracic Surgeons
TAVI	Transcatheter Aortic Valve Implantation
TAVR	Transcatheter Aortic Valve Replacement
TEE	Transesophageal Echocardiogram (same as TOE)
TIA	Transient Ischemia Attack
TTE	Transthoracic Echocardiogram
UADE	Unanticipated Adverse Device Effect
USA	United States of America (same as US)
VARC 2	Valve Academic Research Consortium 2
WBC	White Blood Cell

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APPENDIX II: VARC II ENDPOINTS

Source	Definition
Cardiovascular Mortality (VARC 2)	**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 nonstructural valve dysfunction or other valve-related adverse events • Sudden or unwitnessed death • Death of unknown cause
Myocardial Infarction (VARC 2)	**Peri-procedural MI (less than or equal to (≤) 72 h after the index procedure)** 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, or imaging evidence of new loss of viable myocardium or new wall motion abnormality), ***AND*** Elevated cardiac biomarkers within 72 h after the index procedure consisting of at least one sample post-procedure with a peak value exceeding 15x upper reference limit (troponin) or 5x for CK-MB. If cardiac biomarkers are increased at baseline (>99th percentile), a further increase of at least 50% post-procedure is required AND the peak value must exceed the previously stated limit. **Spontaneous MI (greater than (>) 72 h after the index procedure)** 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: ○ Symptoms of ischemia ○ ECG changes indicative of new ischemia [new ST-T changes or new Left Bundle Branch Block (LBBB)] ○ New pathological Q waves in at least two contiguous leads ○ Imaging evidence of new loss of viable myocardium or new wall motion abnormality • Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST-segment elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/ or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. • Pathological findings of an acute myocardial infarction.
Stroke (FDA/VARC 2)	This study is following the FDA's definition of Stroke per FDA's Current Thinking Regarding Neurological Assessments for Transcatheter Valve Trials (Revised: 25 Aug 2011) and VARC 2 (2012) *1. Definitions:* a. Stroke: Stroke is an acute episode of focal or global neurological dysfunction caused by the brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Sub classifications of stroke: i. Ischemic Stroke is defined as an acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.

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	ii. Hemorrhagic Stroke is defined as an acute symptomatic episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage. Stroke Disability (consistent with VARC 2 Definitions): i. Disabling: an mRS score of 2 or more at 90 days and an increase of at least one mRS category from an individual's pre-stroke baseline ii. Non-disabling: an mRS score of < 2 at 90 days or one that does not result in an increase of at least one mRS category from an individual's pre-stroke baseline b. Cerebral Infarction: Evidence of brain cell death from imaging studies or pathological examination. If there are clinical symptoms, then it is a stroke; otherwise, it is an asymptomatic cerebral infarction. c. Transient Ischemic Attack (TIA): A transient (less than (<) 24 hrs) episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction. No evidence of infarction if imaging performed. d. Encephalopathy: Altered mental state (e.g., seizures, delirium, confusion, hallucinations, dementia, coma, psychiatric episode, etc.). e. Intracranial Hemorrhage: Collection of blood between the brain and skull. Subcategorized as epidural, subdural, and subarachnoid bleeds.
Bleeding (VARC 2)	**Life-threatening or disabling bleeding** • Fatal bleeding (BARC type 5) **OR** • Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) **OR** • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) **OR** • Overt source of bleeding with drop in hemoglobin of greater than or equal to (≥) 5 g/dl or whole blood or packed red blood cells (RBCs) transfusion greater than or equal to (≥) 4 U (BARC type 3b). *Given 1 U of packed RBC typically will raise blood hemoglobin concentration by 1 g/dl, an estimated decrease in hemoglobin will be calculated.* **Major bleeding (BARC type 3a)** • Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dl or requiring transfusion of 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 **Minor bleeding (BARC type 2 or 3a, depending on the severity)** • 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)	Change in serum creatinine (up to 48 h) compared with baseline **Stage 1** Increase in serum creatinine to 150% to 199% (1.5 to 1.99 X increase compared with baseline) or increase of greater than or equal to (≥) 0.3 mg/dl (≥26.4 mmol/l) or Urine output <0.5 ml/kg per hour for > 6 but < 12 hours **Stage 2** Increase in serum creatinine to 200% to 299% (2.0 to 2.99 X increase compared with baseline) or Urine output <0.5 ml/kg per hour for > 12 but < 24 hours

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	Stage 3 Increase in serum creatinine to greater than or equal to (≥) 300% (>)3 X increase compared with baseline) or serum creatinine of ≥ 4.0 mg/dl (≥354 mmol/l) with an acute increase of at least 0.5 mg/dl (44 mmol/l) or Urine output < 0.3 ml/kg per hour for ≥ 24 hours or anuria for ≥ 12 hours. *Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.*
Vascular Access Site and Access-Related Complications (VARC 2)	**Major vascular complications** • Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm or • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) ***leading to*** death, life-threatening or major bleeding*, visceral ischaemia or neurological impairment or • Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage or • The use of unplanned endovascular or surgical intervention ***associated*** with death, major bleeding, visceral ischaemia or neurological impairment or • Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram or • Surgery for access site-related nerve injury or • Permanent access site-related nerve injury **Minor vascular complications** • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysms, hematomas, percutaneous closure device failure) ***not leading to*** death, life-threatening or major bleeding*, visceral ischemia or neurological impairment or • Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage or • Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication or • Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft) or **Percutaneous closure device failure** Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)

Acute Device Success (VARC 2 with modifications)	1. Acute device success defined as:
	  ○ Absence of procedural mortality
	  ○ Correct positioning of a single prosthetic heart valve into the proper anatomical location
	  ○ Intended performance of the prosthetic heart valve (mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, no moderate or severe prosthetic valve regurgitation)
	  ○ Successful access was obtained as intended by group assignment
	Device success is a 'technical' composite endpoint meant to characterize the acute device and procedural factors which underlie vascular access, delivery, and performance of the TAVI system. Echocardiography should be routinely utilized as the standard for measuring prosthetic valve stenosis and regurgitation immediately after TAVI, and should always be performed in a resting state, either within 24–48 h after the index procedure or before hospital discharge.

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FDA

Individual Patient Success

1. Acute device success
2. Discharged alive from the hospital without device-related major AEs (Includes AI ≤ 1+)
3. Survival to one year with:
   - No disabling stroke
   - No device-or procedure-related mortality
   - NYHA class ≤ 2, or improvement in NYHA class by at least 1 level from baseline
   - No re-hospitalizations for valve related complications/dysfunction or CHF due to aortic valve related causes
4. No pacemaker dependency at 1 year (Excluding subjects with pre-procedural conduction abnormalities)

Prosthetic Valve Stenosis Criteria ***In conditions of normal or near normal stroke volume (50–70 ml).*** **(VARC 2)**	**Parameter**	**Normal**	**Mild Stenosis**	**Moderate/ severe Stenosis**
	Peak velocity (m/s)	less than (<) 3	3–4	greater than (>) 4
	Mean gradient (mm Hg)	less than (<) 20	20–40	greater than (>) 40
	Doppler velocity index	greater than or equal to (≥) 0.35	0.35–0.25	less than (<) 0.25
	Effective orifice area (cm^2)	greater than (>) 1.1*	1.1–0.8	less than (<) 0.80
Prosthetic Valve Regurgitation Criteria (VARC 2)	**Diastolic flow reversal in the descending aorta (semi-quantitative parameters)**			
	Diastolic flow reversal in the descending aorta *PW Doppler*	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic
	Circumferential extent of paraprosthetic AR	less than (<) 10%	10–29%	greater than or equal (≥) 30%
	Doppler parameters ***(quantitative)***			
	Regurgitant volume (ml/beat)	less than (<) 30%	30–59%	greater than or equal (≥) 60%
	Regurgitant fraction	less than (<) 30%	30–49%	greater than or equal (≥) 50%
	EROA (cm^2)	0.10 cm^2	0.10-0.29 cm^2	≥0.30 cm^2

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

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APPENDIX III: NON-STUDY SPECIFIC DEFINITIONS

Adverse Event (AE)
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 investigational medical device under clinical investigation.

This definition includes adverse events related to the investigational medical device.
This definition includes events related to the procedures involved.

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

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

A planned hospitalization for a pre-existing condition, or a procedure required by the CIP is not considered a serious adverse event.

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

This definition includes any event resulting from the use error or from intentional misuse of the investigational 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 Adverse Device Effect (UADE)
As defined in 21 CFR §812.3, unanticipated adverse device effects (UADE) are defined as 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 CIP 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.

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.

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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.

Device Deficiency (DD)
A device deficiency is defined as 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.

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APPENDIX IV: STUDY-SPECIFIC ASSESSMENTS

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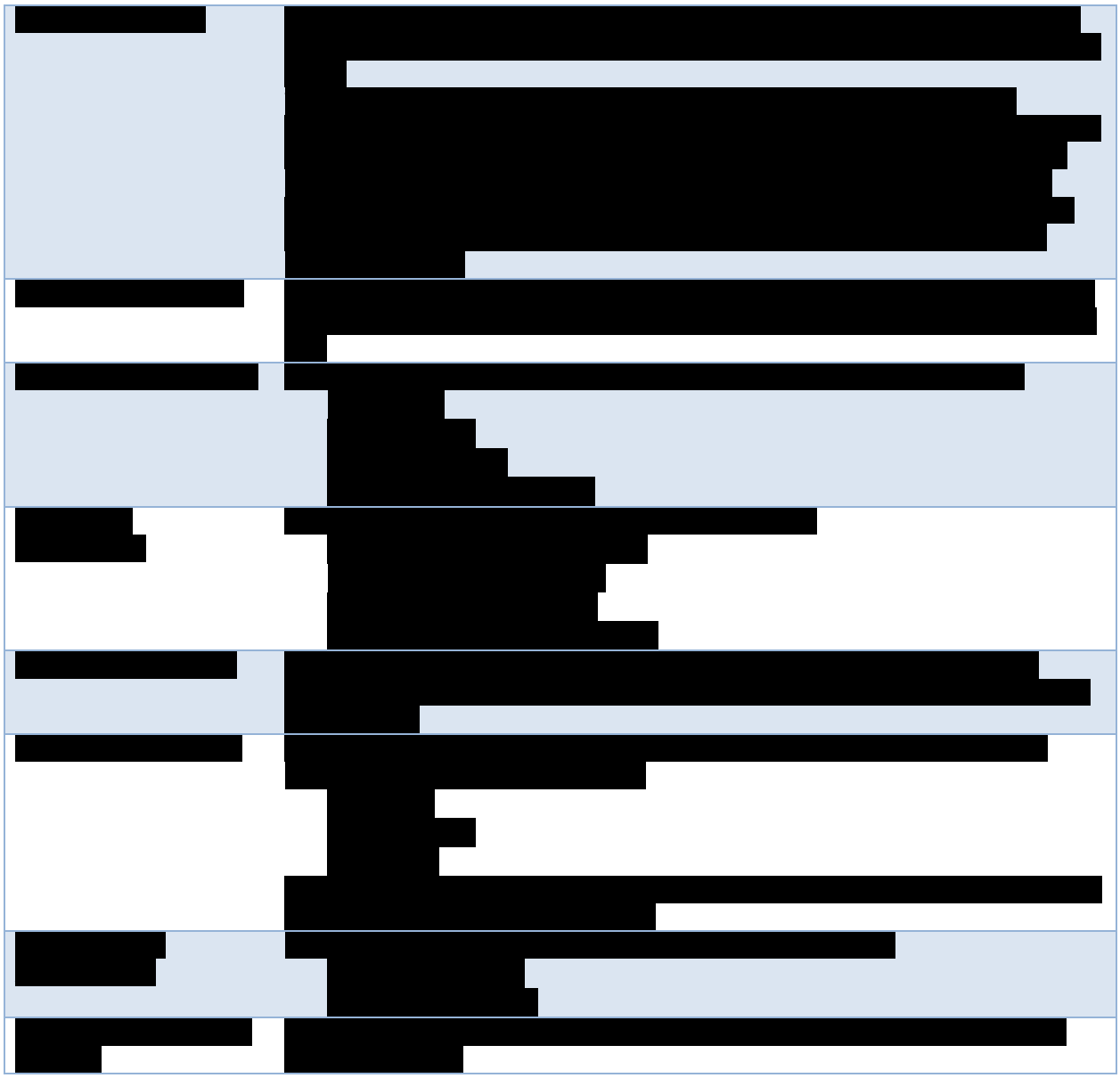

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APPENDIX V: SITE CONTACT INFORMATION

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

[redacted]

Clinical Investigation Plan

APPENDIX VI: SURGICAL RISK ASSESSMENT TOOLS

This clinical study requires the use of two surgical risk assessment tools:

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

Clinical Investigation Plan

APPENDIX VII: FRAILY ASSESSMENT

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

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

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

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

2. Grip strength

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

Grasp 1_____ Grasp 2_____Grasp3_____ Average_____

Clinical Investigation Plan

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

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

3. 5 Meter Walk Time

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

_____seconds

Walk Time, stratified by gender and height

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

Clinical Investigation Plan

APPENDIX VIII: NYHA CLASSIFICATION

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

Clinical Investigation Plan

APPENDIX IX: CANADIAN CARDIOVASCULAR SOCIETY GRADING OF ANGINA PECTORIS

Grade	Description	
Grade I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation	
Grade II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions	
Grade III	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing one flight of stairs in normal conditions and at normal pace	
Grade IV	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest	

Clinical Investigation Plan

APPENDIX X: QUALITY OF LIFE- EQ-5D 3L

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

Mobility

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

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

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

Pain/Discomfort

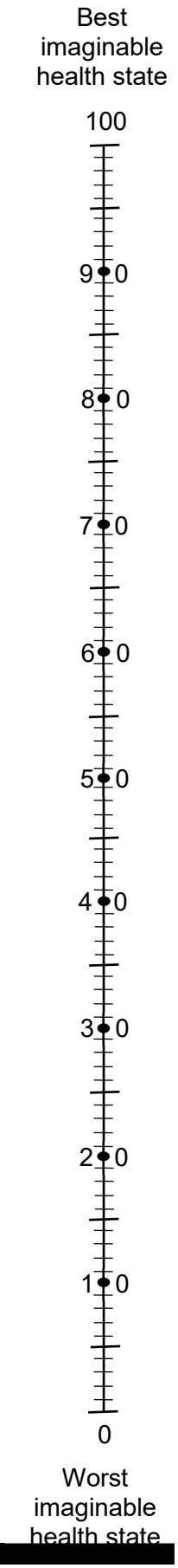
I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety/Depression

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

Clinical Investigation Plan

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



APPENDIX XI: QUALITY OF LIFE – SF-36v2

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities.
Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. **In general, would you say your health is:**

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **<u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Clinical Investigation Plan

6. **During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. **How much bodily pain have you had during the past 4 weeks?**

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. **During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?**

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. **These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. **During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?**

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Clinical Investigation Plan

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Clinical Investigation Plan

APPENDIX XII: QUALITY OF LIFE-KANAS CITY CARDIOMYOPATHY QUESTIONNAIRE (KCCQ)

The KC Cardiomyopathy Questionnaire

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Place an **X** in one box on each line

Activity	Extremely Limited	Quite a bit Limited	Moderately Limited	Slightly Limited	Not at all Limited	Limited for other reasons or did not do the activity
Dressing yourself	☐	☐	☐	☐	☐	☐
Showering/Bathing	☐	☐	☐	☐	☐	☐
Walking 1 block on level ground	☐	☐	☐	☐	☐	☐
Doing yardwork, housework or carrying groceries	☐	☐	☐	☐	☐	☐
Climbing a flight of stairs without stopping	☐	☐	☐	☐	☐	☐
Hurrying or jogging (as if to catch a bus)	☐	☐	☐	☐	☐	☐

2. Compared with 2 weeks ago, have your symptoms of **heart failure** (shortness of breath, fatigue, or ankle swelling) changed?

My symptoms of **heart failure** have become…

Much worse	Slightly worse	Not changed	Slightly better	Much better	I've had no symptoms over the last 2 weeks
☐	☐	☐	☐	☐	☐

Original US English

Clinical Investigation Plan

3. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

4. Over the past 2 weeks, how much has **swelling** in your feet, ankles or legs bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no swelling**
☐	☐	☐	☐	☐	☐

5. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you want?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

6. Over the past 2 weeks, how much has your **fatigue** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no fatigue**
☐	☐	☐	☐	☐	☐

7. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐	☐	☐

Original US English

Clinical Investigation Plan

8. Over the past 2 weeks, how much has your **shortness of breath** bothered you?

It has been ...

Extremely bothersome	**Quite a bit** bothersome	**Moderately** bothersome	**Slightly** bothersome	**Not at all** bothersome	I've had **no shortness of breath**
☐	☐	☐	☐	☐	☐

9. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times a week, but not every day	1-2 times a week	Less than once a week	Never over the past 2 weeks
☐	☐	☐	☐	☐

10. **Heart failure** symptoms can worsen for a number of reasons. How sure are you that you know what to do, or whom to call, if your **heart failure** gets worse?

Not at all sure	**Not very** sure	**Somewhat** sure	**Mostly** sure	**Completely** sure
☐	☐	☐	☐	☐

11. How well do you understand what things you are able to do to keep your **heart failure** symptoms from getting worse? (for example, weighing yourself, eating a low salt diet etc.)

Do not understand at all	Do not understand very well	Somewhat understand	Mostly understand	Completely understand
☐	☐	☐	☐	☐

12. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
☐	☐	☐	☐	☐

13. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
☐	☐	☐	☐	☐

Original US English

14. Over the past 2 weeks, how often have you felt discouraged or down in the dumps because of your **heart failure**?

I felt that way **all of the time**	I felt that way **most of the time**	I **occasionally** felt that way	I **rarely** felt that way	I **never** felt that way
☐	☐	☐	☐	☐

15. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Please place an **X** in one box on each line

Activity	**Severely** limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
Hobbies, recreational activities	☐	☐	☐	☐	☐	☐
Working or doing household chores	☐	☐	☐	☐	☐	☐
Visiting family or friends out of your home	☐	☐	☐	☐	☐	☐
Intimate relationships with loved ones	☐	☐	☐	☐	☐	☐

Original US English

Clinical Investigation Plan

APPENDIX XIII: MINI-MENTAL STATE EXAMINATION (MMSE-2)

MMSE-2™

Standard Version

Blue Form

Date of examination ___/___/___ Examiner _____

Name _____ Age _____ Sex _____

Years of school completed _____ Purpose of exam _____

Assessment of level of consciousness

Alert/ Responsive | Drowsy | Stuporous | Comatose/ Unresponsive

Instructions: Words in boldface type should be read aloud clearly and slowly to the examinee. Item substitutions appear in parentheses. Administration should be conducted privately and in the examinee's primary language. Unless otherwise specified, circle 0 if the response is incorrect or 1 if the response is correct. Begin by introducing the test:

Now I'd like to ask you some questions about your memory.

	RESPONSE	SCORE (circle one)
REGISTRATION		
Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are... MILK [pause], **SENSIBLE** [pause], **BEFORE** [pause]. **Now repeat those words back to me.** [Repeat up to 3 times, but score only the first trial.]		
MILK	_____	0 1
SENSIBLE	_____	0 1
BEFORE	_____	0 1
Now keep those words in mind. I am going to ask you to say them again in a few minutes.		
ORIENTATION TO TIME		
What day is today? What is the...		
year?	_____	0 1
season?	_____	0 1
month of the year	_____	0 1
day of the week	_____	0 1
date?	_____	0 1
ORIENTATION TO PLACE*		
Where are we now? What is the...		
state (or province)?	_____	0 1
county (or city/town)?	_____	0 1
city/town (or part of city/neighborhood)?	_____	0 1
building (name or type)?	_____	0 1
floor of the building (room number or address)?	_____	0 1

*Alternative place words that are appropriate for the setting and increasingly precise may be substituted and noted.

RECALL		
What were those three words I asked you to remember? [Do not offer any hints.]		
MILK	_____	0 1
SENSIBLE	_____	0 1
BEFORE	_____	0 1

If administering the MMSE-2:SV, copy the MMSE-2:BV total raw score to the space provided at the top of page 2 and continue with administration.

MMSE-2:BV total raw score ☐ (16 max. points)

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MMSE-2:BV total raw score ☐ (16 max. points)

ATTENTION AND CALCULATION [*Serial 7s*]

Now I'd like you to subtract 7 from 100. Then keep subtracting 7 from each answer until I tell you to stop.

What is 100 take away 7?	[93]	_____	0	1
If needed, say: **Keep going.**	[86]	_____	0	1
If needed, say: **Keep going.**	[79]	_____	0	1
If needed, say: **Keep going.**	[72]	_____	0	1
If needed, say: **Keep going.**	[65]	_____	0	1

Score 1 point for each correct answer. An answer is considered correct if it is 7 less than the previous answer, even if the previous answer was incorrect.

NAMING

What is this? [*Point to eye.*]	_____	0	1
What is this? [*Point to ear.*]	_____	0	1

REPETITION

Now I am going to ask you to repeat what I say. Ready? IT IS A LOVELY, SUNNY DAY BUT TOO WARM. Now you say that. [*Wait for examinee response and record response verbatim. Repeat up to one time.*]

IT IS A LOVELY, SUNNY DAY BUT TOO WARM.	_____	0	1

Detach the last page of this form. Tear the detached page in half along the horizontal perforation line. Use the upper half of the detached page, which has three shapes on it, as a stimulus form for the Comprehension task. Use the bottom half of the page as a stimulus form for the Reading ("CLOSE YOUR EYES") task. Use the upper back half of the detached page as a stimulus and response form for the Drawing (intersecting pentagons) task and the bottom half of the page (blank) as a response form for the Writing task.

COMPREHENSION

Listen carefully because I am going to ask you to do something. [*Show examinee the geometric figures stimulus page.*] **Look at the pictures and point to the circle, then point to the square, and then point to the triangle.**

Correct response	Observed response		
○		0	1
□		0	1
△		0	1

READING

[*Show examinee the word stimulus page.*] **Please do what this says to do.**

CLOSE YOUR EYES	_____	0	1

WRITING

[*Place the blank piece of paper in front of the examinee and provide a pen or pencil.*] **Please write a sentence.** [*If examinee does not respond, say:* **Write about where you live.**] Score 1 point if the sentence is comprehensible and contains a subject and a verb. Ignore errors in grammar or spelling. 0 1

DRAWING

[*Display the intersecting pentagons on the stimulus form and provide a pen or pencil.*] **Please copy this design.** Score 1 point if the drawing consists of two 5-sided figures that intersect to form a 4-sided figure. 0 1

MMSE-2:SV total raw score ☐ (30 max. points)

Sample

CLOSE YOUR EYES

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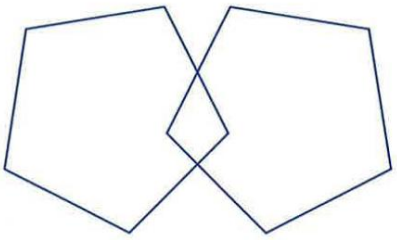

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APPENDIX XIV: BARTHEL INDEX

THE BARTHEL INDEX

Patient Name: _____

Rater Name: _____

Date: _____

Activity	Score
FEEDING 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent	_____
BATHING 0 = dependent 5 = independent (or in shower)	_____
GROOMING 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	_____
DRESSING 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)	_____
BOWELS 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent	_____
BLADDER 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent	_____
TOILET USE 0 = dependent 5 = needs some help, but can do something alone 10 = independent (on and off, dressing, wiping)	_____
TRANSFERS (BED TO CHAIR AND BACK) 0 = unable, no sitting balance 5 = major help (one or two people, physical), can sit 10 = minor help (verbal or physical) 15 = independent	_____
MOBILITY (ON LEVEL SURFACES) 0 = immobile or < 50 yards 5 = wheelchair independent, including corners, > 50 yards 10 = walks with help of one person (verbal or physical) > 50 yards 15 = independent (but may use any aid; for example, stick) > 50 yards	_____
STAIRS 0 = unable 5 = needs help (verbal, physical, carrying aid) 10 = independent	_____
TOTAL (0–100):	_____

Provided by the Internet Stroke Center — www.strokecenter.org

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The Barthel ADL Index: Guidelines

1. The index should be used as a record of what a patient does, not as a record of what a patient could do.
2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
3. The need for supervision renders the patient not independent.
4. A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives and nurses are the usual sources, but direct observation and common sense are also important. However direct testing is not needed.
5. Usually the patient's performance over the preceding 24-48 hours is important, but occasionally longer periods will be relevant.
6. Middle categories imply that the patient supplies over 50 per cent of the effort.
7. Use of aids to be independent is allowed.

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Clinical Investigation Plan

APPENDIX XV: STRUCTURED INTERVIEW FOR THE MODIFIED RANKIN SCORE (mRS)

After the NIHSS has been completed, the mRS (by a certified rater) is to be determined and graded by the same certified rater.

The determination of the scale should be made from 5 to 0.

The purpose of the mRS is to record whether the subject is severely, moderately, or slightly disabled and whether the subject is performing all usual activities without symptoms or not. Because subjects 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 assessor may ask questions but must assess the disability whether or not in agreement with the subject or family.

"Improving the assessment of outcomes in stroke: use of a structured interview to assign grades on the Modified Rankin Scale" (*Stroke*; 33:2243-2246)

Score	Description
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, but does not require constant care *Question: Is assistance essential for eating, using the toilet, daily hygiene, or walking?*
3	• Moderate disability • Need for assistance with some instrumental activities of daily living but not basic activities of daily living. *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 • Independent for activities of daily living. *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

Clinical Investigation Plan

APPENDIX XVI: NIH STROKE SCALE (NIHSS)

N I H
STROKE
SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

Time: ___ ___:___ ___ [ ]am [ ]pm

Person Administering Scale _____

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

Instructions	Scale Definition	Score
1a. Level of Consciousness: The investigator must choose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.	0 = **Alert;** keenly responsive. 1 = **Not alert;** but arousable by minor stimulation to obey, answer, or respond. 2 = **Not alert;** requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic.	_____
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.	0 = **Answers** both questions correctly. 1 = **Answers** one question correctly. 2 = **Answers** neither question correctly.	_____
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to him or her (pantomime), and the result scored (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.	0 = **Performs** both tasks correctly. 1 = **Performs** one task correctly. 2 = **Performs** neither task correctly.	_____
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored, but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI), score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness, or other disorder of visual acuity or fields should be tested with reflexive movements, and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.	0 = **Normal.** 1 = **Partial gaze palsy;** gaze is abnormal in one or both eyes, but forced deviation or total gaze paresis is not present. 2 = **Forced deviation,** or total gaze paresis not overcome by the oculocephalic maneuver.	_____

Clinical Investigation Plan

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat, as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia, is found. If patient is blind from any cause, score 3. Double simultaneous stimulation is performed at this point. If there is extinction, patient receives a 1, and the results are used to respond to item 11.	0 = **No visual loss.** 1 = **Partial hemianopia.** 2 = **Complete hemianopia.** 3 = **Bilateral hemianopia** (blind including cortical blindness).	_____
4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	0 = **Normal** symmetrical movements. 1 = **Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). 2 = **Partial paralysis** (total or near-total paralysis of lower face). 3 = **Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	_____
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** limb holds 90 (or 45) degrees for full 10 seconds. 1 = **Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. 2 = **Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. 3 = **No effort against gravity;** limb falls. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **5a. Left Arm** **5b. Right Arm**	_____ _____
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	0 = **No drift;** leg holds 30-degree position for full 5 seconds. 1 = **Drift;** leg falls by the end of the 5-second period but does not hit bed. 2 = **Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. 3 = **No effort against gravity;** leg falls to bed immediately. 4 = **No movement.** UN = **Amputation** or joint fusion, explain: _____ **6a. Left Leg** **6b. Right Leg**	_____

Clinical Investigation Plan

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	0 = **Absent.** 1 = **Present in one limb.** 2 = **Present in two limbs.** UN = **Amputation** or joint fusion, explain: _____	_____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a=3) are automatically given a 2 on this item.	0 = **Normal;** no sensory loss. 1 = **Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. 2 = **Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	_____
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	0 = **No aphasia;** normal. 1 = **Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient's response. 2 = **Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. 3 = **Mute, global aphasia;** no usable speech or auditory comprehension.	_____
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	0 = **Normal.** 1 = **Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = **Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. UN = **Intubated** or other physical barrier, explain:_____	_____

Clinical Investigation Plan

NIH STROKE SCALE

Patient Identification. ___ ___-___ ___ ___-___ ___ ___

Pt. Date of Birth ___ ___/___ ___/___ ___

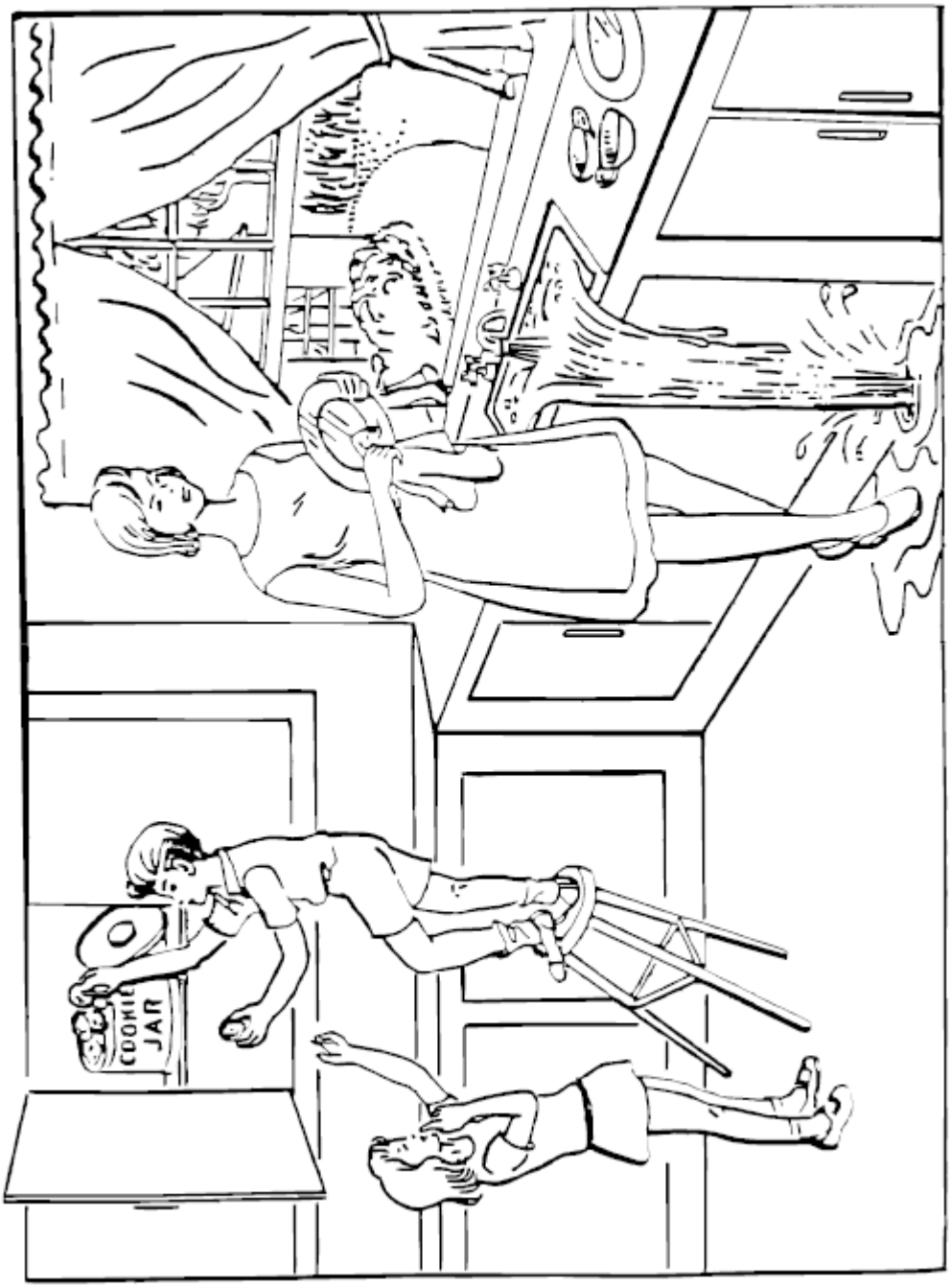
Hospital _____(___ ___-___ ___)

Date of Exam ___ ___/___ ___/___ ___

Interval: [ ] Baseline [ ] 2 hours post treatment [ ] 24 hours post onset of symptoms ±20 minutes [ ] 7-10 days
[ ] 3 months [ ] Other _____(___ ___)

11. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	0 = **No abnormality.** 1 = **Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = **Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.	____

Clinical Investigation Plan



You know how.

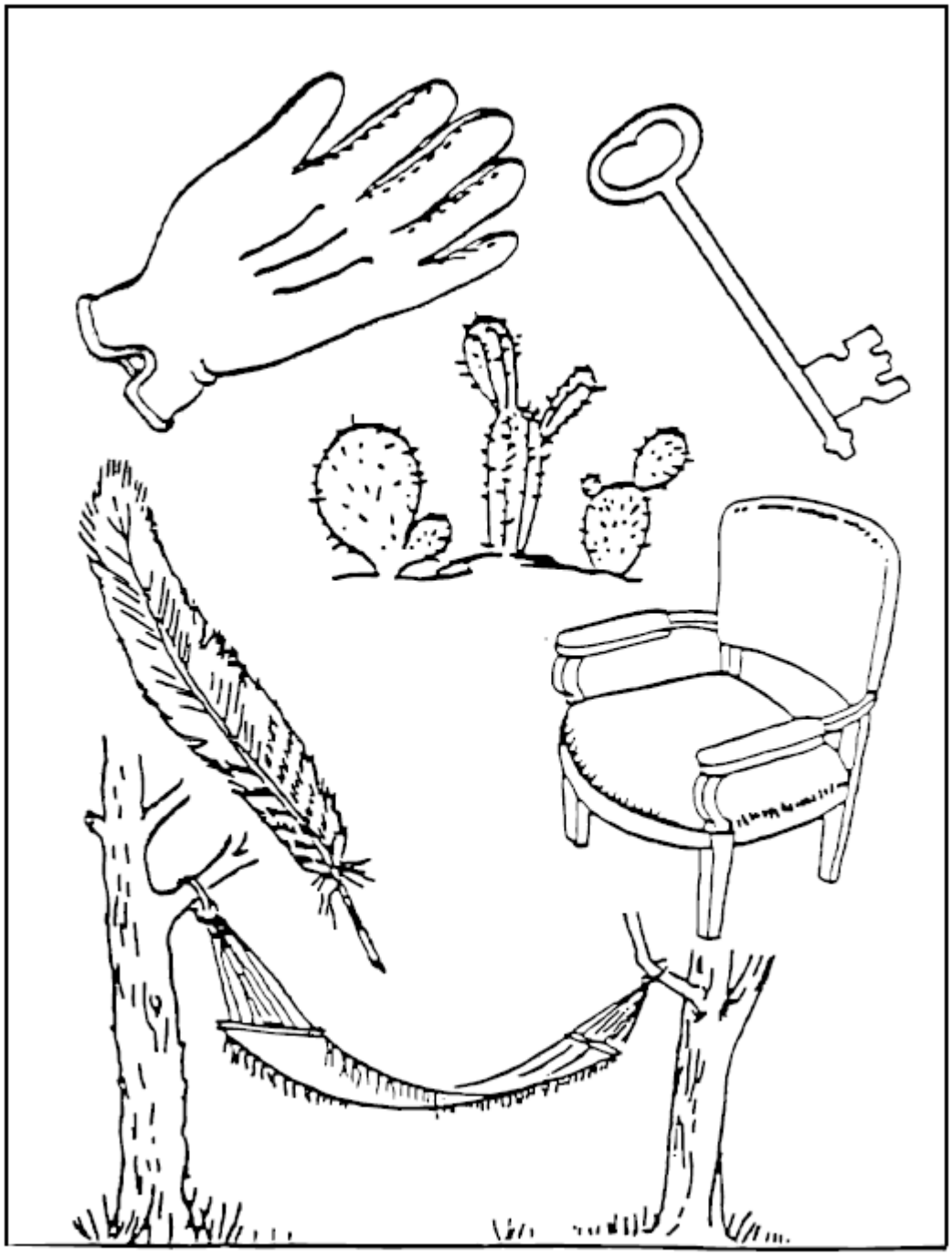
Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.

Clinical Investigation Plan



MAMA

TIP – TOP

FIFTY – FIFTY

THANKS

HUCKLEBERRY

BASEBALL PLAYER

Clinical Investigation Plan

APPENDIX XVII: 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

1. 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.
2. 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.
3. 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.
4. 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.
5. 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.

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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 subject 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.

Clinical Investigation Plan

Baseline Measurements

1. 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."***

Clinical Investigation Plan

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."

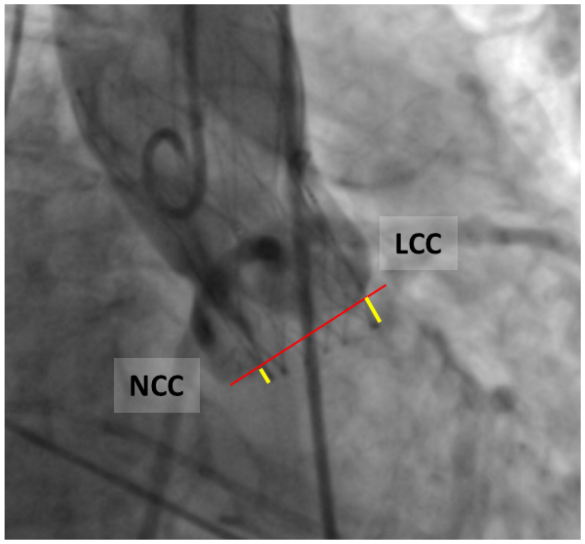
When the timer rings (or buzzes), say this: **"Stop!"**

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

Clinical Investigation Plan

APPENDIX XVIII: PERI-PROCEDURAL GUIDELINES

[redacted]



Clinical Investigation Plan

APPENDIX XIX: EXPLANT, RETURN, AND ANALYSIS OF VALVE

[redacted]

Clinical Investigation Plan

[redacted]

Clinical Investigation Plan

APPENDIX XXI: GERMAN HANDLING OF SERIOUS ADVERSE EVENTS

The scope of this section is to implement the reporting obligation in accordance with §3, section 5 of the German MPSV (Medical Products Safety Ordinance), taking into consideration that notification must be done immediately in accordance § 5, section 2 of the MPSV.

1. Definition of SAE according to §2, Section 5 MPSV:
   Serious Adverse Event: any untoward event occurring within a clinical investigation requiring authorization, which directly or indirectly led to, or which might have led or could lead to death or a serious deterioration in the health of the patient, a user or other person, without taking into account whether the event was caused by the medical device.
2. Notification of SAEs:
   - As soon as the investigator becomes aware of an SAE during the course of a study, the sponsor (Abbott) must be informed immediately, and in no case later than 72 hours after becoming aware.
   - The sponsor (Abbott) also has the obligation to inform the BfArM of all SAEs according to following table.

Condition for reporting to BfArM	**Country of occurrence**	**Timeline for reporting to BfArM**	**Form**
a causal relationship between the SAE and the investigational medical device, a comparator device, diagnostic or therapeutic procedures performed as part of the clinical trial or other conditions of the trial conduct **cannot be excluded**	Germany	immediately	Single report German SAE Report Form Please send to MPSAE@bfarm.de
	all other countries where the clinical trial is performed	immediately	Summary table MEDDEV 2.7/3 SAE report table All SAEs shall be documented using the same Excel file, in a cumulative manner, using the same Excel sheet. Please send to MPSAE@bfarm.de
a causal relationship between the SAE and the investigational medical device, a comparator device, diagnostic or therapeutic procedures performed as part of the clinical trial or other conditions of the trial **conduct can be excluded**	All	quarterly	
		quarterly	Summary table MEDDEV 2.7/3 SAE report table Please complete the MEDDEV Excel sheet as outlined above. Please send to MPSAE@bfarm.de
All SAEs	All	Quarterly	SAE summary evaluation Evaluation Annex 3.1 complication rate

			Please send to MPSAE@bfarm.de Please observe our notes on completing the SAE summary evaluation

- The German SAE Report Form is available on the BfArM homepage: http://www.bfarm.de/SharedDocs/Formulare/EN/MedicalDevices/report_form_clinical_trials_SAE.html

http://www.bfarm.de/DE/Medizinprodukte/form/functions/formmp-node.html

- Please note that the SAE gets a unique ID which consists of 4 Parts:
  - The Study Code (CRD_XXX for the ABBOTT Study Code of this study)
  - The Center ID (ORACLEID = CenterName)
  - The Patient No
  - The Date of SAE in the format (Year(2-digits)MonthDay)

  Example: CRD_910_EU0284_01_160203 for an event which occurred on 3 February for Patient 1 in center EU0284 within the Study CRD_878.
- The German Quarterly Report Template is available on the BfArM Homepage: http://www.bfarm.de/SharedDocs/Formulare/EN/MedicalDevices/sae_template.html
  Table Complication Rates
  http://www.bfarm.de/SharedDocs/Formulare/EN/MedicalDevices/sae_complication_rates.html
  Instructions for completing the quarterly assessment form for serious adverse events
  http://www.bfarm.de/SharedDocs/Formulare/EN/MedicalDevices/sae_template_notes.html

- The investigator will be instructed on this obligation during the initiation visit.
- Information about the obligation must be documented in the "training log".
- Written confirmation that this working procedure has been passed on to the trial center is sent to the investigator and then attached to the study file.

1. Responsibility of the investigators:

   1. The investigator has to notify the SAE to the sponsor without undue delay.
   2. SAEs should be reported either by
      1. eDC (primary reporting tool)
      2. E-Mail: AdverseEvent@sjm.com; study name and patient identification must always be reported in the subject of email.
   - The investigator or main investigator is obliged to respect the deadline for notification of SAEs.
   - A person within the study center will be designated to collect the necessary information.
   - A person within the study center will be designated to pass on this information to the sponsor. A list of people (including a representative) will be prepared for this purpose.

2. Responsibilities of the monitor (Abbott):

   - The monitor will be instructed of his/her responsibilities with regard to SAEs.

- If the monitor discovers an SAE during the course of the study that was not notified or not notified within the notification deadline, the sponsor's action plan will take effect. The BfArM is then notified of the SAE without undue delay and the investigator is informed of it straight away.

3. Responsibilities of the sponsor

- The sponsor (Abbott) shall notify any SAEs without undue delay (at the latest however within 72 hours) after awareness.
- A person will be designated to verify SAEs that occur during the clinical study.
- A list of Abbott people who shall be informed about SAEs is to be drawn up.
- A person will be designated who is responsible for the assessment of any SAEs.
- A person or team will be designated who is responsible for initiating corrective actions if necessary.

4. Responsibilities of the sponsor in Germany

- All people within Abbott who are involved in this clinical study be will instructed of the notification deadlines and are obliged to respect them.
- SAEs/PERs (Product Event Reports) are coordinated by the German project manager (CPL) or by Jörg Scheiner (Manager Clinical Safety/Compliance, Germany).
- SAE notifications to the BfArM and the Ethics Committee are to be made by the CPL or by Clinical Safety.
- The Field Clinical Manager or the study office will take care of SAE/PER notifications should both of the above people be unable to do so.
- Vigilanz-Responsible for this study: Jörg Scheiner (Manager Clinical Study Logistics, Abbott, Germany)
  Phone: +49-6196-7711-241, E-Mail: AdverseEvents-Germany@sjm.com

5. Notification of SAEs in other countries

SAEs are also reported to following countries when participation in the study:

- Denmark
- Italy
- Netherlands
- Sweden
- Ukraine
- United Kingdom

Clinical Investigation Plan

APPENDIX XXII: INDEPENDENT COMMITTEE AND CORE LABORATORY CONTACT DETAILS

[redacted]

Clinical Investigation Plan

APPENDIX XXIII: RATES OF FORSEEABLE ADVERSE EVENTS

[redacted]

[redacted]					
[redacted]					

[redacted]

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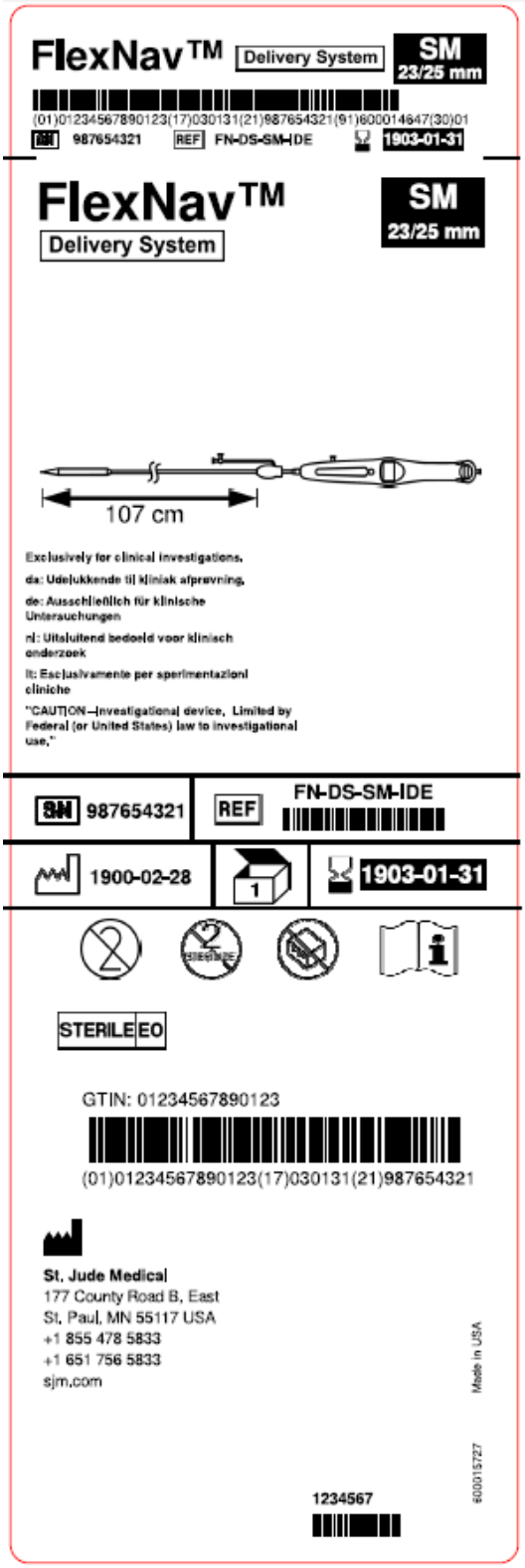
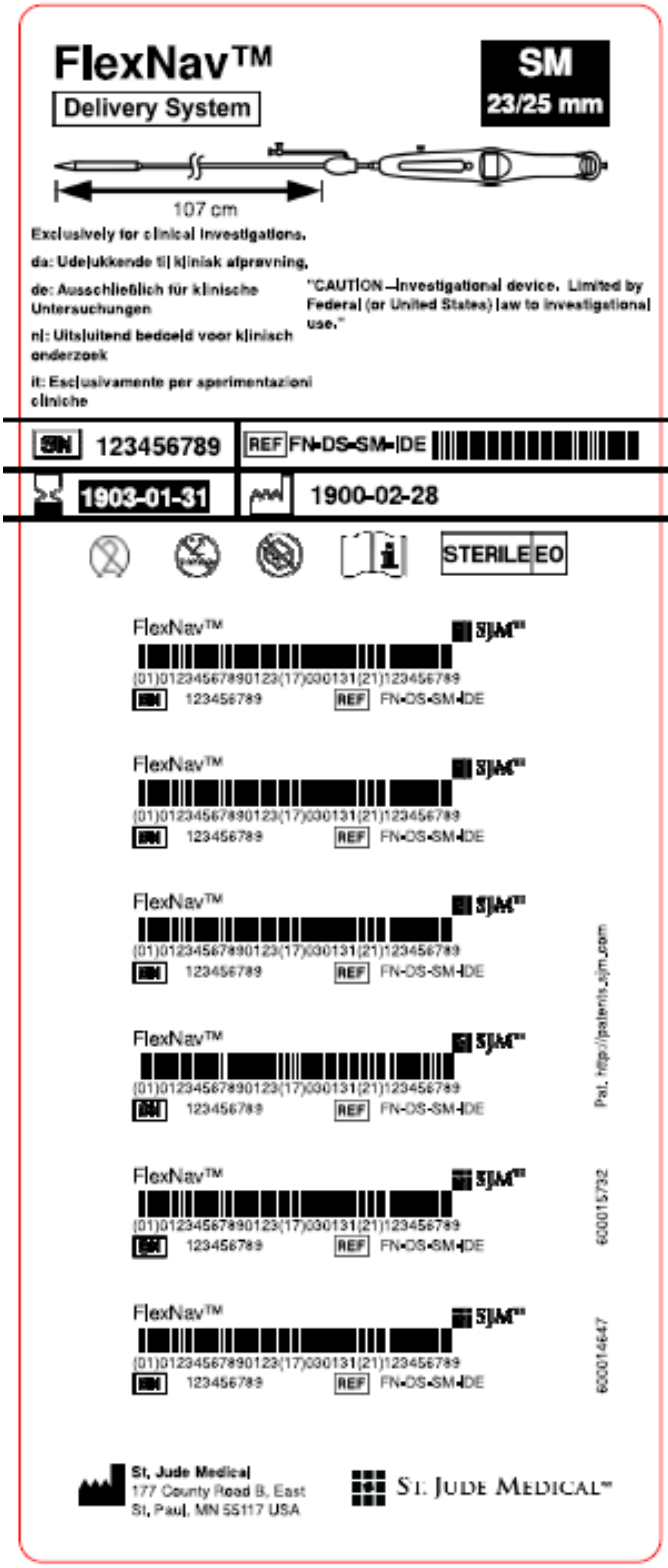
APPENDIX XXIV: LABELS





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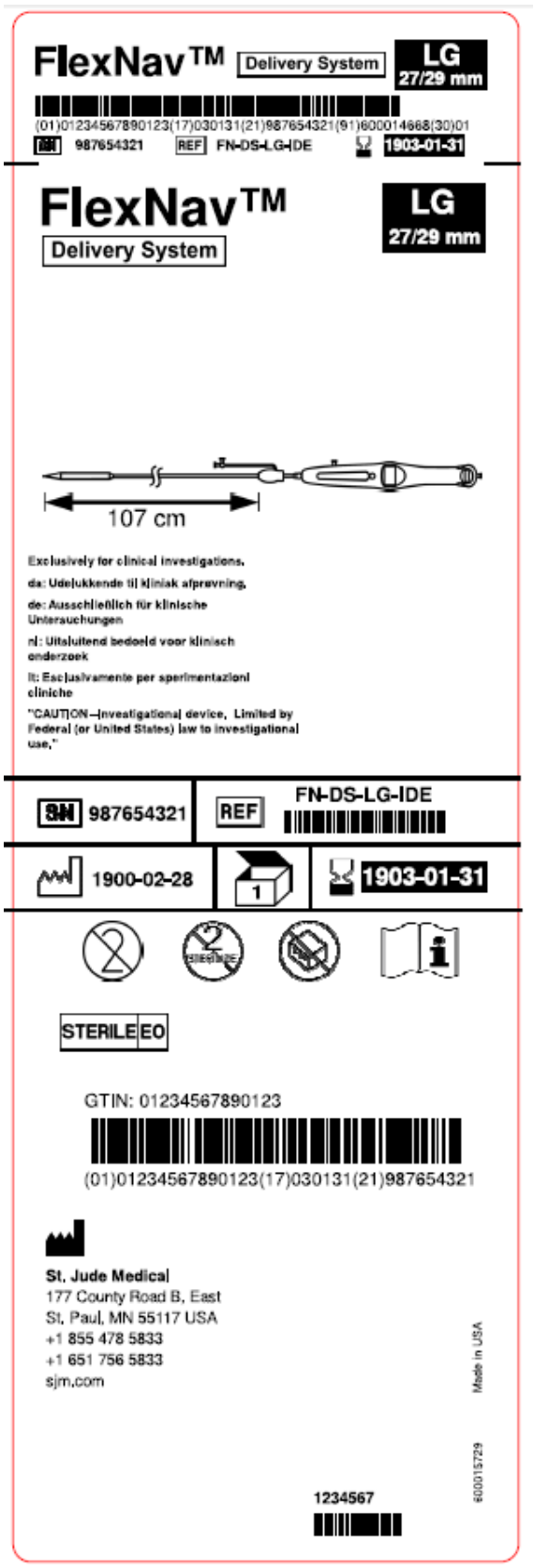

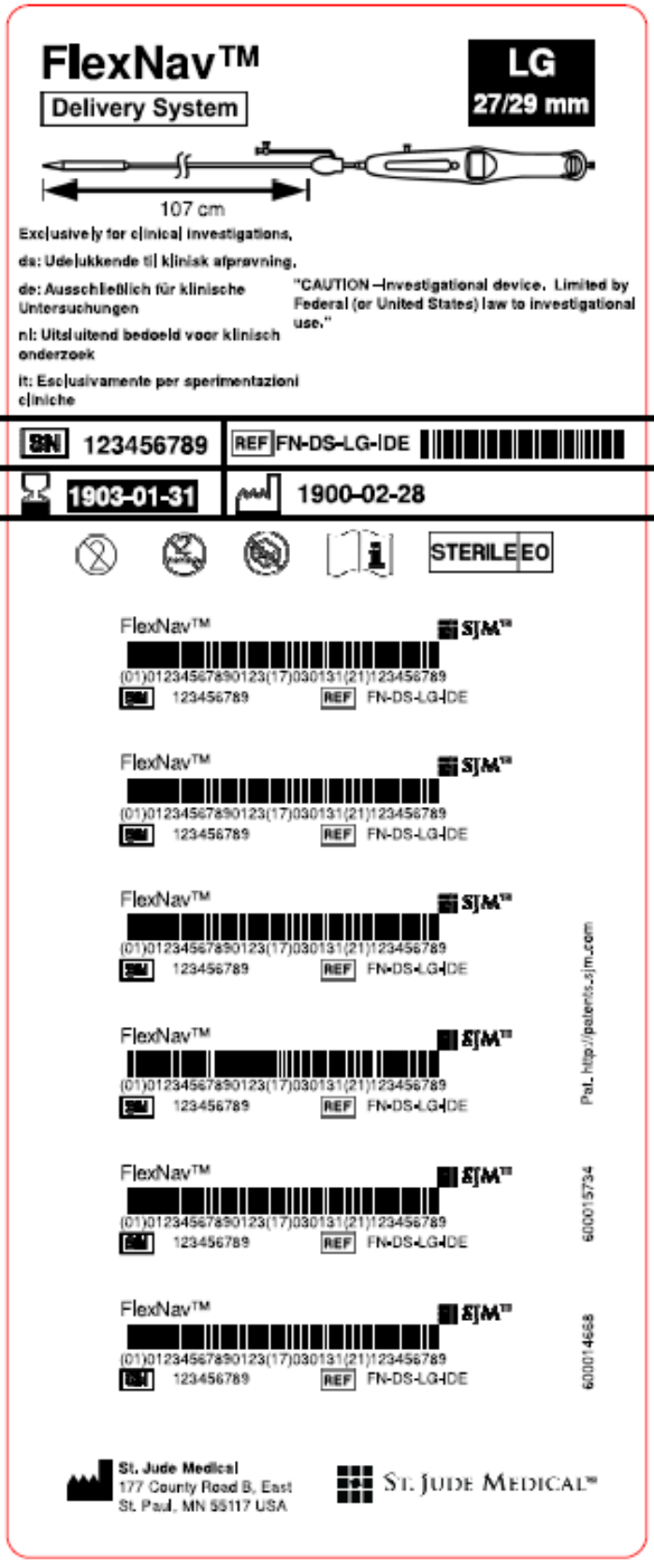

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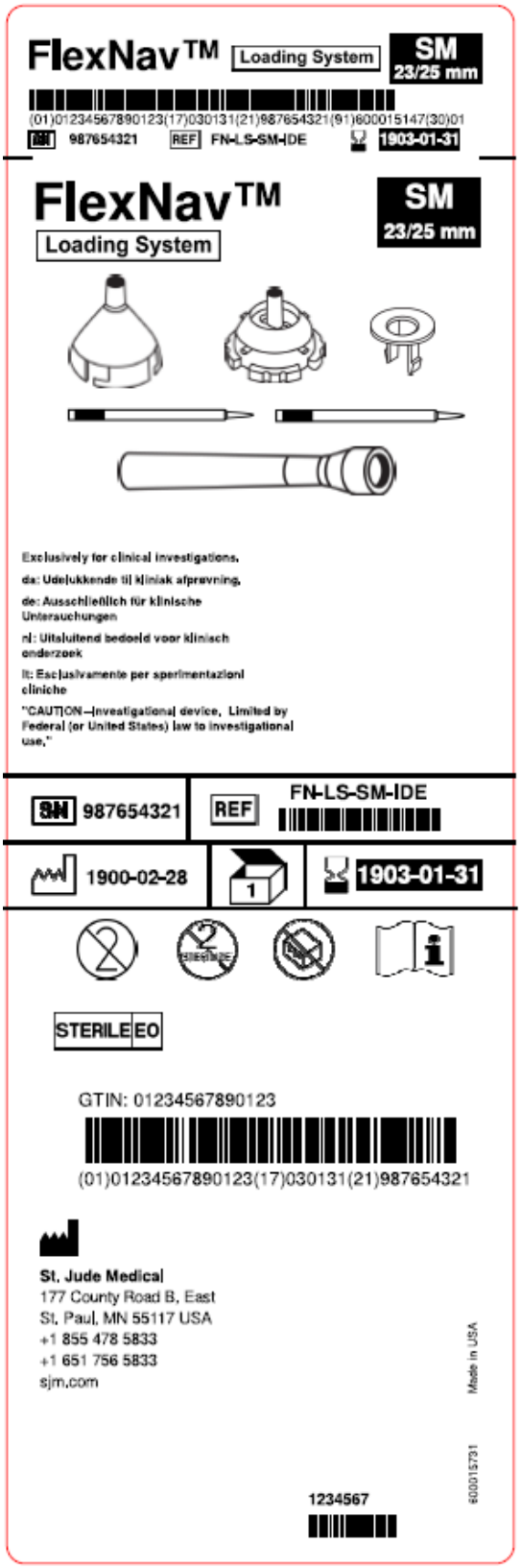

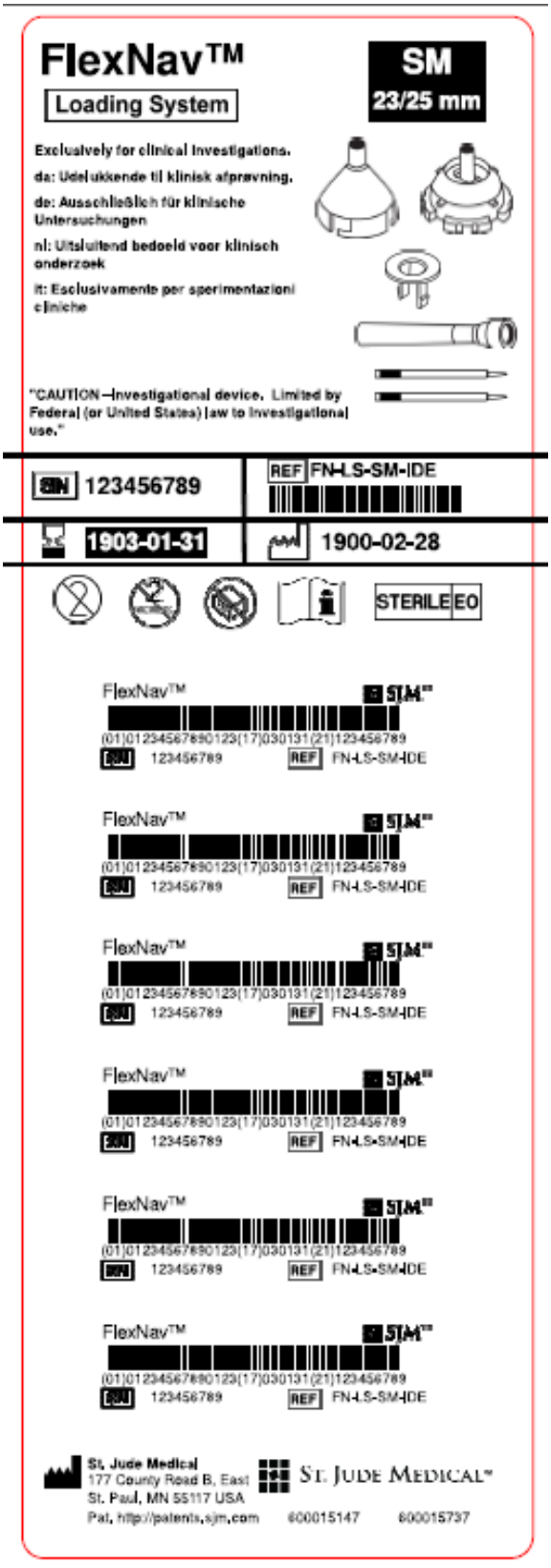

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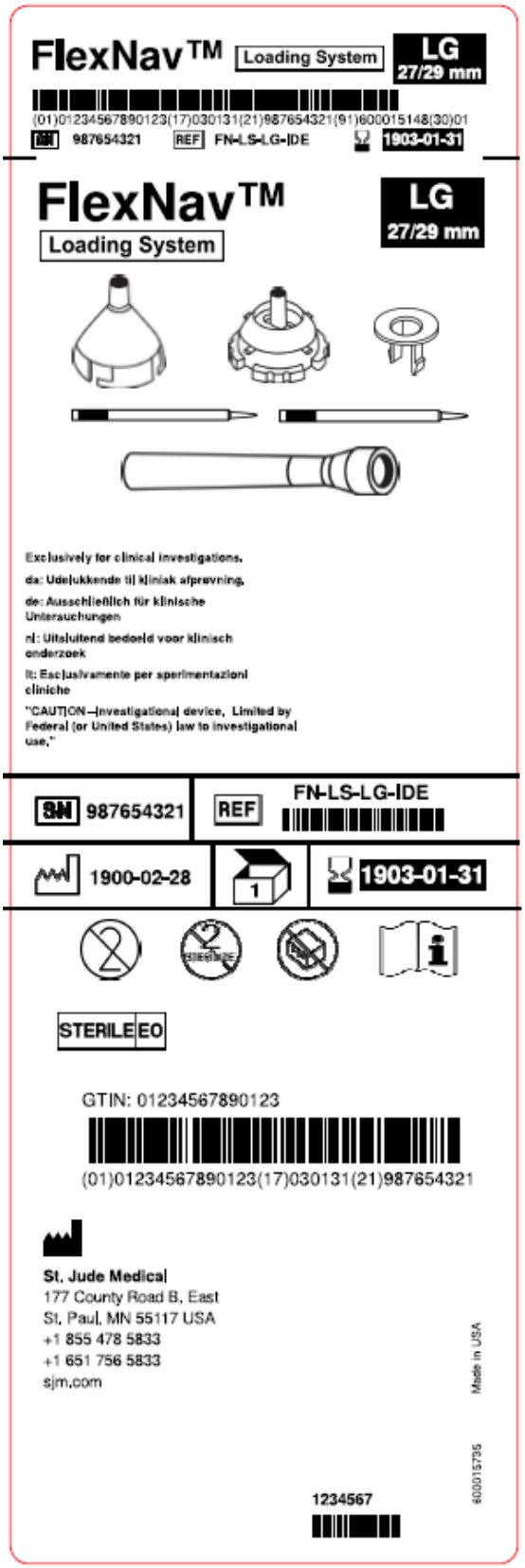

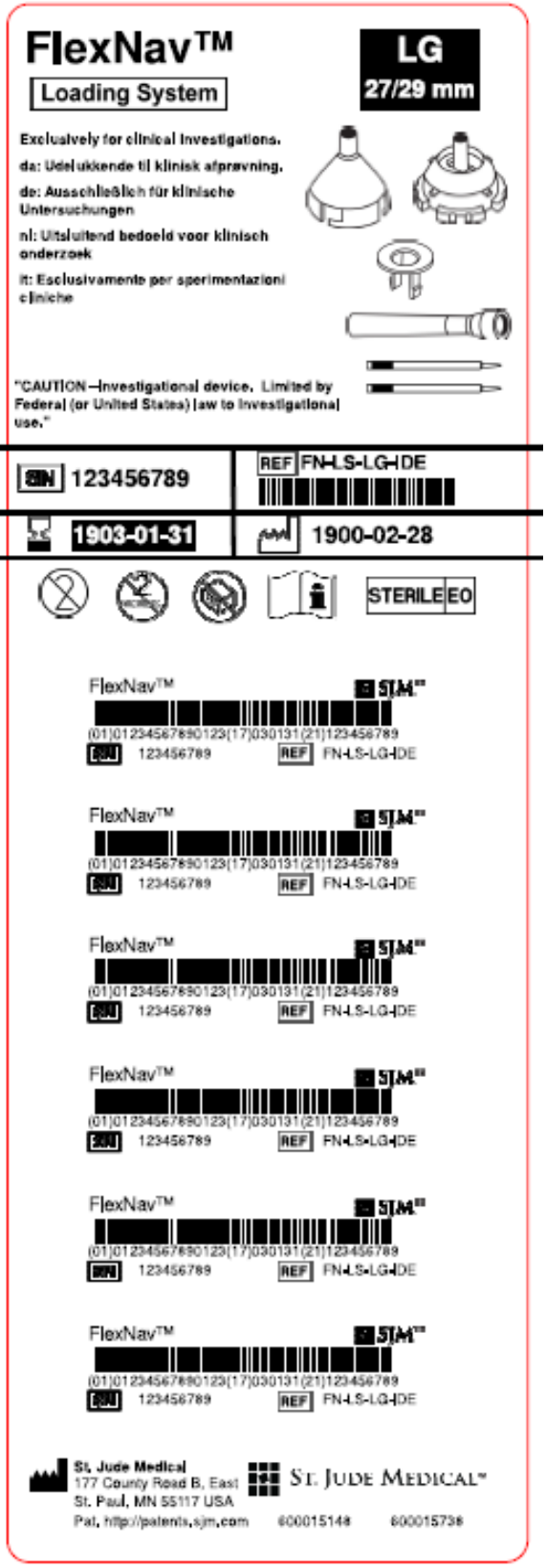

Clinical Investigation Plan

APPENDIX XXV: CASE REPORT FORMS

The case report forms will be kept under a separate cover and is available upon request from the Sponsor Clinical Project Manager for the clinical investigation.

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APPENDIX XXVI: INFORMED CONSENT FORM

The informed consent template will be kept under a separate cover and is available upon request from the Sponsor Clinical Project Manager for the clinical investigation.

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APPENDIX XXVII: MONITORING PLAN

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

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APPENDIX XXVIII: CONTACT INFORMATION

A list of site contacts can be obtained upon request from the Clinical Project Manager for the clinical investigation.

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APPENDIX XXIX: REVISION HISTORY

[redacted]

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APPENDIX XXX: CIP SUMMARY

Clinical Investigation Name and Number	[redacted] FlexNav EU CE Mark Study
Title	Assessment of the Abbott FlexNav™ Delivery System for Portico™ Transcatheter Aortic Valve Implantation in High and Extreme Risk Patients with Symptomatic Severe Aortic Stenosis
Objective(s)	The primary objective of the FlexNav EU CE Mark study is to characterize the safety of the second-generation Portico™ FlexNav™ Delivery System (referred herein as the FlexNav™ Delivery System).
Device Under Investigation	Devices under investigation in this clinical investigation include the FlexNav™ Delivery System(s) (18 F and 19 F) and FlexNav™ Loading System(s) (Small and Large), which are both approved for investigational use only. Other devices to be used in the clinical investigation include all four (4) market released St. Jude Medical (SJM) Portico™ valve sizes (23mm, 25mm, 27mm and 29mm).
Number of Subjects Required for Inclusion in Clinical Investigation	Up to 200 subjects will be enrolled in the clinical investigation, with a predefined minimum of 73 subjects required to analyze the primary safety endpoint. No site may enroll more than 20% of the maximum number of enrolled subjects (n=40).
Clinical Investigation Design	Prospective, single-arm, non-randomized, multi-center, CE Mark investigational study
Primary Endpoint(s)	The primary safety endpoint of the FlexNav EU CE Mark study is VARC II defined major vascular complications at 30 days post index procedure.
Major (Powered) Secondary Endpoints	Not applicable
Subject Follow-up	Subject data will be collected in-person at the investigational site at baseline, pre-procedure, peri-procedure, post-procedure, discharge, 30 days, 6 months and one-year from the index procedure. Echocardiographic data will be collected at screening, peri-procedure (optional), and discharge as well as 30 days, 6 months and 12-months post implantation
Inclusion Criteria	Candidates for High Risk classification must meet all the following inclusion criteria: 1. Subjects must have co-morbidities such that the local heart team concur the predicted risk of operative mortality is ≥15% or a minimum STS score of 8%. a) A candidate who does not meet the STS score criteria of ≥ 8% may be included in the study if at least one surgeon in the local heart team concludes and documents the patient's predicted risk of operative

	mortality is ≥15%. The surgeon's assessment of operative comorbidities (including frailty indices) not captured by the STS score must be documented in the study case report form as well as in the patient medical record. 2. Subject is of legal age or older for consent in the host country. 3. Subject has senile degenerative aortic valve stenosis with echo-derived criteria: mean gradient >40 mmHg or jet velocity greater than 4.0 m/s or doppler velocity index (DVI) <0.25 and an initial aortic valve area (AVA) of ≤ 1.0 cm2 (indexed EOA ≤ 0.6 cm2/m2). (Qualifying AVA baseline measurement must be within 60 days prior to informed consent). 4. Subject has symptomatic aortic stenosis as demonstrated by NYHA Functional Classification of II, III, or IV. 5. The subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site. 6. The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits. 7. Subject's aortic annulus is 19-27mm diameter as measured by CT conducted within 12 months prior to informed consent. If a CT is contraindicated and/or not possible to be obtained for certain subjects, a 3D echo and non-contrast CT of chest and abdomen/pelvis may be accepted. All candidates for Extreme Risk classification must meet # 2, 3, 4, 5, 6, 7 of the above criteria, and 8. After formal consultation with the local heart team (including at least one surgeon) it is agreed that medical factors preclude the subject from undergoing operation, based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. Specifically, the probability of death or serious, irreversible morbidity should exceed 50%. The local heart teams' consult notes shall specify the medical or anatomic factors leading to that conclusion and include a printout of the calculation of the STS score to additionally identify the risks in these patients.
Exclusion Criteria	Candidates will be excluded if any of the following conditions are present: 1. Evidence of an acute myocardial infarction (defined as: ST Segment Elevation as evidenced on 12 Lead ECG) within 30 days prior to index procedure. 2. Aortic valve is a congenital unicuspid or congenital bicuspid valve, or is non-calcified as verified by echocardiography. 3. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation 3-4+).

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	4. Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to index procedure. 5. Pre-existing prosthetic heart valve or other implant in any valve position, prosthetic ring, severe circumferential mitral annular calcification (MAC) which is continuous with calcium in the LVOT, severe (greater than 3+) mitral insufficiency, or severe mitral stenosis with pulmonary compromise. 6. Blood dyscrasias as defined: leukopenia (WBC<3000 mm3), acute anemia (Hb < 9 g/dL), thrombocytopenia (platelet count <50,000 cells/mm³). 7. History of bleeding diathesis or coagulopathy. 8. Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support. 9. Untreated clinically significant coronary artery disease requiring revascularization. 10. Hemodynamic instability requiring inotropic support or mechanical heart assistance. 11. Need for emergency surgery for any reason. 12. Hypertrophic cardiomyopathy with or without obstruction (HOCM). 13. Severe ventricular dysfunction with LVEF <20% as measured by resting echocardiogram. 14. Echocardiographic evidence of intracardiac mass, thrombus or vegetation. 15. Active peptic ulcer or upper GI bleeding within 3 months prior to index procedure. 16. A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media which cannot be adequately premedicated. 17. Recent (within 6 months prior to index procedure date) cerebrovascular accident (CVA) or a transient ischemic attack (TIA). 18. Renal insufficiency (creatinine > 3.0 mg/dL) and/or end stage renal disease requiring chronic dialysis. 19. Life expectancy < 12 months from the time of informed consent due to non-cardiac co-morbid conditions. 20. Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5cm or greater; marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding or ulcerated) or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe “unfolding” and tortuosity of the thoracic aorta. 21. Native aortic annulus size < 19 mm or > 27 mm per the baseline diagnostic imaging.

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	22. Aortic root angulation > 70°. 23. Currently participating in an investigational drug or device study. 24. Active bacterial endocarditis within 6 months prior to the index procedure. 25. Bulky calcified aortic valve leaflets in close proximity to coronary ostia. 26. Non-calcified aortic annulus. 27. Iliofemoral vessel characteristics that would preclude safe insertion of the FlexNav™ delivery system with or without an arterial introducer sheath such as severe obstructive calcification, or severe tortuosity. 28. In the judgment of the investigator, a condition that could limit a patient's ability or willingness to participate in the study, comply with study required testing and/or follow-up visits or that could impact scientific integrity of the study