Clinical Investigation Plan

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Portico NG Approval Study

Evaluation of the Navitor Transcatheter Aortic Valve in High and Extreme Risk Patients with Symptomatic Severe Aortic Stenosis

Version E_US

May 1, 2023

NCT # 04011722

Redaction Date: April 18, 2024

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[redacted]

Portico NG Approval Study

Evaluation of the Navitor Transcatheter Aortic Valve in High and Extreme Risk Patients with Symptomatic Severe Aortic Stenosis

Version Number	E_US
Date	May 1, 2023
Study Principal Investigators	[redacted]
Planned Number of Sites and Region(s)	Up to 22 sites in the United States
Clinical Investigation Type	Prospective, multi-center, international, single-arm, investigational study
Abbott Medical Expert	[redacted] Medical Director, Abbott Structural Heart
Sponsor	Abbott 5050 Nathan Lane N Plymouth, MN 55442
Electronic Data Capture Software	[redacted]
Core Laboratories	[redacted]
Clinical Events Committee Administration	[redacted]
Data Monitoring Committee Administration	[redacted]
CIP Author of Current Version	[redacted] Principal Scientist Clinical Research Structural Heart

[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 study.

Site Principal Investigator

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

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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 study.

Study Principal Investigators

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

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

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COMPLIANCE STATEMENT:

This clinical study will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki, applicable Good Clinical Practices and regulations (e.g., US 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 812, and OUS ISO14155:2020) and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the clinical study will be approved by the appropriate Institutional Review Board (IRB)/Ethics Committee (EC) of the respective investigational site and by the applicable regulatory authorities (e.g., FDA, MHRA, etc.).

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1 INTRODUCTION

This document is a clinical investigational plan (CIP) for a prospective, multi-center, international, single-arm investigational study intended to support regulatory approvals of the Portico™ NG Transcatheter Aortic Heart Valve (Portico NG, to be named Navitor™ upon commercialization) used in combination with the FlexNav™ Delivery System. As of protocol revision D, this study includes a product size extension (Navitor Titan™ valve) analyzed as a separate cohort. When the product is referenced as the Navitor Valve in this document, this language applies to both the Navitor 23-29mm valve sizes and Navitor Titan Valve. The investigational devices are intended for use in patients with symptomatic severe native aortic stenosis, who are considered high or extreme surgical risk. This clinical study is sponsored by Abbott.

The primary objective of the clinical study is to evaluate the acute safety and effectiveness of the Navitor Transcatheter Aortic Heart Valve based on the rates of all-cause mortality at 30 days and moderate or greater paravalvular leak at 30 days.

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

1.1 Background and Rationale

1.1.1 Background

Aortic stenosis (AS) remains the most common valvular disease in the Western population requiring intervention and its prevalence increases with age, estimated at approximately 2% of adults 70-80 years of age and increasing up to 9% after age 80.[1] Clinical risk factors for AS have been identified as smoking, elevated blood pressure, obesity, dyslipidemia, and altered mineral metabolism, which collectively contribute to calcific degeneration of the aortic valve.[2] Although symptoms may remain latent for a period of time, the progression of AS can lead to the narrowing of aortic valve area by up to as much as 0.3 cm^2 per year and an increase in the systolic pressure gradient by as much as 15-19 mmHg per year. Functional deterioration of the aortic valve is more prevalent in the older population and usually coupled with coronary artery disease (CAD) and chronic renal insufficiency, leading to clinical symptoms and the need for treatment.[3]

The primary goals of aortic valve replacement are to reduce the risk for mortality, which can be as high as 25% per year if left untreated, and alleviate clinical symptoms, such as angina and dyspnea. The AHA/ACC revised their guidelines in 2017 to indicate transcatheter aortic valve replacement (TAVR) as a class I indication for the treatment of aortic valve stenosis in patients at prohibitive or high surgical risk, and a reasonable alternative for patients deemed intermediate surgical risk based on evidence from recent clinical trials.[4] In a recent meta-analysis, clinical studies with newer generation TAVR devices have demonstrated low rates of early mortality (pooled estimate: 2.2%, 95% CI: 1.6%-2.8%) and disabling stroke (pooled estimate: 1.1%, 95% CI: 0.7%-1.5%) along with improved valve functional outcomes in

[1] Iung, B, Vahanian, A. Epidemiology of valvular heart disease in the adult. Nat Rev Cardiol 2011; 8:162-172.
[2] Chen HY, Engert JC, Thanassoulis G. Risk factors for valvular calcification. Curr Opin Endocrinol Diabetes Obes 2019; 26:1-7.
[3] Bonow RO, Carabello BA, Kanu C, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2006; 114(5): e84-231.
[4] Nishimura RA, Otto CM, Bonow RA, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease. J Am Coll Cardiol 2017; 70(2): 252-289.

over 10,000 patients treated, thus maintaining TAVR as a standard of care as well as providing evidence to support expansion of the treatment option to a wider patient population.[5]

Several transcatheter aortic valves are currently available in global markets and include design modifications as compared to first generation products intended to improve clinical outcomes and performance. Specifically, updated valve designs include addition of an outer skirt or wrap intended to minimize the risk of paravalvular leak (PVL) following implantation. Reported clinical outcomes demonstrate the safety of devices with these design modifications based on low rates of mortality (1.4%-4.2% at 30 days), disabling stroke (0.9%-2.8% at 30 days), and stage 2/3 acute kidney injury (1.7%-2.8% at 30 days);[6,7,8,9,10,11,12] in addition, the rates of moderate post-procedural PVL, ranging from 0% to 3.4% at 30 days, appear lower than those reported for earlier generation balloon expandable and self-expanding transcatheter aortic valves, such as CoreValve (ranging from 9% to 21%) and SAPIEN XT (reported as 6% to 13.9%).[13] Furthermore, while data from the Portico I study demonstrated a reasonably low rate of moderate PVL of 3.9% at 30 days, mild PVL was still observed in approximately two thirds of patients.[14] As the occurrence of PVL has been linked to increased mortality, there is a clinical need for devices that can reduce the risk for PVL. Overall, the results from the literature review demonstrate low rates of periprocedural mortality, adverse clinical events, and moderate/severe paravalvular leak following implantation with newer generation TAVR devices, supporting the clinical benefit of these valve design modifications.

The Portico™ Transcatheter Heart Valve is designed to be implanted in the native aortic valve without removal of the failed native valve; [redacted]. The Navitor Transcatheter Aortic Valve is a design iteration that builds upon the Portico Transcatheter Heart Valve system, which is indicated for patients with symptomatic severe native AS, who are considered high or extreme surgical risk for surgery. Key design elements of the Navitor valve includes: [redacted]

[5] Barbanti M, Buccheri S, Rodés-Cabau J, et al. Transcatheter aortic valve replacement with next generation devices: a systematic review and meta-analysis. Int J Cardiol 2017; 15(245): 83-89.
[6] Kodali S, Thourani VH, White J, et al. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. Eur Heart J. 2016; 37(28): 2252-2262.
[7] Herrmann H, Thourani VH, Kodali SK, et al. One-year clinical outcomes with SAPIEN 3 transcatheter aortic valve replacement in high-risk and inoperable patients with severe aortic stenosis. Circulation 2016; 134:130-140.
[8] Feldman TE, Reardon MJ, Rajagopal VK, et al. Effect of mechanically expanded vs self-expanding transcatheter aortic valve replacement on mortality and major adverse clinical events in high-risk patients with aortic stenosis the REPRISE III randomized clinical trial. JAMA 2018; 319(1): 27-37.
[9] Forrest JK, Mangi AA, Pompa JJ, et al. Early outcomes with the Evolut PRO repositionable self-expanding transcatheter aortic valve with pericardial wrap. J Am Coll Cardiol Intv 2018; 11: 160-168.
[10] Hellhammer K, Piayda K, Afzal S, et al. The latest evolution of the Medtronic CoreValve system in the era of transcatheter aortic valve replacement. J Am Cardiol Intv 2018; 11: 2314-2322.
[11] Meredith IT, Dumonteil N, Blackman DJ, et al. Repositionable percutaneous aortic valve implantation with the LOTUS valve: 30-day and 1-year outcomes in 250 high risk surgical patients. EuroIntervention 2017; 13(7): 788-795.
[12] Tarantini G, Lefevre T, Terkelsen CJ, et al. One-year outcomes of a European transcatheter aortic valve implantation cohort according to surgical risk: a subanalysis of the SOURCE 3 registry. Circ Cardiovasc Interv 2019; epub ahead of print.
[13] Genereux P, Head SJ, Hahn R, et al. Paravalvular leak after transcatheter aortic valve replacement: the new Achilles' heel? J Am Coll Cardiol 2013; 61: 1125-1136.
[14] Sondergaard L, Rodés-Cabau J, Hans-Peter Linke A, et al. Transcatheter Aortic Valve Replacement With a Repositionable Self-Expanding Prosthesis: the Portico-1 Trial 1-Year Outcomes. J Am Coll Cardiol 2018;72(23A):2859-2867.

[redacted]

[redacted] A larger size valve (Navitor Titan) is being added to the Navitor product line to provide a treatment option for patients with larger annulus diameters (27-30mm). Collectively, these design modifications are intended to improve clinical outcomes and ease of use for the Navitor TAVI system.

1.1.2 Rationale for Conducting this Clinical Study

The rationale for conducting the Portico NG study is to collect acute safety and effectiveness data in a high or extreme surgical risk patient population to support CE Mark and FDA approval. Accordingly, the study population will consist of high or extreme risk subjects with symptomatic, severe native AS who meet study eligibility criteria.

It is anticipated that the rate of all-cause mortality observed in this study at 30 days and the rate of moderate or greater PVL at 30 days will be comparable to rates reported for FDA approved TAVR devices studied in the same patient population (e.g., high and extreme surgical risk) reported in the literature.

2 CLINICAL STUDY OVERVIEW

2.1 Clinical Study Objective

2.1.1 Primary objective

The primary objective of this clinical study is to evaluate the acute safety and effectiveness of the Navitor Transcatheter Aortic Heart Valve as assessed by the rate of all-cause mortality at 30 days and the rate of moderate or greater paravalvular leak at 30 days. The results for the primary safety endpoint will be descriptively compared to published data on FDA approved TAVR devices, and the results for the primary effectiveness endpoint will be compared to a performance goal derived from published results of FDA approved TAVR devices studied in the same patient population (e.g., high and extreme surgical risk).

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

2.2.1 Name of the Device(s) Under Investigation

Devices in this clinical study include investigational devices labeled as the Portico NG Valve (23mm, 25mm, 27mm and 29mm sizes), FlexNav Delivery System(s) (small and large) and Portico NG Loading System(s) (small and large), all of which are currently approved for investigational use only. Navitor Titan (35 mm valve) and the Navitor Loading System – LG+ are added as a product size extension.

Model numbers for the valve, delivery system, loading system are provided below in Table 1.

Table 1: Identification of Devices Included in the Study

Device name	Model/Type	Serial/Lot Controlled	Manufacturer	Regions	Regulatory Status*
Portico NG 23mm Valve	PRT-NG-23	Serial numbered	St. Jude Medical	United States, Europe, Australia	Investigational
Portico NG 25mm Valve	PRT-NG-25	Serial numbered	St. Jude Medical	United States, Europe, Australia	Investigational

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Device name	Model/Type	Serial/Lot Controlled	Manufacturer	Regions	Regulatory Status*
Portico NG 27mm Valve	PRT-NG-27	Serial numbered	St. Jude Medical	United States, Europe, Australia	Investigational
Portico NG 29mm Valve	PRT-NG-29	Serial numbered	St. Jude Medical	United States, Europe, Australia	Investigational
Navitor Titan	PRT-NG-35	Serial numbered	Abbott	United States, Europe, Australia	Investigational
FlexNav Small Delivery System	FN-DS-SM-IDE/ FNAV-DS-SM*	Serial numbered	St. Jude Medical	United States, Europe, Australia	Investigational/ Commercial*
FlexNav Large Delivery System	FN-DS-LG-IDE/ FNAV-DS-LG*	Serial numbered	St. Jude Medical	United States, Europe, Australia	Investigational/ Commercial*
Portico NG Small Loading System	PRT-NG-LS-SM	Serial numbered	St. Jude Medical	United States, Europe, Australia	Investigational
Portico NG Large Loading System	PRT-NG-LS-LG	Serial numbered	St. Jude Medical	United States, Europe, Australia	Investigational
Navitor Loading System – LG+	PRT-NG-LS-35	Serial numbered	Abbott	United States, Europe, Australia	Investigational

Note: the regulatory status listed is current as of the version date of this CIP. Updated information will be provided, as applicable.
*Abbott anticipates the FlexNav Delivery System will receive FDA approval during this clinical study and CE Mark approval was granted in December 2019, however sites will continue to use clinically labeled product in the trial.

2.2.2 Intended Indication for Use

In accordance with the Portico NG Instructions for Use:

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

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

The Portico NG Loading System is indicated for loading the Portico NG Valve in the FlexNav Delivery System.

In accordance with the Navitor Titan Instructions for Use:

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

The FlexNav Delivery System is indicated for transfemoral or subclavian/axillary delivery of the Navitor Titan valve.

The Navitor Loading System - LG + is indicated for loading the Navitor Titan Valve in the FlexNav Delivery System.

The Navitor Valve, FlexNav Delivery System and the Navitor Loading System will be used in accordance with the Instructions for Use (IFU). Please refer to the Portico NG or Navitor Titan Transcatheter Aortic Valve Implantation System IFU for further details.

2.2.3 Description of the Device(s) Under Investigation

[redacted]

2.2.3.1 Portico NG (Navitor) Valve

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[redacted]

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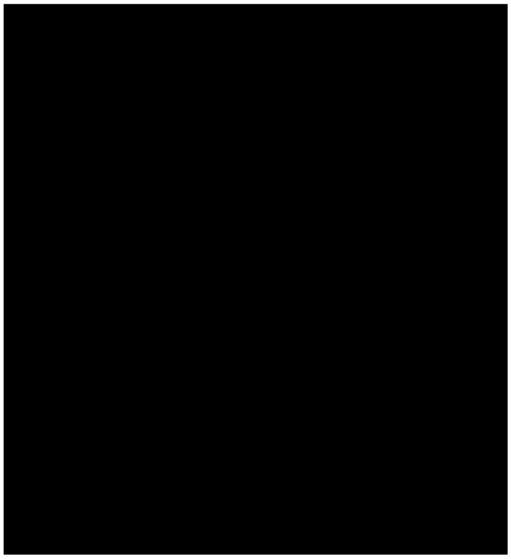

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

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2.2.3.2 Navitor Titan

[redacted]

[redacted]

2.2.3.3 FlexNav Delivery System

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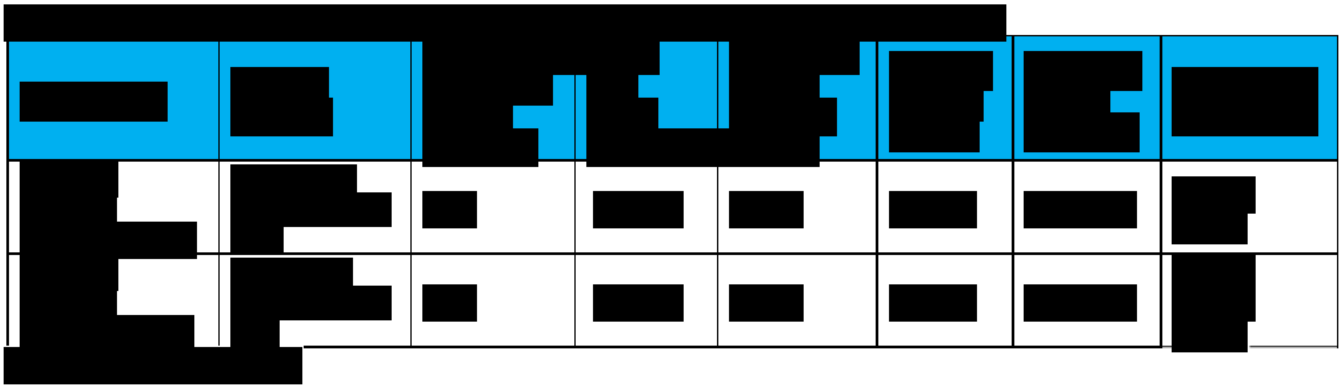
[redacted]



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[redacted]

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2.2.3.4 Portico NG (Navitor) Loading System

[redacted]

2.2.4 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 STUDY DESIGN

The Portico NG Approval study is a prospective, multi-center, international, single-arm investigational study designed in accordance with ISO standards 14155:2011 and 5840-3:2013. To be eligible for study participation, a patient must have symptomatic, severe native aortic stenosis and be considered high or extreme risk for surgical valve replacement. This clinical study will be conducted at up to twenty-two (22) sites in the United States. Implanting physicians must either have prior Portico TAVI system experience or must complete roll-in cases. Upon provision of informed consent and approval by the subject selection committee, subjects will undergo Navitor Valve implantation via a transfemoral or alternative access approach according to the site's anesthesia protocol for TAVR procedures.

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To support PMA approval of the Navitor Valve, data from a minimum of 152 subjects who undergo a Navitor implant attempt (excluding roll-ins) will be analyzed and at least 40 of the 152 analysis subjects will be implanted with a 23 mm or 25 mm Navitor valve, with at least 10 subjects receiving a 23 mm valve. To ensure sufficient number of subjects for primary endpoint analysis (described in detail in section 8.3), a total of 169 subjects may undergo a Navitor implant attempt in the PMA cohort for the 23-29mm Navitor sizes (Portico NG cohort). Furthermore, at least 50% of the subjects in the Portico NG analysis cohort (n=85 subjects) will be enrolled at sites in the United States.

A separate cohort of 60 subjects (Titan cohort) will undergo an implant attempt with the Navitor Titan valve. Data from the Titan cohort will be analyzed separately to support submissions for regulatory approval. At least 50% of the subjects in the Titan analysis cohort (n=30 subjects) will be enrolled at sites in the United States. Prospective data from Titan subjects enrolled under a separate, regional OUS protocol may be combined with US subjects to meet the minimum required sample size for the PMA submission. Importantly, both protocols enroll high and extreme surgical risk subjects with severe symptomatic AS who undergo Navitor Titan valve implantation with the FlexNav Delivery System in a premarket setting and are aligned in terms of inclusion/exclusion criteria, devices being studied, training requirements and Instructions for Use, follow-up requirements and data collection. Furthermore, subjects enrolled in the Titan cohort will undergo the same screening, baseline, procedure and follow-up assessments as the Portico NG cohort.

In addition, up to a total of 20 roll-in subjects may be enrolled and undergo a Navitor implant attempt. While there is no pre-specified minimum number of extreme risk patients required for the study, a maximum of 20% of the analysis population may be classified as extreme risk (n=33 subjects for the Portico NG cohort and n=12 for the Titan cohort) to enroll a similar patient population as the Portico IDE and FlexNav studies. No investigational site may enroll more than 20% of the total analysis population (n=33 for the Portico NG cohort and n=12 for the Titan cohort).

Subjects participating in the clinical study will be followed for a total of 5 years with data collected at screening, baseline, procedure, prior to hospital discharge, and follow-up at 30 days, 12 months and annually thereafter up to 5 years. Key assessments required at each visit are described below in Section 6. The expected duration of enrollment is 12 months, and the total duration of the clinical study is expected to be 6.5 years. Abbott plans to submit safety and effectiveness data for Navitor when a minimum of 152 analysis subjects (meeting the valve size requirements) have completed 30-day follow-up to support PMA approval in the United States; an analysis of the first 80 subjects with 30-day follow-up data will be provided to support the CE Mark submission. Global regulatory submissions for the Navitor Titan valve will be completed when 60 subjects have 30-day follow-up data. Follow-up data through 5 years will be submitted as part of a final report to respective regulatory agencies.

3.1 Clinical Study Procedures and Follow-up Schedule

Subjects will be screened for study eligibility by the investigator as well as the site's heart team per the inclusion and exclusion criteria listed in Section 5.3. Upon submission of medical history information and screening exams to the sponsor and independent core laboratory, subjects will be reviewed by an independent Subject Selection Committee to confirm anatomical suitability and surgical risk classification assigned by the site's Heart Team.

If the Subject Selection Committee determine the subject's anatomy precludes implantation of the Navitor Valve using the FlexNav Delivery System or if the Subject Selection Committee deems the assigned surgical risk classification outside of the study inclusion criteria, the subject will be exited from the study as a screen failure.

Clinical study assessments will occur at baseline, implant procedure, discharge, 30 days, 12 months and annually thereafter to 5 years post-implantation (Figure 6). It is strongly recommended the procedure be

scheduled to occur within 14 days of Subject Selection Committee approval. Clinical study assessments and the follow-up schedule will be the same for the Titan cohort as the Portico NG cohort.

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 until 5 years post implantation. At the conclusion of the 5-year follow-up, participation in the clinical study will end and subjects will be followed as part of standard of care. The clinical study has been designed to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects. Refer to the Risk Analysis section of this CIP for details.

The Flow Chart and the follow-up requirements of this clinical study are described below.

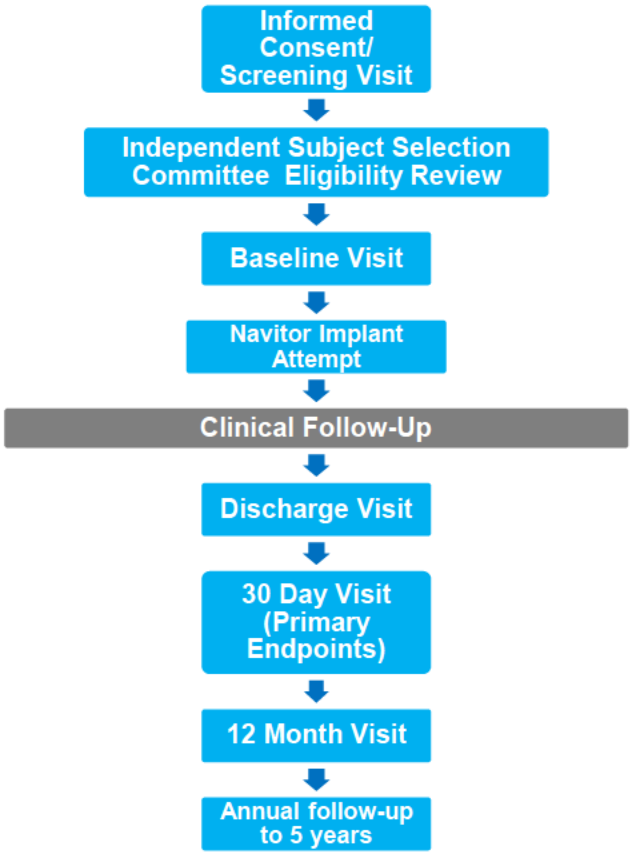

Figure 6: Clinical Study Flow Chart

3.2 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 interdisciplinary heart team at the site
- Assessment of anatomical suitability by a Computed Tomography (CT) 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
- Maintaining high rates of follow-up compliance
- Standardized administration of patient-reported outcomes assessments

These are described in further detail below.

3.2.1 Screening by an interdisciplinary Heart Team

At each investigational site, a 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 study. It is strongly recommended for the heart team to assess all available TAVR patients as potential candidates for the study.

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

An independent Computed Tomography (CT) Core Laboratory will be used for anatomical assessments of each patient prior to approval for implantation with the Navitor valve. 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 and route, and valve size selection. Use of an independent core laboratory to confirm anatomical criteria minimizes variability of critical measurements and provides an objective assessment for the SSC to review.

3.2.3 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 comorbidities) and anatomic suitability for implant in conjunction to the protocol and sizing recommendations provided in the IFU. SSC review and approval are required prior to implanting a subject with the Navitor Valve.

The composition, guiding policies, and operating procedures governing the SSC in this clinical study are further defined in the SSC Charter.

3.2.4 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 in the clinical study as defined in the CEC Charter. Pre-specified clinical events defined in the primary and descriptive endpoints will be adjudicated according to the Valve Academic Research Consortium 2 (VARC-2) definitions. The CEC will have final adjudication responsibilities for subject outcomes related to primary and descriptive outcome measures.

3.2.5 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.

The screening echocardiogram will be assessed for aortic stenosis severity (including valve hemodynamic performance parameters; aortic valve area, mean transvalvular gradient, peak velocity). Echocardiograms

collected post implantation will be assessed for hemodynamic performance and aortic regurgitation (total regurgitation and paravalvular leak (PVL) according to the Echo Core Laboratory Standard Operating Procedure Manual. Each site is responsible for performing the echocardiogram according to the core laboratory imaging protocol, forwarding the exam to the core laboratory for analysis and providing local interpretation of the echocardiogram for clinical assessment. The echocardiographic core laboratory will be responsible for completing the relevant case report forms and submitting these to the Sponsor.

3.2.6 Maintaining High Rates of 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 study, 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 study conduct.

3.2.7 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. Standardized PRO measures and assessment scales minimize bias in the reporting of clinical events and perceived patient outcomes, thus allowing for a more robust comparison to results captured from other studies utilizing these same measures.

3.3 Suspension or Early Termination of the Clinical Study

The Sponsor reserves the right to discontinue the clinical study 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 (UADE) occurs and it presents an unreasonable risk to the participating subjects
- Data monitoring committee or study principal investigator(s) makes a recommendation to stop or terminate the clinical study (such as higher frequency of anticipated adverse device effects)
- Further product development is cancelled.

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

A Principal Investigator, IRB/EC or regulatory authority may suspend or prematurely terminate participation in the clinical study at the investigational site(s) 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 study 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. Details for such subject's follow-up will be provided. The Principal Investigator or authorized designee will promptly inform the enrolled subjects at his/her site, if appropriate.

4 ENDPOINTS

4.1 Primary Endpoints and Rationale

This clinical study has two (2) co-primary endpoints. The same primary endpoints will be evaluated in both the Portico NG and Titan cohorts and analyzed independently for each cohort.

The primary safety endpoint is all-cause mortality at 30 days. The 30-day primary safety endpoint is established by VARC-2 as the most appropriate time period to assess the safety of the procedure.[15] It is also consistent with the primary safety endpoint used in the Portico TAVI System CE Mark Study (NCT01493284) and is consistent with the timepoint of assessment of the primary safety endpoint for multiple pivotal TAVR trials.[8,9,21]

The primary effectiveness endpoint is moderate or greater paravalvular leak at 30 days. The primary effectiveness endpoint will characterize the ability of the new fabric outer cuff that has been added to the exterior portion of the valve stent to optimize valve sealing and minimize paravalvular leak (PVL). Moderate or greater PVL was selected as the primary effectiveness endpoint based on the clinical relevance and associated link to increased risk of mortality. Hermann et al.[16] reported that moderate or greater PVL was associated with a statistically significant increase in the risk of mortality at 1 year as compared to none/trace (HR: 3.65, $p<0.01$) or mild PVL (HR: 3.29, $p<0.01$), thus supporting the relevance of moderate or greater PVL as the primary effectiveness endpoint. For additional details on the primary endpoints including analysis and success criteria, please refer to section 8.2 (Statistical Analyses).

4.2 Secondary Endpoint and Rationale

This clinical study has one secondary endpoint, a non-hierarchical composite of all-cause mortality, disabling stroke, life threatening bleeding, acute kidney injury (stage 3), or major vascular complications at

[15] Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol 2012; 60(15): 1438-1454

[16] Hermann H, Thourani V, Kodali S, et al. One-year clinical outcomes with SAPIEN 3 transcatheter aortic valve replacement in high-risk and inoperable patients with severe aortic stenosis. Circulation 2016;134:130-140.

30 days. The secondary endpoint is the same for the Titan cohort as the Portico NG cohort and will be analyzed independently for each cohort.

The non-hierarchal composite safety endpoint is reasonably consistent with the primary safety endpoint in the Portico US IDE pivotal trial (NCT02000115), with minor modifications to life-threatening bleeding (removed 'requiring transfusion') and acute kidney injury (removed 'requiring dialysis') to better align with recent TAVR studies of commercially approved devices in a similar patient population.[8,9]

4.3 Descriptive Endpoints

The following key outcomes (relevant to characterizing the safety profile and outcomes based on the design modifications) will be assessed as descriptive endpoints for the study (for both the Portico NG and Titan cohorts, but analyzed independently for each cohort):

- Technical device success defined as successful vascular access, delivery and deployment of the Navitor Valve; retrieval with the delivery system and correct positioning of a single valve in the proper anatomical location and the absence of procedural mortality
- All-cause mortality at 12 months from the index procedure
- Cardiovascular-related mortality at 30 days and 12 months from the index procedure
- Disabling stroke at 30 days and 12 months from the index procedure
- Life threatening and major bleeding at 30 days from the index procedure
- Acute kidney injury at 30 days from the index procedure
- Major and minor vascular complications at 30 days from the index procedure
- Permanent pacemaker insertion at 30 days and 12 months from the index procedure
- Changes in functional status from baseline to follow-up assessments at 30 days and 12 months (e.g., NYHA classification, six-minute walk test, quality of life measures)
- Paravalvular leak at discharge, 30 days and 12 months from the index procedure
- Changes in echocardiographic parameters from baseline to follow-up at 30 days and 12 months (e.g., mean effective orifice area, mean transvalvular gradient, mean peak velocity)
- Symptomatic valve thrombosis at 30 days and 12 months from the index procedure

Additional outcomes to be collected and assessed during the study:

- Myocardial infarction at 30 days and 12 months from the index procedure
- New-onset atrial fibrillation at 30 days and 12 months from the index procedure
- Coronary obstruction requiring intervention at 30 days from the index procedure
- Valve embolization during procedure, and at 30 days and 12 months from the index procedure
- Reintervention to treat valve-related dysfunction at 30 days and 12 months from the index procedure
- Total aortic valve regurgitation (transvalvular plus paravalvular leak) at discharge, 30 days and 12 months from the index procedure

5 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This clinical study will enroll male and female subjects who have symptomatic, severe native AS and are determined to be at high or extreme surgical risk. Subjects must sign and date the informed consent prior to undergoing 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 assessment by the local heart team and confirmation by the SSC. The assessment of surgical risk will include the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Risk Calculator score and the EuroSCORE II score, indices of frailty, and comorbidities not captured by the STS calculator, as described below, and based on current TAVR practice guidelines.[17,18]

Subject case review will be conducted by the SSC to determine the patient's anatomical eligibility to receive a Navitor 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 ≥7%.

Patients with an STS risk score that is <7% 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, mitral regurgitation, moderate tricuspid regurgitation, diabetes, chronic kidney disease, chronic and/or 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 >7%, aged >90 years and with a frailty index ≥ 2 will automatically be classified as extreme risk. No more than 20% of subjects (n=33 for the Portico NG cohort and n=12 for the Titan cohort) in the total analysis population or the first 80 subjects (n=16) who undergo a Navitor implant attempt may be classified as extreme risk.

[17] Otto CM, Kumbhani DJ, Alexander KP et al. 2017 ACC Expert Consensus Decision Pathway for Transcatheter Aortic Valve Replacement in the Management of Adults with Aortic Stenosis: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2017; 69(10): 1313-1346.
[18] Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the Management of Valvular Heart Disease. Eur Heart J 2017; 38(36):2739-2791.

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 study, 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 study-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)
2. Medical History (including major cardiovascular, vascular, and other coexisting medical conditions)
3. Physical Exam (including weight, heart rate, blood pressure)
4. Surgical Risk Assessment tools (STS Risk Score and EuroSCORE II)
5. New York Heart Association (NYHA) Functional Classification
6. Frailty Index Assessment (Katz index of Activates of Daily Living, Grip Strength, 5 meter walk test)
7. Forced Expiratory Volume (FEV1) Test, if clinically indicated
8. 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)
9. Lab Measurements (including CBC and Platelet count, BUN and creatinine, BNP or ProBNP, and Albumin)
10. 12 Lead Electrocardiogram (ECG)
11. Computed Tomography Scan with Angiography for chest, abdomen and pelvis: aortic root and valve annulus sizing, assessment of suitability of iliofemoral or alternate 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.
12. 3D Transesophageal Echocardiogram (TEE) if CT is contraindicated
13. 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.
14. Adverse Event Assessment

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

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 90 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.

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In case the subject does not meet all inclusion criteria or meets any of the exclusion criteria, the subject is considered a screen failure. The Principal Investigator or the delegated clinical study personnel will record the screen failure in the hospital records and on a screening log as required. 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 study. These patients will also be entered into the screening log.

Upon initial screening of eligibility of patients by the heart team, subject case reviews will be conducted by an independent SSC to confirm a patient's eligibility to receive a Navitor Valve via transfemoral or alternate access implantation (specified per the IFU). 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 implantation with the Navitor Valve and will be exited from the study as a screen failure. If the SSC does not approve the subject for study participation, the subject will be exited from the study as a screen failure and will not be counted toward the sample size of 169 analysis subjects in the Portico NG cohort or 60 analysis subjects for the Titan cohort.

Subject data will be collected following enrollment into the clinical study.

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 IRB or EC. This process will include a verbal discussion with the subject on all aspects of the clinical study that are relevant to the subject's decision to participate, such as details of clinical study procedures, anticipated benefits, and potential risks of clinical study participation. Subjects must be informed about their right to withdraw from the clinical study 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 study 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. Financial incentives will not be given to the subject. Subjects may be compensated for time and travel directly related to the participation in the clinical study. 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 IRB or 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 study-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.

Prior to consideration of live cases at congresses, the investigator must request Sponsor approval prior to performing a Live Case, which may be accepted or denied at the discretion of the Sponsor. If approved, the patient needs to sign a specific Live Case Informed Consent Form (ICF), approved by the IRB/EC and by the Sponsor, as well as by the competent authorities (e.g., FDA), as applicable.

Failure to obtain informed consent from a subject prior to clinical study enrollment should be reported to Sponsor as soon as possible and to the reviewing center's IRB/EC according to the respective reporting requirements.

If, during the clinical study, 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 Special Circumstances for Informed Consent

Consistent with the study exclusion criteria listed in section 5.3.3, incapacitated individuals, defined as persons who are mentally ill, mentally handicapped, or individuals without legal authority, are excluded from the study population. Individuals under the age of 18 or age of legal consent are excluded from the study population. Individuals unable to read or write are excluded from the study population. Pregnant or breastfeeding women are also excluded from the study population.

All other aspects of the Informed Consent process will be in compliance with Section 5.2.2. In addition, an authorization for use and disclosure of the subject's protected health information, in accordance with the Health Insurance Portability and Accountability Act (HIPAA), must be obtained from the subject or their legally acceptable representative.

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 study. If ANY of the exclusion criteria are met, the patient is excluded from the clinical study and cannot be enrolled.

5.3.2 Inclusion Criteria

5.3.2.1 General Inclusion Criteria

1. Subjects must have a Society of Thoracic Surgeons (STS) score of ≥7% OR documented heart team agreement of high or extreme risk for surgical aortic valve replacement due to frailty or co-morbidities not captured by the STS score.
2. Subject is of legal age or older for consent in the host country.
3. Subject has symptomatic aortic stenosis as demonstrated by NYHA Functional Classification of II, III, or IV.
4. 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) or Ethics Committee (EC) of the respective clinical site.
5. The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits.

5.3.2.2 Imaging Inclusion Criteria

1. Subject has senile degenerative aortic valve stenosis with echo-derived criteria, defined as: aortic valve area (AVA) of ≤ 1.0 cm^2 (or indexed EOA ≤ 0.6 cm^2/m^2) AND mean gradient ≥40 mmHg or peak jet velocity ≥ 4.0 m/s or doppler velocity index (DVI) ≤0.25. (Qualifying AVA baseline measurement must be within 90 days prior to informed consent).
2. Portico NG cohort (only): aortic annulus diameter of 19-27mm and ascending aorta diameter of 26-42 mm for the specified valve size listed in the IFU, 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 echocardiogram and non-contrast CT of chest and abdomen/pelvis may be accepted).

[redacted]

3. Titan cohort (only): aortic annulus diameter of 27-30 mm and ascending aorta diameter of 27-44 mm per the IFU, 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 echocardiogram and non-contrast CT of chest and abdomen/pelvis may be accepted).

5.3.3 Exclusion Criteria

5.3.3.1 General Exclusion Criteria

1. Pregnant or breastfeeding subjects and those who plan pregnancy during the clinical study follow-up period.
2. Need for emergency surgery for any reason.
3. Life expectancy < 12 months from the time of informed consent due to non-cardiac co-morbid conditions.
4. In the judgment of the investigator, subject presents with a medical, social or psychological condition that could limit the 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. Incapacitated individuals, defined as persons who are mentally ill, mentally handicapped, or individuals without legal authority
6. Individuals who are unable to read or write
7. Currently participating in an investigational drug or device study that has not reached the primary endpoint or may confound the results of this study

5.3.3.2 Medical Exclusion Criteria

8. Evidence of an acute myocardial infarction (defined as: ST Segment Elevation as evidenced on 12 Lead ECG) within 30 days prior to index procedure.
9. Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to index procedure.
10. Blood dyscrasias as defined: leukopenia (WBC<3000 mm^3), acute anemia (Hb < 9 g/dL), thrombocytopenia (platelet count <50,000 cells/mm^3). History of bleeding diathesis or coagulopathy.
11. Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support.
12. Untreated clinically significant coronary artery disease requiring revascularization
13. Hemodynamic instability requiring inotropic support or mechanical heart assistance
14. Hypertrophic cardiomyopathy with obstruction.
15. Active peptic ulcer or upper GI bleeding within 3 months prior to index procedure that would preclude anticoagulation
16. A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), bivalirudin or clopidogrel (Plavix), sensitivity to contrast media which cannot be adequately premedicated, or clinical condition that precludes contrast CT or TEE imaging.
17. Recent (within 6 months prior to index procedure date) cerebrovascular accident (CVA) or a transient ischemic attack (TIA).

[redacted]

18. Renal insufficiency (creatinine > 3.0 mg/dL) and/or end stage renal disease requiring chronic dialysis.
19. Sepsis or active bacterial endocarditis within 6 months prior to the index procedure.
20. Liver failure (Child-Pugh class C)
21. Untreated atrial fibrillation (e.g., patients with atrial fibrillation not on anticoagulants)
22. Severe pulmonary hypertension with pulmonary systolic pressure greater than two-thirds of systemic pressure

5.3.3.3 Imaging Exclusion Criteria

23. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation 3-4+).
24. Aortic valve is a congenital unicuspid or congenital bicuspid valve or is non-calcified as verified by echocardiography.
25. Severe ventricular dysfunction with LVEF <25% as measured by resting echocardiogram.
26. 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 left ventricular outflow tract (LVOT), severe (greater than or equal to 3+) mitral insufficiency, or severe mitral stenosis with pulmonary compromise.
27. Echocardiographic or multi-slice computed tomography (MSCT) evidence of intracardiac mass, thrombus or vegetation.
28. 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 (applicable for transfemoral access only)
29. Native aortic annulus size < 19 mm or > 27 mm per the baseline diagnostic imaging.
30. Aortic root angulation > 70°
31. Undue risk of coronary obstruction (e.g., bulky aortic valve leaflets in close proximity to coronary ostia)
32. Non-calcified aortic annulus
33. 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, protruding thrombus or severe tortuosity (applicable for transfemoral access only)
34. Severe tricuspid regurgitation or severe right ventricle dysfunction
35. Minimum access vessel diameter of <5.0mm for small FlexNav™ Delivery System and <5.5 mm for large FlexNav™ Delivery System
36. Ascending aorta anatomy that would preclude safe delivery of the valve to the native aortic annulus
37. Sinus of Valsalva anatomy that would prevent adequate coronary perfusion
38. Annulus eccentricity ratio <0.73

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5.4 Subject Enrollment

The point of a subject's enrollment in the clinical study is completion of signing the informed consent.

Consented subjects who undergo study-specific testing and are found to have met exclusion criteria or not all inclusion criteria (or if a site disagrees with the Subject Selection Committee's decision regarding risk classification) will be considered screen failures; these subjects will not be counted toward the sample size of 169 analysis subjects and will be exited from the study without further follow-up.

In addition, consented subjects who undergo study-specific testing and meet study criteria but do not undergo a Navitor implant attempt (defined as insertion of the delivery system into the vasculature) will not be counted toward the sample size of 169 analysis subjects and will be exited from the study without further follow up.

All subjects who undergo a Navitor implant attempt will be included in the analysis population or designated as roll-in as described in Section 5.4.1. Subjects who undergo a Navitor implant attempt but are not implanted with the Navitor Valve will be followed for 30 days and then exited from the study; similarly, any subject who undergoes explant of the Navitor Valve during the study follow-up period will be exited from the study 30 days following the explant procedure.

5.4.1 Roll-in Cohort

The requirement for roll-in cases will be determined based on experience of the implanting physicians. If neither of the implanting physicians have previous Portico with FlexNav clinical experience, a minimum of one roll-in subject will be required. Data from roll-in subjects will be analyzed separately as the "roll-in arm" and will not be included in the analysis population. A maximum of 20 roll-in subjects will be permitted in the study. Designation of roll-in or analysis subject will be made by the Sponsor in advance of the procedure. The combined Portico NG and Titan cohorts will not exceed a total of 20 roll-in subjects.

The total number of roll-in subjects required per site will be at the discretion of the Sponsor and will be based on the primary implanting physician's recent Portico implant experience.

5.4.2 Enrollment of Medicare Beneficiaries

This clinical study will enroll subjects with Medicare benefits and therefore conforms to all standards of Medicare coverage requirements. The Risks and Benefits section describes how all enrolled subjects, including Medicare beneficiaries, may be affected by the device under investigation.

Subjects enrolled in the clinical study are expected to be consistent with the Medicare population based on age and as such, the clinical study results are expected to be generalizable to the Medicare population.

5.4.3 Historically Under-Represented Demographic Subgroups

The Sponsor intends to ensure adequate representation of women and other traditionally under-represented demographic subgroups in this clinical study. Some barriers to participation of women and ethnic minorities in clinical studies have traditionally been:

- Lack of understanding about main obstacles to participation of such subgroups in clinical research
- Inclusion/exclusion criteria potentially not needed to define the clinical study population may unintentionally exclude specific subgroups
- Under diagnosis of disease etiologies and pathophysiology leading to lower referral rates of demographic subgroups

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- Avoidance of specific subgroups by investigators and Sponsors due to the perception that it takes more time and resources to recruit them
- Family responsibilities limiting women's ability to commit time for follow-up requirements

Historically, TAVR clinical studies performed in a similar patient population have shown the treatment population to be approximately 50% or higher female.[8,9,11] Furthermore, the traditional barriers to enrollment of women (such as fear of fetal consequences, family responsibilities that may limit the ability for time commitment to trial follow-up) are not applicable in this study due to the expected average age of the patient population (> 80 years). Additionally, aortic stenosis is prevalent in traditionally underrepresented non-white subgroups based on data collected from over 18.9 million patients treated in the U.S. from 2002 to 2012 (74.8% White, 12.6% Black, 7.3% Hispanic, 1.9% Asian or Pacific Islander, 0.6% Native American, 2.8% other ethnicity).[19]

In the Portico IDE randomized cohort, which enrolled subjects at sites in the United States and Australia, the study population was approximately 50% female and nearly 8% of non-white ethnicity. As the Portico NG study will also enroll subjects in the U.S., which has a diverse population, the proportion of females and the proportion of non-white subjects are expected to be comparable to that enrolled in the Portico IDE which had nearly identical inclusion/exclusion criteria. Therefore, there is no expected impact of the inclusion/exclusion criteria on the enrollment of females and ethnic minorities for the Portico NG study; specifically, the anatomical parameters required and devices sizes available allow for inclusion of female subjects and ethnicities with smaller anatomical measurements (i.e., small annulus diameters), and medical exclusion criteria are translatable to a general TAVR patient population deemed high or extreme risk for surgical valve replacement without any gender or racial bias. For the Titan cohort, the same principles apply, with the exception that due to the large annulus use range, it is anticipated there will be a larger proportion of male subjects as observed in clinical studies for FDA approved large valve devices (i.e., Evolut R 34mm).[20]

The Sponsor will take the following steps to ensure adequate representation of women and racial or ethnic minorities in this clinical study:

- The Sponsor will provide training to investigational site personnel to ensure adequate representation of these demographic subgroups
- The Sponsor will regularly review enrollment data to investigate whether there is under-representation of these demographic subgroups
- The Sponsor will regularly review withdrawal rates for under-represented subgroups and compare these rates with that in the overall clinical study population
- As appropriate and necessary, the Sponsor will retrain sites on the importance of recruiting and retaining subjects in the clinical study
- The Sponsor will approach sites without bias or consideration for specific demographic subgroups

[19] Beydoun HA, Beydoun MA, Liung H, et al. Sex, Race, and Socioeconomic Disparities in Patients With Aortic Stenosis (from a Nationwide Inpatient Sample). Am J Cardiol 118 (6): 860-865.
[20] Tang GHL, Reardon MJ, Kodali SK, et al. Comparison of Clinical and Echocardiographic Outcomes After Transcatheter Aortic Valve Implantation with 31-mm CoreValve versus 34-mm Evolut R Bioprostheses from the STS/ACC TVT Registry. Am J Cardiol 2019;124:1091-1098.

- The Sponsor will have informed consent materials in alternative languages and will work with sites and IRBs/ECs on recruitment materials

5.5 Subject Withdrawal

Each enrolled subject shall remain in the clinical study until completion of the required follow-up period; however, a subject's participation in any clinical study 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 3.3.

The Sponsor must be notified by the site of subject's discontinuation as well as the reason(s) for subject discontinuation. Investigators must also report subject discontinuations to their respective IRB/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 study. However, if a subject withdraws from the study 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 study.

5.5.1 Lost-to-Follow-up

If the subject misses two consecutive scheduled follow-up visits 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 study cardiologist or relative will be considered as subject contact for the purpose of collecting vital status information. The center shall retain records of the contact.

5.6 Number of Subjects

A total of 169 analysis subjects (up to a total of 189 subjects including roll-ins) will undergo an attempted Navitor implant in order to analyze the primary endpoints for the Portico NG cohort. Furthermore, a total of 60 analysis subjects will undergo an attempted Navitor Titan implant for the PMA submission. To ensure

enrollment balance across study sites, no site may enroll more than 20% of the analysis population (n=33 for the Portico NG cohort and n=12 for the Titan cohort).

5.7 Duration of the Clinical Study

The expected duration of each subject's participation in the clinical study is 5 years, including the scheduled visits and data collection as listed in Section 6.5.5. All enrolled subjects will be followed until their 5-year visit, subject withdrawal, or study closure, whichever occurs first. Subjects that are exited from the study after providing Informed Consent but prior to enrollment in the study will not require any additional follow-up.

Overall, the total duration of the clinical study is expected to be approximately [redacted] years, based on an expected enrollment period of 12 months, 5 years of follow-up for each subject, and approximately 6 months for study closure activities and results reporting.

6 TREATMENT AND EVALUATION OF ENDPOINTS

6.1 Baseline

For subjects that have successfully completed screening, scheduled visits will be performed in the following order: Baseline, Index Procedure, Discharge, 30 days,12 months, and annual follow-up assessments to 5 years.

6.1.1 Baseline Assessments

Subjects who are deemed eligible for implantation of a Navitor Valve using the FlexNav Delivery System will undergo a baseline visit prior to the procedure (may occur on the day of, procedure prior to the implant procedure).

The following baseline assessments will be performed for all subjects prior to the index procedure.

1. Chest X-ray (if standard of care)
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)
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/Anticoagulant 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 Tests

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 Procedures Involved in the Use of the Device Under Investigation

Please refer to IFU for instructions on handling and preparation of the Navitor Valve, FlexNav Delivery System, Navitor Loading System. All Investigators must read and understand the IFU and Investigator Brochure, as applicable.

6.2.2 Procedural Anticoagulation

Anticoagulation use during the procedure is left to the physician's discretion or should be established as with any other transcatheter 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 Implant Procedure

It is recommended (required for US sites per the Medicare National Coverage Decision) that the heart team's interventional cardiologist(s) and cardiac surgeon(s) jointly participate in the intra-operative technical aspects of the TAVR procedure.

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

A Navitor Valve may be implanted in a subject who has signed the ICF and Data Protection Form (if applicable) and approved by the SSC. 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.

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 capillary wedge pressure (PCWP) immediately pre- and post implant
4. Cardiac rhythm monitoring and rhythm changes throughout the duration of the procedure

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 XIII for a description of standardized methods for measuring aortic regurgitation according to VARC-2 criteria and instructions for assessing implant depth in the LVOT.

During the procedure, the implanting physician may determine implantation of the Navitor 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 be considered a procedural exclusion.

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

All the required information must be recorded on the applicable CRF. Following the procedure, the FlexNav Delivery System and Navitor Loading System should be securely disposed as per hospital requirements for hazardous materials. If there are any concerns noted with the Navitor Valve, FlexNav Delivery System, or the Navitor Loading System during the procedure, these products should be returned to the Sponsor for evaluation.

6.2.4 Post-procedure Imaging

Subjects implanted with a Navitor Valve will be required to undergo an echocardiogram between 24 and 48 hours after the procedure.

6.3 Post–procedure (In-hospital)

6.3.1 Post-procedure Laboratory Tests

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

1. Troponin, or CK / CK-MB should be collected between approximately 12 and 24 hours after procedure, between approximately 36 and 48 hours after the procedure, 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 Assessments

The discharge visit will take place at the time of hospital discharge or at 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. Modified Rankin Scale (mRS)
3. NIH Stroke Scale (NIHSS)

4. Barthel Index
5. Echocardiogram (if not performed during the post procedure testing within 48 hours after procedure)
6. 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)
7. Cardiovascular medications documentation
8. Adverse events assessment
9. 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 Assessments

6.5.1 Follow-up Medications

Medications administered to subjects during the follow-up period will be at the physician's discretion.

6.5.2 Follow-up for All Subjects

Required clinical follow-up will be performed at the following intervals for all subjects who were implanted with a Navitor valve:

- 30 days (+21 days) follow-up site visit (visit must be conducted even if subject is in hospital)
- 12 months (365 days -30/+45 days) follow up site visit
- Annual follow-up at 2, 3, 4 and 5 years (±60 days)

Subjects with a Navitor implant attempt that did not have a Navitor Valve implanted will only be required to complete the 30-day follow-up visit prior to exiting the study.

Dates for 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 by the same individual who performed the baseline tests whenever possible.

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. If necessary, in-home assessment by an authorized health care representative (e.g. Hawthorne Effect) may be conducted. 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. Any missed testing will be considered a protocol deviation.

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. If medically indicated, a subject may undergo additional imaging per standard of

care (e.g., contrast CT scan or TEE) to evaluate device specific findings (e.g., valve thrombosis); if performed, this additional imaging will be sent to the Sponsor for analysis.

6.5.2.1 30-day Follow-Up

The 30-day follow-up visit will occur 30 days (+21 days) post-index procedure, and will include the following assessments:

1. Physical exam (weight, heart rate, blood pressure)
2. Modified Rankin Scale (mRS)
3. NIH Stroke Scale (NIHSS)
4. Barthel Index
5. Echocardiography
6. 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)
7. 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)
8. NYHA Functional Classification
9. Frailty Index Assessment (Katz Index of Activities of Daily Living, Grip Strength, 5 meter walk test)
10. Quality of Life Assessment (SF-36)
11. MMSE-2:SV
12. Six Minute Walk Test (6MWT)
13. Cardiovascular medications documentation
14. Adverse events assessment

6.5.2.2 12-Month Follow-Up

The 12-month follow-up visit will take place at 12 months (365 days -30 /+45 days) post-index procedure, and will include the following assessments:

1. Physical exam (weight, heart rate, blood pressure)
2. Modified Rankin Scale (mRS)
3. NIH Stroke Scale (NIHSS)
4. Barthel Index
5. Echocardiography
6. 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)
7. 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)

8. NYHA Functional Classification
9. Frailty Index Assessment (Katz Index of Activities of Daily Living, Grip Strength, 5 meter walk test)
10. Quality of Life Assessment (SF-36)
11. MMSE-2:SV
12. Six Minute Walk Test (6MWT)
13. Cardiovascular medications documentation
14. Adverse events assessment

6.5.2.3 Annual Follow-up

The following data should be collected at years 2, 3, 4 and 5 years (± 60 days) post index procedure (note: remote follow-up either in-home or by phone may be conducted):

1. Physical exam (if an in-person office visit is conducted)
2. NYHA Functional Classification (if an in-person office visit is conducted)
3. Cardiovascular medications
4. Adverse event assessment
5. Modified Rankin Stroke Scale (if an in-person office visit is conducted)
6. Echocardiography (required at 2-year, 4-year, and 5-year follow-up visits)

Note: if the 12-month or annual follow-up visits are conducted prior to the nominal due date (e.g., before day 365 for the 12-month visit), it may be requested to conduct a vitality status check to document the subject's status prior to the next follow-up visit.

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 (e.g., trans-ischemic attack (TIA), stroke, or encephalopathy) within 2 years post implantation, 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 X for a copy of the Modified Rankin Score and APPENDIX XI for a copy of the NIH Stroke Scale.

6.5.3.2 Unscheduled Follow-Up Visits Including an Echocardiographic Assessment

All echocardiograms performed as part of an unscheduled visit will be analyzed by the echocardiographic core laboratory. See Section 3.2.5 for detailed information on site responsibility.

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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 study:

- SF-36
- Mini-Mental State Examination (MMSE-2)
- New York Heart Association Functional Classification
- Barthel Index

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 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 VII for the sample questionnaire.

6.5.4.2 Mini-Mental State Examination-2

The Mini Mental State Examination-2 (MMSE-2) is a validated, 11-question tool used to assess mental status. The MMSE-2 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-2 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 VIII for the sample questionnaire.

6.5.4.3 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 NYHA 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 VI for the sample questionnaire.

6.5.4.4 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 approximately 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 IX for the sample questionnaire.

6.5.5 Schedule of Events

Table 5 provides a tabulated schedule of the study-required activities and standard of care data collection in the clinical study.

Table 5: Table of Assessments

Study Activity	Screening	Baseline	Procedure	Discharge	30 days [+21 days]	12 months[1] [-30/+45 days]	Annual visits (2 through 5 years) [±60 days]
Subject Interview and Informed Consent	X						
Demographics	X						
Medical History	X						
Physical Exam	X			X	X	X	X[9]
NYHA Classification	X				X	X	X[9]
Cardiovascular Medications documentation		X		X	X	X	X
Coronary and Aortic Angiogram (with runoff if clinically indicated)	X (within 12 months prior to consent)						
National Institute of Health Stroke Scale (NIHSS)		X		X	X	X	
Modified Rankin Scale (mRS)		X		X	X	X	X[9]
Barthel Index		X		X	X	X	
MMSE-2:SV		X			X	X	
Neurological Assessment	A neurological assessment must be performed at 90 days (±14 days) from the date of a suspected neurological event within 2 years post implantation						
Surgical Risk Assessment (STS, EuroSCORE II)	X						
Six Minute Walk Test		X			X	X	
Frailty Index (Katz Index of ADLs, Grip strength, 5 m walk)	X				X	X	
FEV1	X (if clinically indicated)						
Non-Invasive Tests							
12 lead Electrocardiogram (ECG)[2]	X			X	X	X	
Cardiac rhythm monitoring			X				
Echocardiogram	X		X[3]	X[4]	X	X	X[10]
Angiogram			X				
3D Transesophageal Echocardiogram (TEE)	X[5] (if CT is contraindicated) TEE is also						

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Study Activity	Screening	Baseline	Procedure	Discharge	30 days [+21 days]	12 months[1] [-30/+45 days]	Annual visits (2 through 5 years) [±60 days]
	recommended after adverse events of ischemic stroke and myocardial infarction.						
CT Scan with Angiography for chest, abdomen and pelvis	X (within 12 months of consent)						
Chest X-Ray		X					
Quality of Life Measures							
SF-36		X			X	X	
Lab Measurements							
CBC and Platelet count	X			X	X	X	
BUN and Creatinine	X		X[6]	X	X	X	
BNP *or* ProBNP	X				X	X	
INR (if subject is on Coumadin or Warfarin[8])		X			X	X	
Troponin *or* CK / CK-MB		X	X[7]	(X)	X	X	
Albumin (for Frailty Index)	X				X	X	
Other							
Adverse Event Assessment	X	X	X	X	X	X	X
Deviation	(X)	(X)	(X)	(X)	(X)	(X)	(X)
Device Deficiency			(X)	(X)	(X)	(X)	(X)
Withdrawal			(X)	(X)	(X)	(X)	(X)
Death	(X)	(X)	(X)	(X)	(X)	(X)	(X)

[1] In the event a 12 month visit per the requirements in the clinical investigational plan is not completed, the site may call the subject to document survival.
[2]For subjects receiving a new permanent pacemaker, ECG should be completed showing the underlying rhythm as well as the current pacing programming.
[3]Copy of echocardiographic exam to be stored at the site and available to the Sponsor upon request.
[4]To be done within 24-48 hours after procedure, or as close to discharge as possible (but no more than 7 days after procedure).
[5]If CT is contraindicated and/or not possible to be obtained for certain subjects, a 3D TEE and non-contrast CT of chest and abdomen/pelvis may be accepted if approved by the subject selection committee.
*[6]To be collected within 72 hours **before** index procedure and within 72 hours **after** index procedure*
*[7]To be collected within 72 hours **before** index procedure and approximately 12-24 hours **after** the procedure, approximately 36-48 hours after the procedure, and at approximately 72 hours (or at discharge, if patient is discharged prior to 72 hours post procedure) to be consistent with VARC II guidelines.*
[8]Subjects may take other anticoagulants/vitamin K antagonists in lieu of warfarin
[9]Only required if an in-person office visit is conducted
[10]Required at all annual follow-up visits except for the 3-year visit
(X) indicates if applicable

6.6 Requirement for Core Laboratories

Independent core laboratories will be utilized for evaluating CT scans and echocardiograms collected in the clinical study. Each investigational site will submit CT scans and echocardiograms to the respective core laboratories for evaluation. The core laboratories will provide the study required interpretation and documentation of each data submission according to their Standard Operating Procedures and study specific charter.

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 the data provided by the core laboratories in data analyses, where measurements were collected by the core laboratory. If the core laboratory determines that the imaging exam is 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 study 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, in the context of a clinical investigation, whether or not related to the investigational medical device.

As part of ISO14155 Section 3.2, the adverse event definition has the following notes:

Note 1: This definition includes events related to the investigational medical device or the comparator.

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

Note 3: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

7.1.2 Serious Adverse Event

Serious adverse event is an AE that led to any of the following:

a) Death,

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

   1. Life-threatening illness or injury,
   2. Permanent impairment of a body structure or a body function,
   3. Hospitalization or prolongation of patient hospitalization,
   4. Medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function,
   5. Chronic disease

c) Fetal distress, fetal death or a congenital physical or mental impairment or birth defect.

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

7.1.3 Device Deficiency

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

Note 1: The definition includes device deficiencies related to investigational medical device or the comparator.

Note 2: Cyber-security incidents related to the investigational product shall be reported as device deficiencies.

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

7.2 Device Relationship

Determination of whether there is a reasonable possibility that an investigational product or device under investigation caused or contributed to an AE is to be determined by the Investigator and recorded on the appropriate CRF form. Determination should be based on 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

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.

7.2.2 Serious Health Threat

Serious Health Threat is a signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons
Note: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

7.3 Adverse Event and Device Deficiency Reporting

7.3.1 Adverse Event Reporting

Safety surveillance and reporting starts as soon as the subject is enrolled in the clinical study. Safety surveillance and reporting will continue until the last follow-up visit has been performed, the subject is deceased, the subject concludes participation in the clinical study or the subject withdraws from the

clinical study. 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.

For the purposes of this study, the following event types will be reported:

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. All Device Deficiencies

Cardiac and non-cardiac related abnormal laboratory values will not be considered AEs unless:

1. the investigator determined that the value is clinically significant,
2. the abnormal lab value required intervention, or
3. the abnormal lab value required subject withdrawal from the clinical study.

An offline form will be made available to allow the investigator to report SAEs in the event the entry cannot be made in the Electronic Data Capture (EDC). This does not replace the EDC reporting system. All information must still be entered in the EDC system as soon as feasible.

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 above.

The date the site 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 IRB/EC according to the institution's IRB/EC reporting requirements.

7.3.2 Unanticipated Serious Adverse Device Effect Reporting to Sponsor and IRB

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 IRB/EC per IRB/EC requirements.

7.3.3 Device Deficiency Reporting

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 IRB/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 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.

8 STATISTICAL CONSIDERATIONS

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

8.1 Analysis Population

The analysis population will include all subjects in whom a Navitor implant is attempted, excluding roll-in cases. A Navitor implant attempt is defined as insertion of the FlexNav Delivery System (loaded with a Navitor Valve) into the subject's vasculature.

8.2 Statistical Analyses

8.2.1 Primary Safety Endpoint Analysis (Portico NG cohort)

The primary safety endpoint for the Portico NG cohort is all-cause mortality at 30 days post index procedure.

The proportion of Portico NG subjects experiencing a primary safety endpoint will be estimated from the binomial model. The 95% confidence intervals will be calculated using the exact Clopper–Pearson method. The estimated primary safety endpoint rate at 30 days will be descriptively compared with the all-cause mortality rates (and 95% confidence intervals) of FDA approved TAVR devices studied in the same

patient population (e.g., high and extreme risk), [redacted], and additional published data on high and extreme surgical risk subjects available at the time of PMA submission.

[redacted]

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

The analysis population will include subjects who undergo a Navitor implant attempt that is described in Section 8.1.

8.2.2 Primary Safety Endpoint Analysis (Titan cohort)

The primary safety endpoint for the Titan cohort is all-cause mortality at 30 days post index procedure.

The proportion of Titan subjects experiencing a primary safety endpoint will be estimated from the binomial model. The 95% confidence intervals will be calculated using the exact Clopper–Pearson method. The estimated primary safety endpoint rate at 30 days will be descriptively compared with the all-cause mortality rates (and 95% confidence intervals) of FDA approved large valve TAVR devices studied in the same patient population (e.g., high and extreme risk) as well as results from the Portico NG cohort.

The analysis population will include subjects who undergo a Navitor Titan implant attempt that is described in Section 8.1.

[redacted]

8.2.3 Primary Effectiveness Endpoint Analysis (Portico NG cohort)

The primary effectiveness endpoint for the Portico NG cohort is moderate or greater paravalvular leak at 30 days.

Let π be the proportion of Portico NG subjects who experience a primary effectiveness endpoint event at 30 days. The following hypothesis will be tested:

H_0: $\pi \geq 8.5\%$
H_a: $\pi < 8.5\%$

π will be estimated as a binomial proportion. The hypothesis will be tested at the 0.05 significance level and the null hypothesis will be rejected if the 95% upper confidence bound (UCB) for the proportion, π, is less than the performance goal of 8.5%. [redacted]

The results for the primary effectiveness endpoint will be considered successful if the null hypothesis is rejected.

[redacted]

[redacted]

[redacted]

[redacted]

The analysis population will include subjects who undergo a Navitor implant attempt that is described in Section 8.1 and who have 30-day paravalvular leak status as determined by the echocardiography core laboratory.

8.2.4 Primary Effectiveness Endpoint Analysis (Titan cohort)

The primary effectiveness endpoint for the Titan cohort is moderate or greater PVL at 30 days post index procedure.

The proportion of Titan subjects experiencing a primary effectiveness endpoint will be estimated from the binomial model. The 95% confidence intervals will be calculated using the exact Clopper–Pearson method. The estimated primary effectiveness endpoint rate at 30 days will be descriptively compared with 30-day moderate or greater PVL rates (and 95% confidence intervals) of FDA approved large valve TAVR devices studied in the same patient population (e.g., high and extreme risk) as well as results from the Portico NG cohort.

The analysis population will include subjects who undergo a Navitor Titan implant attempt that is described in Section 8.1 and who have 30-day paravalvular leak status as determined by the echocardiography core laboratory.

8.2.5 Secondary Endpoint Analysis

The secondary endpoint is a non-hierarchical composite of all-cause mortality, disabling stroke, life threatening bleeding, acute kidney injury (stage 3), or major vascular complications at 30 days. This endpoint will be analyzed for both the Portico NG and Titan cohorts separately.

The proportion of subjects experiencing a secondary endpoint will be estimated from the binomial model. The 95% confidence intervals will be calculated using the exact Clopper–Pearson method. The estimated secondary endpoint rate at 30 days will be descriptively compared with rates observed with FDA approved TAVR devices studied in the same patient population (e.g., high and extreme risk), including the observed rates and 95% confidence intervals from published sources shown in Table 8 below and data from FDA approved devices available at the time of PMA submission.

[redacted]

Clinical Investigation Plan

[redacted]

[redacted]

8.3 Sample Size Calculation and Assumptions

The total sample size required for the Portico NG cohort (to ensure adequate number of subjects for analysis of the primary endpoints) is 169 subjects as described in more detail below.

[redacted]

For the Titan cohort, a total of 60 analysis provides an adequate sample size to descriptively compare to results from competitor studies of a larger valve size (e.g., Evolut R 34mm) and the Portico NG cohort.

[redacted]

8.4 Timing of Analysis

The analysis for the PMA submission will be conducted on a dataset locked after a minimum of 152 analysis subjects in the Portico NG cohort have had a 30-day study visit and have PVL data assessed by the echocardiography core laboratory. As stated in section 3, an analysis of the first 80 subjects (with a Navitor implant attempt) with 30-day follow-up data will be provided to support the CE Mark submission.

Data from the Titan cohort will be analyzed independently from the Portico NG cohort. The analysis for the Titan cohort will be conducted on a dataset locked after 60 analysis subjects have had a 30-day study visit and have PVL data assessed by the echocardiography core laboratory, excluding any subjects who die or are lost to follow-up within 30 days.

8.5 Subgroup Analysis

No subgroup analyses are planned for this clinical study.

8.6 Multiplicity

The clinical study has two (2) co-primary endpoints with hypothesis testing only for the primary effectiveness endpoint in the Portico NG cohort. Therefore, there is no multiplicity adjustment planned in this clinical study.

8.7 Pooling Strategy

Additional information regarding the planned pooling strategy in this clinical study will be maintained in a separate Statistical Analysis Plan (SAP).

8.8 Procedures for Accounting for Missing Data

There is no plan to impute missing data for this clinical study.

[redacted]

8.9 Planned Interim Analysis

No interim analyses are planned for this clinical study.

8.10 Statistical Criteria for Termination

There are no statistical criteria for termination of this clinical study.

8.11 Success Criteria

Study success will be determined independently for the Portico NG and Titan cohorts. The Portico NG cohort will be considered successful if the rate for the primary safety endpoint (all-cause mortality within 30 days) is within expected ranges as compared to previous commercially approved devices studied in the same patient population (e.g., high and extreme surgical risk) and the null hypothesis is rejected for the primary effectiveness endpoint (moderate or greater PVL at 30 days).

The Titan cohort will be considered successful if three (3) or fewer deaths occur within 30 days of the index procedure in 60 analysis subjects.

8.12 Deviations from Statistical Plan

Any major changes to the statistical plan will be documented in an amendment to the statistical plan. Less significant changes to the planned analyses will be documented in the final report.

9 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

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

Subjects providing informed consent are agreeing to allow clinical study monitors or regulatory authorities including foreign countries to review, in confidence, any records identifying the subjects in this clinical study. 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

The Sponsor will select investigators qualified by training and experience to participate in the clinical study. Sites will be selected based upon review of a recent site assessment, if applicable, and the qualifications of the investigators who will participate in the clinical study. A list of the participating sites will be provided upon request.

10.2 Site Principal Investigator Responsibilities

The role of the Site Principal Investigator is to implement, oversee the management of the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation. The principal investigator shall support monitoring and reporting to IRB/EC and local competent authorities as necessary, throughout the conduct of the clinical investigation.

Clinical Investigation Plan

The principal investigator is responsible for ensuring adequate training and qualification of the investigation site team and for maintaining oversight of their activities. The principal investigator may

delegate tasks to members of the investigation site team but retains responsibility for the clinical investigation. This also applies when activities are outsourced to an external organization by the principal investigator in which case he/she shall exercise oversight to ensure the integrity of all tasks performed and any data generated by this external organization.

10.3 Clinical Study Finances and Agreements

The clinical study will be financed by Abbott. Investigational sites will be compensated by Abbott for participation in the clinical study per the conditions of agreement between the Sponsor and the Investigational site.

10.4 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 IRB/EC or equivalent committee of the CIP amendment (administrative changes) or obtaining IRB's/EC's approval of the CIP amendment (changes in subject care or safety), according to the instructions provided by the Sponsor with the CIP amendment.

The Sponsor will submit the CIP Amendment to regulatory bodies per applicable regulation and await regulatory approval before implementing the CIP amendment.

Acknowledgement/approval by the IRB/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.

10.5 Training

10.5.1 Site Training

Investigators and clinical study personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit, or other appropriate training sessions. Over-the-phone or self-training may take place as required. Training of Investigators and clinical study personnel will include, but is not limited to, the CIP requirements, investigational device usage, electronic case report form completion and clinical study personnel responsibilities. All Investigators and clinical study personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Prior to signing the training log, Investigators and clinical study personnel must not perform any CIP-related activities that are not considered standard of care at the site.

10.5.2 Training Required for the Use of the Device

Training on the Navitor TAVI System will be conducted with implanting physicians prior to their first case in accordance with the appropriate training plan(s). Proof of training records will be controlled documents managed by the Sponsor in an appropriate archiving system. If updates are made to the training plan, physicians will be required to complete the revised training plan prior to their next case.

10.6 Monitoring

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

Clinical Investigation Plan

Prior to initiating any procedure, the Sponsor monitor (or delegate) will ensure that the following criteria are met:

- The investigator understands and accepts the obligation to conduct the clinical study according to the CIP and applicable regulations, and has signed the Investigator Agreement or Clinical Trial Agreement
- The Investigator and his/her staff should have sufficient time and facilities to conduct the clinical study and should have access to an adequate number of appropriate subjects to conduct the clinical study.
- Source documentation (including original medical records) must be available to substantiate proper informed consent procedures, adherence to CIP procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information.
- The Investigator/site will permit access to such records. A monitoring visit sign-in log will be maintained at the site. The Investigator will agree to dedicate an adequate amount of time to the monitoring process. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator will provide the monitor with a suitable working environment for review of clinical study-related documents.

10.7 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 determine the cause of deviations, implement corrective actions and inform their IRB or EC of all CIP deviations in accordance with their specific IRB or EC 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 study 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 study.

10.8 Quality Assurance Audit

A Sponsor representative or designee may request access to all clinical study 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 study, 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 study (e.g., Form FDA 483, Inspectional Observations, Warning Letters, Inspection Reports, etc.). Sponsor may provide any needed assistance in responding to regulatory audits.

10.9 Sponsor Auditing

Sponsor audits may be conducted for the clinical study in accordance with the below requirements:

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.

10.10 Committees

The clinical study will utilize the following separate committees:

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

10.10.1 Subject Selection Committee

The Subject Selection Committee (SSC) will consist of cardiac surgeons and cardiac interventionalists who will be responsible for ensuring subject eligibility in the clinical study according to the CIP. After Informed Consent is obtained and study eligibility is confirmed by the local heart team, subject data will be reviewed by the SSC to confirm anatomic suitability for the Navitor 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 a Navitor implant attempt in the study.

10.10.2 Data Monitoring Committee (DMC)

The Data Monitoring Committee (DMC) is an independent multidisciplinary group restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. The DMC will be composed of at least two physicians with experience relevant to the clinical study (e.g., cardiologist, cardiac surgeon, neurologist) and a biostatistician.

The DMC will serve in an advisory role to the Sponsor to ensure safety by reviewing cumulative data from the clinical study at prescribed intervals for the purpose of safeguarding the interests of enrolled subjects and those patients yet to be enrolled, as well as the continuing validity and scientific merit of the clinical

study. The composition, frequency of the meetings and the statistical monitoring guidelines are described in detail in the DMC charter.

The DMC may consider a recommendation for modifications or termination of the clinical study based on any perceived safety concerns regardless of statistical significance. The recommendations of the DMC are not binding, and all final decisions related to clinical study modifications rest with the Sponsor.

10.10.3 Clinical Events Committee (CEC)

The Clinical Events Committee (CEC) is an independent adjudication body comprised of qualified physicians (e.g., an interventional cardiologist, cardiothoracic surgeon, and a neurologist) who are not participants in the clinical study. The CEC will review and have final adjudication responsibilities for pre-specified adverse events reported by investigators or identified by Safety personnel for the clinical study as defined in the CEC Standards of Operation Charter and according to definitions provided in this CIP.

10.10.4 Publication and Steering Committee

A Steering and Publication Committee may be established to oversee the clinical study and its publications, including publication planning and authorship determinations as applicable. 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 study generated data. The committee will also review all external requests for accessing clinical study-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 study.

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 study, 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.

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

11.1 Protection of Personally Identifiable Information

The Sponsor respects and protects personally identifiable information collected or maintained for this clinical study.

Clinical Investigation Plan

The Sponsor implements technical and physical access controls to ensure that Personal Information is accessible only to and processed only on a 'need to know' basis, including periodic review of access rights, and revocation of access when an individual's employment is terminated or the individual transitions to a role that does not require access to Personal Information, and appropriate restrictions on physical access to premises, facilities, equipment, and records containing Personal Information.

The Sponsor requires the investigational sites to transfer into Sponsor's data management systems only pseudonymous Personal Information (key-coded) necessary to conduct the clinical study, such as the patient's medical condition, treatment, dates of treatment, etc. The Sponsor discloses as part of the clinical study informed consent process that some Sponsor representatives still may see Personal Information at the participating sites for technical support of the participating physicians on the device implant or procedures, monitoring and quality control purposes. Confidentiality of Personal Information will be observed by all parties involved at all times throughout the clinical study. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data.

The Sponsor data management systems and processes were designed, developed, and tested according to industry standards to appropriately safeguard Confidential Information (including any Personal Information) against unauthorized access and/or interference by third parties, intrusion, theft, destruction, loss or alteration. Clinical study data are encrypted in transit and at rest.

The Sponsor maintains a Privacy Incident procedure that complies in all respects with Applicable Law and industry best practices.

11.2 Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data review, data cleaning, issuing and resolving data discrepancies, and database locking. If appropriate, the DMP may be updated throughout the duration of the clinical study. 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 study:

- Medical history/physical condition of the subject before involvement in the clinical study sufficient to verify CIP entry criteria
- Dated and signed notes on the day of entry into the clinical study 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 study (including start and stop dates)
- Subject's condition upon completion of or withdrawal from the clinical study

- Any other data required to substantiate data entered into the CRF
- Patient reported outcome measures may be completed using CRF worksheets. These serve as the source documentation.

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 study 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 study 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 Institutional Review Board/Medical Ethics Committee Review and Approval

Institutional Review Board (IRB) or 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 study. The approval letter must be received prior to the start of this clinical study 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 IRB/EC requirements.

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

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

13 CLINICAL STUDY CONCLUSION

Upon completion of the study, a final report will be generated and submitted to all sites, competent authorities, reviewing IRBs and all ECs within one year of the end of the study. For sites in the United States, the final report will be submitted to the FDA and reviewing IRBs within 6 months of study completion per 21 CFR 812.150.

The clinical study will be concluded following completion when:

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

14 PUBLICATION POLICY

The data and results from the clinical study 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 study. The Investigators will not use this clinical study-related data without the written consent of the Sponsor for any purpose other than for clinical study 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.

Upon receiving IDE approval from the FDA, this clinical study will be registered on ClinicalTrials.gov. 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 study. A full report of the pre-specified outcomes, regardless of the results, will be made public through the ClinicalTrials.gov website no later than 12 months after clinical study completion. If this clinical study is terminated early, the Sponsor will make every effort to hasten the release of the pre-specified outcomes through the ClinicalTrials.gov website.

15 RISK ANALYSIS

15.1 Anticipated Clinical Benefits

While there are no guaranteed clinical benefits associated with participation in this clinical study, it is expected that patients implanted with a Navitor valve with the FlexNav delivery system will experience similar improvements in symptoms related to severe aortic stenosis as patients implanted with other

commercially available transcatheter valves. This includes improvements in chest pain, fatigue, shortness of breath, dizziness and fainting.

Although the Navitor Valve and FlexNav Delivery System is not anticipated to add new clinical benefits, the design modifications to the Navitor valve may result in reduced risk for paravalvular leak, minimize vessel trauma, and improved valve expansion, stability and sealing as compared to the first-generation Portico valve.

Similarly, the design features of the FlexNav Delivery System are intended to improve deliverability and deployment accuracy and enhance overall ease of use. Additionally, the Navitor Loading system is designed to accommodate the newly scaled stent aortic heights of the Navitor Valve and a new stent guard component is added to accommodate the atraumatic aortic cells.

15.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

Risks associated with the specified device and procedure, together with their likely incidence, are described in Appendix XV. There may be risks related to the devices under investigation that are unknown at present. Likewise, the exact frequency of the risk may be unknown.

15.2.1 Potential Anticipated Adverse Events

The Navitor TAVI System is not intended or anticipated to introduce any new risks beyond that observed for the current (first-generation) Portico system. For that reason, the potential anticipated adverse events associated with use of the Navitor TAVI System are similar to those associated with any routine TAVR 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:

- access site complications (e.g., pain, bleeding, infection, hematoma, pseudoaneurysm, etc.)
- acute coronary obstruction
- acute myocardial infarction
- allergic reaction to antiplatelet agents, contrast medium, or valve components
- aortic rupture
- ascending aorta trauma
- atrio-ventricular node block
- cardiac arrhythmias
- conduction system injury
- dissection
- embolism
- endocarditis
- heart failure
- hemodynamic compromise
- hemolysis
- hemolytic anemia
- hemorrhage (bleeding)
- hypotension or hypertension
- infection
- myocardial ischemia
- mitral valve insufficiency

- multi-organ failure
- non-structural dysfunction (i.e., entrapment by pannus, paravalvular leak, inappropriate sizing or positioning)
- pericardial effusion
- perforation of the myocardium, ventricle, or a blood vessel
- pannus
- regurgitation
- renal insufficiency or renal failure (acute kidney injury)
- respiratory failure
- sepsis
- stroke
- structural deterioration (i.e., calcification, leaflet tear)
- thrombosis
- tamponade
- valve embolization or migration
- vessel dissection or spasm.

It is possible these complications could lead to:

- transfusion
- conversion to open surgical procedure
- reoperation
- emergent balloon valvuloplasty
- emergent percutaneous coronary intervention (PCI)
- emergent surgery (i.e., coronary artery bypass, heart valve replacement)
- explantation
- permanent disability
- death
- permanent pacemaker

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

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

Risk analysis for the Navitor Transcatheter Aortic Heart Valve, FlexNav Delivery System, and Navitor Loading System will be performed in accordance with the Risk Analysis Plan (internal ref: 90163677). The risk analysis utilizes Hazard Analysis (internal ref: 90163681) and Failure Mode Effect Analysis (FMEA) tools to systematically identify potential hazards associated with the design (internal refs: 90336360, 90163680) and use (internal ref: 90078354) of the devices. All potential harms and hazards associated with Navitor Valve and the FlexNav Delivery System were identified and documented in risk management report. All risks will be reduced as far as possible. Information of residual risks and safety will be provided in the Instruction for Use.

15.4 Risks Associated with Participation in this Clinical Study

Protocol-required assessments are summarized in Table 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 procedures.

Study-specific assessments that are not considered standard of care include the six-minute walk test, blood collection for laboratory tests, and echocardiogram exam during scheduled follow-up visits (excluding at discharge). Risk associated with blood collection is similar to any routine blood collection and is minimal (e.g., temporary pain and small risk of infection, bleeding, or bruising/swelling at the puncture site), which are mitigate by appropriate cleansing and adherence to standard blood collection procedures. There are no know clinical risks associated with echocardiogram; however a subject may experience mild discomfort from the pressure of the transducer during the exam. A subject may experience fatigue, shortness of breath, chest pain and/or leg cramps during six minute walk test; this is mitigated by performing this test under the supervision of a trained professional and in a testing area where medical care is immediately available.

15.5 Steps Taken to Control or Mitigate Risks

In-depth recommendations, special precautions and instructions regarding patient anatomical evaluation, vessel sizing, pre-implantation, implantation and post-implantation precautions are included in the IFU. Furthermore, the IFU also states that the devices can only be used by physicians who have received appropriate training on how to use the device. This statement is interpreted to mean that the physician users are expected to be aware of the known and foreseeable safety risks associated with the use of the devices including the surgical and/or non-surgical treatment of these conditions.

Risks associated with the use of the device under investigation are minimized through device design, investigator selection and training, pre-specified patient eligibility requirements, study monitoring by the sponsor to ensure adherence to the protocol as well as to assess ongoing patient safety.

Device Design: Specific features of the device design that to minimize potential risk to subjects are described below.

Navitor Valve:

The Navitor transcatheter heart valve is a pericardial tri-leaflet valve in a self-expanding stent designed for intra-annular placement using minimally invasive techniques.

The Navitor Valve maintains several design features of the first-generation Portico Valve including: same valve sizes and use range, open stent cell design to provide easy coronary access and blood flow, repositionable with full ability to re-sheath and retrieve, leaflets derived from pericardial bovine tissue, and low placement of leaflets/cuff within the stent frame for early valve function to maintain hemodynamic stability during implant.

The Navitor Valve incorporates the following key design enhancements to improve upon the first-generation Portico™ valve:

- Addition of a fabric outer cuff to the exterior portion of the stent to optimize valve sealing and improve paravalvular leak performance.

- Replacement of the inner porcine tissue cuff with the same fabric used for the new exterior cuff to maintain delivery system profile.
- Addition of a slight inward curvature to the aortic end of the stent to minimize vessel trauma and aid retainer release from the FlexNav™ Delivery System
- Adjusted scaling of the stent across all valve sizes to normalize the aortic/annular to stent height ratio.
- Minor stent modifications to the 23 mm and 25mm Navitor Valves to deliver uniform minimum stent/valve chronic outward radial (COR) force across the Portico family to improve valve expansion, stability and sealing.

Similarly, the Navitor Titan Valve maintains those same design features of the first-generation Portico valve and includes the outer fabric cuff and slight inward curvature of the aortic end of the stent. The Navitor Titan valve is designed to provide comparable COR forces as the other Navitor sizes in patients with larger annulus diameters (27-30mm).

FlexNav Delivery System:

The Navitor valve is loaded onto the FlexNav™ Delivery System which has an equivalent integrated sheath diameter of 14 French for 23 and 25 mm valves and 15 French for 27 and 29 mm valves. The FlexNav Delivery System offers several key features to mitigate risks to patients:

- The delivery system features an integrated sheath with hydrophilic coating on the exterior, which serves as an introducer sheath to decrease the insertion profile into the vasculature.
- Added stability layer on outer membrane shaft acts as a stabilizing layer during deployment by isolating motion between the introducer/vasculature and delivery system to minimize the number of manipulations required during valve deployment
- Stainless steel multifilar shaft increases delivery system tensile strength and flexibility to aid in valve alignment and improve re-sheath closure
- Proximal end of nose cone tip has been modified to be more tapered to minimize potential dislodging of the valve during removal of the delivery system.
- Nose cone profile has been lengthened to facilitate sheathless introduction.
- Handle features an automatically engaged partial deployment release button to retract the outer sheath, releasing the valve.
- The delivery system deploys the valve annulus first to allow gradual deployment of the annular cells. A partially deployed valve's position can be evaluated, and the valve can be re-sheathed and re-deployed (if needed) provided the valve has not been released past the aortic cells. Complete re-sheathing of the partially deployed valve at the implant site is possible by reversing the deployment mechanism.

Navitor Loading System:

The Navitor Loading System facilitates valve preparation/loading onto the FlexNav Delivery System; the small Navitor loading system is used for loading the 23 or 25mm valves on the small delivery system (14 F equivalent integrated sheath), and the large Navitor loading system is used for loading the 27 or 29mm

valves on the large delivery system (15 F equivalent integrated sheath). The Navitor Loading System – LG+ is used for loading the Navitor Titan valve on the large delivery system.

- The loading base has been modified to include an integrated guide tune to eliminate the potential for the tip of the delivery system to interact with valve leaflets during loading of the vale onto the delivery system.
- The loading base insert has been modified to fit the new integrated guide tube

Investigator Selection and Training: The following risk control measures will be implemented at the investigational site level to minimize potential clinical risks to subjects participating in this clinical study:

- Investigators will be carefully selected based on their knowledge of, and experience implanting and managing, TAVR devices, including Portico TAVI system.
- Interventional cardiologists and cardiovascular surgeons performing procedures must be board certified and experienced with TAVR implantation procedures.
- The local Heart Team's interventional cardiologist(s) and cardiac surgeon(s) jointly participate in the intra-operative technical aspects of TAVR (required for US sites per Medicare NCD).
- Investigators will be extensively trained with regards to implantation technique of the Navitor Valve using the FlexNav Delivery System.
- Investigators will be provided with a Clinical Instructions for Use (IFU) as a reference.
- Procedure setting to include either a hybrid catheterization/operating room suite and/or a fixed C-arm angiography imaging capability in the operative suite for quality imaging.

Adherence to the Clinical Investigational Protocol: The clinical study will be monitored by the Sponsor to ensure adherence to the CIP. Subjects will be carefully selected through rigorous screening by both the site's heart team and independent SSC using pre-specified inclusion and exclusion criteria as stated in section 5.3. Additionally, as stated in section 10.9.2, an independent DMC will monitor cumulative data at prescribed intervals and may consider a recommendation for modifications or termination of the study based on any safety concerns. 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

Current medical management guidelines have established TAVR as first-line treatment (Class I indication) for symptomatic severe aortic stenosis in patients considered to be high or extreme risk for surgical aortic valve replacement. Risks associated with the Portico family of valves are the same as other transcatheter heart valves. The anticipated risks are stated in Section 15.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects.

Protocol-required clinical assessments are primarily standard of care assessments for cardiac/structural heart interventional procedures and will be administered per Hospital guidelines. Risks to the subject undergoing study-specific assessments (not considered standard of care) have been addressed in the clinical investigational protocol with appropriate mitigation for each risk to the lowest level possible.

The benefits of the Navitor valve are anticipated to be similar to other transcatheter aortic valves, which may include improvements in chest pain, fatigue, shortness of breath, dizziness and fainting. Clinical evaluation of the Portico valve and first-generation Portico Delivery System in the Portico TAVI System CE

Clinical Investigation Plan

Mark study and Portico I study support the safety and performance of these devices. While the clinical benefit of the Navitor valve used with the FlexNav delivery system has not been established, the design modifications are not intended to or anticipated to introduce new risks. Collectively, the prior clinical experience with the Portico TAVI system and bench data support that the benefits outweigh the risks associated with the evaluation of this device in a clinical study.

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
LVOT	Left Ventricular Outflow Tract
MAC	Mitral Annular Calcification
MI	Myocardial Infarction

[redacted]

Clinical Investigation Plan

MMSE	Mini-mental state examination
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
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: STUDY ENDPOINT DEFINITIONS

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 hr 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 hr 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: o Symptoms of ischemia o ECG changes indicative of new ischemia [new ST-T changes or new Left Bundle Branch Block (LBBB)] o New pathological Q waves in at least two contiguous leads o Imaging evidence of new loss of viable myocardium or new wall motion abnormality • Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST-segment elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/ or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. • Pathological findings of an acute myocardial infarction.
Stroke (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.

	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 hr) 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 hours but < 24 hours

	Stage 3 Increase in serum creatinine to greater than or equal to (≥) 300% (>)3 X increase compared with baseline) or serum creatinine of ≥ 4.0 mg/dl (≥354 mmol/l) with an acute increase of at least 0.5 mg/dl (44 mmol/l) or Urine output < 0.3 ml/kg per hour for ≥ 24 hours or anuria for ≥ 12 hours. *Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.*
Valve Thrombosis (VARC 2)	Any thrombus attached to or near an implanted valve that occludes part of the blood flow path (as confirmed by imaging), interferes with valve function, or is sufficiently large to warrant treatment.
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)

Prosthetic Valve Stenosis Criteria ***In conditions of normal or near normal stroke volume (50–70 ml).***	**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

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(VARC 2)	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.

[redacted]

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APPENDIX III: ADDITIONAL DEFINITIONS

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

As part of ISO14155 Section 3.2, the adverse event definition has the following notes:

Note 1: This definition includes events related to the investigational medical device or the comparator.

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

Note 3: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

Serious Adverse Event (SAE)
Serious adverse event is an AE that led to any of the following:

d) Death,

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

1. Life-threatening illness or injury,
2. Permanent impairment of a body structure or a body function,
3. Hospitalization or prolongation of patient hospitalization,
4. Medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function,
5. Chronic disease

f) Fetal distress, fetal death or a congenital physical or mental impairment 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 a SAE.

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)

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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)
Anticipated serious adverse device effect (ASADE) 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 previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other anticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

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.

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

Note 1: The definition includes device deficiencies related to investigational medical device or the comparator.

Note 2: Cyber-security incidents related to the investigational product, shall be reported as device deficiencies

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

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APPENDIX IV: 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 (http://riskcalc.sts.org/STSWebRiskCalc273/de.aspx)

2. Euro SCORE II (http://euroscore.org/calc.html)

Clinical Investigation Plan

APPENDIX V: FRAILTY ASSESSMENT

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

The frailty assessment consists of four evaluations:

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

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.

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Grasp 1_____ Grasp 2_____Grasp3_____ Average_____

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

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

3. 5 Meter Walk Time

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

_____seconds

Walk Time, stratified by gender and height

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

4. Serum Albumin

Serum albumin (measured at screening) will contribute as one frailty factor if measuring less than 3.5 g/dL.

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APPENDIX VI: 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 VII: 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

Clinical Investigation Plan

3. The following questions are about activities you might do during a typical day. Does your health now limit you 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

Clinical Investigation Plan

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

Clinical Investigation Plan

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

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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!

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APPENDIX VIII: 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
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

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

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

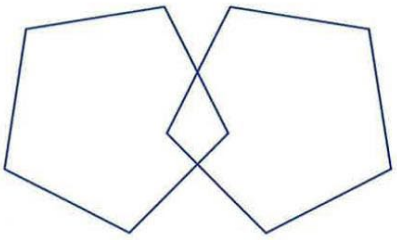
MMSE-2:SV total raw score ☐ (30 max. points)

Clinical Investigation Plan

Sample

CLOSE YOUR EYES

Clinical Investigation Plan



Clinical Investigation Plan

APPENDIX IX: 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

Clinical Investigation Plan

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.

References

Mahoney FI, Barthel D. "Functional evaluation: the Barthel Index."
Maryland State Medical Journal 1965;14:56-61. Used with permission.

Loewen SC, Anderson BA. "Predictors of stroke outcome using objective measurement scales."
***Stroke.* 1990;21:78-81.**

Gresham GE, Phillips TF, Labi ML. "ADL status in stroke: relative merits of three standard indexes."
***Arch Phys Med Rehabil.* 1980;61:355-358.**

Collin C, Wade DT, Davies S, Horne V. "The Barthel ADL Index: a reliability study."
***Int Disability Study.* 1988;10:61-63.**

Copyright Information

Clinical Investigation Plan

APPENDIX X: 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 XI: 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 ___ ___/___ ___/___ ___

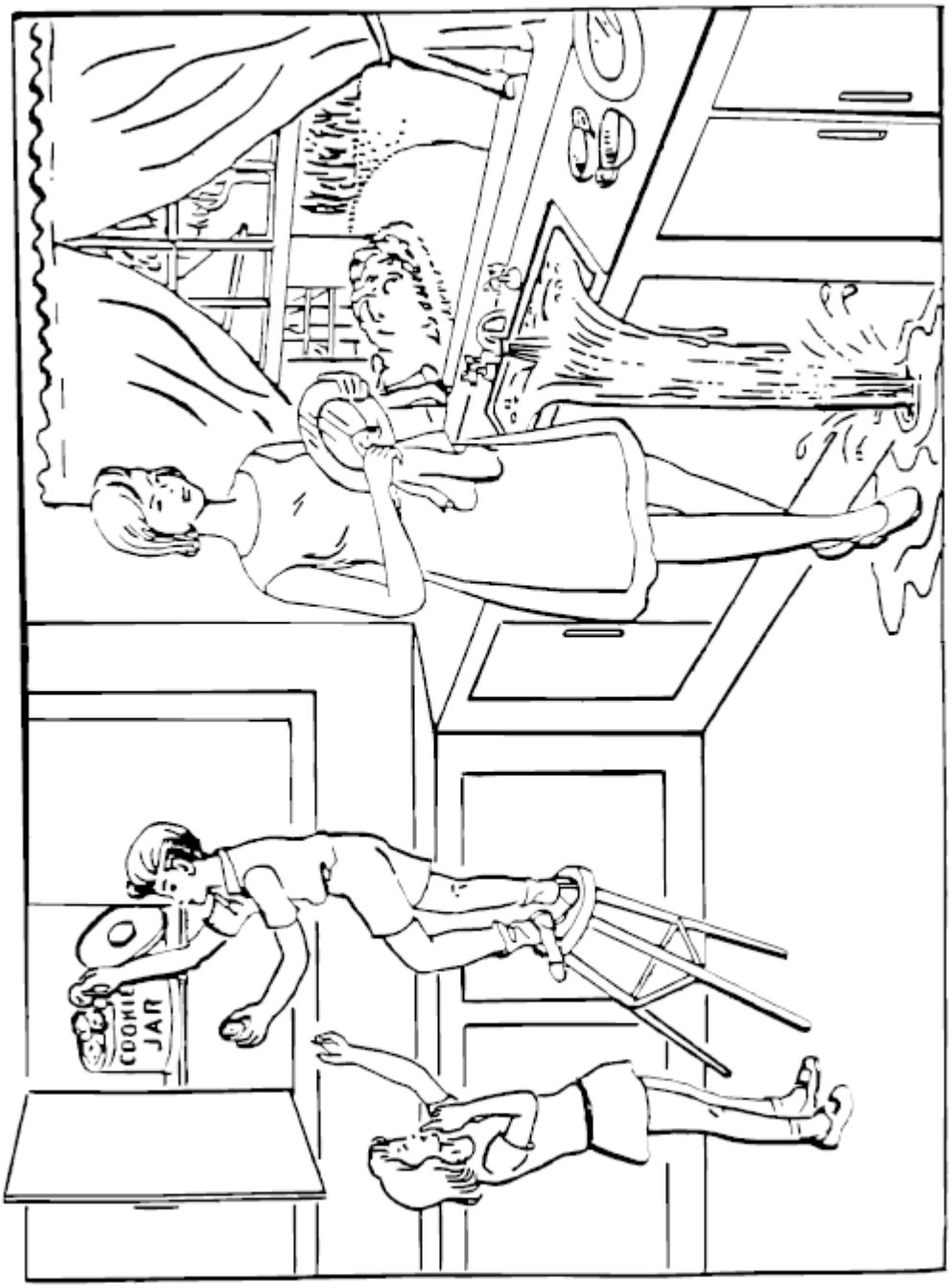
Hospital _____(___ ___-___ ___)

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



Clinical Investigation Plan

You know how.

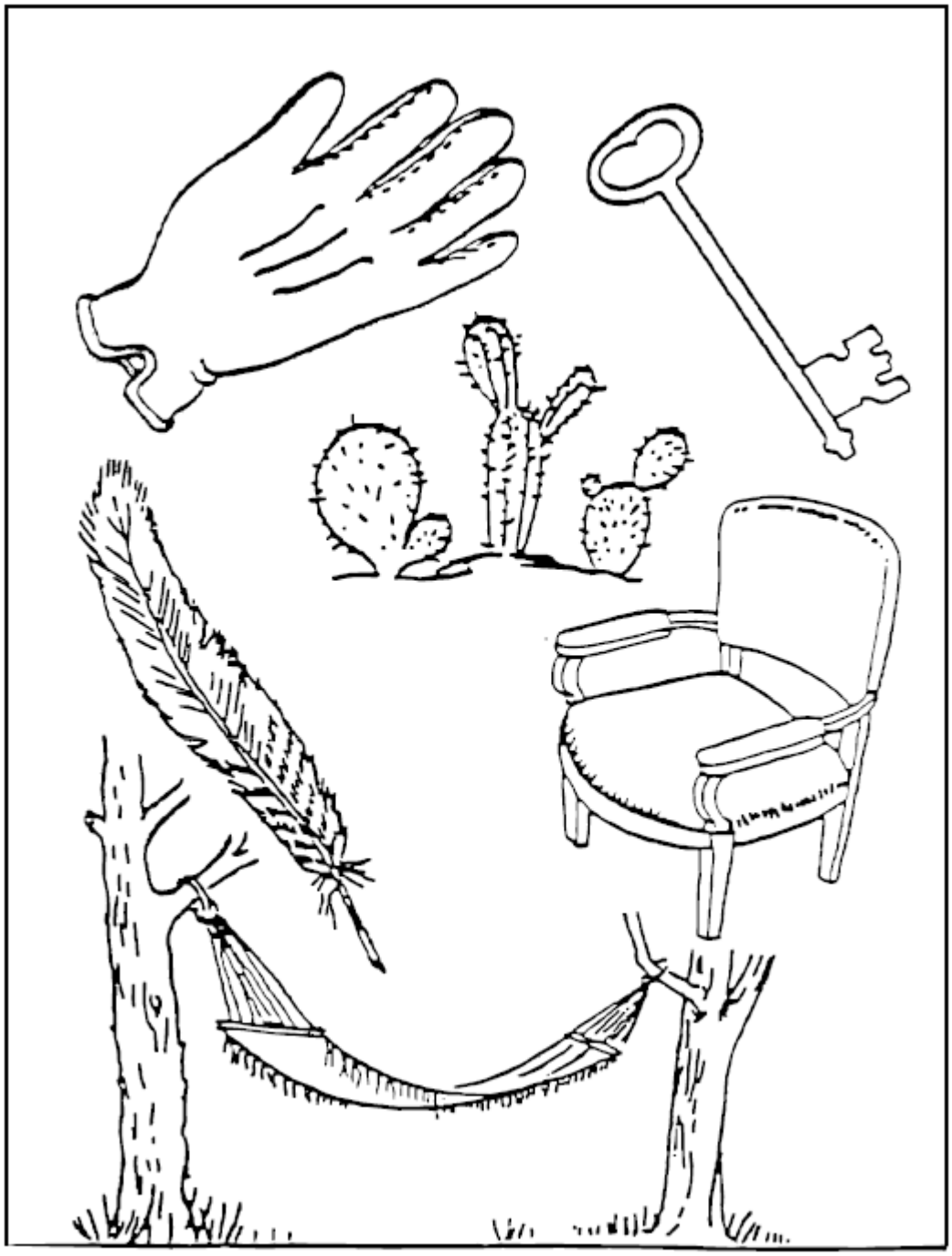
Down to earth.

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 XII: 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.

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.

Clinical Investigation Plan

LOCATION

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

PROCEDURE

REQUIRED EQUIPMENT

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

PATIENT PREPARATION

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

Baseline Measurements

1. 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."***

[redacted]

Clinical Investigation Plan

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

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

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

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

After the first minute, tell the patient the following (in even tones):

> ***"You are doing well. You have 5 minutes to go."***

When the timer shows 4 minutes remaining, tell the patient the following:

> ***"Keep up the good work. You have 4 minutes to go."***

When the timer shows 3 minutes remaining, tell the patient the following:

> ***"You are doing well. You are halfway done."***

When the timer shows 2 minutes remaining, tell the patient the following:

> ***"Keep up the good work. You have only 2 minutes left."***

When the timer shows only 1 minute remaining, tell the patient:

> ***"You are doing well. You have only 1 minute to go."***

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

If the patient stops walking during the test and needs a rest, say this:

> ***"You can lean against the wall if you would like; then continue walking whenever you feel able."***

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

When the timer is 15 seconds from completion, say this:

> ***"In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."***

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

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

Clinical Investigation Plan

APPENDIX XIII: PERI-PROCEDURAL GUIDELINES

Assessment of aortic regurgitation

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

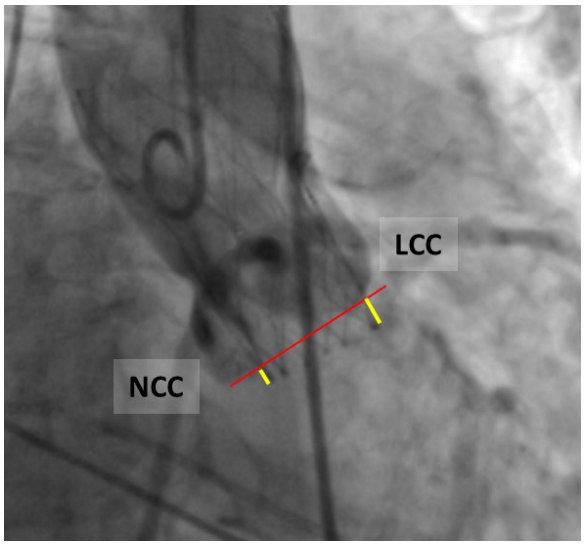
Echocardiography: Use color-Doppler in the short-axis view of the ventricular part of the valve frame. The circumferential extent of the regurgitant jet determine the degree of paravalvular leak (PVL); <10% = mild (I), 10-29% = moderate (II), >30% = severe (III-IV).

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

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

Assessment of implant depth

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



Clinical Investigation Plan

APPENDIX XIV: SITE CONTACT INFORMATION

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

[redacted]

Clinical Investigation Plan

APPENDIX XV: RATES OF FORSEEABLE ADVERSE EVENTS

Potential risks associated with Navitor implant procedure are similar to those for standard TAVI procedure. Although anticipated risks for Navitor are described below, due to the nature of this study, there may also be other risks, which are not known at this time. Likewise, the exact frequency of the risk may be unknown.

The frequencies of the foreseeable events indicated in the table below are based on literature on TAVI procedures, and clinical study data (Portico TF EU CE Mark study (n=222), Portico I study (n= 941)).

Potential Adverse Event	Very common (≥10%)	Common or frequent (≥1.0% to <10%)	Uncommon or infrequent (≥0.1% to <1.0%)	Rare (≥0.01% to <0.1%)	Very rare (< 0.01%)
access site complications (e.g., pain, bleeding, infection, hematoma, pseudoaneurysm, etc.)	X				
acute coronary obstruction			X		
acute myocardial infarction		X			
allergic reaction to antiplatelet agents, contrast medium, or valve components				X	
aortic rupture			X		
ascending aorta trauma			X		
atrio-ventricular node block	X				
cardiac arrhythmias	X				
conduction system injury	X				
dissection			X		
embolism		X			
endocarditis		X			
heart failure		X			
hemodynamic compromise	X				
hemolysis				X	
hemolytic anemia					X

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Potential Adverse Event	Very common (≥10%)	Common or frequent (≥1.0% to <10%)	Uncommon or infrequent (≥0.1% to <1.0%)	Rare (≥0.01% to <0.1%)	Very rare (< 0.01%)
hemorrhage (bleeding)	X				
hypotension or hypertension			X		
infection		X			
myocardial ischemia		X			
mitral valve insufficiency				X	
multi-organ failure					X
non-structural dysfunction (i.e., entrapment by pannus, paravalvular leak, inappropriate sizing or positioning)		X			
pericardial effusion		X			
perforation of the myocardium or a blood vessel		X			
pannus			X		
regurgitation	X				
renal insufficiency or renal failure	X				
respiratory failure		X			
sepsis		X			
stroke		X			
structural deterioration (i.e., calcification, leaflet tear)				X	
thrombosis	X				
tamponade		X			
valve embolization or migration		X			
vessel dissection or spasm		X			
transfusion	X				
conversion to open surgical procedure			X		
reoperation		X			

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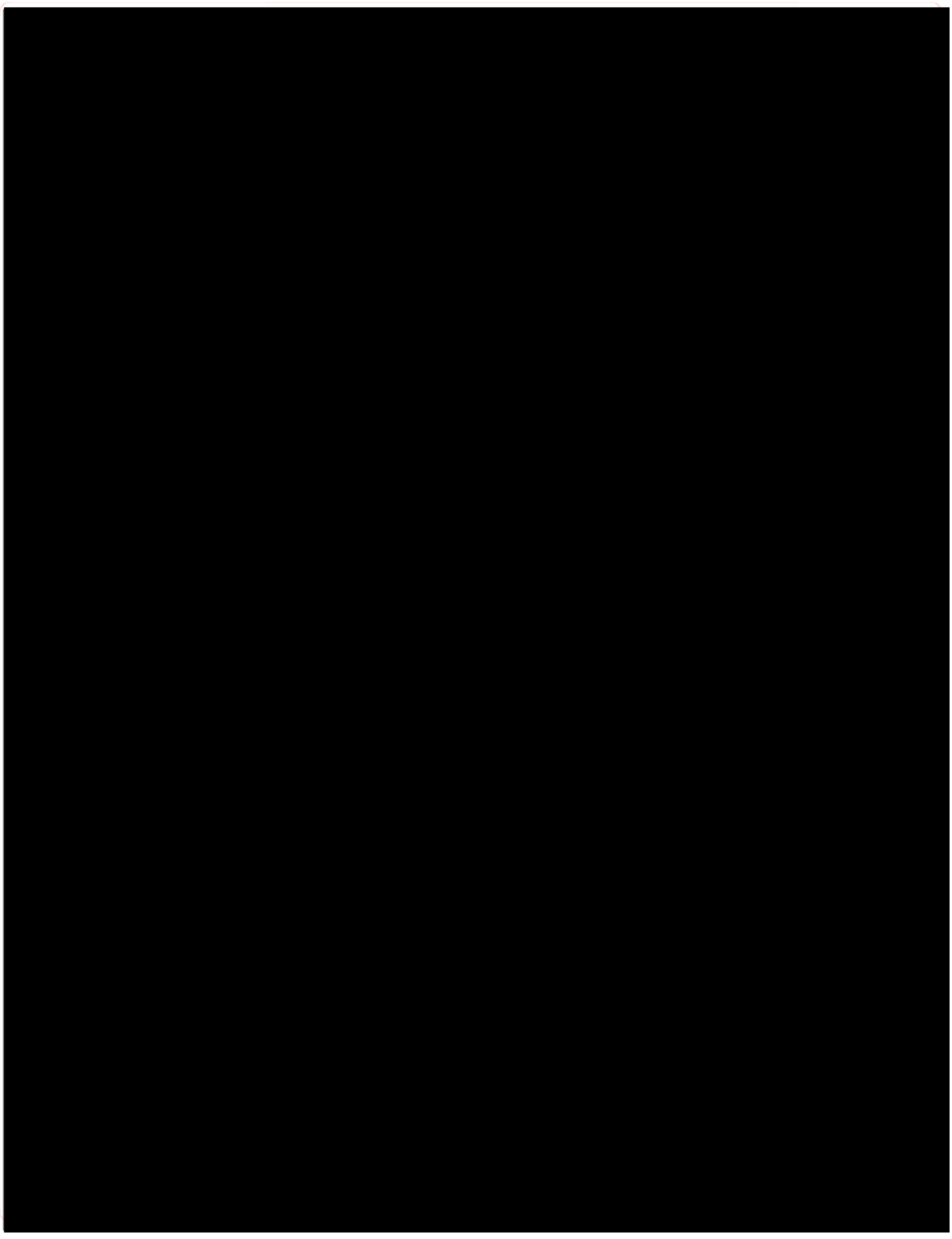
Potential Adverse Event	Very common (≥10%)	Common or frequent (≥1.0% to <10%)	Uncommon or infrequent (≥0.1% to <1.0%)	Rare (≥0.01% to <0.1%)	Very rare (< 0.01%)
emergent balloon valvuloplasty				X	
emergent percutaneous coronary intervention (PCI)				X	
emergent surgery (i.e., coronary artery bypass, heart valve replacement)		X			
explantation		X			
permanent disability				X	
death		X			
permanent pacemaker	X				

Clinical Investigation Plan

APPENDIX XVI: LABELS

A sample of the device labeling is provided below.



Clinical Investigation Plan

[redacted]

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APPENDIX XVII: CASE REPORT FORMS

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

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APPENDIX XVIII: INFORMED CONSENT FORM

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

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APPENDIX XIX: 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 XX: REVISION HISTORY

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

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

[redacted]

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[redacted]

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APPENDIX XXI: CIP SUMMARY

Clinical Investigation Name and Number	Portico NG Approval Study [redacted]
Title	Evaluation of the Navitor Transcatheter Aortic Valve in High and Extreme Risk Patients with Symptomatic Severe Aortic Stenosis
Objective(s)	The primary objective of this clinical study is to evaluate the acute safety and effectiveness of the Navitor Transcatheter Aortic Heart Valve as assessed by the rate of all-cause mortality at 30 days and the rate of moderate or greater paravalvular leak at 30 days.
Device Under Investigation	Portico NG (Navitor) Valve (23mm, 25mm, 27mm and 29mm) Navitor Titan Valve (35mm) FlexNav Delivery System (small and large) Portico NG (Navitor) Loading System (small and large) Navitor Loading System – LG+
Number of Subjects Required for Inclusion in Clinical Investigation	169 analysis subjects (up to a total of 189 subjects including roll-ins) with an attempted Navitor implant will be enrolled in order to analyze the primary endpoints for the PMA submission of the Navitor 23-29mm valve sizes. To ensure enrollment balance across study sites, no site may enroll more than 20% of the analysis population (n=33). A separate cohort of 60 analysis subjects will undergo a Navitor Titan valve implant attempt to analyze the primary endpoints for the PMA submission.
Clinical Investigation Design	Prospective, multi-center, international, single-arm, investigational study
Primary Endpoint(s)	The primary safety endpoint is all-cause mortality at 30 days. The primary effectiveness endpoint is moderate or greater paravalvular leak at 30 days.
Secondary Endpoint	The secondary endpoint is the non-hierarchical composite of all-cause mortality, disabling stroke, life threatening bleeding, acute kidney injury (stage 3), or major vascular complications at 30 days.
Subject Follow-up	Subject data will be collected at baseline, procedure, discharge, 30 days, 12 months, and annually thereafter to 5 years post implant procedure. Echocardiographic data will be collected at screening, procedure (optional), and discharge as well as 30 days, 12 months, and at 2, 4, and 5 years post implant procedure.
Inclusion Criteria	Key inclusion criteria, refer to the complete inclusion criteria in the body of the CIP (section 5.3.2): 1. Subjects must have a Society of Thoracic Surgeons (STS) score of ≥7% OR documented heart team agreement of high or extreme risk for surgical aortic valve replacement due to frailty or co-morbidities not captured by the STS score.

	2. Subject has symptomatic aortic stenosis as demonstrated by NYHA Functional Classification of II, III, or IV. 3. Subject has senile degenerative aortic valve stenosis with echo-derived criteria, defined as: aortic valve area (AVA) of ≤ 1.0 cm^2 (or indexed EOA ≤ 0.6 cm^2/m^2) AND mean gradient ≥40 mmHg or peak jet velocity ≥ 4.0 m/s or doppler velocity index (DVI) ≤0.25. (Qualifying AVA baseline measurement must be within 90 days prior to informed consent). 4. Portico NG cohort (only): aortic annulus diameter of 19-27mm and ascending aorta diameter of 26-42 mm for the specified valve size listed in the IFU, 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 echocardiogram and non-contrast CT of chest and abdomen/pelvis may be accepted). 5. Titan cohort (only): aortic annulus diameter of 27-30mm and ascending aorta diameter of 27-44mm per the IFU, 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 echocardiogram and non-contrast CT of chest and abdomen/pelvis may be accepted).
Exclusion Criteria	Key exclusion criteria, refer to the complete inclusion criteria in the body of the CIP (section 5.3.3): 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. Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to index procedure. 3. Active peptic ulcer or upper GI bleeding within 3 months prior to index procedure that would preclude anticoagulation 4. Recent (within 6 months prior to index procedure date) cerebrovascular accident (CVA) or a transient ischemic attack (TIA). 5. Renal insufficiency (creatinine > 3.0 mg/dL) and/or end stage renal disease requiring chronic dialysis. 6. Sepsis or active bacterial endocarditis within 6 months prior to the index procedure. 7. Liver failure (Child-Pugh class C) 8. Untreated atrial fibrillation (e.g., patients with atrial fibrillation not on anticoagulants) 9. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation 3-4+) 10. Aortic valve is a congenital unicuspid or congenital bicuspid valve, or is non-calcified as verified by echocardiography

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	11. Severe ventricular dysfunction with LVEF <25% as measured by resting echocardiogram 12. 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 left ventricular outflow tract (LVOT), severe (greater than or equal to 3+) mitral insufficiency, or severe mitral stenosis with pulmonary compromise 13. Echocardiographic or multi-slice computed tomography (MSCT) evidence of intracardiac mass, thrombus or vegetation 14. 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 (applicable for transfemoral access only) 15. Aortic root angulation > 70° 16. Undue risk of coronary obstruction (e.g., bulky aortic valve leaflets in close proximity to coronary ostia) 17. Non-calcified aortic annulus 18. 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, protruding thrombus or severe tortuosity (applicable for transfemoral access only) 19. Severe tricuspid regurgitation or severe right ventricle dysfunction 20. Minimum access vessel diameter of <5.0mm for small FlexNav Delivery System and <5.5 mm for large FlexNav Delivery System