Portico™ Re-sheathable Transcatheter Aortic Valve System US IDE Trial
(PORTICO)
NCT02000115

Clinical Investigation Plan (CIP): [redacted]

Investigational Devices	
Description:	St. Jude Medical (SJM) Portico™ Transcatheter Aortic Valve
Trade Name:	Portico™ Transcatheter Heart Valve: Portico 23mm valve Portico 25mm valve Portico 27mm valve Portico 29mm valve
Model Numbers:	PRT-23-IDE or PRT-23 PRT-25-IDE or PRT-25 PRT-27-IDE PRT-29-IDE (or equivalent model numbers in respective geographies)
Associated Investigation Devices:	Portico Delivery Systems FlexNav Delivery Systems Portico Loading Systems FlexNav Loading Systems
Model Numbers:	PRT-DS-TF-18F-IDE, PRT-DS-TF-19F-IDE PRT-DS-ALT-18F-IDE, PRT-DS-ALT-19F-IDE PRT-LS-TFALT-18FID, PRT-LS-TFALT-19FID FN-DS-SM-IDE, FN-DS-LG-IDE, FN-LS-SM-IDE, FN-LS-LG-IDE(or equivalent model numbers in respective geographies)

Study Sponsor
St. Jude Medical (now Abbott) [redacted]

National Co-Principal Investigators	
[redacted]	[redacted]

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CIP Number: [redacted]

Study Device: Portico™ Transcatheter Heart Valve and Delivery Systems

I, the undersigned, have read and understand the Clinical Investigation Plan specified above and agree to follow its content.

_____
Site Principal Investigator Name (please print)

_____ _____
Site Principal Investigator Signature Date

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Table of Contents

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List of Tables

List of Figures

List of Appendices

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1 Purpose (Pivotal IDE and Continued Access Protocol (CAP))

1.1 Indication for Use

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

1.2 Study Design and Objectives

The PORTICO clinical study is an investigational device exemption (IDE) study comprised of the PORTICO pivotal IDE trial (pivotal IDE) and the PORTICO IDE Continued Access Protocol (CAP) study. The study design and objectives of these two separate study arms within the PORTICO clinical study are described below.

1.2.1 Study Design and Objectives (Pivotal IDE)

The PORTICO pivotal IDE trial is a prospective, multi-center, randomized, controlled clinical investigation study designed to evaluate the safety and effectiveness of the SJM Portico Transcatheter Heart Valve and Delivery Systems (Portico) via transfemoral and alternative delivery methods in high-risk and extreme-risk patients.

As shown in Figure 1, the pivotal IDE trial includes a randomized cohort of 750 patients that will be used to support a Premarket Approval (PMA) application for the Portico™ Transcatheter Aortic Heart Valve in the United States. Prior to randomization, patients will be classified as high or extreme risk and stratified by vascular access within each risk group. At the time of the primary analysis, the risk cohorts will be combined.

There are two nested-registries within the pivotal IDE trial (Roll-in registry and Valve-in-Valve registry). Data from the IDE Valve-in-Valve registry will be used to support an expanded indication for transcatheter delivery of the Portico valve in a failed surgical bioprosthesis (TAVR-in-SAVR). [redacted] The objective of the FlexNav study is to characterize the safety of the second-generation Portico Delivery System (“FlexNav™ Delivery System”). Thirty-day outcomes data from the FlexNav study will be used to support the PMA application for the Portico™ Transcatheter Aortic Heart Valve and the FlexNav™ Delivery System. A synopsis of the FlexNav study which includes details such as objectives, endpoints, and other study information is provided in Appendix W.

This protocol conforms to all the standards of Medicare coverage requirements. The PORTICO subject characteristics are consistent with Medicare population and the results are expected to be generalizable to the Medicare population.

Investigators enrolling subjects in the pivotal IDE trial under protocol version L or later will implant the Portico valve using the FlexNav™ Delivery System across all active study arms.

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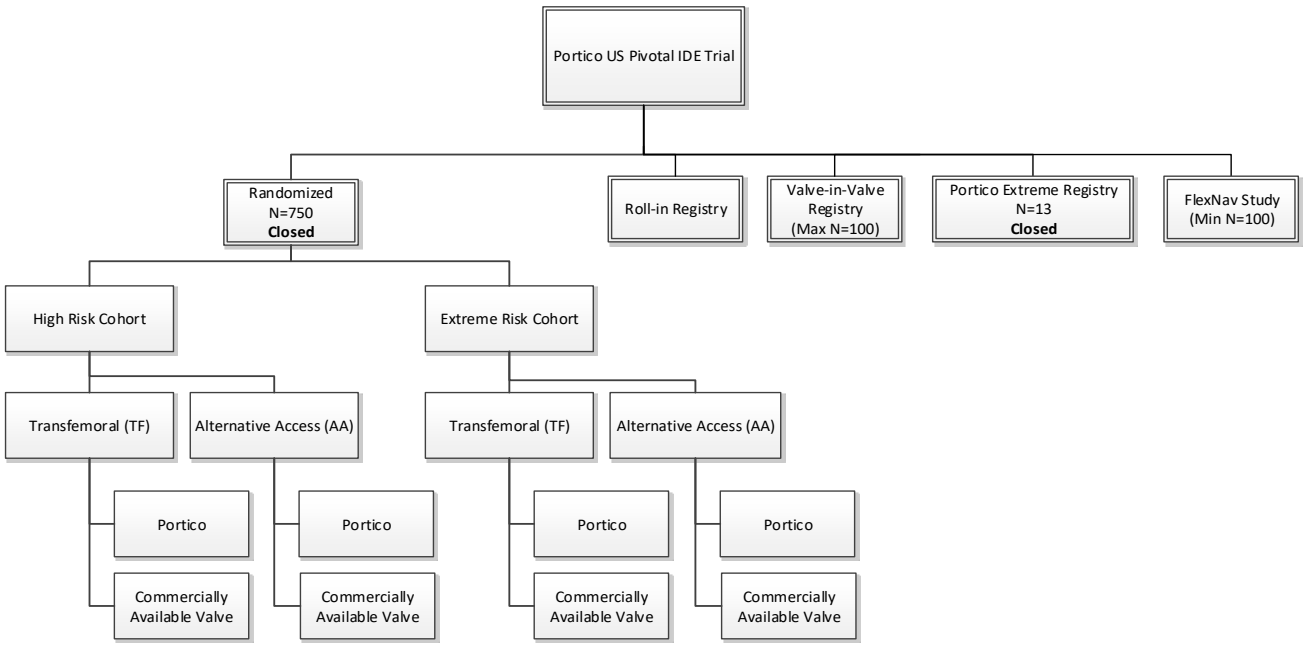

Figure 1: PORTICO US Pivotal IDE Trial

1.2.2 Study Design and Objectives (CAP)

The PORTICO IDE Continued Access Protocol (CAP) study is a prospective, multicenter, single-arm investigational study designed to collect additional safety and clinical effectiveness data on the SJM Portico Transcatheter Aortic Heart Valve and Delivery System following completion of enrollment of subjects in the randomized cohort and FlexNav study of the PORTICO pivotal IDE trial.

[redacted]

Conduct of the CAP will follow the same protocol outlined for the pivotal IDE trial except where indicated. The main differences between the CAP and pivotal IDE trial include:

- A 6-month visit is not required for CAP subjects
- CAP subjects will not be randomized. All CAP subjects will receive a Portico device.
- The 6 Minute Walk Test (6MWT) and SF-36 questionnaire will not be required at any follow-up visit for CAP subjects.

[redacted]

A synopsis of the CAP which includes details such as objectives, endpoints, and other study information are provided in Appendix V.

[redacted]

1.3 Study Endpoints (Pivotal IDE and CAP)

1.3.1 Pivotal IDE Endpoints (Randomized Cohort and Registries)

Primary Effectiveness Endpoint: A composite of all-cause mortality or disabling stroke at one year.

Primary Safety Endpoint: Non-hierarchical composite of all-cause mortality, disabling stroke, life threatening bleeding requiring blood transfusion, acute kidney injury requiring dialysis, or major vascular complications at 30 days.

Secondary Endpoints:

1. Severe aortic regurgitation (AR) at one year
2. Kansas City Cardiomyopathy Questionnaire (KCCQ) at one year
3. Moderate or severe aortic regurgitation at one year
4. Six-minute walk at one year

Descriptive Endpoints:

1. Acute device success defined as:
   - Absence of procedural mortality AND
   - Correct positioning of a single prosthetic heart valve into the proper anatomical location AND
   - Intended performance of the prosthetic heart valve (mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, no moderate or severe prosthetic valve regurgitation) AND
   - Successful access was obtained as intended by group assignment
2. Kansas City Cardiomyopathy Questionnaire (KCCQ) at one year for Centers for Medicare and Medicaid Services (CMS) National Coverage Decision primary quality of life endpoint
3. Major vascular complications at 30 days from the index procedure
4. NYHA functional classification at 30 days, 6 months, and one year
5. Six-minute walk test at 30 days, 6 months, and one year
6. Paravalvular Leak (PVL) at 30 days, 6 months, and one year

[redacted]

7. Aortic insufficiency greater than trace at 30 days, 6 months, one year, and two years
8. Reintervention to treat aortic insufficiency at 1 year and 2 years
9. Permanent pacemaker insertion at 30 days from the index procedure
10. Major bleeding at 30 days from the index procedure
11. Acute kidney injury at 30 days from the index procedure
12. Individual components of the primary effectiveness endpoint
    - All-cause mortality at 30 days, 6 months, one year and two years
    - Disabling stroke at 30 days, 6 months, one year and two years
13. Non-disabling Stroke and Transient Ischemic Attack (TIA) at 30 days, 6 months, one year, and two years
14. Atrial fibrillation at one year and two years
15. Quality of Life (QOL) from baseline to 30 days, 6 months and one year

1.3.2 Pivotal IDE FlexNav™ Study Endpoints

Primary Safety Endpoint: VARC II defined major vascular complication rate at 30 days.

Descriptive Endpoints:

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

[redacted]

1.3.3 CAP Endpoints

Primary Safety Endpoint: A composite of VARC II defined all-cause mortality or disabling stroke at 30 days.

Descriptive Endpoints:

1. Technical device success defined as successful vascular access, delivery and deployment of the Portico Valve; retrieval with the delivery system and correct positioning of a single valve in the proper anatomical location
2. Life threatening bleeding requiring blood transfusion and major bleeding at 30 days from the index procedure
3. Acute kidney injury at 30 days from the index procedure
4. Major and minor vascular access complication rate at 30 days from the index procedure
5. Permanent pacemaker insertion at 30 days from the index procedure
6. Paravalvular Leak (PVL) at 30 days and one year from the index procedure
7. NYHA functional classification at 30 days and one year from the index procedure
8. Disabling stroke at 30 days and one year from the index procedure
9. All-cause mortality at 30 days and one year from the index procedure
10. KCCQ Quality of Life (QOL) score from baseline to 30 days and one year from the index procedure

[redacted]

2 Clinical Protocol (Pivotal IDE)

2.1 Background Information

2.1.1 Disease State and Patient Population

Aortic stenosis (AS) is currently the most common valvular disease in the Western population[1] and its prevalence tends to increase with age, being present in 4.6% of adults ≥75 years.[2] Aortic stenosis (AS) can be primarily attributed to rheumatic disease and senile

[redacted]

degenerative calcification. Senile degenerative calcific AS is most common in the United States (U.S.) present in individuals older than 65 years. This calcification phenomenon is present in congenitally bicuspid or normal trileaflet valves. Calcific changes are due to an active disease process characterized by lipid accumulation, inflammation, and calcification.[3,4] This calcification process eventually leads to a restricted valve leaflet motion with obstruction to left ventricular outflow.[3-5]

Patients with AS are typically free from cardiovascular symptoms until late courses of the disease. However, once symptomatic, patients with severe AS have a poor prognosis, especially when combined with heart failure.[5,7]

Despite the tendency to grade the degree of AS based on a variety of hemodynamic measurements and natural history, ACC/AHA guideline authors describe aortic stenosis as a continuum.

The progression of AS can lead to the narrowing of aortic valve area by approximately 0.3 cm^2 per year. Also, the systolic pressure gradient across the valve can increase by as much as 15.19 mmHg per year. This 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.[8]

Severe symptomatic AS is considered Class I indication for surgery.[8,20] The Joint ACC/AHA Task Force's published guidelines for the management of patients with valvular heart disease includes classification criteria for determining the severity of aortic stenosis (Table 1)[20].

Table 1. Classification of severity of aortic valve disease in adults

Indicator	Mild	Moderate	Severe
Jet velocity (m/s)	< 3.0	3.0-4.0	> 4.0
Mean Gradient (mmHg)	< 25	25-40	> 40
Valve area (cm^2)	> 1.5	1.0-1.5	< 1.0
Valve area index (cm^2/m^2)			< 0.6

After the onset of symptoms of angina pectoris, dyspnea, or syncope, annual mortality of patients with moderate-to-severe AS approaches 25%[3] and average survival is only 2 to 3 years. Other data also suggest the 2-year mortality rate can range from 44.4% for symptomatic AS patients[9] to as high as 79%[10] for predominant AS patients. Following symptomatic patients with severe aortic stenosis in whom operation was declined, O'Keefe[11] reported mortality rates of 45%, 63% and 75% at 1 year, 2 year, and 3 year follow-up, respectively. More recently, it has been established that inoperable patients with severe AS had a one year mortality rate of 50%.[12]

Relief of aortic valve obstruction typically results in an improvement of symptoms, hemodynamic parameters, and global left ventricle systolic function, as well as reversal of left ventricular hypertrophy.[13]

[redacted]

2.1.2 Therapy for Severe Aortic Stenosis

Several treatment options are available to patients with symptomatic AS including optimal medical treatment. Until recently, surgical aortic valve replacement (SAVR) was the only effective treatment in adults with severe AS.[8] SAVR has been documented to significantly improve long-term survival in patients with AS.[7,9,10] Despite these proven positive outcomes of SAVR, the decision on whether to undergo SAVR can be influenced by prohibitive operative risk.[9]

Many patients with severe AS are considered high surgical risk and do not undergo SAVR due to severe comorbidities. Though some of these patients may be candidates for balloon valvuloplasty, this procedure has not offered any improvement in mortality.[14] SAVR has an average operative mortality of 3% to 8%, however primary patient characteristics and comorbidities, such as age and reduced left ventricular (LV) function, are associated with increased mortality within that range.[15-18] In addition, surgeon experience and hospital volume also affect outcomes with an absolute 2% lower mortality rate in the highest-volume compared with the lowest-volume hospitals.[19]

2.1.3 Transcatheter Aortic Valve Replacement

A variety of conventional mechanical and bioprosthetic heart valves are readily accessible and commercially available in the U.S. However, some individuals are considered too high risk for open heart surgery, and may benefit from a less invasive procedure. With technological advancements, an alternative to SAVR, known as PAVR or TAVR (Percutaneous or Transcatheter Aortic Valve Replacement) and TAVI (Transcatheter Aortic Valve Implantation) has been under active investigation by a number of groups.[21-28] This concept was first demonstrated by Andersen et al[29] in 1992, who delivered a porcine bioprosthesis attached to a wire-based stent at various aortic sites with satisfactory hemodynamic results. In 2002, Cribier, et al,[30]reported the first successful human TAVR for the treatment of severe symptomatic aortic stenosis. Several single-center trials followed which demonstrated that this new approach was feasible for the treatment of severe aortic stenosis in patients who were inoperable or at a very high risk to undergo SAVR.

2.1.4 Status of TAVR in the United States

The safety and effectiveness of TAVR has been confirmed with the recently published results of the Prospective, Randomized Placement of Aortic Transcatheter Valves (PARTNER) trial for high risk patients (Cohort A)[34] and inoperable patients (Cohort B)[12] (PMA # P100041). In 2011, with the FDA PMA approval of PARTNER Cohort A the Centers for Medicare and Medicaid Services (CMS) issued a coverage determination (NCD) for TAVR studies in the US (CAG-00430N).[31] The CMS national coverage decision provides requisite guidance on patient selection, post market surveillance methods and further clinical investigations of transcatheter aortic valve technologies in the extreme risk and high risk patient populations. The PARTNER trial has provided definitive data confirming TAVR as an alternative to SAVR. TAVR was found to be non-inferior to SAVR in both Cohort A (High Risk

patients) and Cohort B (Inoperable Risk patients) with severe aortic stenosis. When compared with standard therapy, TAVR significantly reduced the rates of all-cause mortality or repeat hospitalization, and cardiac symptoms, despite the higher incidence of major strokes and major vascular events, in the inoperable patients with severe AS.[31]

2.1.5 Valve-in-Valve

There is a growing need for treatment options for patients with a failed bioprosthetic valve as the population ages, life expectancy improves, and the use of bioprosthetic valves increases. Operative mortality for elective redo aortic valve surgery is generally low (2% to 7%), but it can increase to more than 30% in high-risk and non-elective patients. Because transcatheter aortic valve (TAV)-in-surgical aortic valve (SAV) implantation represents a minimally invasive alternative to conventional redo surgery, it may prove to be as safe and effective as a redo surgery. Prospective comparisons with a large number of patients and long-term follow-up are required to confirm these potential advantages.

The most common reasons for an aortic valve implant redo, or valve-in-valve, are 1) wear and tear, 2) calcific degeneration, 3) pannus, 4) endocarditis, and 5) thrombus, where calcification and wear and tear are the most common reasons for bioprosthetic valve failure.[36]

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2.1.7 Results of Literature Search

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2.1.8 Primary Effectiveness Endpoint

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2.1.9 Primary Safety Endpoint

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2.2 Summary of St. Jude Medical Portico Transcatheter Valve Clinical Experience

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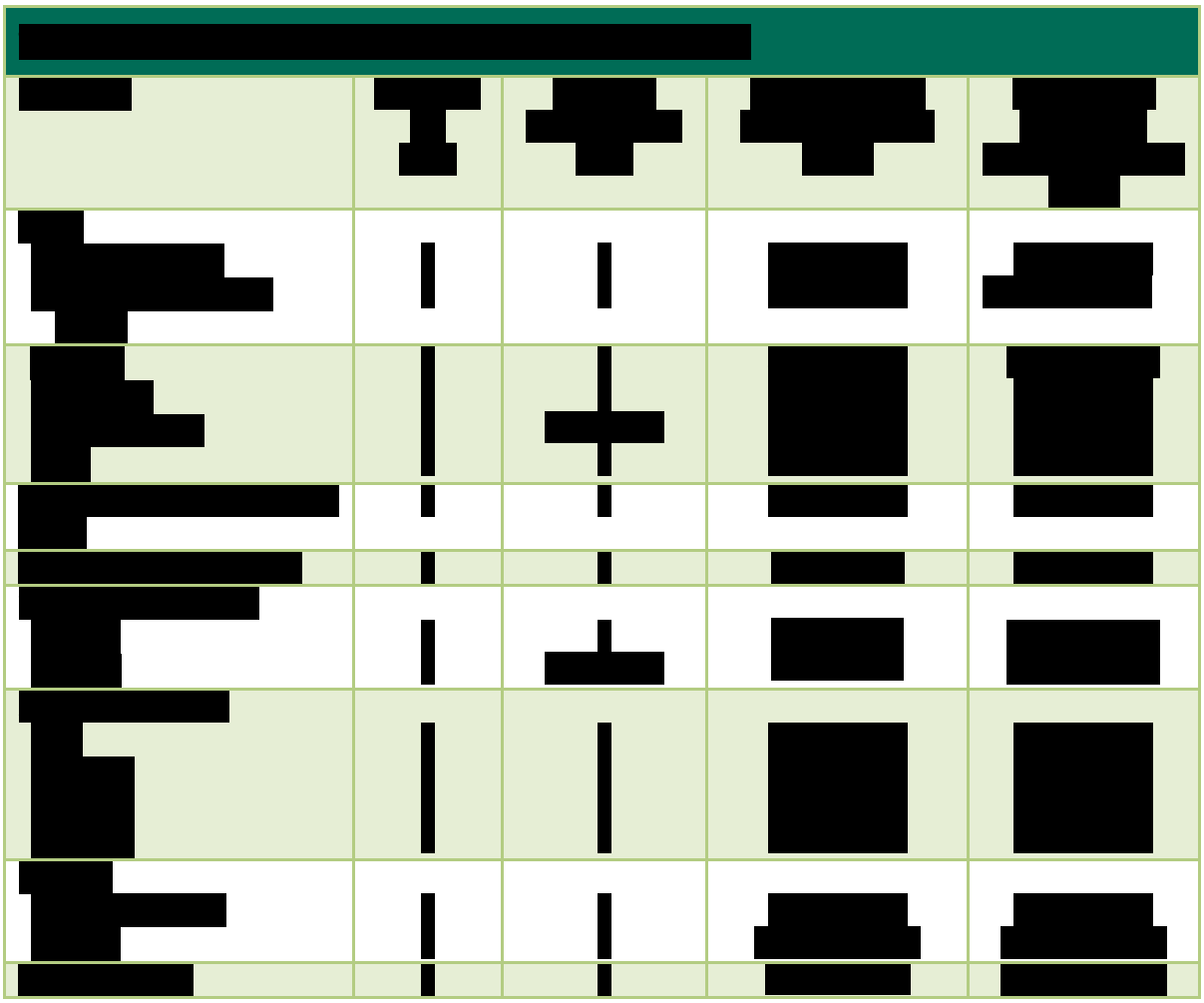

2.3 Rationale (Pivotal IDE and CAP)

2.3.1 Pivotal IDE Rationale

The rationale for this study is to potentially offer a SJM transcatheter Portico valve that is safe and effective for subjects with symptomatic, severe aortic valve stenosis who are considered at high or extreme risk for conventional surgical aortic valve replacement.

The rationale for conducting the FlexNav study as a separate arm of the pivotal IDE trial is to enable the direct comparison of 30-day safety outcomes data for the FlexNav™ Delivery System to the first-generation Portico Delivery System. Results from the FlexNav study will be included in a PMA application to support US approval of the Portico Transcatheter Heart Valve and FlexNav™ Delivery System.

2.3.2 CAP Rationale

The rationale for the CAP is to allow current IDE study implanters to maintain their technical proficiency in Portico device implantation.

2.4 Name and Description of the Investigational Device (Pivotal IDE and CAP)

The investigational devices used in the PORTICO clinical study consist of the Portico™ Transcatheter Aortic Heart Valve, the first-generation Portico Delivery System and the FlexNav™ Delivery System.

The PORTICO clinical study is utilizing the 23mm, 25mm, 27mm and the 29mm St. Jude Medical Portico™ Transcatheter Aortic Heart Valve. The Portico valve will be implanted using the Transfemoral access (TF), or alternative access (AA) consisting of Subclavian/Axillary and Transaortic access.

The Portico valve model number and reference dimensions are provided Table 7. Model numbers for equivalent devices may vary based on respective geographies.

Table 7. Valve Model Number and Reference Dimensions

Model Number	Intended to Treat Aortic Annulus Diameter
PRT-23-IDE	19 – 21mm
PRT-25-IDE	21 – 23mm
PRT-27-IDE	23 – 25mm
PRT-29-IDE	25 – 27mm

The model numbers of the first-generation and second-generation ("FlexNav") Portico delivery systems and loading systems associated with the Portico valve are provided in Table 8. Part numbers are subject to change, but SJM maintains a list, which is available upon request. Model numbers for equivalent delivery and loading systems may vary based on respective geographies.

[redacted]

Table 8. Delivery and Loading Systems and Model Numbers	
Model Number	**Delivery System Diameter**
PRT-DS-TF-18F-IDE	18 Fr
PRT-DS-ALT-18F-IDE	18 Fr
FN-DS-SM-IDE[1]	18 Fr
PRT-DS-TF-19F-IDE	19 Fr
PRT-DS-ALT-19F-IDE	19 Fr
FN-DS-LG-IDE[1]	19 Fr
PRT-LS-TFAL-18FID	N/A (loading system)
FN-LS-SM-IDE[2]	N/A (loading system)
PRT-LS-TFALT-19FID	N/A (loading system)
FN-LS-LG-IDE[2]	N/A (loading system)
[1]Indicates second-generation FlexNav™ Delivery System. Only allowed under protocol version L or later [2]Indicates second-generation FlexNav™ Loading System. Only allowed under protocol version L or later	

3 Portico Transcatheter Aortic Heart Valve

The Portico Transcatheter Aortic Heart Valve (Figure 2) is designed to be implanted in the native aortic heart valve without open heart surgery and without concomitant surgical removal of the failed native valve.

The valve stent is made from nitinol, a material that has self-expanding properties and is radiopaque. The valve cuff is made from porcine pericardium that is sutured to the stent frame.

The cuff provides the sealing area for implantation. The valve orifice is made by suturing three valve leaflets, each made from a single layer of bovine pericardium, into a trileaflet configuration on the stent frame. The cuff and leaflet pericardial tissue is preserved and crosslinked in glutaraldehyde. Glutaraldehyde, formaldehyde and ethanol are used in the valve sterilization process.

The valve leaflets and valve cuff are processed using Linx™ anti-calcification treatment. The valve is supplied sterile and non-pyrogenic.

[redacted]

Figure 2. Portico Transcatheter Heart Valve

3.1 Portico Delivery Systems

3.1.1 First-Generation Portico Delivery System

The first-generation Portico Delivery System is an over-the-wire, 0.035”-compatible system with an outer diameter ranging between 18 French (Fr) and 19 Fr depending on valve size.

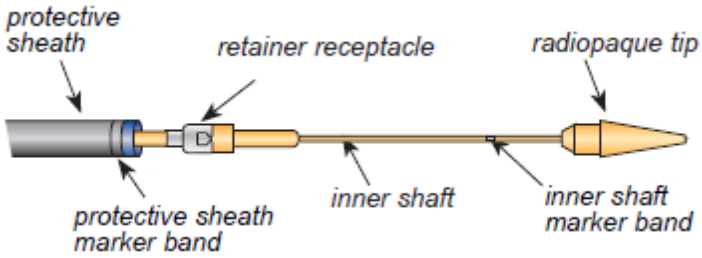

Figure 3. First-Generation Portico Delivery System (deployment end)

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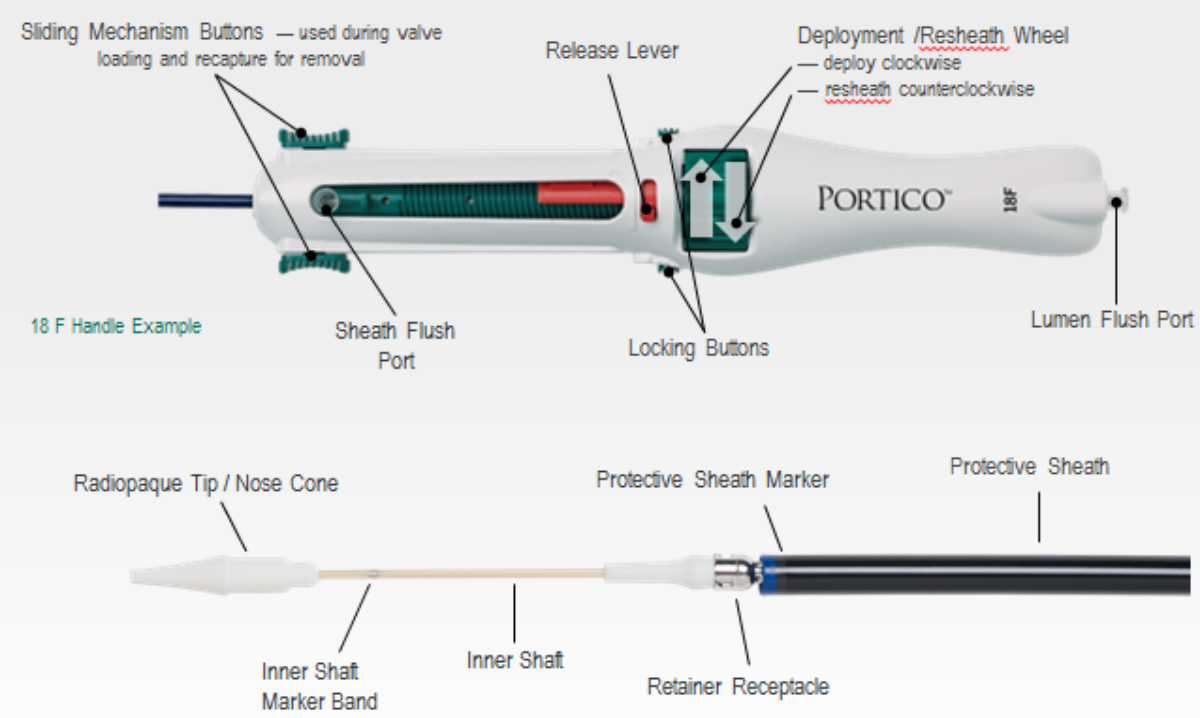

Figure 4. First-Generation Portico Delivery System

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The first-generation Portico Delivery System model number and reference dimensions are provided in the Instruction For Use (IFU) of the Portico™ Transcatheter Aortic Heart Valve.

3.1.2 Second-Generation FlexNav™ Delivery System

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

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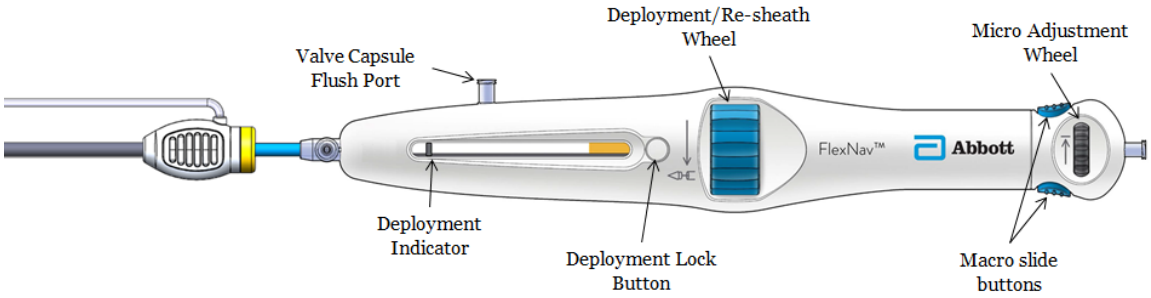

Figure 5: Second-Generation FlexNav™ Delivery System Handle Detail

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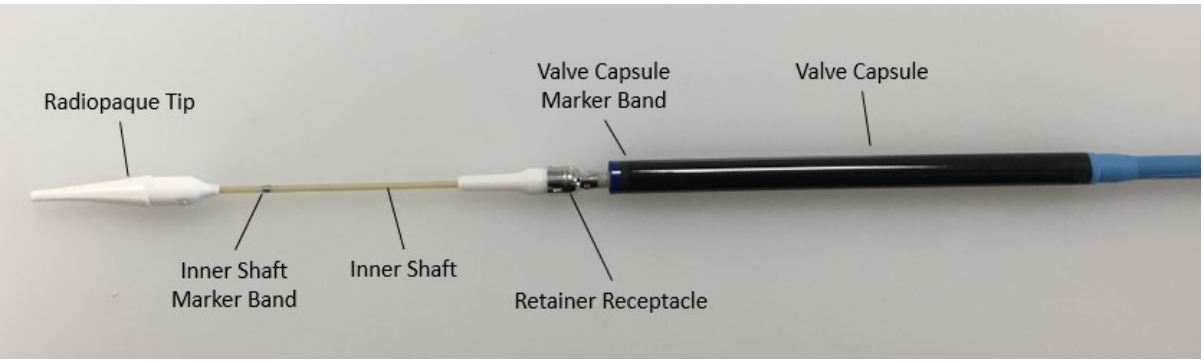

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3.2 Portico Instructions for Use

For instructions for use (IFU) of the Portico valve and the associated delivery and loading systems please refer to the following IFUs (Note: Model numbers for equivalent devices may vary based on respective geographies):

- Portico™ Transcatheter Heart Valve (Models PRT-23-IDE, PRT-25-IDE, PRT-27-IDE, and PRT-29-IDE)
- Portico™ Transfemoral Delivery Systems (Model PRT-DS-TF-18F-IDE and PRT-DS-TF-19F-IDE)
- Portico™ Alternative Access Delivery Systems (Model PRT-DS-ALT-18F-IDE and PRT-DS-ALT-19F-IDE)
- Portico™ Transfemoral/Alternative Access Loading Systems (Model PRT-LS-TFALT-18FID and PRT-LS-TFALT-19FID)
- FlexNav™ Delivery System (FN-DS-SM-IDE, FN-DS-LG-IDE)
- FlexNav™ Loading System (FN-LS-SM-IDE, FN-LS-LG-IDE)

4 Risk and Benefits of the Study Device and Clinical Study (Pivotal IDE and CAP)

Participation in the pivotal IDE and CAP is expected to be associated with a similar risk and benefits profile to other commercially-available TAVR systems.

Please refer to the IFU of the Portico Transcatheter Aortic Heart Valve (which includes a description of risks and benefits), the risks listed below and to the adverse events section in this protocol for a list of the potential adverse events.

[redacted]

4.1 Risks

There are potential risks associated with the use of transcatheter procedure with the study valve and commercially available control transcatheter valves. The potential risks 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
- Access site injury
- Allergic reaction to antiplatelet agents, contrast medium, anesthesia, or valve components
- Anaphylactic shock/toxic reaction
- Annulus rupture
- Aortic rupture
- Ascending aorta trauma
- Atrio-ventricular node block
- AV fistula
- Bleeding
- Cardiac arrhythmias
- Cardiovascular or vascular injury, such as perforation or damage (dissection) of vessels, ventricle, myocardium or valvular structures that may require intervention
- Conduction system injury
- Death
- Endocarditis
- Embolism: air, calcification or thrombus
- Exercise intolerance (weakness)
- Fever
- Heart failure
- Hematoma
- Hemodynamic compromise
- Hemolysis
- Hemolytic anemia
- Hemorrhage
- Hypotension or hypertension
- Immunological reaction
- Infection
- Leakage, regurgitation
- Left ventricular failure/rupture

[redacted]

- Left ventricular impairment (due to apical scar)
- Myocardial ischemia
- Mitral valve insufficiency
- Multi-organ failure
- Neurological changes including stroke/transient ischemic attack;
- Non-structural dysfunction (i.e., entrapment by pannus, paravalvular leak, inappropriate sizing or positioning)
- Pannus
- Paravalvular leak
- Pericardial effusion
- Perforation of the myocardium or a blood vessel
- Potential coronary obstruction
- Renal failure
- Renal insufficiency
- Respiratory failure (shortness of breath)
- Sepsis
- Septal rupture
- Stenosis (high gradient)
- Stroke
- Structural valve deterioration (i.e., calcification, leaflet tear)
- Systemic peripheral ischemia
- Tamponade
- Valve explant
- Valve embolization
- Valve migration or malposition
- Valve stenosis
- Valve thrombosis
- Ventricular failure (acute)
- Ventricular rupture
- Vessel dissection or spasm

[redacted]

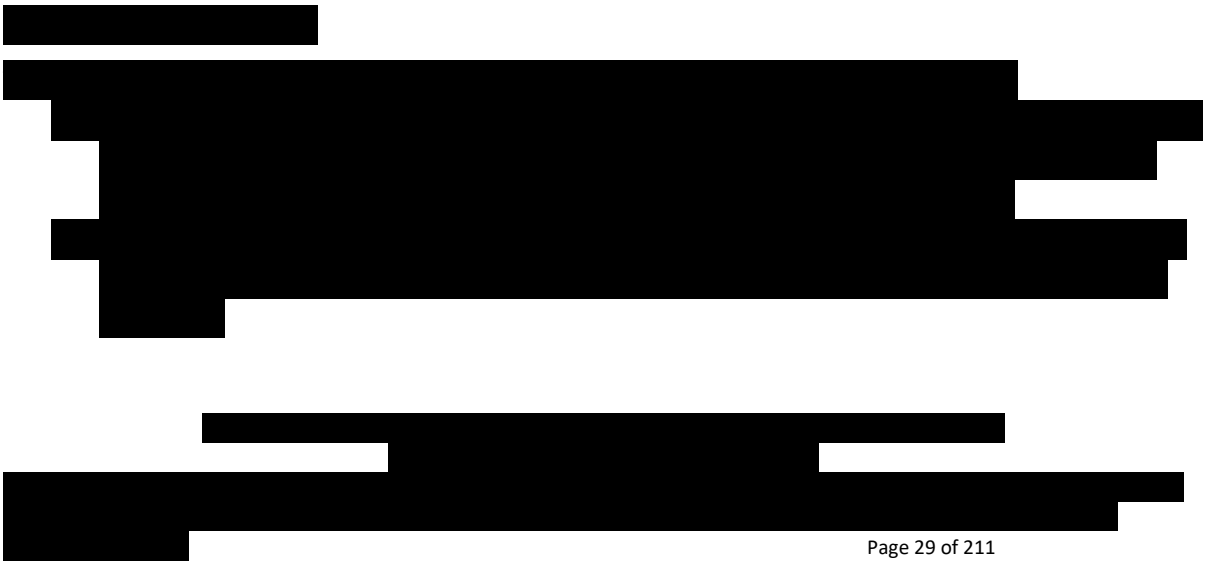
It is possible these complications could lead to:

- 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

All the listed risks may include the symptoms associated with the above mentioned medical conditions.

4.2 Gender-Based Risks

A TAVR literature and background information search, pertaining to sex or gender differences in the intended patient population, did not reveal either a gender disparity favoring one gender over the other, or a race or ethnic disparity. This review shows that in over 50 studies, the median female percentage is 52% with a maximum of 94% female participation.[39] It is however evidenced in the literature that the risks experienced in TAVR can be observed in a higher rate within the female groups. The CoreValve ADVANCE[40] study revealed that females experienced a higher rate of stroke, major vascular complications, and major bleeding. Similarly, Buchanan et al. (2011) concluded that female sex was a predictor of major vascular complications with females requiring more transfusion. No differences were noted amongst patients undergoing TAVI in composite safety and efficacy endpoints according to sex.[41] Female subjects, however, had a better 1 year survival rate in the Sapien PARTNER trial.[12,34] Also, Humphries et al. (2012) in a study of 641 consecutive patients (51.3% female) showed that female gender is associated with better short- and long-term survival after TAVR. This is also evidenced in the PARTNER 1A findings.



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4.4 Benefits

There are no guaranteed benefits from participation in this study. Implantation of the transcatheter heart valve in the annular position may result in one or more of the following: improved valvular function, acute alleviation of symptoms related to aortic stenosis, improved morbidity and mortality.

Additionally, information gained from the conduct of this study may be of benefit to other people with the same medical condition in the future. The long-term results of using the study valve are not known at the present time. Alternative treatments include palliative medical therapy, aortic balloon valvuloplasty, transcatheter aortic valve delivery and surgical replacement of the aortic valve.

5 Study Population (Pivotal IDE and CAP)

The PORTICO clinical study is limited to two subject cohorts with severe, symptomatic aortic stenosis who are determined to be at high or extreme operative risk for surgical aortic valve replacement. The operative risk determination of study candidates will be based on the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Risk Calculator. Subject case review

[redacted]

will be conducted by the Subject Selection Committee to determine the patient's eligibility to receive Portico valve.

These subject cohorts are defined as follows:

High risk cohort:

The **high risk** cohort is defined as subjects with severe aortic stenosis symptoms for whom conventional aortic valve replacement surgery is associated with high risk equivalent to an STS risk score that is ≥8%.

Extreme risk cohort:

The **extreme risk** cohort is defined as subjects with severe aortic stenosis symptoms and 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.

The surgical risk of study candidates will be determined by the heart team's interventional cardiologist(s) and cardiac surgeon(s) assessments taking into consideration the STS Adult Cardiac Surgery Risk Calculator.[35]

5.1 Inclusion Criteria

High Risk Cohort:

All candidates for the High Risk Cohort of this study must meet **all** the following inclusion criteria:

1. Subjects must have co-morbidities such that the surgeon and cardiologist Co-Investigators concur that the predicted risk of operative mortality is ≥15% or a minimum STS score of 8%. A candidate who does not meet the STS score criteria of ≥ 8% can be included in the study if a peer review by at least two surgeons concludes and documents that the patient's predicted risk of operative mortality is ≥15%. The surgeon's assessment of operative comorbidities not captured by the STS score must be documented in the study case report form as well as in the patient medical record.
2. Subject is 21 years of age or older at the time of consent.
3. Subject has senile degenerative aortic valve stenosis with echocardiographically derived criteria: mean gradient >40 mmHg or jet velocity greater than 4.0 m/s or Doppler Velocity Index <0.25 and an initial aortic valve area (AVA) of ≤ 1.0 cm^2

[redacted]

(indexed EOA ≤ 0.6 cm^2/m^2). (Qualifying AVA baseline measurement must be within 60 days prior to informed consent).

4. Subject has symptomatic aortic stenosis as demonstrated by NYHA Functional Classification of II, III, or IV.
5. The subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site.
6. The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits.
7. Subject's aortic annulus is 19-27mm diameter as measured by CT conducted within 12 months prior to informed consent. Note: if CT is contraindicated and/or not possible to be obtained for certain subjects, a 3D echo and non-contrast CT of chest and abdomen/pelvis may be accepted if approved by the subject selection committee.

Extreme Risk Cohort:

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

1. The subject, after formal consults by a cardiologist and two cardiovascular surgeons agree that medical factors preclude operation, based on a conclusion that the probability of death or serious, irreversible morbidity exceeds the probability of meaningful improvement. Specifically, the probability of death or serious, irreversible morbidity should exceed 50%. The surgeons' consult notes shall specify the medical or anatomic factors leading to that conclusion and include a printout of the calculation of the STS score to additionally identify the risks in these patients.

All Candidates:

Additionally, all candidates for the study must meet the following inclusion criteria for the TAVR Leaflet Motion Sub-study, until the minimum sub-study sample size has been achieved, as described in Appendix S. This sub-study is not applicable for subjects enrolled under protocol Version K or later (including CAP subjects) as the minimum sub-study sample size has been achieved:

Be willing and able to undergo, at both 30 days and 6 months post-implant, a Multi-Slice Computed Tomography (MSCT) scan (or TEE, if medically or technically contraindicated for a MSCT) of the heart and cardiac structures.

[redacted]

5.2 Exclusion Criteria

High and Extreme Risk Cohort:

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

1. Evidence of an acute myocardial infarction (defined as: ST Segment Elevation as evidenced on 12 Lead ECG) within 30 days prior to index procedure.
2. Aortic valve is a congenital unicuspid or congenital bicuspid valve, or is non-calcified as verified by echocardiography.
3. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation 3-4+).
4. Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to index procedure.
5. Pre-existing prosthetic heart valve or other implant in any valve position, prosthetic ring, severe circumferential mitral annular calcification (MAC) which is continuous with calcium in the LVOT, severe (greater than 3+) mitral insufficiency, or severe mitral stenosis with pulmonary compromise. ***Subjects with pre-existing surgical bioprosthetic aortic heart valve should be considered for the Valve-in-Valve registry.***
6. Blood dyscrasias as defined: leukopenia (WBC<3000 mm^3), acute anemia (Hb < 9 g/dL), thrombocytopenia (platelet count <50,000 cells/mm^3).
7. History of bleeding diathesis or coagulopathy.
8. Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support.
9. Untreated clinically significant coronary artery disease requiring revascularization.
10. Hemodynamic instability requiring inotropic support or mechanical heart assistance.
11. Need for emergency surgery for any reason.
12. Hypertrophic cardiomyopathy with or without obstruction (HOCM).
13. Severe ventricular dysfunction with LVEF <20% as measured by resting echocardiogram.
14. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
15. Active peptic ulcer or upper GI bleeding within 3 months prior to index procedure.
16. A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine (Ticlid), or clopidogrel (Plavix), or sensitivity to contrast media which cannot be adequately premedicated.
17. Recent (within 6 months prior to index procedure date) cerebrovascular accident (CVA) or a transient ischemic attack (TIA).

[redacted]

18. Renal insufficiency (creatinine > 3.0 mg/dL) and/or end stage renal disease requiring chronic dialysis.
19. Life expectancy < 12 months from the time of informed consent due to non-cardiac co-morbid conditions.
20. Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5cm or greater; marked tortuosity (hyperacute bend), aortic arch atheroma (especially if thick [> 5 mm], protruding or ulcerated) or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe "unfolding" and tortuosity of the thoracic aorta (applicable for transfemoral patients only).
21. Native aortic annulus size < 19 mm or > 27 mm per the baseline diagnostic imaging.
22. Aortic root angulation > 70° (applicable for transfemoral patients only).
23. Currently participating in an investigational drug or device study.
24. Active bacterial endocarditis within 6 months prior to the index procedure.
25. Bulky calcified aortic valve leaflets in close proximity to coronary ostia.
26. Non-calcified aortic annulus
27. Iliofemoral vessel characteristics that would preclude safe placement of the introducer sheath such as severe obstructive calcification, or severe tortuosity (applicable for transfemoral patients only).

5.3 Screening Process

At the time the patient agrees to participate after receiving information and all the patient's questions have been answered satisfactorily, the study informed consent form will be signed. Patients who sign an informed consent form and meet all the inclusion criteria and none of the exclusion criteria will be reviewed and confirmed by the Subject Selection Committee for participation eligibility. Subject selection should take place within 30 days from the date the subject provided informed consent. Once the subject is selected to participate in the study, baseline assessments and randomization (if applicable) can be completed. The index procedure should take place no later than 14 calendar days from subject enrollment.

Subjects who meet the subject selection criteria and are confirmed by the Subject Selection Committee will be assigned to cohorts based on their surgical risk level and either randomized into the pivotal IDE randomized cohort or enrolled into a study-defined registry (Roll-in or Valve-in-Valve), the FlexNav study or the CAP. Subjects who do not meet the selection criteria will not be scheduled for an implant procedure and will not be considered enrolled into the study.

If a subject is consented and undergoes study-specific testing (i.e., testing that would not be done if they were not being considered for the study) but is not enrolled in the study, the

subject should be followed for adverse events for 30 days from informed consent and then withdrawn from study participation.

For subjects consented under protocol version L or later, if a subject undergoes study-specific testing but does not undergo a Portico implant attempt with the FlexNav™ Delivery System the subject will not be considered enrolled in the study and will not require any further follow-up.

Figure 7 summarizes subjects' screening and enrollment flow.

Subject screening depends on the joint collaboration of investigators (including designated interventional cardiologist(s) and designated cardiac surgeon(s)) at each site. All suitable subjects must undergo the established institutional specific multidisciplinary team assessment to confirm both appropriateness for transcatheter aortic valve placement and high-risk designation. Both a cardiologist investigator and a cardiac surgeon investigator must be involved in the subject selection and screening process. All subjects evaluated for severe aortic stenosis in medical and surgical departments that are high or extreme risk candidates for AVR should be screened for study eligibility.

The investigators are responsible for ensuring subject eligibility. Study sites will maintain a log of all the screened subjects and subjects enrolled. Reasons for meeting study criteria but failing to be enrolled will be captured on the screening log and may be monitored by SJM.

5.3.1 Additional Exclusion Criteria (Transcatheter Access-Related)

For subjects who do not qualify for transfemoral access, the following exclusion criteria will be used to screen for an appropriate alternative access delivery method.

5.3.1.1 Transaortic Subject Cohort Specific Exclusion Criteria

1. Subject has pre-existing patent RIMA graft that would preclude access.
2. Subject has a hostile chest or other condition that complicates transaortic access.
3. Subject has a porcelain aorta, defined as an extensive circumferential calcification of the ascending aorta that would complicate TAo access.

For subjects enrolled under version L of the protocol, the following exclusion criteria apply for transaortic access using the FlexNav™ Delivery System:

1. Subject has a distance between the annular plane and the aortic access site <7 cm (2.8")
2. Subject has a distance between the annular plane and the separate introducer sheath distal tip <6 cm (2.4")

5.3.1.2 Subclavian/Axillary Subject Cohort Specific Exclusion Criteria

1. Subject's access vessel (subclavian/axillary) diameter will not allow for introduction of the applicable 18 Fr or 19 Fr delivery system.
2. Subject's subclavian/axillary arteries have severe calcification and/or tortuosity.

[redacted]

3. Subject‘s aortic root angulation is:
    - Left Subclavian/Left Axillary: >70°
    - Right Subclavian/Right Axillary: >30°
4. Subject has a history of patent LIMA/RIMA graft that would preclude access

For subjects enrolled under version L of the protocol, the following exclusion criteria apply for subclavian/axillary access using the FlexNav™ Delivery System:

1. Subject’s access vessel (subclavian/axillary) has a distance between the annular plane and the integrated sheath distal tip <17 cm (6.7")
2. Subject’s access vessel requires the delivery system to be advanced through a separate introducer sheath

For selection of the appropriate alternative access method, subjects will be screened using the access specific exclusion criteria, and the selection of the alternative access method will be based on the evaluation by the site and the Subject Selection Committee.

[redacted]

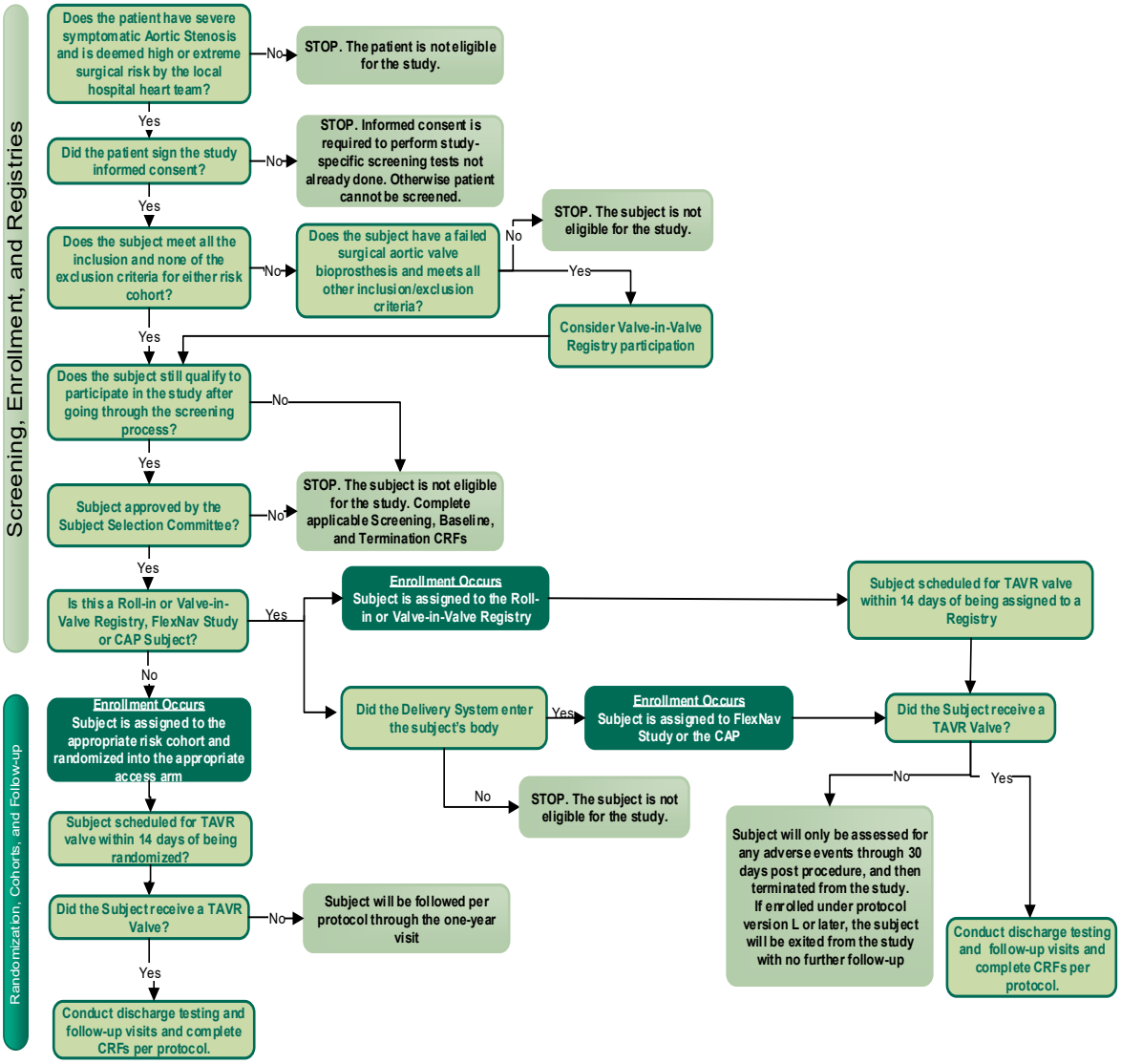


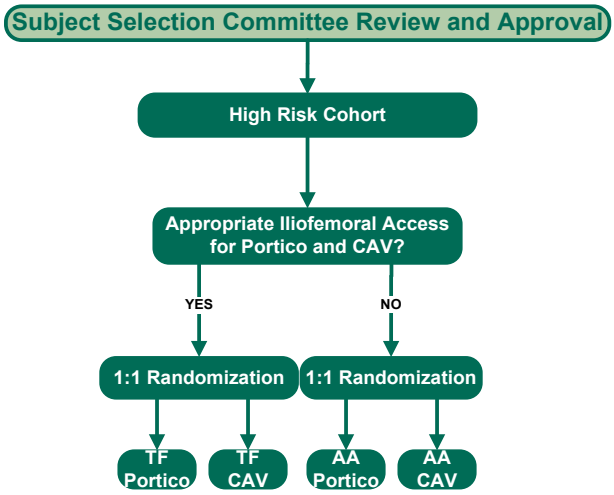
Figure 7: Study Conduct Flowchart (Pivotal IDE and CAP)

6 Subject Assignments

Subjects will be assigned to one of the following cohorts:

6.1 High Risk Cohort (Pivotal IDE)

High risk subjects with an annular size between 19-27mm who qualify for transfemoral access and have a suitable iliofemoral vasculature for both Portico valve and an FDA approved commercially available transcatheter valve (CAV) will be randomized into the transfemoral arm to receive either the Portico valve or the CAV. Subjects who do not qualify for the transfemoral access arm (iliofemoral vasculature is not suitable for both Portico and CAV) will be randomized within the alternative access arm to receive either the Portico valve or CAV (Figure 8).



TF=Transfemoral, CAV= Commercially Available Transcatheter Valve, AA=Alternative Access

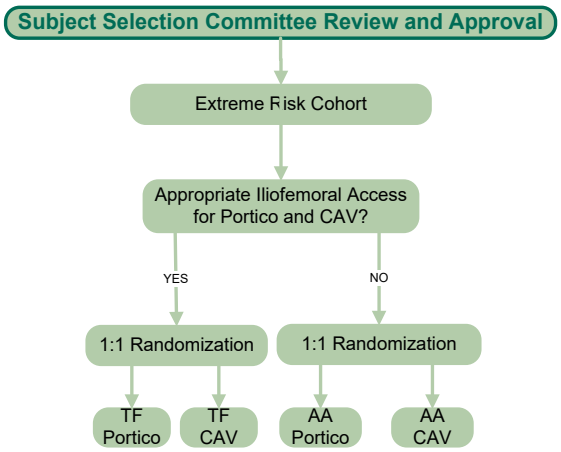
Figure 8. High Risk Cohort Flow Chart

6.2 Extreme Risk Cohort (Pivotal IDE)

Extreme risk subjects will be assigned to the Extreme Risk Cohort as follows:

Extreme risk subjects with annular size between 19-27mm who qualify for transfemoral access and have suitable iliofemoral vasculature suitable for both Portico and CAV will be randomized into the transfemoral arm to receive either the Portico valve or CAV. Subjects who do not qualify for the transfemoral access arm (iliofemoral vasculature is not suitable for both Portico and CAV) will be randomized within the alternative access arm to receive either the Portico valve or CAV (Figure 9).

[redacted]



TF=Transfemoral, CAV= Commercially Available Transcatheter Valve, AA=Alternative Access

Figure 9. Extreme Risk Cohort Flow Chart

6.3 Valve-in-Valve Registry

Subjects who have documented failed aortic surgical valve prosthesis and are deemed eligible to receive a transcatheter Portico valve into the existing bioprosthesis will be considered for eligibility in the Valve-in-Valve registry. The Valve-in-Valve registry will enroll up to 100 qualified subjects from the pivotal IDE trial or CAP.

Valve-in-valve registry subjects must meet all the applicable inclusion criteria and none of the applicable exclusion criteria for the high or extreme risk cohort (Sections 5.1 & 5.2).

Examples of criteria that may not apply include inclusion criterion numbers **3** and **4** (the bioprosthetic valve may be stenotic or require replacement due to other forms of structural valve deterioration), and exclusion criterion numbers **2, 3, 5** (existing surgical bioprosthetic aortic valve), **21**, and **26**. If the subject has a bioprosthetic valve in another location, the subjects will be excluded from the PORTICO clinical study.

Valve-in-valve subjects' data will not be included in the randomized population nor the primary data analysis; however, the data will be analyzed and presented separately to support an expanded indication for Valve-in-Valve use (Portico-in-SAVR).

All Valve-in-Valve subjects enrolled under protocol version L or later will have a Portico valve implanted using the FlexNav™ Delivery System. Implanting physicians will be required to have completed a minimum of one (1) roll-in subject in the FlexNav study before enrolling a subject in the IDE Valve-in-Valve registry.

6.4 Roll-in Registry

Prior to enrolling subjects in the pivotal IDE randomized cohort, sites will be required to complete a minimum of two (2) and up to three (3) roll-in patients per primary implanting physician. However, implanting physicians with prior Portico experience and with a minimum of 3 implants in the last 6 months will not be required to include roll-in patients.

[redacted]

For subjects enrolled under protocol version L or later, all primary implanting physicians irrespective of prior Portico implant experience will be required to complete a minimum of one (1) and up to three (3) roll-in patients using the FlexNav™ Delivery System.

All roll-in subjects will be added to the IDE Roll-in Registry. The roll-in subjects must meet all the inclusion criteria and none of the exclusion criteria and be approved by the Subject Selection Committee. These subjects will be followed per protocol for the duration of the study, or until subject's withdrawal or death. The roll-in subjects' data will not be included in the randomized population nor the primary data analysis; however, the data will be analyzed and presented separately.

6.5 FlexNav Study

High and extreme risk subjects with an annular size between 19-27mm with suitable anatomy for transfemoral or alternative access valve implantation using the FlexNav™ Delivery System (minimum vessel requirement ≥ 5mm) will be enrolled in the FlexNav study. All FlexNav study subjects will receive a Portico device (no randomization).

The number of roll-in patients required by a site before they can contribute to the FlexNav study will be at the discretion of the Sponsor. All roll-in subjects will be designated as such prior to enrollment and will be added to the IDE Roll-in Registry.

Following the successful completion of roll-in subjects, sites will enroll subjects into the FlexNav study. These enrolled subjects will be considered part of the 'analysis population'.

Analysis subject data (excluding roll-ins) will be summarized and presented separately to the randomized cohort in the PMA application.

6.6 Continued Access Protocol (CAP)

After the pivotal IDE trial has met its minimum sample-size for the randomized cohort and the FlexNav study, sites may choose to participate in the CAP and enroll high and extreme risk subjects with an annular size between 19-27mm with suitable anatomy for transfemoral or alternative access valve implantation. All CAP subjects will receive a Portico valve (no randomization). [redacted]

6.7 Screening

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

[redacted]

After subject informed consent is obtained, study-specific screening evaluation may be conducted to determine inclusion in the study. All cardiac medications and all medications given for cardiovascular effect may be continued at their prescribed dosages.

1. Demographics
2. Medical History
3. Canadian Cardiovascular Society (CCS) Angina Scale Assessment
4. Surgical Risk Assessment tools (STS Risk Score, and EuroSCORE II)
5. Forced Expiratory Volume (FEV1), if clinically indicated
6. Physical Exam
7. Echocardiography to include comprehensive transthoracic or transesophageal 2D echocardiogram, including assessment of aortic valve gradients (mean and peak), areas, indices, degree of regurgitation, cardiac output and cardiac index, left ventricle systolic function (global and segmental)
8. Lab Measurements (per Table 9, Table of Assessments)
9. 12 Lead Electrocardiogram (ECG)
10. Computed Tomography Scan with Angiography for chest, abdomen and pelvis: aortic root and valve annulus sizing, assessment of suitability of iliofemoral access, and determination of appropriate coaxial angles for optimizing the valve implantation procedure. CT scan performed up to 12 months prior to consent will be acceptable.
11. 3D Transesophageal Echocardiogram (TEE) if CT is contraindicated
12. New York Heart Association (NYHA) Functional Classification
13. Frailty Index Assessment
    a. Katz Index of Activities of Daily Living
    b. Grip strength
    c. 15 ft. walk
14. Coronary and aortic angiogram (arteriograms of the lower abdominal aorta to the femoral arteries), with runoff if clinically indicated. Coronary and aortic angio performed up to 12 months prior to consent will be acceptable.

6.8 Baseline Assessments

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

1. Chest X-ray
2. Cardiovascular medications documentation
3. Modified Rankin Scale (mRS)
4. NIH Stroke Scale (NIHSS)
5. Barthel Index
6. Quality of Life Measures (QoL) (For CAP subjects enrolled under Ver. K or later, only the KCCQ and EQ-5D are required.)
7. MMSE-2:SV
8. Six Minute Walk Test (6MWT) (Not required for CAP subjects enrolled under Ver. K or later)

[redacted]

9. Troponin or CK/CK-MB, INR (if subject is on Coumadin or Warfarin)

6.9 Subject Enrollment and Randomization

All subjects who meet the study eligibility requirements will be assigned into an applicable registry (Roll-in or Valve-in-Valve), the FlexNav study, the CAP or one of the pivotal IDE randomized cohorts for operability, followed by delivery method determination based on vascular access (Figure 10).

Subjects will be considered enrolled into the study after completion of all of the following steps:

1. Signed informed consent is obtained.
2. Based on the screening assessments, it is determined that the subject meets all of the inclusion and none of the exclusion criteria.
3. Subject is approved by the subject selection committee.
4. The trial cohort has been determined, and understood by the subject.
5. The subject is randomized (pivotal IDE only) or assigned to the appropriate registry or CAP.

In the FlexNav study and the CAP (under protocol version L), the subject will be considered enrolled once steps 1-4 above are complete and when the FlexNav™ Delivery System enters the subjects' body.

For the pivotal randomized IDE cohort, the subject will be randomized based on the cohort assignment as follows:

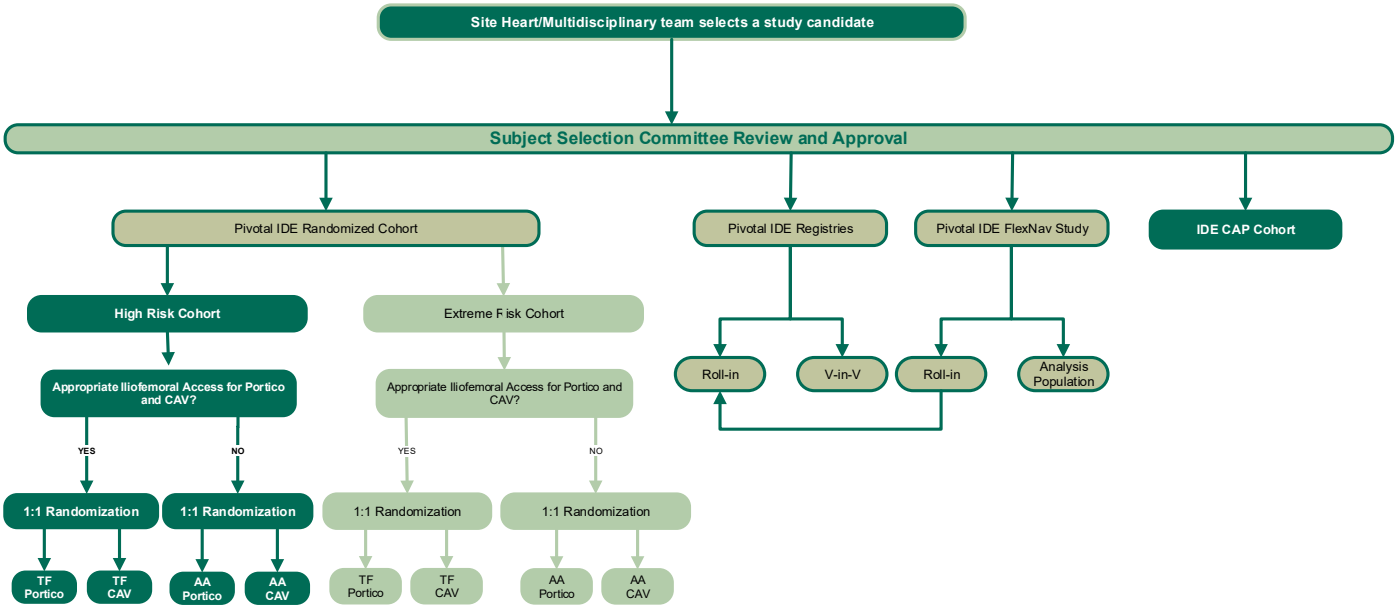
- The high risk cohort will be randomized against an FDA-approved and commercially-available transcatheter valve on a 1:1 basis.
- The extreme risk cohort will be randomized against an FDA-approved and commercially-available transcatheter valve on a 1:1 basis.

It is strongly recommended the implant procedure take place no later than 14 calendar days from subject enrollment/randomization

Once a subject is randomized in the pivotal IDE, crossover from one arm to the other is not allowed. However, following randomization or enrollment in the FlexNav Study, registry or the CAP, those subjects who are scheduled to receive a transcatheter valve via transfemoral access and found not to be suitable for this delivery modality (per the heart team medical decision) can receive a transcatheter valve using an alternate access modality and vice versa. However, this will be considered a protocol deviation unless multiple access routes were pre-approved by the Subject Selection Committee. The rationale for this decision must be documented.

In the pivotal IDE trial, when subjects are randomized to receive a CAV, the subject selection and procedure must follow the FDA-approved instructions for use (IFU).

[redacted]



TF=Transfemoral, CAV= FDA approved and commercially available transcatheter valve, AA=Alternative Access, V-in-V=Valve-in-Valve

Figure 10. PORTICO Clinical Study Flow Chart

[redacted]

7 Study Conduct (Pivotal IDE and CAP)

7.1 Subject Informed Consent

Prior to enrolling in the clinical investigation, subjects shall be fully informed of the details of clinical investigation participation as required by applicable regulations and the center's IRB. Informed consent must be obtained from each subject prior to any clinical investigation participation (including the study-specific screening phase), using the Informed Consent Form (ICF). The ICF must be signed and dated by the subject and by the person obtaining the consent.

The subject shall be provided ample time to meet with the Site Principal Investigator or site personnel conducting the consent, and must be given the opportunity to ask questions of and receive satisfactory answers. The subject will then be allowed additional time, if requested, to take a copy of the informed consent form home with him or her to allow for additional time to thoroughly review this documentation.

All information pertinent to the clinical investigation shall be provided in writing and in native, non-technical language that is understandable to the subject.

The process of informed consent shall avoid any coercion of or undue influence of patients to participate, not waive or appear to waive patient's legal rights, use language that is non-technical and understandable to the patient, provide ample time for the patient to consider participation, and include dated signatures of the patient and of the clinical investigator or person obtaining the consent.

Prior to the subject signing the ICF, the Investigator or authorized delegate will fully explain to the subject the nature of the research, clinical investigation procedures, anticipated benefits, and potential risks of participation in the clinical investigation. The Investigator or delegate will allow adequate time for the subject to read and review the informed consent form and to ask questions.

The Investigator or authorized delegate must document in the subject's medical records that the subject was consented and the date on which the consent was obtained. The original signed informed consent form will be retained in the subject's clinical investigation records. A copy of the signed informed consent form and will be provided to the subject and a copy placed in the subject's medical record.

If new information becomes available during the clinical investigation that can significantly affect a subject's future health and medical care, or willingness to continue in the study, that information will be provided to the subject(s) in written form.

7.2 Subject Selection Committee

The Subject Selection Committee will be responsible for ensuring all subjects' clinical eligibility and technical suitability for implant according to the protocol. The composition and detailed process is further defined in the Subject Selection Committee Charter.

[redacted]

Subject Selection Committee review and approval is required prior to enrollment of any subject into any randomized cohort, FlexNav study, registry or the CAP.

7.3 Index Procedure

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

The index procedure should occur within 14 calendar days following subject randomization, registry or CAP assignment. The procedure must be performed according to the instructions for use (IFU) for the assigned device. Antiplatelet/Anticoagulation and other medications should be administered per the standard of care.

Cardiac enzymes must be obtained prior to the index procedure and within approximately 72 hours after the procedure.

Cardiac rhythm should be monitored and recorded at the following time points:

1. Upon crossing native valve with the guidewire
2. Upon positioning of the guidewire
3. Prior to valvuloplasty (if performed)
4. Immediately post valvuloplasty (if performed)
5. Before valve crosses the AV valve
6. After valve crosses the annulus
7. After valve is deployed in final position

The following data should be collected pre and post implant:

1. Aortic systolic/diastolic pressure, Mean aortic pressure, Mean AV gradient, Peak AV gradient
2. Simultaneous Aortic and LV pressure measurements for valve area calculation
3. A supra-aortic angiogram for valve performance and coronary patency
4. Device deployment information
5. If performed, right atrial (RA) pressure, pulmonary artery (PA) systolic/diastolic pressure, Mean PA pressure, pulmonary wedge pressure (PCWP)

The activated clotting time (ACT) should be monitored and recorded on source documentation during the procedure and adjusted to attempt to keep the subject's ACT>250 seconds.

If an enrolled subject is not implanted with a TAVR valve, the following will apply:

- Randomized subjects will be followed per protocol through the one-year visit, as part of the primary analysis intent to treat (ITT) population, and then terminated from the study.
- Registry-assigned (Roll-in or Valve-in-Valve), FlexNav study and CAP subjects will be assessed for any adverse events through 30 days post procedure, and then terminated from the study.

[redacted]

Post Procedure Activities

1. Echocardiogram within 24-48 hours of procedure (or at discharge)
2. Troponin, or CK / CK-MB should be collected within approximately 12-24 hours after procedure, 24 hours thereafter, and at approximately 72 hours after the procedure (*or at discharge, if patient is discharged prior to 72 hours post procedure*)
3. BUN and Creatinine should be collected within 72 hours after index procedure

7.4 Discharge Visit (or up to 7 days post procedure, whichever occurs first)

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

1. Physical exam
2. CCS Status of angina
3. Modified Rankin Scale (mRS)
4. NIH Stroke Scale (NIHSS)
5. Barthel Index
6. Echocardiogram (if not performed during the post procedure testing within 24-48 hours after procedure)
7. 12 lead ECG (for subjects receiving a new permanent pacemaker, ECG should be completed showing the underlying rhythm as well as the current pacing programming)
8. Cardiovascular medications documentation
9. Adverse events assessment
10. Lab Measurements (per Table 9, Table of Assessments)

7.5 Follow-up Visits

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

7.6 30 Day Visit (±7 days)

The 30 Day visit will take place 30 days (±7 days) post index procedure, and will include the following:

[redacted]

1. Physical exam
2. CCS status of angina
3. Modified Rankin Scale (mRS)
4. NIH Stroke Scale (NIHSS)
5. Barthel Index
6. Echocardiography
7. 12 lead ECG (for subjects receiving a new permanent pacemaker, ECG should be completed showing the underlying rhythm as well as the current pacing programming)
8. Lab Measurements (per Table 9, Table of Assessments)
9. NYHA Functional Classification
10. Frailty Index assessment
11. Quality of Life Measures (For CAP subjects enrolled under Ver. K or later, only the KCCQ and EQ-5D are required.)
12. MMSE-2:SV
13. Six Minute Walk Test (6MWT) (Not required for CAP subjects enrolled under Ver. K or later)
14. Cardiovascular medications
15. Adverse events assessment
16. Multi-Slice CT (MSCT) Scan (or TEE if MSCT is medically or technically contraindicated), as described in Appendix S: TAVR Leaflet Motion Sub-study until sub-study enrollment is complete. (Not required for subjects enrolled under Ver. K or later)

7.7 6 Month (±30 days) (This visit is not required for CAP subjects enrolled under Ver. K or later)

The following data must be collected at 6 Months post index procedure:

1. Physical exam
2. CCS status of angina
3. Modified Rankin Scale (mRS)
4. NIH Stroke Scale (NIHSS)
5. Barthel Index
6. Echocardiography
7. 12 lead ECG (for subjects receiving a new permanent pacemaker, ECG should be completed showing the underlying rhythm as well as the current pacing programming)
8. Lab Measurements (per Table 9, Table of Assessments)
9. NYHA Functional Classification
10. Frailty Index assessment
11. Quality of Life Measures (QoL)
12. MMSE-2:SV

[redacted]

13. Six Minute Walk Test (6MWT)
14. Cardiovascular medications
15. Adverse events assessment
    Multi-Slice CT (MSCT) Scan (or TEE if MSCT is medically or technically contraindicated), as described in Appendix S: TAVR Leaflet Motion Sub-study until sub-study enrollment is complete.

7.8 One-Year Visit (-30 days, + 45 days)

The following data must be collected at one-year (-30 days, + 45 days) post index procedure:

1. Physical exam
2. CCS status of angina
3. Modified Rankin Scale (mRS)
4. NIH Stroke Scale (NIHSS)
5. Barthel Index
6. Echocardiography
7. 12 lead ECG (for subjects receiving a new permanent pacemaker, ECG should be completed showing the underlying rhythm as well as the current pacing programming)
8. Lab Measurements (per Table 9, Table of Assessments)
9. NYHA Functional Classification
10. Frailty Index assessment
11. Quality of Life Measures (QoL) (For CAP subjects enrolled under Ver. K or later, only the KCCQ and EQ-5D are required.)
12. MMSE-2:SV
13. Six Minute Walk Test (6MWT) (Not required for CAP subjects enrolled under Ver. K or later)
14. Cardiovascular medications documentation
15. Adverse events assessment

7.9 Annual Visits (2 year, 3 year, 4 year and 5 year (±60 days))

The following data should be collected at years 2, 3, 4 and 5 post index procedure:

1. Physical exam
2. CCS status of angina
3. NYHA Functional Classification
4. Cardiovascular medications
5. Adverse event assessment
6. NIH Stroke Scale (NIHSS)
7. Modified Rankin Stroke Scale
8. Barthel Index

[redacted]

9. 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)
10. Echocardiography
11. Quality of Life Measures (QoL) (For CAP subjects enrolled under Ver. K or later, only the KCCQ and EQ-5D are required.)

7.10 Unscheduled Visits

7.10.1 Unscheduled Visits for Evaluation of Suspected Neurological Event

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

1. Neurological Assessment conducted by a neurologist or a neurology fellow
2. NIH Stroke Scale
3. Modified Rankin Scale (mRS)

7.11 Evaluation of Ischemic Stroke and Myocardial Infarction

All ischemic strokes and myocardial infarctions should be investigated per standard of care to include an assessment for leaflet motion (TEE is recommended) and evaluation of sources for an embolus (e.g., left atrial appendage).

7.12 Subject Withdrawal

All living and enrolled subjects are required to complete clinical follow-up. A study subject that has been withdrawn from the study will not be replaced. All data collected up to the point of their study discontinuation will be reported and included in the data analysis as applicable.

If a subject cannot be reached for a follow-up visit, the investigator will complete a Protocol Deviation Case Report Form. The efforts undertaken to contact the subject, referring physicians, including internists as well as cardiologists, family members, or other alternate contacts should be noted in the subject's records. These efforts should include at least three (3) attempts of telephone contact on separate dates, and a registered letter before considering the subject lost-to-follow-up.

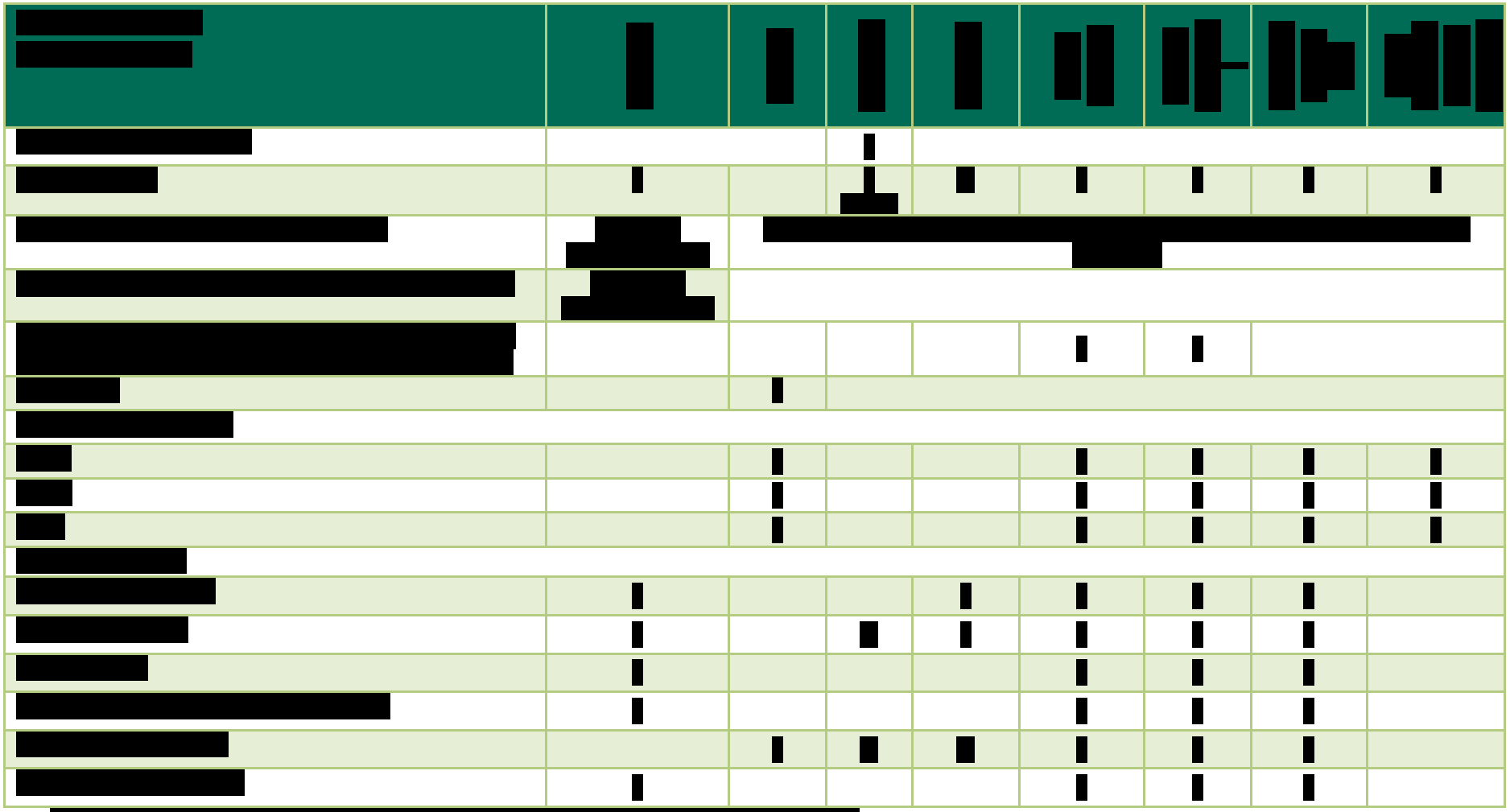
7.13 Table of Assessments

Subject data and data collection timeline are summarized in Table 9.

* FDA's Current Thinking Regarding Neurological Assessments for Transcatheter Valve Trials (Revised: August 25, 2011)

[redacted]

Table 9. Table of Assessments (IDE Pivotal Trial and CAP)



7.14 Study Activity Definitions

Table 10 summarizes the study activity definitions.

Table 10. Study Activity Definitions

Study Activity	Definition
Adverse Event Assessment	All adverse events will be documented according to Adverse Events section 9.
Lab Measurements	The following lab tests will be collected at each required interval per Table 9, Table of Assessments: • CBC and Platelet count • BUN • Creatinine • BNP or ProBNP • INR (only if subject is taking Coumadin or Warfarin) • Albumin (for Frailty Index) • Troponin or CK / CK-MB
Barthel Index	A scale used to measure performance in activities of daily living (ADL). Each performance item is rated on this scale with a given number of points assigned to each level or ranking. It uses ten variables describing ADL and mobility where a higher number is associated with a greater likelihood of being able to live at home with a degree of independence following discharge from the hospital.
Cardiac Rhythm Monitoring	Assessment of heart rate, QRS and dominant rhythm pre-procedure, during and after the procedure.
CCS Angina	Canadian Cardiovascular Society grading of angina pectoris (Appendix I)
Coronary and Aortic Angiogram (with runoff if clinically indicated)	Coronary and aortic imaging conducted per institutional guidelines.
CT Scan/MSCT Scan	Computed Tomography (CT) with minimum of 64-detectors is recommended for image acquisition. The complete cardiac cycle will be captured, encompassing both the diastolic and systolic phases of the heart (Multi-Slice). Scan records that leave the institution will be modified to remove subject identifiers. CT Scan images will be provided to a CT core lab for evaluation.
Echocardiography	Each site is responsible for performing the echocardiogram according to the Echocardiographic protocol. Echocardiogram will be provided to an Echocardiographic core lab for evaluation.
12 lead Electrocardiogram (ECG)	Assessment of heart rate, QRS and dominant rhythm using 12 lead ECG. For subjects receiving a permanent pacemaker during the study, an ECG will be completed showing the underlying rhythm as well as the current pacing programming. Electrocardiograms will be provided to an Electrocardiographic core lab for evaluation.
FEV1	The volume exhaled during the first second of a forced expiratory maneuver started from the level of total lung capacity.
Frailty Index	Used to assess if frailty is a high risk factor for subjects prior to enrollment.
Informed Consent	An IRB- and Sponsor-approved Informed Consent must be obtained before subject enrollment
Medical History	General medical history of the subject:

[redacted]

	• Previous cardiovascular operations • Coexisting cardiovascular diseases • Clinically significant peripheral vascular disease (PVD) • Previous peripheral vascular operations • Other coexisting medical conditions (e.g., diabetes, hypertension, kidney and lung disease, endocarditis)
Cardiovascular Medications	Only the following Cardiovascular medications will be collected at each visit: • Beta Blockers • Calcium Channel Blockers • Anticoagulants • Antiplatelet agents including Aspirin • Diuretics • Ace-Inhibitors • Angiotensin Receptor Blocker (ARBs) • Hydralazine • Antiarrhythmics
MMSE-2:SV	Mini Mental State Exam -2:SV is a screening tool for cognitive impairment
Modified Rankin Stroke Scale*	The modified Rankin Scale (mRS) is functional measurement to assess the degree of disability or dependence in the daily activities of people who have suffered a stroke. *This assessment must be completed by a rater who has a current certificate that demonstrates completion of an accredited training program for this stroke scale, or by a neurologist or neurology fellow.
Multidisciplinary Heart Team	All suitable subjects must undergo the established institutional specific multidisciplinary/Heart team (as defined in the CMS Decision Memo for TAVR (CAG-00430N) assessment to confirm both appropriateness for transcatheter aortic valve placement and high-risk designation. Both co- investigators must be involved in the subject selection and screening process. All subjects evaluated for severe aortic stenosis in medical and surgical departments that are high or extreme risk candidates for AVR should be screened for study eligibility.
Neurological Assessment	A neurological assessment will be conducted on subjects 90 days (±14 days) after any neurological event (stroke, TIA, encephalopathy). The neurological assessment should be conducted by a **neurologist or a neurology fellow** and should include physical functioning as well as a basic neurocognitive evaluation to cover the major domains.
NIH Stroke Scale**	The NIHSS is a 15-item neurologic examination stroke scale used to evaluate the effect of acute cerebral infarction on the levels of consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss. Certified personnel rate the subject's ability to answer questions and perform activities. Ratings for each item are scored with 3 to 5 grades with 0 as normal, and there is an allowance for untestable items. The single subject assessment requires less than 10 minutes to complete. ** National Institute of Health (NIH) Stroke Scale - All personnel conducting any study required NIHSS evaluations are required to have received training and certification per nationally accepted guidelines such as American Stroke Association, or American Academy of Neurology, or National Institute of

[redacted]

	Neurological Disorders and Stroke, or must be a neurologist or neurology fellow.
NYHA Classification	The New York Heart Association (NYHA) Functional Classification provides a simple way of classifying the extent of heart failure. It places subjects in one of four categories based on how much they are limited during physical activity; the limitations/symptoms are in regards to normal breathing and varying degrees in shortness of breath and or angina pain
Physical Assessment	At the baseline visit the following measurement must be assessed: • Age on consent date • Gender • Ethnicity • Height (only at baseline) The following measurements must be assessed at all visits: • Weight • Heart rate • Heart rhythm • General physical state
Procedure Information	Procedure information must be collected including: • Pre-procedure Information • Procedure Information • Post-procedure Information
Quality of Life Measures	EQ-5D 3L is a standardized instrument for use as a measure of health outcomes. The process to complete this questionnaire is indicated. SF-36 is a survey of subject health to determine cost-effectiveness of a health treatment KCCQ is a 23 item questionnaire that quantifies physical function, symptoms, social function, self-efficacy and knowledge, and quality of life
Surgical Risk Assessment	Surgical Risk Assessment tools consist of EuroSCORE II and STS Risk Score.
Six Minute Walk Test	The six-minute walk test (6MWT) measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface. The goal is for the individual to walk as far as possible in six minutes. The individual is allowed to self-pace and rest as needed as they traverse back and forth along a marked walkway.
Subject Selection Committee	The Subject Selection Committee will be responsible for ensuring all subjects' clinical eligibility and technical suitability for implant according to the protocol. The composition and detailed process is further defined in the Subject Selection Committee Charter.

7.15 Determination of the Aortic Annulus Size

[redacted]

The PORTICO clinical study requires that all annulus sizing be determined using a CT scan for all participants in the study. However, if 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 if approved by the Subject Selection Committee.

7.16 Core Laboratories

Independent core laboratories will be utilized for evaluating CT images, ECG rhythms and echocardiograms for the pivotal IDE cohort. The same core laboratories and processes will be used for the CT images and echocardiograms for the CAP cohort.

Each site is responsible for performing the CT scan and echocardiogram according to the core laboratory imaging protocol. Also, ECG data collection and reporting must be completed according to the ECG core laboratory protocol.

CT scan, echocardiography, and ECG data will be forwarded to the respective core laboratories for interpretation. It is the responsibility of each site to perform the local interpretation of the echocardiogram for clinical assessment.

The core laboratories will not be responsible for notifying the site of any abnormal findings that are identified in the study. The responsibility of the core laboratories is to complete the data collection forms and submit these to the Sponsor.

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

7.17 Medications

If a subject is taking any of the following classes of cardiovascular medications, they will be reviewed at each applicable visit and documented on the visit CRF:

1. Beta Blockers
2. Calcium Channel Blockers
3. Anticoagulants
4. Antiplatelet agents including Aspirin
5. Diuretics
6. Ace-Inhibitors
7. Angiotensin Receptor Blocker (ARBs)
8. Hydralazine
9. Antiarrhythmics

[redacted]

8 Data Collection and Management (Pivotal IDE and CAP)

A study-specific Data Management Plan will be created to document measures ensuring data quality and completeness. All required study data will be recorded on study-specific electronic Case Report Forms (eCRFs), as provided by SJM.

Subject data will be collected using a web-based remote electronic data capture (EDC/RDC) system supported by SJM. The Investigator or his/her designee is responsible for timely recording of all data onto the study eCRFs. The data used to complete these forms has to be verified by authorized site personnel.

If additional documentation (e.g., procedural notes, discharge summaries) is required for any reason (such as an adverse event) it should be appropriately redacted (e.g., blacked out) to remove the subject's name and any additional identifying information, and the subject's unique study ID code inserted, prior to being submitted to SJM.

8.1 Source Data and Subject Files

The Investigator has to keep a written or electronic subject file for every subject participating in the clinical study. In this subject file, the available demographic and medical information of a subject has to be documented, in particular the following:

1. Name
2. Birth date
3. Sex
4. Height
5. Weight
6. Ethnicity (if available)
7. Medical history
8. Concomitant diseases and concomitant medications (including changes during the course of the study)
9. Statement of entry into the study
10. Study identification
11. Date of informed consent
12. All study visit dates
13. Predefined performed examinations and clinical findings
14. Observed AEs and source documents related to the AE
15. Reason for withdrawal from the study, if applicable.

It should be possible to verify the inclusion and exclusion criteria for the study from the available data in this file.

It must be possible for the investigator to identify each subject by using this subject file.

Additionally, any other documents with source data that were generated by technical equipment have to be filed. This may include 12 lead ECG recordings, X-ray films, CT scans and laboratory value listings, as applicable. All these documents have to bear at least the subject identification. The medical evaluation of such records should be

[redacted]

documented as necessary. All data recorded on the eCRF must be found in the subject's source data.

9 Adverse Events (Pivotal IDE and CAP)

9.1 Unanticipated Adverse Device Effect

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 the device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3 (s)).

9.2 Anticipated Adverse Events

Adverse Events will be classified as either a Serious Adverse Event or an Adverse Event.

Serious Adverse Event- is defined as those adverse events resulting in the following: death, life-threatening adverse event, unplanned inpatient hospitalization or prolongation of existing hospital stay, persistent or significant disability/incapacity, congenital anomaly/birth defect or medically significant event.

Adverse Event - is defined as an event which does not meet the definition of a serious adverse event but is still an undesirable clinical occurrence and is a negative change from baseline, whether or not device related

9.3 Potential Anticipated Adverse Events

The potential anticipated adverse events include but are not limited to, the following:

1. Access site complications (e.g., pain, bleeding, infection, hematoma, pseudoaneurysm, etc.)
2. Acute coronary obstruction
3. Acute myocardial infarction
4. Access site injury
5. Allergic reaction to antiplatelet agents, contrast medium, anesthesia, or valve components
6. Anaphylactic shock/toxic reaction
7. Annulus rupture
8. Aortic rupture
9. Ascending aorta trauma
10. Atrio-ventricular node block
11. AV fistula
12. Bleeding
13. Cardiac arrhythmias
14. Cardiovascular or vascular injury, such as perforation or damage (dissection) of vessels, ventricle, myocardium or valvular structures that may require intervention
15. Conduction system injury
16. Death

[redacted]

17. Endocarditis
18. Embolism: air, calcification or thrombus
19. Exercise intolerance (weakness)
20. Fever
21. Heart failure
22. Hematoma
23. Hemodynamic compromise
24. Hemolysis
25. Hemolytic anemia
26. Hemorrhage
27. Hypotension or hypertension
28. Immunological reaction
29. Infection
30. Leakage, regurgitation
31. Left ventricular failure/rupture
32. Left ventricular impairment (due to apical scar)
33. Myocardial ischemia
34. Mitral valve insufficiency
35. Multi-organ failure
36. Neurological changes including stroke/transient ischemic attack;
37. Non-structural dysfunction (i.e., entrapment by pannus, paravalvular leak, inappropriate sizing or positioning)
38. Pannus
39. Paravalvular leak
40. Pericardial effusion
41. Perforation of the myocardium or a blood vessel
42. Potential coronary obstruction
43. Renal failure
44. Renal insufficiency
45. Respiratory failure (shortness of breath)
46. Sepsis
47. Septal rupture
48. Stenosis (high gradient)
49. Stroke
50. Structural valve deterioration (i.e., calcification, leaflet tear)
51. Systemic peripheral ischemia
52. Tamponade
53. Valve explant
54. Valve embolization
55. Valve migration or malposition
56. Valve stenosis
57. Valve thrombosis
58. Ventricular failure (acute)
59. Ventricular rupture

[redacted]

60. Vessel dissection or spasm

It is possible these complications could lead to:

1. Transfusion
2. Conversion to open surgical procedure
3. Reoperation
4. Emergent balloon valvuloplasty
5. Emergent percutaneous coronary intervention (PCI)
6. Emergent surgery (i.e., coronary artery bypass, heart valve replacement)
7. Explantation
8. Permanent disability
9. Death
10. Permanent pacemaker

There are no known interactions of the Portico Transcatheter Heart Valve with concomitant medical treatment.

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

9.4 Adverse Event Reporting

9.4.1 Reporting All Adverse Events

Investigators are responsible for promptly reporting ALL adverse events to SJM by completing the Adverse Event eCRF. Serious Adverse Events must be reported to the Sponsor no later than three (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. All unresolved adverse events should be followed by the investigator until resolution.

For subjects enrolled under version L or later of the protocol, the reporting of adverse events will commence at the time of the Portico implant attempt.

9.4.2 Paravalvular Leak

Paravalvular leak should be reported as an adverse event in the following cases:

- When paravalvular leak remains moderate or severe after balloon dilatation, or
- When valve-in-valve, surgical conversion or other intervention is required for any grade of paravalvular leak after implant.

9.4.3 Reporting Unanticipated Adverse Device Effects

An investigator shall submit to the Sponsor and the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation no later than three (3) calendar days from the day the site personnel first learns of the effect.

[redacted]

9.5 Classification of Causal Relationships

For each adverse event, the causal relationship between the adverse event and the Portico Transcatheter Heart Valve and Delivery System, and the causal relationship between the event and the index procedure, will be assessed by the Investigator and reported as such on the Adverse Event case report form. Final causal relationships for events related to primary and secondary endpoint criteria according to the Valve Academic Research Consortium (VARC 2) definitions will be determined per CEC adjudication.

9.6 Subject Death

Subject death is a potential outcome of a Serious Adverse Event that will be reported within three (3) calendar days from the time of the site personnel knowledge of the event, if the event occurs from the time of signed informed consent until the subject exits the study.

Subject death will be subdivided specifically denoting cardiovascular and non-cardiovascular mortality:

1. Cardiovascular mortality includes any one of the following criteria:
    a. Any death due to proximate cardiac cause (such as MI, tamponade, worsening heart failure)
    b. Sudden or unwitnessed death
    c. Death of unknown cause
    d. All procedure-related deaths including those related to a complication of the procedure or treatment for a complication of the procedure
    e. Death caused by non-coronary vascular conditions such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease.
2. Non-cardiovascular mortality includes any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide)

An Adverse Event CRF, Death CRF and relevant source documentation including the death certificate should be submitted to SJM.

10 Independent Boards (Pivotal IDE and CAP)

10.1 Clinical Events Committee

An independent Clinical Events Committee (CEC), consisting of, at a minimum, an interventional cardiologist, cardiologist, cardiothoracic surgeon, and a neurologist will adjudicate events related to primary and secondary endpoint criteria according to the Valve Academic Research Consortium (VARC 2) definitions. The CEC will have final adjudication responsibilities for subject outcomes related to primary and secondary endpoint criteria. Members of the CEC cannot be investigators on the PORTICO Clinical

[redacted]

Study. A charter that is agreed upon by both the Sponsor and the independent CEC governs the event adjudication process.

10.2 Data Safety Monitoring Board (DSMB) (Pivotal IDE)

An independent Data Safety Monitoring Board (DSMB) will be utilized to regularly review study progress with regard to safety of the pivotal IDE trial. Members of the DSMB cannot be investigators on the PORTICO Clinical Study. Board membership may consist of, but not limited to, a cardiologist, cardiac surgeon, neurologists, and a biostatistician.

The primary responsibilities of the DSMB include:

- Review and validate the subject sample (i.e., review inclusion/exclusion deviations and other protocol deviations)
- Provide oversight for issues affecting general subject welfare
- Recommend premature study termination or modification of the trial for any perceived safety concerns

At any time during the course of the study, the DSMB may offer opinions or make formal recommendations concerning aspects of the study that impact subject safety (e.g., safety-related protocol changes or input regarding adverse event rates associated with the investigational study). Additionally, the DSMB may act as an advisory panel for questions regarding informed consent, subject enrollment, protocol implementation, study endpoints, data discrepancies, and other issues that may present during the course of the study. A charter that is agreed upon by both the sponsor and the DSMB members governs the role and responsibility of this committee.

The recommendations of the DSMB are not binding, and all final decisions related to modifications to the clinical investigational protocol rest with the Sponsor.

11 Statistical Methods and Analysis (Pivotal IDE)

This section describes the statistical methods and analysis of the pivotal IDE randomized cohort unless otherwise specified. The analysis will be performed on combined high-risk cohort and extreme-risk cohort.

11.1 Analysis Populations

The primary analysis will be based on the intention-to-treat (ITT) population. The ITT population is defined [redacted]

Additional populations will be used to confirm the results of the ITT population.

[redacted]

[redacted]

11.2 Randomization and Stratification

[redacted]

11.3 Primary Endpoints

11.3.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is the composite endpoint of all-cause mortality or disabling stroke at one year. This endpoint will be evaluated by a non-inferiority test comparing the Portico test group to the control (CAV) group, and the primary analysis will be conducted on the ITT population. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

11.3.2 Primary Safety Endpoint

The primary safety endpoint is the non-hierarchical composite endpoint of all-cause mortality, disabling stroke, life-threatening bleeding requiring blood transfusion, acute kidney injury requiring dialysis, or major vascular complications at 30 days. This endpoint will be evaluated by a non-inferiority test comparing Portico test group to the control group, and the primary analysis will be conducted on the ITT population. [redacted]

[redacted]

11.4 Sample Size Calculations

[redacted]

[redacted]

11.4.1 Sample Size for the Primary Effectiveness Endpoint

[redacted]

[redacted]

11.4.2 Sample Size for the Primary Safety Endpoint

[redacted]

11.4.3 Total Sample Size

The total sample size required for evaluating the primary effectiveness and safety endpoints is 750 and 750 subjects respectively. Thus the total sample size is 750 for the study.

[redacted]

11.5 Secondary Endpoints

All secondary endpoints are defined in section 1.3. Among these, 4 have hypotheses to be tested. The secondary study hypotheses are:

- Severe aortic regurgitation (AR) at one year
- Kansas City Cardiomyopathy Questionnaire (KCCQ) at one year
- Moderate or severe aortic regurgitation at one year

[redacted]

- 6-minute walk at one year

Non-inferiority tests will be performed for each endpoint. [redacted]

11.6 Multiplicity Adjustment

[redacted]

[redacted]

[redacted]

11.7.4 Analysis of Descriptive Endpoints

The descriptive endpoints listed in section 1.3 will be summarized using descriptive statistics including mean, standard deviation, median and range for continuous data and count and percentage for categorical data.

[redacted]

[redacted]

11.10 Statistical Methods and Analysis (FlexNav Study, Registries and CAP)

[redacted]

12 Study Termination/Withdrawal (Pivotal IDE and CAP)

Active subject participation in the pivotal IDE is expected to last for five (5) years after index procedure unless the subject was randomized or assigned to a registry or FlexNav study but not implanted with a TAVR valve. Enrolled CAP subjects successfully implanted with a Portico valve will be followed for a minimum of one year and up to 5 years or upon study completion (whichever is reached first).

If an enrolled subject was not implanted with a TAVR valve, the following will apply:

- Randomized subjects will be followed per protocol through to the one-year visit, as part of the primary analysis intent to treat (ITT) population, and then terminated from the study.
- Registry-assigned (Roll-in or VIV Registry), FlexNav study or CAP subjects will be assessed for any adverse events through 30 days post procedure, and then terminated from the study.

The study will be closed at the investigational site following the distribution of the final clinical study report for all study locations. A copy of the final report will be provided to the IRB and Competent Authorities, if applicable, and acknowledgement requested.

Early termination of the study by either SJM or the Investigator, if applicable, will be communicated to the IRB.

Upon completion of subject participation in this study, the subject will be followed-up in accordance with institutional standards.

Possible reasons for early termination of the study and/or investigation site's participation in the study may include, but are not limited to:

- Request from the Clinical Investigation Site Principal Investigator
- Delivery system or device fails to perform as intended
- Occurrence of UADE which cannot be prevented in future cases
- SJM management decision to discontinue the study

[redacted]

- Request from Regulatory bodies
- Site's noncompliance with the requirements of the CIP and/or applicable laws and regulations
- Falsification of data or any other breach of ethics or scientific principles

Subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the subject is otherwise entitled and withdrawal from the study will not jeopardize their future medical care or their relationship with the Principal Investigator. Subjects will be asked what the reason for termination is but have the right not to answer.

The Principal Investigator may withdraw a subject from the study at any time if s/he believes it is in the subject's best interest.

The subject's future care will not be changed by a decision, voluntary or otherwise, to withdraw from the study. All reasonable efforts should be made to retain the subject in the clinical study until completion of the clinical study.

Reasons for subject's termination or withdrawal include, but are not limited to, the following:

- Subject death (in case of subject death, cause must be documented)
- Subject and/or family request, if applicable
- Subject non-compliance
- Subject lost to follow-up, defined as the following: a subject will be considered "lost to follow-up" after a minimum of 3 documented phone calls of a physician or designee at the study site to the subject or emergency contact and a letter sent to the last known address
- Subject's participation terminated by the Principal Investigator
- Study discontinued due to management decision by sponsor or request from Regulatory bodies
- Investigational site ends participation in the study

The study will be terminated according to locally applicable regulations. If applicable, the study may be temporarily suspended or terminated, either at the local, national, or international level, at the request of the IRB and/or the FDA. Justification and request for resuming the clinical investigation after suspension will be communicated to the IRB and the FDA.

[redacted]

13 Study Management (Pivotal IDE and CAP)

SJM, as the study sponsor, is responsible for:

- the design, overall conduct, analysis, and reporting of the results from this study as described in this CIP
- conducting CIP and technical training of the Principal Investigator and Co-Investigator(s)
- conducting CIP training of clinical staff, including but not limited to, research coordinator(s), echocardiographers, procedural staff
- monitoring the study
- performing those actions necessary to protect the rights of subjects and the scientific credibility of this study is conducted
- selecting qualified study Investigators, study monitors and research staff
- safety reporting to Competent Authorities
- providing support from a Field Clinical Specialist at each Portico valve implant
- providing a proctor as support for each Portico valve implant until the proctor/SJM determines the site can function independently

SJM reserves the right to obtain data clarification and/or additional medical documentation on subjects enrolled in this study until the study is terminated or closed by study final report.

The Sponsor of this study and manufacturer of the investigational device is:

[redacted]

SJM will retain, at a minimum, the following reports, records, publications:

- Signed Clinical Investigation Plan and all amendments
- Blank, revision controlled eCRFs
- Informed Consent Form template, and all IRB-approved versions
- Signed Study Agreements and all amendments completed
- Investigator Financial Disclosure information and all updates thereto
- IRB approval letters
- Regulatory approval letters
- All significant correspondence relating to the conduct of this study between SJM the study site, and IRB
- Signed CVs and professional licenses (if applicable) for all study personnel
- Training records relevant to conduct of the Clinical Investigation
- CIP/device related training records for all applicable study personnel

[redacted]

- Site personnel signatures and documentation of the Investigator's delegation of study related responsibilities
- Investigational device inventory information including the date, quantity, and unique identifier of all investigational devices shipped and received
- Appropriate tracking of each investigational device to include implant, explant, return, and analysis
- Publication Agreement
- IRB Registration Number
- List of IRB voting members (optional)
- Insurance Certificate
- Relevant Source Documentation (de-identified).

13.1 Study Investigators

Study Investigators are those who have been qualified and sufficiently trained by SJM on the study CIP requirements. Implanting Study Investigators have to complete required training as per the Training Plan prior to implanting the Portico Transcatheter Heart Valve.

13.2 National Principal Investigators

[redacted]

13.3 Investigator Responsibilities

[redacted]

13.4 Reports

[redacted]

13.5 Records

[redacted]

13.6 Record Retention

[redacted]

[redacted]

13.7 Confidentiality

All subject information collected during the course of this study will be kept strictly confidential according to applicable country-specific laws and regulations. All data and information concerning subjects and their participation in this study are considered confidential by Sponsor, and its affiliates (located in the U.S.A. and European Economic Area (EEA), and other countries), and other people who work for Sponsor to provide services related to the device and this study (collectively referred to as “SJM”). All public reporting of the results of the study will eliminate identifiable references to the subjects. Information on paper will be kept in secured locations. Electronic information will be kept on password-protected computers.

[redacted]

[redacted]

Study subjects have a right to gain access and to correct inaccuracies in information about them as permitted by applicable law. In order to help keep subject medical records and personal information confidential only certain authorized investigators and sponsor personnel, or approved contracted agents of the sponsor, will have access to confidential records. These include researchers in the hospital who are part of this study, the sponsor and its affiliates and representatives that perform study-related services who may be located in the USA, European Economic Area (EEA) and other countries. The IRB and other regulatory authorities also have the right to inspect and copy records pertinent to this study. It is necessary for them to review study data, portions of study subject records and information so that they can follow the study progress, which may include without limitation:

1. monitor the accuracy and completeness of the study
2. perform scientific analysis and develop the medical product
3. and/or obtain approval to market the medical products in the USA, Canada, EEA, and other countries.

Any information about subjects that leaves the institution conducting the study will be modified to remove certain information that could identify the subject (e.g., subject's name, address, and hospital number) and only be identifiable by a study ID code. Study data provided to sponsor that is published in medical journals and/or presented at scientific conferences will not allow the identification of study subjects.

The results of the study will be made available to the sponsor and its affiliates (located in the U.S.A., EEA, and other countries) along with other people who work for the sponsor to provide services related to the device and this study and study center.

A summary of the information on all subjects may be provided to governmental agencies (including regulatory agencies), regulatory authorities in the U.S.A., Canada, EEA and other countries who may also need to review study data and portions of medical records. Results from this study may also be published in scientific journals or presented at conferences as an oral or poster presentation; however, the identity of a study subject will not be disclosed.

13.8 Amendment Procedure

If an amendment becomes necessary during the study, the site along with SJM will submit the CIP amendment to the IRB. SJM will submit the amendment to the FDA, as required. Prior approval from the FDA and IRB will need to be obtained, when applicable, prior to the implementation of the change except in an emergency situation to protect the health and welfare of the subject(s) as deemed necessary by the Principal Investigator.

[redacted]

A justification statement shall be included with each amended section of the CIP documentation, and the version number and dates of amendments will be documented.

13.9 Ethical Basis

The PORTICO clinical study will be performed in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) and 21 CFR Parts 50 and 56.

This clinical investigation will be performed in accordance with the World Medical Association Declaration of Helsinki and 21 CFR parts 54 and 812.

IRB approval letter should clearly identify:

- the date of the meeting
- duration of approval or expiration date of approval
- the approved version of the Clinical Investigation Plan
- the approved version of the informed consent form and any other advertising or subject recruitment materials
- the approved version of the Instructions for Use (IFU)

Approval from the IRB is necessary prior to the start of the investigation. The original approval is to be filed in the Investigator Study Binder and a copy of the approval is provided to SJM prior to the first investigational assessment.

Any amendments to the CIP should be submitted to the FDA. Approval of amendments shall be obtained in written form from the FDA and IRB prior to implementation.

The IRB will be informed about SAEs, UADEs, and protocol deviations in accordance with local and national requirements.

13.10 Insurance

Subjects will be allowed to participate in the study regardless of their personal health insurance status.

13.11 Subpopulations

The PORTICO clinical study will include study patients with severe, symptomatic aortic stenosis that can be considered as one of three subpopulations:

- High operative risk for surgical aortic valve replacement
- Extreme operative risk for surgical aortic valve replacement
- Patients at either high or extreme operative risk who will have a TAVR valve implanted in an existing failed bioprosthetic surgical aortic valve.

[redacted]

13.12 Underrepresented Group Considerations

Since findings based on data collected from trials are commonly used to support the application of therapies across the general population, it is important that the enrolled patient population be as representative as possible of the eligible population in terms of the racial, ethnic and gender mix.

The PORTICO clinical study inclusion and exclusion criteria do not unduly exclude any particular underrepresented group. In order to facilitate access to the study by underrepresented groups, the PORTICO clinical study will be conducted at sites throughout the United States and Australia and will consist of urban as well as rural facilities. Steps (e.g., translation of ICF to native language, financial hardship program, etc.) will be taken to ensure inclusion of underrepresented groups.

13.13 Study Monitoring

Investigational sites will be monitored to ensure the study is being conducted in accordance with this Clinical Investigation Plan, Investigator Agreement, applicable laws and regulations and SJM policies and procedures. Qualified clinical representatives will be selected to monitor this study. If required, a study-specific Monitoring Plan will be created. The Monitoring Plan will be in accordance with SJM procedures and will be updated as appropriate.

[redacted]

13.14 Regulatory Inspections

The Investigator and/or designee should contact SJM immediately upon notification of an impending FDA inspection.

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

An Investigator, or designee, shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to inspect and copy all records relating to an investigation.

An Investigator shall permit authorized FDA employees to inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator,

[redacted]

to the sponsor or IRB have not been submitted or are incomplete, inaccurate, false, or misleading.

[redacted]

13.16 Protocol Deviation

The Principal Investigator and delegates are required to adhere to the Clinical Investigation Plan, signed Study Agreement, applicable national or local laws and regulations, and any conditions required by the reviewing IRB or applicable regulatory authorities.

A protocol deviation is used to describe situations in which the CIP was not followed. All deviations must be reported to SJM on the Protocol Deviation Case Report Form. Deviations must be reported to the IRB per their requirements. Any corrective and preventive actions required by the IRB must be completed by the site.

The Investigator must notify SJM and the IRB (as required by the IRB's requirements) of any deviation from the Investigation Plan to protect the life or physical well-being of a subject in an emergency as soon as possible, but no later than 5 working days after the deviation has occurred.

SJM retains the right to terminate the participation of a study Investigator for any of, but not limited to, the following reasons:

- Concern for subject safety and welfare
- Failure to secure informed consent prior to any study activity
- Failure to report unanticipated adverse device effects without unjustified delay
- Repeated non-compliance with this Investigation Plan or the Study Agreement
- Inability to successfully implement this Investigation Plan
- Violation of the Declaration of Helsinki
- Violation of applicable national or local laws and regulations
- Falsification of data, or any other breach of ethics or scientific principles
- Loss of or unaccounted use of investigational device inventory
- Management decision by SJM

[redacted]

13.17 Device Accountability

The study site must maintain device accountability records documenting the receipt, expiration date, and final disposition (e.g., subject ID if implanted, attempted, or returned to SJM) of all investigational devices. The unique device identifiers and date received must be documented on the log for all valves and delivery systems upon receipt and include the initials of the person completing the log. All devices that are opened must be accounted for on the device accountability log, even if they are not used.

SJM must also maintain device accountability documenting all shipments and returns of investigational devices by unique device identifier, date, and person completing the log. Storage locations for the investigational devices will be locked with access restricted only to investigators or designee.

13.18 Economic and Quality of Life Analysis

[redacted]

13.19 Publications

Upon receiving Investigational Device Exemption from FDA, the PORTICO clinical study will be registered on www.clinicaltrials.gov. The trial will adhere to the publication principles of the International Committee of Medical Journal Editors (ICMJE).

[redacted]

13.20 Investigational Site Start-up

13.20.1 Study Initiation Visit

Prior to beginning the study, SJM personnel will contact the Investigator to discuss the CIP and review the data requirements in detail.

[redacted]

13.20.2 Site Activation

[redacted]

14 Sponsor Contact Information

[redacted]

15 Bibliography

[redacted]

48. [redacted]

16 APPENDICES

Appendix A: Abbreviations

Abbreviation	Term
6MWT	Six Minute Walk Test
AA	Alternative Access
ACC	American College of Cardiology
ACT	Activated Clotting Time
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AHA	American Heart Association
ARB	Angiotensin Receptor Blocker
AS	Aortic Stenosis
AV	Aortic Valve
AVA	Aortic Valve Area
AVR	Aortic Valve Replacement
BARC	Bleeding Academic Research Consortium
BNP	B-type Natriuretic Peptide
CAD	Coronary Artery Disease
CAP	Continued Access Protocol
CAV	FDA Approved and Commercially Available Transcatheter Valve
CBC	Complete Blood Count
CCS	Canadian Cardiovascular Society
CE	Conformité Européene (European Conformity)
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CMS	Centers for Medicare & Medicaid Services
CPB	Cardiopulmonary Bypass
eCRF	Electronic Case Report Form
CT	Computed Tomography
CV	Curriculum Vitae
CVA	Cerebral Vascular Accident
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
Echo	Echocardiography
eDC	Electronic Data Capture
EEA	European Economic Area
EF	Ejection Fraction

[redacted]

Abbreviation	Term
EOA	Effective Orifice Area
EU	European Union
FDA	Food and Drug Administration
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
IRB	Institutional Review Board
ITT	Intent To Treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
Kg	Kilogram
LBBB	Left Bundle Branch Block
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
MAC	Mitral Annular Calcification
MI	Myocardial Infarction
MMSE	Mini-mental state examination
MR	Mitral Regurgitation
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
MSCT	Multi-Slice Computed Tomography
NCD	National Coverage Determination
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
PAVR	Percutaneous Aortic Valve Replacement
PMA	Premarket Approval
PVD	Peripheral Vascular Disease
PVL	Paravalvular Leak
RA	Right Atrium
RV	Right Ventricular
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event

[redacted]

Abbreviation	Term
SAV	Surgical Aortic Valve
SAVR	Surgical Aortic Valve Replacement
SD	Standard Deviation
SJM	St. Jude Medical, Cardiovascular Division
SSC	Subject Selection Committee
STS	Society of Thoracic Surgeons
TA	Trans Apical
TAV	Transcatheter Aortic Valve
TAVI	Transcatheter Aortic Valve Implantation
TAVR	Transcatheter Aortic Valve Replacement
TEE	Transesophageal Echocardiogram (same as TOE)
TF	Trans Femoral
TIA	Transient Ischemia Attack
TAo	Transaortic
TTE	Transthoracic Echocardiogram
UADE	Unanticipated Adverse Device Effect
US	United States (same as USA)
USA	United States of America (same as US)
VARC 2	Valve Academic Research Consortium 2
VIV	Valve in Valve
WBC	White Blood Cell
WMA	World Medical Association

[redacted]

[redacted]

Appendix C: 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 h after the index procedure)** New ischemic symptoms (e.g., chest pain or shortness of breath), or new ischemic signs (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, or imaging evidence of new loss of viable myocardium or new wall motion abnormality), ***AND*** Elevated cardiac biomarkers within 72 h after the index procedure consisting of at least one sample post-procedure with a peak value exceeding 15x upper reference limit (troponin) or 5x for CK-MB. If cardiac biomarkers are increased at baseline (>99th percentile), a further increase of at least 50% post-procedure is required AND the peak value must exceed the previously stated limit. **Spontaneous MI (greater than (>) 72 h after the index procedure)** Any one of the following criteria: • Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with evidence of myocardial ischemia with at least one of the following: ○ Symptoms of ischaemia ○ ECG changes indicative of new ischemia [new ST-T changes or new Left Bundle Branch Block (LBBB)] ○ New pathological Q waves in at least two contiguous leads ○ Imaging evidence of new loss of viable myocardium or new wall motion abnormality • Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST-segment elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/ or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. • Pathological findings of an acute myocardial infarction.
Stroke (FDA/VARC 2)	This study is following the FDA's definition of Stroke per FDA's Current Thinking Regarding Neurological Assessments for Transcatheter Valve Trials (Revised: 25 Aug 2011) and VARC 2 (2012) *1. Definitions:* a. Stroke: Stroke is an acute episode of focal or global neurological dysfunction caused by the brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction.

[redacted]

Source	Definition
	Subclassifications 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 h) compared with baseline **Stage 1**

[redacted]

Source	Definition
	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 **<u>Stage 2</u>** Increase in serum creatinine to 200% to 299% (2.0 to 2.99 X increase compared with baseline) or Urine output <0.5 ml/kg per hour for > 12 but < 24 hours **<u>Stage 3</u>** 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 <u>≥</u> 24 hours or anuria for <u>≥</u> 12 hours. *Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.*
Vascular Access Site and Access-Related Complications (VARC 2)	**Major vascular complications** • Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm or • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) ***leading to*** death, life-threatening or major bleeding*, visceral ischaemia or neurological impairment or • Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage or • The use of unplanned endovascular or surgical intervention ***associated*** with death, major bleeding, visceral ischaemia or neurological impairment or • Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram or • Surgery for access site-related nerve injury or • Permanent access site-related nerve injury **Minor vascular complications** • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneuysms, hematomas, percutaneous closure device failure) ***not leading to*** death, life-threatening or major bleeding*, visceral ischaemia or neurological impairment or • Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage or • Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication or • Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft) or **Percutaneous closure device failure** Failure of a closure device to achieve haemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)

[redacted]

Source	Definition			
Acute Device Success (VARC 2 with modifications)	1. Acute device success defined as: ○ Absence of procedural mortality ○ Correct positioning of a single prosthetic heart valve into the proper anatomical location ○ Intended performance of the prosthetic heart valve (mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, no moderate or severe prosthetic valve regurgitation) ○ Successful access was obtained as intended by group assignment Device success is a 'technical' composite endpoint meant to characterize the acute device and procedural factors which underlie vascular access, delivery, and performance of the TAVI system. Echocardiography should be routinely utilized as the standard for measuring prosthetic valve stenosis and regurgitation immediately after TAVI, and should always be performed in a resting state, either within 24–48 h after the index procedure or before hospital discharge.			
FDA	Individual Patient Success 1. Acute device success 2. Discharged alive from the hospital without device-related major AEs (Includes AI ≤ 1+) 3. Survival to one year with: ○ No disabling stroke ○ No device-or procedure-related mortality ○ NYHA class ≤ 2, or improvement in NYHA class by at least 1 level from baseline ○ No re-hospitalizations for valve related complications/dysfunction or CHF due to aortic valve related causes 4. No pacemaker dependency at 1 year (Excluding subjects with pre-procedural conduction abnormalities)			
Prosthetic Valve Stenosis Criteria ***In conditions of normal or near normal stroke volume (50–70 ml).*** **(VARC 2)**	**Parameter**	**Normal**	**Mild Stenosis**	**Moderate/ severe Stenosis**
	Peak velocity (m/s)	less than (<) 3	3–4	greater than (>) 4
	Mean gradient (mm Hg)	less than (<) 20	20–40	greater than (>) 40
	Doppler velocity index	greater than or equal to (≥) 0.35	0.35–0.25	less than (<) 0.25
	Effective orifice area (cm^2)	greater than (>) 1.1*	1.1–0.8	less than (<) 0.80
Prosthetic Valve Regurgitation Criteria (VARC 2)	**Diastolic flow reversal in the descending aorta (semi-quantitative parameters)**			
	Diastolic flow reversal in the descending aorta *PW Doppler*	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic

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

[redacted]

Source	Definition			
	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

[redacted]

Appendix D: Surgical Risk Assessment Tools

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

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

[redacted]

Appendix E: Quality of Life – EQ-5D 3L

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

Mobility

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

Self-Care

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

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

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

Pain/Discomfort

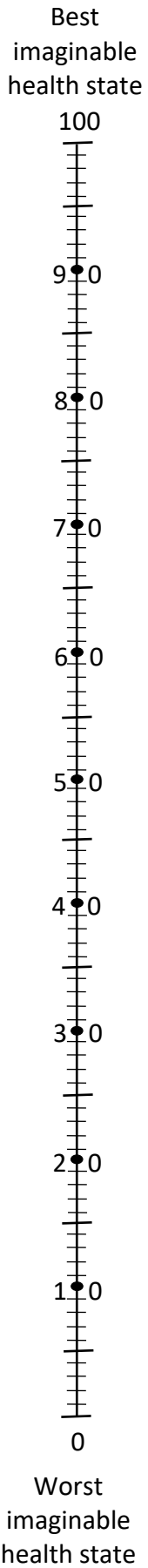
I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety/Depression

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

[redacted]

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



[redacted]

Appendix F: 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

[redacted]

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

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

[redacted]

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?

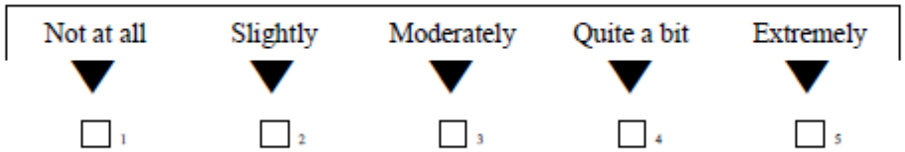
	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Were limited in the kind of work or other activities	☐ 1	☐ 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)?

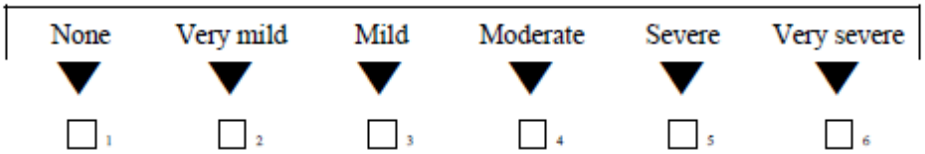
	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Did work or other activities less carefully than usual	☐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

[redacted]

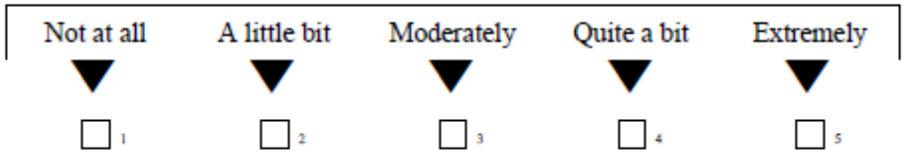
6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**



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



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



[redacted]

9. **These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. 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 <u>past 4 weeks</u>…**

	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 <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> 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

[redacted]

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!

[redacted]

Appendix G: Quality of Life – Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KC Cardiomyopathy Questionnaire

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

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

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

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

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

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

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

Original US English

[redacted]

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

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

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

It has been ...

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

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

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

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

It has been ...

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

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

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

Original US English

[redacted]

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

It has been ...

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

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

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

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

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

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

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

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

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

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

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

Original US English

[redacted]

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

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

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

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

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

Original US English

[redacted]

Appendix H: Mini-Mental State Examination (MMSE-2)

MMSE-2™

Standard Version

Blue Form

Date of examination ___/___/___ Examiner _____

Name _____ Age _____ Sex _____

Years of school completed _____ Purpose of exam _____

Assessment of level of consciousness

Alert/ Responsive | Drowsy | Stuporous | Comatose/ Unresponsive

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

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

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

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

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

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

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

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[redacted]

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

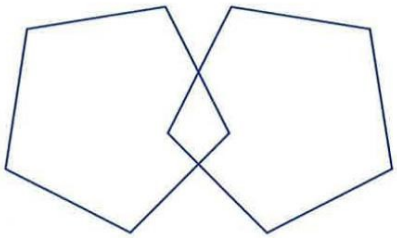
MMSE-2:SV total raw score ☐ (30 max. points)

[redacted]

Sample

CLOSE YOUR EYES

[redacted]



[redacted]

Appendix I: Canadian Cardiovascular Society grading of angina pectoris

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

[redacted]

Appendix J: Frailty Assessment

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

1. Katz Index of Independence in Activities of Daily Living
2. Grip Strength
3. 15 Foot walk test

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:_____		

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

Grasp 1_____ Grasp 2_____ Grasp3_____
Average_____

[redacted]

15 Foot Walk _____seconds

Men	*Cutoff for grip strength (Kg) criterion for frailty*
BMI ≤ 24	≤ 29
BMI 24.1-26	≤ 30
BMI 26.1-28	≤ 30
BMI > 28	≤ 32

Women	*Cutoff for grip strength (Kg) criterion for frailty*
BMI ≤ 23	≤ 17
BMI 23.1-26	≤ 17.3
BMI 26.1-29	≤ 18
BMI > 29	≤ 21

(Appendix, Fried et al)

Appendix K: Structured Interview for the Modified Rankin Scale (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, i.e., the order presented.

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

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

Question: Does the person require constant care?

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

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

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

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

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

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

1_No significant disability; symptoms present but not 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.

[redacted]

Appendix N: 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.

Appendix O: ATS Guidelines for the Six Minute Walk Test

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

SAFETY ISSUES

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.

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.

[redacted]

- 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."***

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."***

[redacted]

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.

[redacted]

Appendix P: 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

[redacted]

The Barthel ADL Index: Guidelines

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

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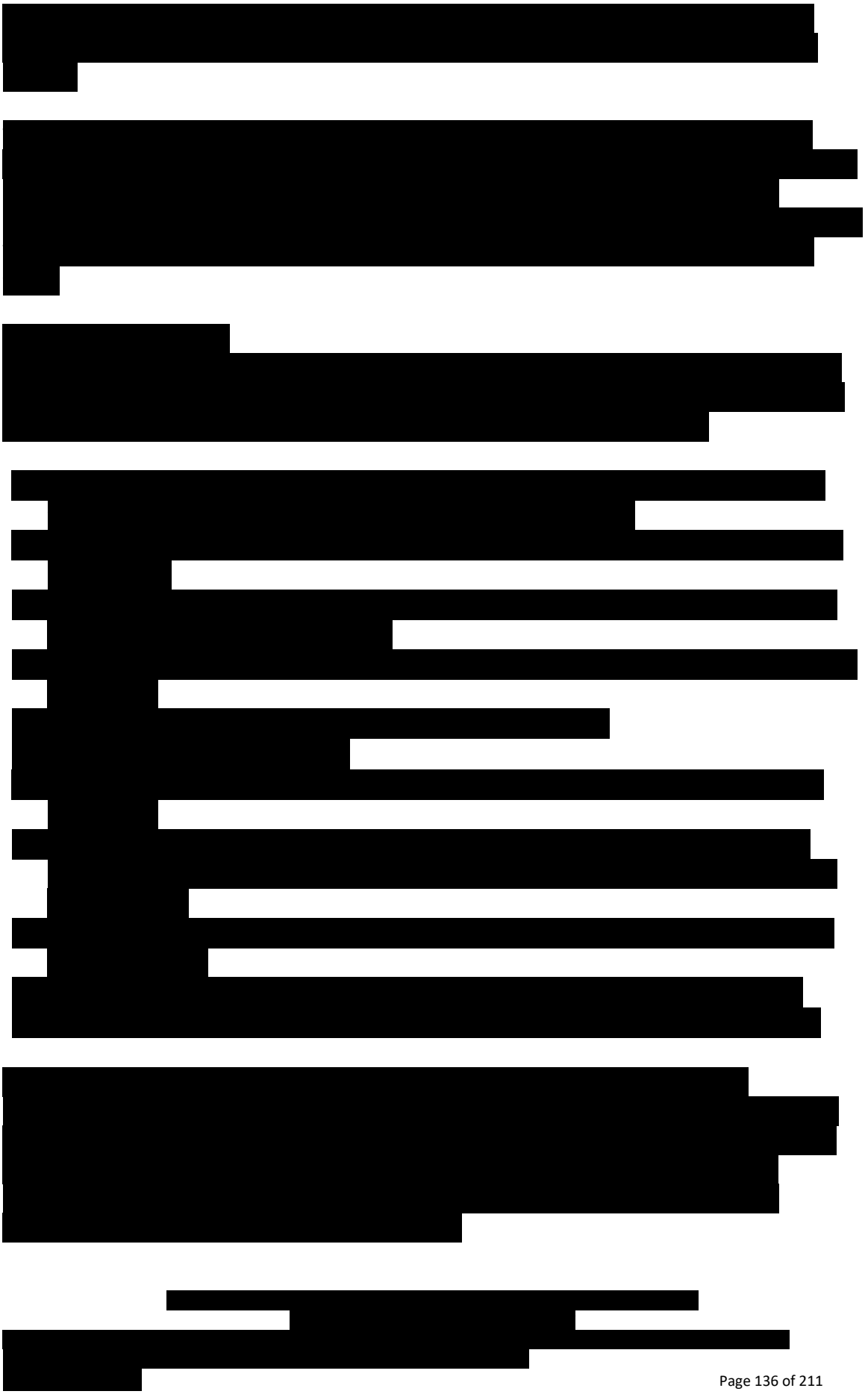

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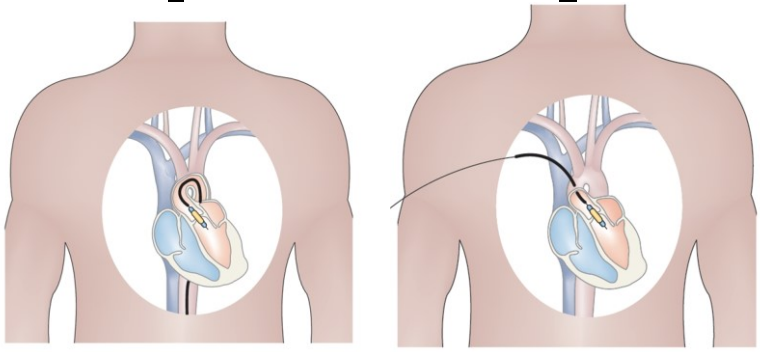

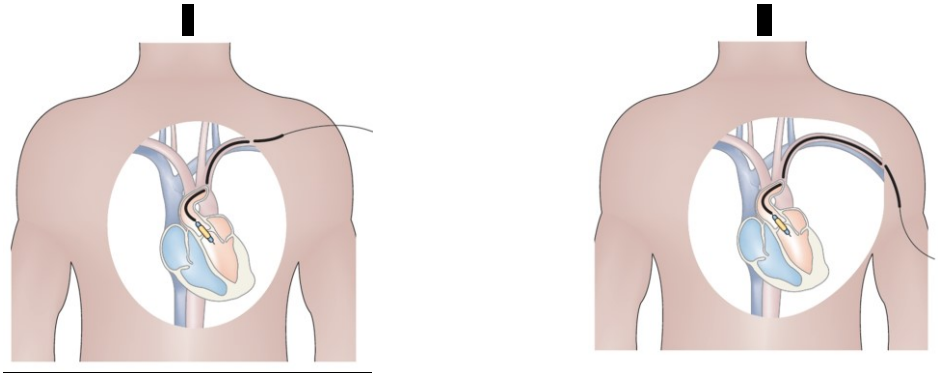

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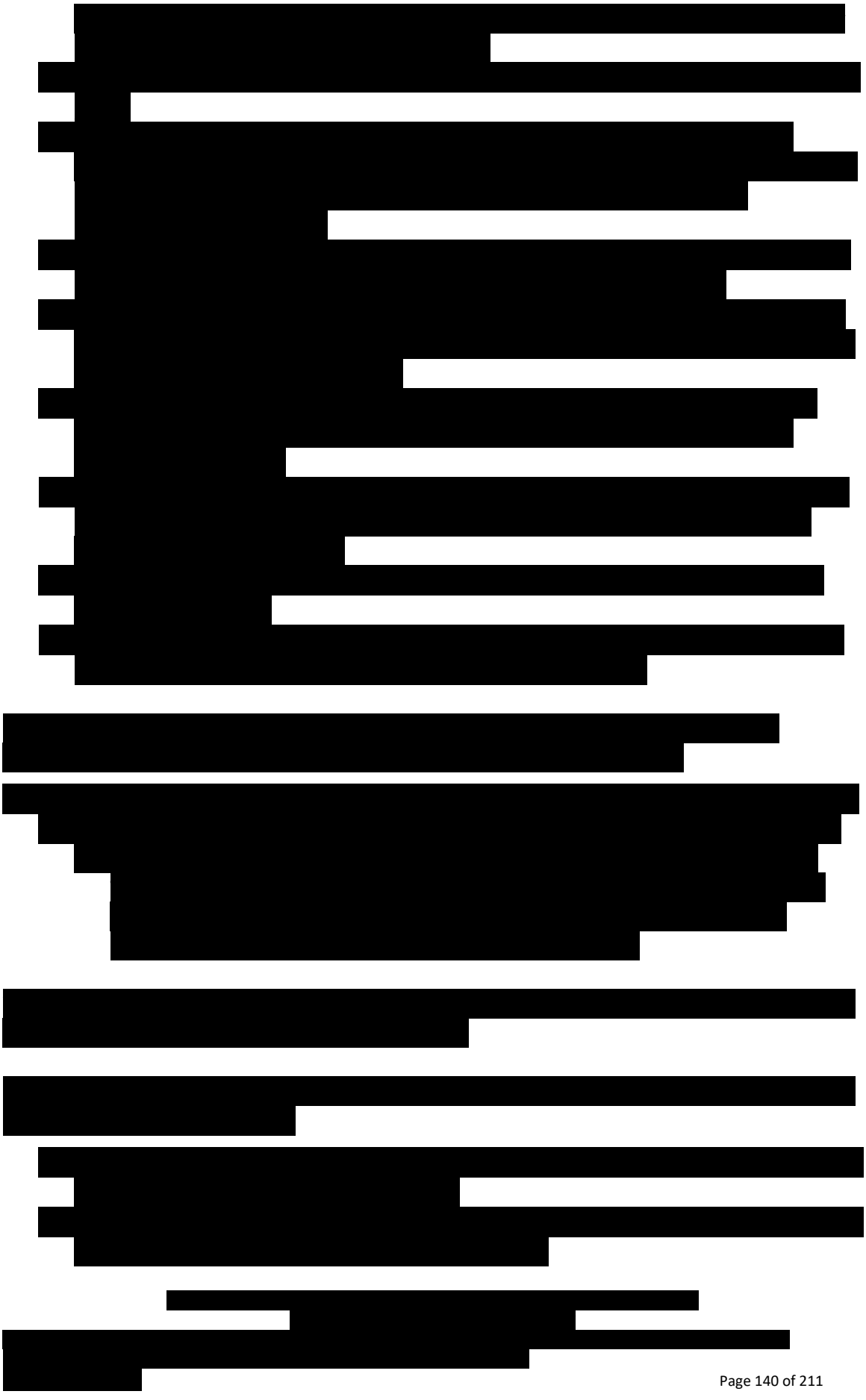

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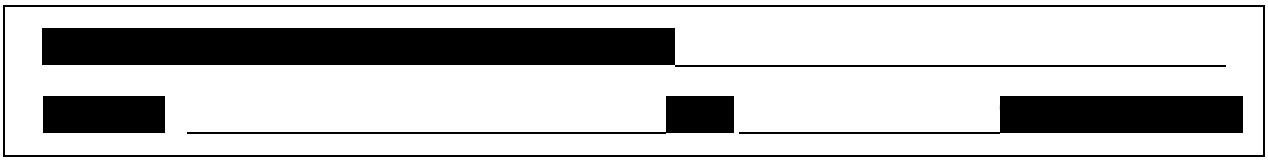

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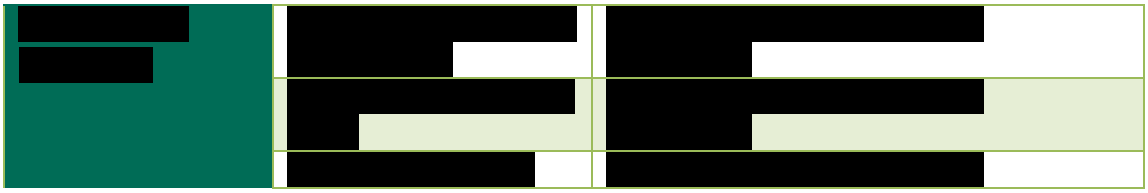

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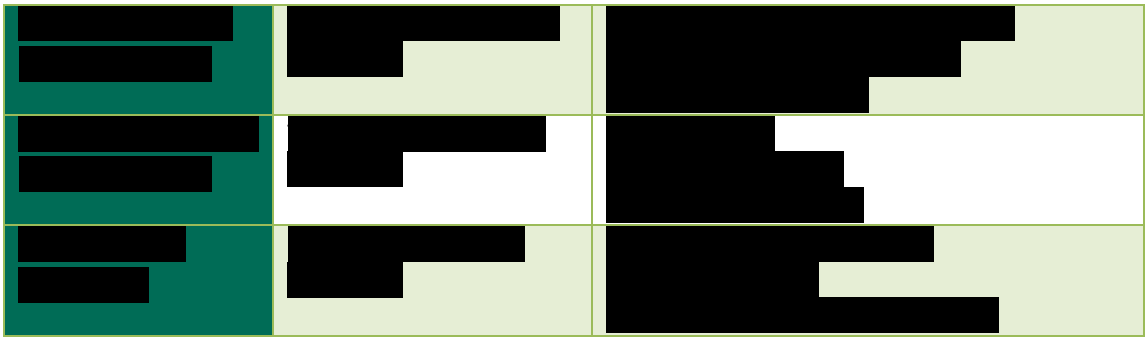

Appendix U: NIH Stroke Scale (NIHSS)

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.	_____

[redacted]

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**	_____

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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:_____	____

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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.	____

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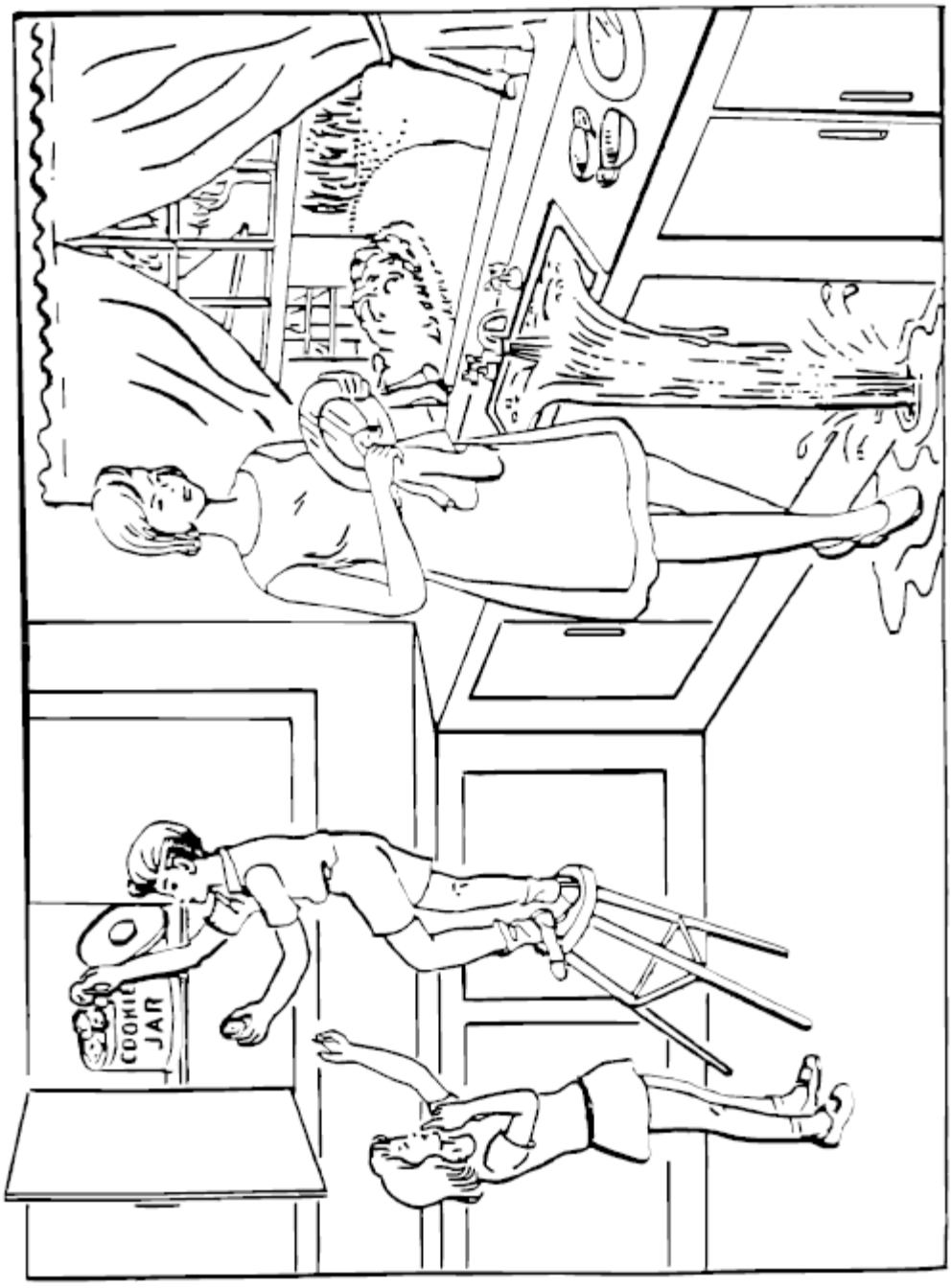

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You know how.

Down to earth.

I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.

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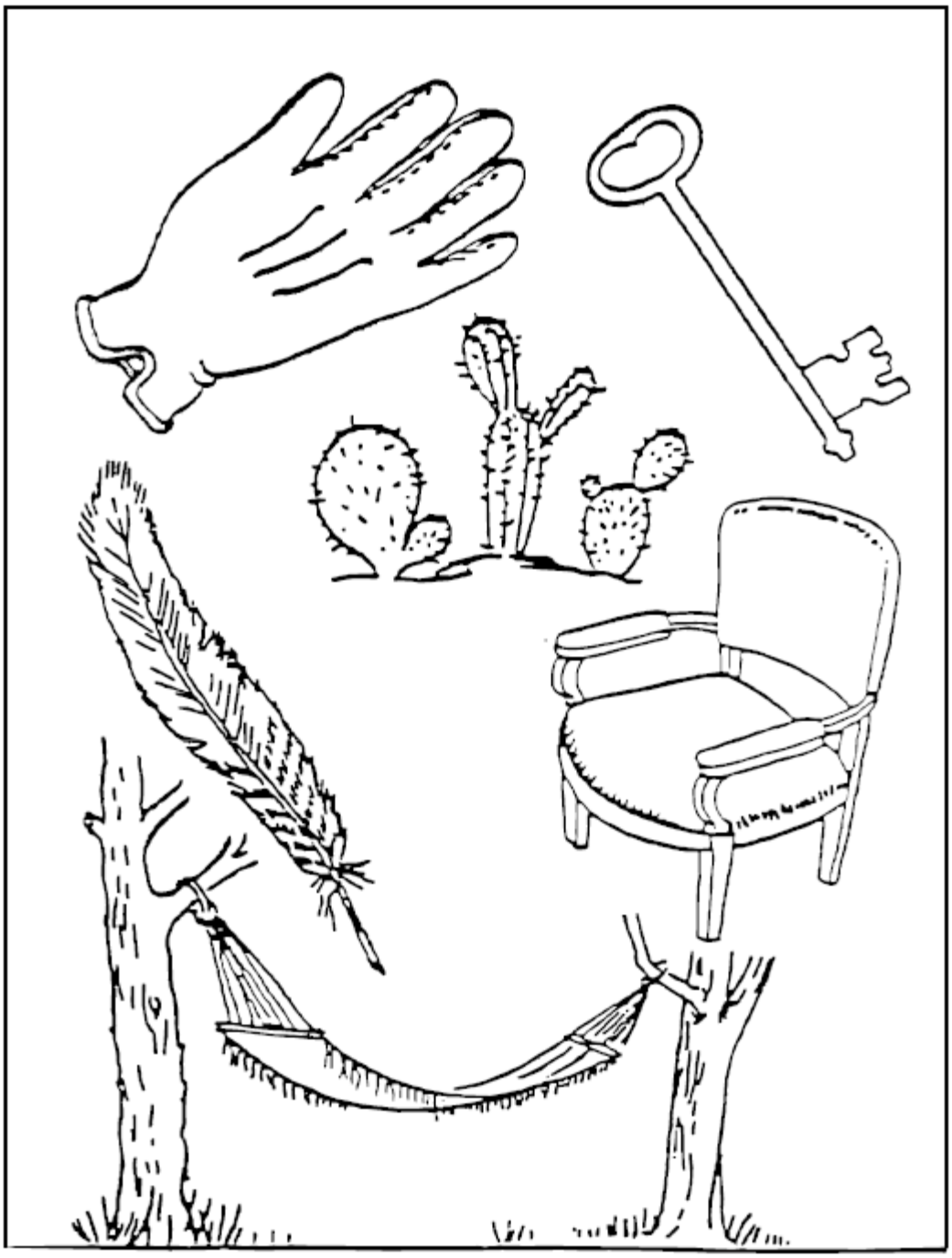

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FIFTY – FIFTY

THANKS

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Appendix W: Portico IDE FlexNav Study Synopsis

1. PURPOSE

1.1 Indications for Use

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

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

1.2 Study Design and Objectives

The primary objective of the PORTICO pivotal IDE FlexNav study ("FlexNav study") is to characterize the safety of the second-generation FlexNav™ Delivery System ("FlexNav™ Delivery System).

The FlexNav study will be conducted as a prospective, multicenter, investigational study arm of the PORTICO pivotal IDE trial. Up to 200 patients (includes a maximum of 100 roll-ins) with symptomatic, severe aortic stenosis considered by a local Heart Team to be high or extreme risk for surgical aortic valve implantation will be enrolled from up to 70 US and Australian IDE sites. Upon provision of informed consent, subjects will undergo Portico valve implantation via a transfemoral or alternative access approach. Subject selection and key data collection will follow the pivotal IDE protocol to facilitate direct comparison of safety outcomes with the randomized cohort.

[redacted]

1.3 Study Endpoints

1.3.1 Primary Endpoint

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

[redacted]

[redacted]

1.3.2 Descriptive Endpoints

A selection of endpoints from the pivotal IDE trial including valve performance parameters, clinical function assessments and adverse events defined according to VARC II[1] criteria will be assessed at 30 days and included in the PMA application:

Descriptive Endpoints:

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

Additional endpoints to be assessed at one year but not included in the PMA application:

1. Composite of all-cause mortality or disabling stroke at one year from the index procedure
2. All-cause mortality at one year from the index procedure
3. Disabling stroke at one year from the index procedure
4. Non-disabling stroke at one year from the index procedure
5. Paravalvular Leak (PVL) at one year from the index procedure
6. KCCQ Quality of Life (QOL) score from baseline and one year from the index procedure
7. NYHA functional classification at one year from the index procedure

[redacted]

2. CLINICAL PROTOCOL

2.1 Background Information

In 2017, the AHA/ACC revised their guidelines in a focused update to make TAVR a class I indication (previously a class IIa indication) for the treatment of aortic valve stenosis in patients at prohibitive or high-surgical risk.[2] As the use of TAVR expands into younger, lower risk populations, minimizing vascular complications which are amongst the most frequent and serious complications of TAVR is of paramount importance as studies show vascular and bleeding complications during the procedure are associated with increased morbidity and mortality risk.[3,4]

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

The safety and effectiveness of the Abbott (legacy St. Jude Medical) family of CE Marked Portico™ Transcatheter Aortic Heart Valves (size range 23-29mm) is currently being assessed in the PORTICO pivotal US IDE trial. [redacted]

[redacted]

The proposed FlexNav study will be conducted as separate arm of the pivotal IDE trial and will include a minimum of 100 analysis patients. [redacted]

Characterizing the safety profile of the FlexNav™ Delivery system with respect to rate of major vascular complications, which is expected to be directly impacted by the recent design modifications to the delivery system, is the primary focus of the clinical investigation.

2.2 Rationale

The rationale for conducting the FlexNav study within the PORTICO pivotal IDE trial is to enable the direct comparison of 30-day safety outcomes data for the FlexNav™ Delivery System to the first-generation Portico Delivery System. Results from the FlexNav study will be included in a PMA application to support US approval of the Portico Transcatheter Heart Valve and FlexNav™ Delivery System.

[redacted]

[redacted]

3.3 Instructions for Use

For instructions for use (IFU) of the Portico™ Transcatheter Aortic Heart Valve and FlexNav™ Delivery System please refer to the IFU (Number 600014467) which includes the following:

- Portico™ Transcatheter Aortic Valve (PRT-23-IDE, PRT-25-IDE, PRT-27-IDE, PRT-29-IDE)
- FlexNav™ Delivery System (FN-DS-SM-IDE, FN-DS-LG-IDE)
- FlexNav™ Loading System (FN-LS-SM-IDE, FN-LS-LG-IDE)

[redacted]

[redacted]

[redacted]

4. RISK AND BENEFITS OF THE STUDY DEVICE AND CLINICAL STUDY

There are no changes to the risk or benefits reported in the pivotal IDE trial for subjects participating in the FlexNav Study. Please refer to the Portico™ Transcatheter Aortic Heart Valve and FlexNav Delivery System IFU for a description of risk to benefits and a list of the potential adverse events.

5. STUDY POPULATION

5.1 Study Cohort

The FlexNav study is limited to subjects with symptomatic, severe aortic stenosis who are determined to be at high or extreme operative risk for surgical aortic valve replacement. The operative risk determination will be based on the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Risk Calculator. A surgeon's assessment of operative comorbidities, including medical and anatomic factors not captured by the STS risk calculator will also be considered in determining a subject's operative risk.

[redacted]

5.2 Inclusion/Exclusion Criteria

The inclusion/exclusion criteria for the FlexNav Study is the same as the pivotal IDE trial. Refer to Sections 5.1 and 5.2 of the main protocol for details.

Additional exclusion criteria for subjects being considered for Portico valve implantation via an alternative access approach using the FlexNav™ Delivery System include:

For transaortic access using the FlexNav™ Delivery System:

1. Subject has a distance between the annular plane and the aortic access site <7 cm (2.8")
2. Subject has a distance between the annular plane and the separate introducer sheath distal tip <6 cm (2.4")

For subclavian/axillary access using the FlexNav™ Delivery System:

[redacted]

1. Subject's access vessel (subclavian/axillary) has a distance between the annular plane and the integrated sheath distal tip <17 cm (6.7")
2. Subject's access vessel requires the delivery system to be advanced through a separate introduce sheath

5.3 Screening Process

Subject case reviews will be conducted to determine a patient's eligibility to receive a Portico valve (roll-in and analysis population) by the same independent Subject Selection Committee used in the pivotal IDE trial.

The risk definitions will be the same as the pivotal IDE trial to ensure a consistent patient population is enrolled. The Subject Selection Committee will provide final determination of a subject's risk classification and primary access approach. If a site disagrees with the Subject Selection Committee's final decision regarding risk classification and/or primary access approach the subject will not be eligible for enrollment in the study.

6. SUBJECT ASSIGNMENTS

Subjects in the FlexNav study are not randomized. All subjects will undergo a Portico valve implant attempt.

Subject assignments (roll-in or analysis population) will be assigned by the Sponsor after Subject Selection Committee approval and prior to enrollment, based on the primary implanting physician's recent Portico experience.

6.1 Subject Enrollment

Subjects will be considered enrolled into the FlexNav study after completion of all of the following steps:

1. Signed informed consent is obtained.
2. Based on the screening assessments, it is determined that the subject meets all of the inclusion and none of the exclusion criteria.
3. Subject is approved by the Subject Selection Committee.
4. Subject assignment (roll-in or analysis) has been determined by the Sponsor.
5. The Portico delivery system enters the subjects' body.

Subjects who are approved by the Subject Selection Committee to receive a Portico valve via transfemoral access and are found during the procedure not to be suitable for this delivery modality (per the heart team medical decision) may receive a Portico valve using an alternate access modality and vice versa. This will be considered a protocol deviation unless the Subject Selection Committee pre-approved the subject for multiple access sites. The rationale for this decision must be documented by the site.

[redacted]

6.2 Roll-in Cohort

A minimum of one (1) and up to three (3) roll-in subjects will be required per primary implanting physician at each site. Data from roll-in subjects will be added to the IDE Roll-in Registry and will not be included in the analysis population of 100 subjects. A maximum of 100 roll-in subjects will be permitted in the study.

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.

[redacted]

6.3 Proctoring

[redacted]

7. STUDY CONDUCT

Assessments required at screening, baseline, pre- and post-procedure, prior to hospital discharge and during follow-up in the FlexNav study will be the same as that in the pivotal IDE trial. Stroke ascertainment and evaluation will be performed according to VARC II recommendations and the pivotal IDE protocol. Detailed information can be found in Section 7.0 of the main protocol.

Subjects enrolled in the FlexNav study will be followed for a minimum of one year and annually thereafter for up to 5 years.

7.1 Core Laboratories

[redacted] independent core laboratories and processes used in the pivotal IDE trial will be utilized for evaluating CT images, ECG rhythms and echocardiograms for the FlexNav study.

7.2 Subject Selection Committee

The independent Subject Selection Committee will be responsible for final approval of a study subjects':

1. risk classification (high vs extreme) based on patients' clinical history, STS score, non-STS comorbidities (including frailty indices) and key patient demographics.

[redacted]

2. primary access route based on independent core-laboratory CT imaging. A secondary access route may also be approved.

As in the pivotal IDE trial, the Subject Selection Committee will provide guidance with respect to Portico valve size selection based on CT-measured annular dimensions (area, perimeter, diameter, eccentricity) and calcification. However, the investigational site has the final decision for which Portico valve size is selected for implantation.

8. DATA COLLECTION AND MANAGEMENT

The schedule for data collection and management of data will follow the pivotal IDE trial. Refer to Section 8.0 of the main protocol for details.

Enrolled subjects who undergo a Portico implant attempt but do not receive a Portico valve will be assessed for any adverse events through to 30 days post-procedure, and will then be terminated from the study.

If a subject is consented and undergoes study-specific testing (i.e., testing that would not be done if they were not being considered for the study) but is not enrolled in the study (FlexNav™ Delivery System does not enter the subject's body), the subject will be exited from the study without any further follow-up.

9. INDEPENDENT BOARDS

9.1 Clinical Events Committee

All adverse events will be adjudicated by the same independent Clinical Events Committee used in the pivotal IDE trial according to the Valve Academic Research Consortium (VARC II) definitions[1]. The independent Clinical Events Committee will have final adjudication responsibilities for subject outcomes related to the primary safety endpoint at 30 days and descriptive endpoints at 30 days and one-year follow-up.

The independent Clinical Events Committee will be responsible for adjudicating the following adverse events at 30 days:

- mortality (all-cause and cardiovascular related)
- stroke (non-disabling and disabling)
- life-threatening bleeding requiring blood transfusion
- major bleeding
- acute kidney injury requiring dialysis
- major vascular complications (access-site related and access related)
- minor vascular complications
- permanent pacemaker insertion

The independent Clinical Events Committee will be responsible for adjudicating the following adverse events at one year:

- mortality (all-cause and cardiovascular related)

[redacted]

- stroke (non-disabling and disabling)

9.2 Data and Safety Monitoring Board

[redacted] independent Data and Safety Monitoring Board used in the pivotal IDE trial will be engaged to review the progress and safety of subjects enrolled in the FlexNav study.

10. STATISTICAL METHODS AND ANALYSIS

[redacted]

[redacted]

10.3 Primary Endpoint

Acceptable safety of the FlexNav™ Delivery System will be determined from a predefined precision estimate for VARC II-defined major vascular complications at 30 days. Results will be summarized and descriptively compared in context of results for the first-generation Delivery System in the randomized cohort (Portico arm) of the pivotal IDE trial.

A comparison to published results for the Portico valve and latest-generation commercially- available transcatheter valves will also be provided.

10.4 Descriptive Endpoints

Descriptive endpoints will be summarized and presented for the analysis population (n=100 subjects) and according to access route (transfemoral vs alternative access). Additionally, all descriptive endpoints at 30 days will be summarized and descriptively compared to rates reported in the randomized cohort of the pivotal IDE trial as well as published results for Portico and latest-generation commercially available valves.

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11.0 Bibliography

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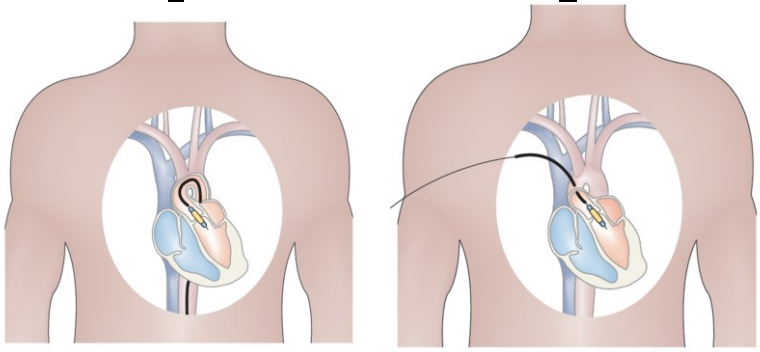

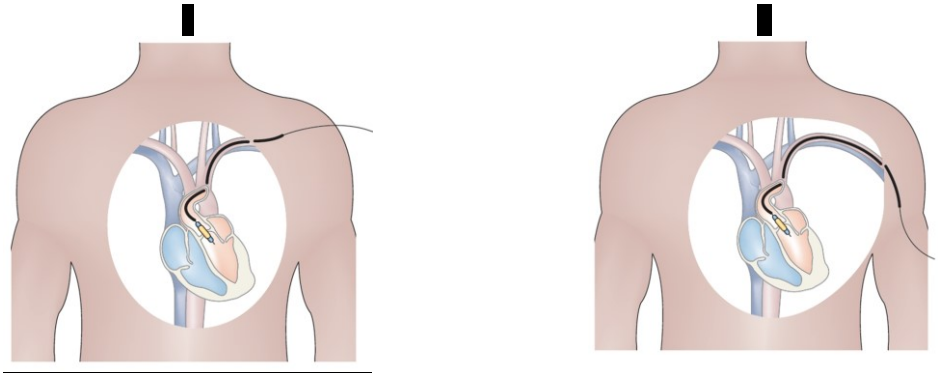

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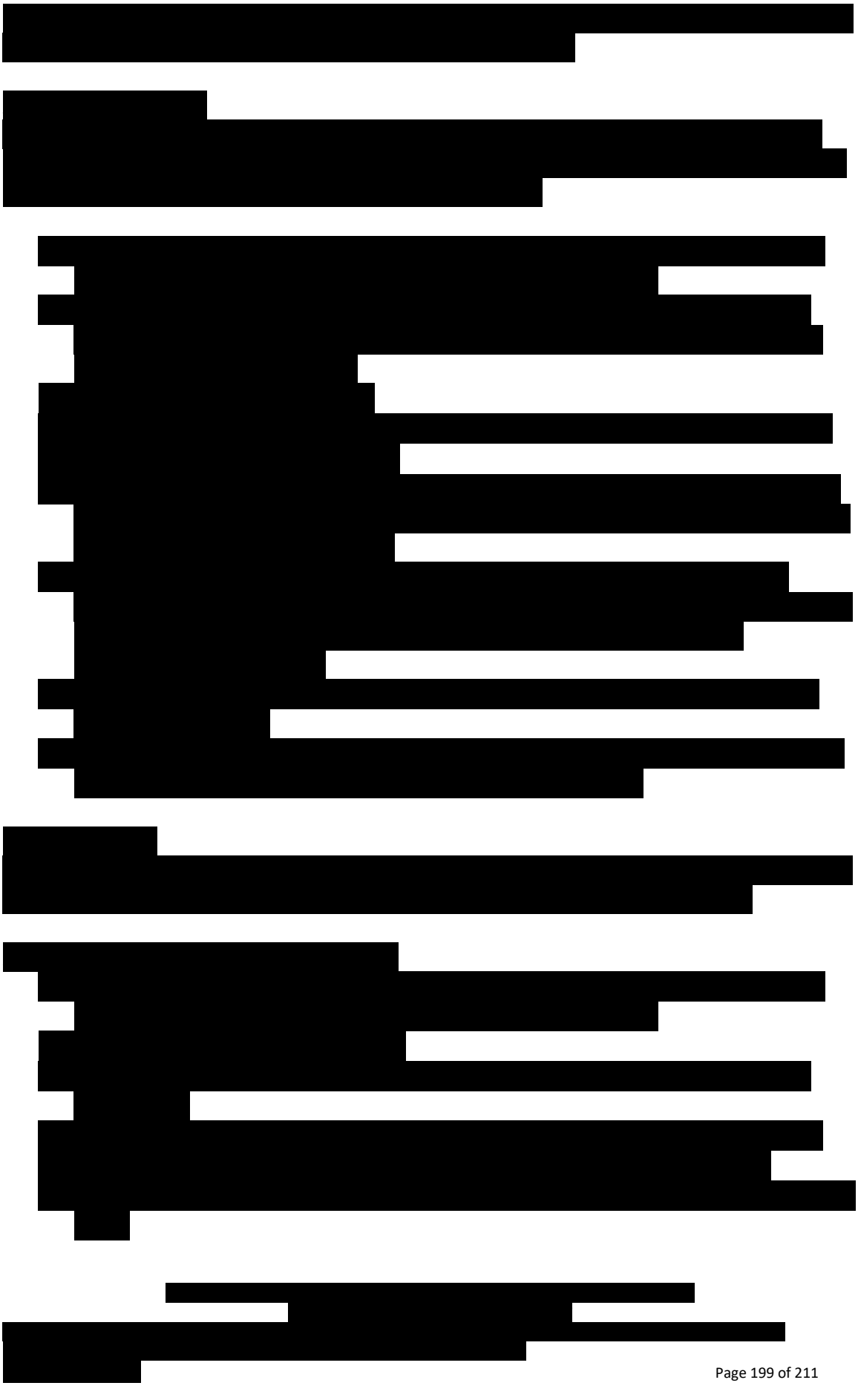

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