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

Clinical Investigation Plan (CIP):

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**Study Sponsor**

St. Jude Medical (now Abbott)

**National Co-Principal Investigators**

- [Name]
- [Name]
- [Name]
- [Name]

**Document Version**

| Version: | August 8, 2018 |
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CIP Number: [masked]

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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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).

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.
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.

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

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:
      o Absence of procedural mortality AND
      o Correct positioning of a single prosthetic heart valve into the proper anatomical location AND
      o 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
      o 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
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
   o All-cause mortality at 30 days, 6 months, one year and two years
   o 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
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
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 \(\geq 75\) years.\(^2\) Aortic stenosis (AS) can be primarily attributed to rheumatic disease and senile
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. This calcification process eventually leads to a restricted valve leaflet motion with obstruction to left ventricular outflow.

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.

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.

Severe symptomatic AS is considered Class I indication for surgery. 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).

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<th>Moderate</th>
<th>Severe</th>
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<td>3.0-4.0</td>
<td>&gt; 4.0</td>
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<tr>
<td>Mean Gradient (mmHg)</td>
<td>&lt; 25</td>
<td>25-40</td>
<td>&gt; 40</td>
</tr>
<tr>
<td>Valve area (cm(^2))</td>
<td>&gt; 1.5</td>
<td>1.0-1.5</td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td>Valve area index (cm(^2)/m(^2))</td>
<td>&lt; 0.6</td>
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After the onset of symptoms of angina pectoris, dyspnea, or syncope, annual mortality of patients with moderate-to-severe AS approaches 25% 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 to as high as 79% for predominant AS patients. Following symptomatic patients with severe aortic stenosis in whom operation was declined, O’Keefe 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%.

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.
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. SAVR has been documented to significantly improve long-term survival in patients with AS. Despite these proven positive outcomes of SAVR, the decision on whether to undergo SAVR can be influenced by prohibitive operative risk.

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. 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. 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.

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. This concept was first demonstrated by Andersen et al 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, 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) and inoperable patients (Cohort B) (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). 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

2.1.7 Results of Literature Search
2.1.8 Primary Effectiveness Endpoint

![Table 2: Mean Cumulative Rates of Effectiveness Endpoints]

<table>
<thead>
<tr>
<th>Effectiveness Endpoint</th>
<th>Extreme Risk (%)</th>
<th>High Risk (%)</th>
<th>All —cause mortality</th>
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<tbody>
<tr>
<td>All —cause mortality</td>
<td>24.68</td>
<td>22.20</td>
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<tr>
<td>Major Stroke</td>
<td>4.92</td>
<td>0.70</td>
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<tr>
<td>Composite event rate</td>
<td>29.6</td>
<td>22.9</td>
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2.1.9 Primary Safety Endpoint

![Table 3: Mean Cumulative Rates of Safety Endpoints Across Studies]

<table>
<thead>
<tr>
<th>Safety Endpoint</th>
<th>Extreme Risk (%)</th>
<th>High Risk (%)</th>
<th>All —cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>All —cause mortality</td>
<td>6.03</td>
<td>8.28</td>
<td></td>
</tr>
<tr>
<td>Major Stroke</td>
<td>3.06</td>
<td>2.62</td>
<td></td>
</tr>
<tr>
<td>Life threatening bleeding</td>
<td>12.14</td>
<td>4.24</td>
<td></td>
</tr>
<tr>
<td>Vascular Complications</td>
<td>11.33</td>
<td>9.42</td>
<td></td>
</tr>
<tr>
<td>Renal failure/Complications</td>
<td>11.13</td>
<td>3.03</td>
<td></td>
</tr>
<tr>
<td>Composite event rate</td>
<td>43.69</td>
<td>27.59</td>
<td></td>
</tr>
</tbody>
</table>
2.2 Summary of St. Jude Medical Portico Transcatheter Valve Clinical Experience

In 2011, following preclinical (bench and animal studies) testing, SJM started conducting clinical investigations in Canada and Europe. The study device includes the Portico transcatheter heart valve and its delivery systems. A series of six (6) prospective clinical evaluations have been conducted on the SJM Portico Transcatheter Aortic Valve System (Table 4). The objective of the collective series of evaluations is to establish a robust portfolio of safety and performance data on the Portico valve and transfemoral delivery system in patients with severe symptomatic AS, who are at high risk for conventional surgical aortic valve replacement. SJM purposely designed the series of evaluations under the following key considerations for consistency and to facilitate interpretation of results:

- Ensure comparable patient cohort and outcome definitions, eligibility criteria, safety and effectiveness endpoints, sample size and overall methods across series
- Include Valve Academic Research Consortium (VARC2) definitions and standards in criteria and assessment methods
- Include U.S. FDA's current guidance regarding neurological assessment methods
- Utilize global expert advisory committee for oversight including subject selection committee to confirm all subjects were appropriate candidates for transcatheter aortic valve placement and met the high-risk designation.
<table>
<thead>
<tr>
<th>Study Series</th>
<th>Sample Size</th>
<th>Geography</th>
<th>Status</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU First in Human TF</td>
<td>10 patients</td>
<td>EU (1 site)</td>
<td>Enrollment complete</td>
<td>12 month follow-up complete and results presented</td>
</tr>
<tr>
<td>Canadian Special Access First in Human TF</td>
<td>13 patients</td>
<td>Canada (2 sites)</td>
<td>Implanted complete</td>
<td>30 day results published on first 10 subjects</td>
</tr>
<tr>
<td>Canadian Special Access Long Term Follow-up</td>
<td>13 patients</td>
<td>Canada (2 sites)</td>
<td>TF 12 month follow-up</td>
<td>Completion</td>
</tr>
<tr>
<td>TF EU CE Mark Trial: 23mm</td>
<td>50 patients</td>
<td>EU (5 sites)</td>
<td>TF 23mm enrollment complete (N=50)</td>
<td>30 day and 12 month follow-up complete and results published</td>
</tr>
<tr>
<td>TF EU CE Mark Trial: 25mm</td>
<td>50 patients</td>
<td>EU (7 sites)</td>
<td>TF 25mm enrollment complete (N=50)</td>
<td>30 day and 12 month follow-up complete and results published</td>
</tr>
<tr>
<td>TF EU CE Mark Trial: 27-29mm</td>
<td>120 patients</td>
<td>EU/AUS (12 sites)</td>
<td>27mm and 29mm enrollment complete (N=120)</td>
<td>30 day and 12 month follow-up complete and results published</td>
</tr>
</tbody>
</table>

1 Manoharan, G. Prospective, Multicenter Evaluation of the Portico Transcatheter Aortic Valve: Acute Results and one year Outcomes. TCT 2012.

As summarized in Table 5 below, the primary endpoints and objectives were comparable across all prospective clinical evaluations of the Portico device. As previously referenced, VARC standardized outcome definitions were routinely implemented within all of the Portico clinical evaluations.
Table 5. Primary Endpoints and Objectives for Portico Valve Evaluations

<table>
<thead>
<tr>
<th>Primary Safety Endpoint(s)/Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality, MI, stroke, bleeding, acute kidney injury, vascular complications, prosthetic valve performance, prosthetic valve associated complications</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Efficacy Endpoint(s)/Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical benefit: NYHA functional classification and QoL.</td>
</tr>
<tr>
<td>Procedural outcomes, delivery, deployment, removal, and closure</td>
</tr>
<tr>
<td>Functional improvement from baseline to 30 days for NYHA functional classification, 6-minute walk test, effective orifice area (EOA)</td>
</tr>
</tbody>
</table>

The consistent primary safety endpoint for the Portico clinical evaluation series is 30-day all-cause mortality. St. Jude Medical follows all European CE mark study subjects to 12 months per clinical study protocol. SJM follows Portico subjects enrolled in the CE Mark studies for a minimum of 5 years post implant under a separate post-market surveillance study to assess long-term safety and performance outcomes, enabling the assessment of long-term clinical durability for the valve.

Safety and performance of the clinical series is summarized in Table 6.
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>
<thead>
<tr>
<th>Model Number</th>
<th>Intended to Treat Aortic Annulus Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRT-23-IDE</td>
<td>19 – 21mm</td>
</tr>
<tr>
<td>PRT-25-IDE</td>
<td>21 – 23mm</td>
</tr>
<tr>
<td>PRT-27-IDE</td>
<td>23 – 25mm</td>
</tr>
<tr>
<td>PRT-29-IDE</td>
<td>25 – 27mm</td>
</tr>
</tbody>
</table>

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.
Table 8. Delivery and Loading Systems and Model Numbers

<table>
<thead>
<tr>
<th>Model Number</th>
<th>Delivery System Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRT-DS-TF-18F-IDE</td>
<td>18 Fr</td>
</tr>
<tr>
<td>PRT-DS-ALT-18F-IDE</td>
<td>18 Fr</td>
</tr>
<tr>
<td>FN-DS-SM-IDE¹</td>
<td>18 Fr</td>
</tr>
<tr>
<td>PRT-DS-TF-19F-IDE</td>
<td>19 Fr</td>
</tr>
<tr>
<td>PRT-DS-ALT-19F-IDE</td>
<td>19 Fr</td>
</tr>
<tr>
<td>FN-DS-LG-IDE¹</td>
<td>19 Fr</td>
</tr>
<tr>
<td>PRT-LS-TFAL-18FID</td>
<td>N/A (loading system)</td>
</tr>
<tr>
<td>FN-LS-SM-IDE²</td>
<td>N/A (loading system)</td>
</tr>
<tr>
<td>PRT-LS-TFALT-19FID</td>
<td>N/A (loading system)</td>
</tr>
<tr>
<td>FN-LS-LG-IDE²</td>
<td>N/A (loading system)</td>
</tr>
</tbody>
</table>

¹Indicates second-generation FlexNav™ Delivery System. Only allowed under protocol version L or later
²Indicates 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.
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.

![First-Generation Portico Delivery System (deployment end)](image)

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

---

**Figure 4. First-Generation Portico Delivery System**
The FlexNav™ Delivery System allows for transfemoral, subclavian/axillary or transaortic access methods with the current range of Portico valves size (23, 25, 27 and 29mm). The FlexNav™ Delivery System has a working length of 107cm and is composed of a handle at the proximal end, connected to a shaft that is 13 Fr at the proximal end and 18F or 19F at the distal end (Figure 5).

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

The FlexNav™ Delivery System shaft includes a stability layer over the outer member to improve control during positioning and deployment of the valve. The FlexNav™ Delivery System handle functions in a similar manner as the first-generation Portico Delivery system with modifications and added labeling. The macro slide that facilitates opening and closure of the delivery system has been moved and incorporated into the proximal end of the handle with two release buttons.

The distal end of the FlexNav™ Delivery System features an atraumatic, radiopaque tip with hydrophilic coating and a radiopaque inner member marker band to aid in visualizing. The FlexNav™ delivery system includes the same retainer design as the first-generation Portico Delivery System (Figure 6).

Summary of key design improvements to the FlexNav™ Delivery System:

- Integrated sheath to allow sheathless insertion
- Hydrophilic coating for smoother insertion and tracking to the target area
- Stability Layer to improve valve handling and improve placement accuracy during deployment
- Improved handle design to provide easier user operation
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.
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
- 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
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. 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 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. Female subjects, however, had a better 1 year survival rate in the Sapien PARTNER trial. 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.
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
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\(^2\)
(indexed EOA ≤ 0.6 cm²/m²). (Qualifying AVA baseline measurement must be within 60 days prior to informed consent).

4. Subject has symptomatic aortic stenosis as demonstrated by NYHA Functional Classification of II, III, or IV.

5. The subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Institutional Review Board (IRB) of the respective clinical site.

6. The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits.

7. Subject’s aortic annulus is 19-27mm diameter as measured by CT conducted within 12 months prior to informed consent. 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.
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.


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).
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.
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.
Does the patient have severe symptomatic Aortic Stenosis and is deemed high or extreme surgical risk by the local hospital heart team?

STOP. The patient is not eligible for the study.

Did the patient sign the study informed consent?

STOP. Informed consent is required to perform study-specific screening tests not already done. Otherwise patient cannot be screened.

Did the subject meet all the inclusion and none of the exclusion criteria for either risk cohort?

STOP. The subject is not eligible for the study.

Does the subject have a failed surgical aortic valve bioprosthesis and meets all other inclusion/exclusion criteria?

Consider Valve-in-Valve Registry participation

Does the subject still qualify to participate in the study after going through the screening process?

STOP. The subject is not eligible for the study. Complete applicable Screening, Baseline, and Termination CRFs

Subject approved by the Subject Selection Committee?

Enrollment Occurs

Subject is assigned to the appropriate risk cohort and randomized into the appropriate access arm

Subject scheduled for TAVR valve within 14 days of being assigned to a Registry

Did the Subject receive a TAVR Valve?

Subject will only be assessed for any adverse events through 30 days post procedure, and then terminated from the study. If enrolled under protocol version L or later, the subject will be exited from the study with no further follow-up

Subject will be followed per protocol through the one-year visit

Subject scheduled for TAVR valve within 14 days of being assigned to a Registry

Did the Delivery System enter the subject’s body

Enrollment Occurs

Subject is assigned to the Roll-in or Valve-in-Valve Registry

Did the Subject receive a TAVR Valve?

Enrollment Occurs

Subject is assigned to FlexNav Study or the CAP

Enrollment Occurs

Subject is assigned to the Roll-in or Valve-in-Valve Registry

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).

![Figure 8. High Risk Cohort Flow Chart](image-url)

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

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).
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.
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).

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

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<th>Study Activity</th>
<th>Visit window [days]</th>
<th>30 days [±7 days]</th>
<th>6 Month [±30 days]</th>
<th>7 One Year [−30,+45 days]</th>
<th>1 Annual Follow-up [−30,+45 days]</th>
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<td>Surgical Risk Assessment (STS, EuroSCOREII)</td>
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<td>Six Minute Walk Test</td>
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<td>Procedure</td>
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**Quality of Life Measures**

- SF-36
- EQ-5D
- KCCQ

**Lab Measurements**

- CBC and Platelet count
- BUN and Creatinine
- BNP or ProBNP
- INR (if subject is on Coumadin or Warfarin)
- Troponin or CK / CK-MB
- Albumin (for Frailty Index)

1. In the event a 12 month visit per the requirements in Section 7.8 is not completed, the site may call the subject to document survival.
2. For subjects receiving a new permanent pacemaker, ECG should be completed showing the underlying rhythm as well as the current pacing programming.
3. To be done within 24-48 hours after procedure, or as close to discharge as possible (but no more than 7 days after procedure).
4. If CT is contraindicated and/or not possible to be obtained for certain subjects, a 3D TEE and non-contrast CT of chest and abdomen/pelvis may be accepted if approved by the subject selection committee.
5. To be collected within 72 hours before index procedure and within 72 hours after index procedure.
6. To be collected within 12-24 hours after the procedure, approximately 24 hours thereafter, and at approximately 72 hours (or at discharge, if patient is discharged prior to 72 hours post procedure) to be consistent with VARC 2 guidelines.
7. Not required for CAP subjects enrolled under Ver. K or later. See Appendix V.
8. Not required for subjects enrolled under Ver. K or later. TAVR Leaflet Motion Sub-study now closed.
### 7.14 Study Activity Definitions

Table 10 summarizes the study activity definitions.

<table>
<thead>
<tr>
<th>Study Activity</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Event Assessment</strong></td>
<td>All adverse events will be documented according to Adverse Events section 9.</td>
</tr>
</tbody>
</table>
| **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: |
- 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)

<table>
<thead>
<tr>
<th>Cardiovascular Medications</th>
<th>Only the following Cardiovascular medications will be collected at each visit:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Beta Blockers</td>
</tr>
<tr>
<td></td>
<td>• Calcium Channel Blockers</td>
</tr>
<tr>
<td></td>
<td>• Anticoagulants</td>
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<tr>
<td></td>
<td>• Antiplatelet agents including Aspirin</td>
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<td></td>
<td>• Diuretics</td>
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<tr>
<td></td>
<td>• Ace-Inhibitors</td>
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<tr>
<td></td>
<td>• Angiotensin Receptor Blocker (ARBs)</td>
</tr>
<tr>
<td></td>
<td>• Hydralazine</td>
</tr>
<tr>
<td></td>
<td>• Antiarrhythmics</td>
</tr>
</tbody>
</table>

| MMSE-2:SV                  | Mini Mental State Exam -2:SV is a screening tool for cognitive impairment      |

<table>
<thead>
<tr>
<th>Modified Rankin Stroke Scale*</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*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.</td>
</tr>
</tbody>
</table>

| 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. |

<table>
<thead>
<tr>
<th>NIH Stroke Scale**</th>
<th>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.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>** 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</td>
</tr>
</tbody>
</table>
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
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
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
documented as necessary. All data recorded on the eCRF must be found in the subject’s source data.

<table>
<thead>
<tr>
<th>Schedule of Data Collection (Case Report Forms)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening</strong></td>
</tr>
<tr>
<td>• Inclusion Exclusion</td>
</tr>
<tr>
<td>• Screening</td>
</tr>
<tr>
<td>Prior to subject selection committee review</td>
</tr>
<tr>
<td><strong>Randomization</strong></td>
</tr>
<tr>
<td>• Subject Selection Decision/Randomization</td>
</tr>
<tr>
<td>At subject selection committee review/randomization</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
</tr>
<tr>
<td>• Baseline</td>
</tr>
<tr>
<td>• Barthel Index</td>
</tr>
<tr>
<td>• SF-36 v2 Health Survey (IDE Only)</td>
</tr>
<tr>
<td>• KCCQ</td>
</tr>
<tr>
<td>Prior to Index Procedure</td>
</tr>
<tr>
<td><strong>Procedure</strong></td>
</tr>
<tr>
<td>• Procedure</td>
</tr>
<tr>
<td>• Lab Measurements Procedure</td>
</tr>
<tr>
<td>• Device Portico Valve and Loading &amp; Delivery</td>
</tr>
<tr>
<td>• Device Commercially Available Valve</td>
</tr>
<tr>
<td>• Healthcare Utilization/Hospitalization</td>
</tr>
<tr>
<td>At time of Index Procedure</td>
</tr>
<tr>
<td><strong>Discharge</strong></td>
</tr>
<tr>
<td>• Discharge</td>
</tr>
<tr>
<td>• Lab Measurements</td>
</tr>
<tr>
<td>• Barthel Index</td>
</tr>
<tr>
<td>At hospital discharge</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
</tr>
<tr>
<td>• 30 Days, 6 Month (IDE Only) &amp; Annual Follow-Up Visit</td>
</tr>
<tr>
<td>• Barthel Index</td>
</tr>
<tr>
<td>• SF-36 v2 Health Survey (IDE Only)</td>
</tr>
<tr>
<td>• KCCQ</td>
</tr>
<tr>
<td>• 30 Day</td>
</tr>
<tr>
<td>• 6 month (pivotal IDE trial only)</td>
</tr>
<tr>
<td>• One year</td>
</tr>
<tr>
<td>• Annually through year five</td>
</tr>
<tr>
<td><strong>Adverse Event</strong></td>
</tr>
<tr>
<td>• Adverse Event</td>
</tr>
<tr>
<td>• Healthcare Utilization/Hospitalization (for cardiovascular event requiring treatment and/or is device-related)</td>
</tr>
<tr>
<td>At the time of occurrence or notification of event</td>
</tr>
<tr>
<td><strong>Suspected Neurological Event</strong></td>
</tr>
<tr>
<td>• Neurological Assessment</td>
</tr>
<tr>
<td>• Adverse Event</td>
</tr>
<tr>
<td>A neurological assessment must be performed at 90 days (±14 days) from the date of a suspected neurological event</td>
</tr>
<tr>
<td><strong>Protocol Deviation</strong></td>
</tr>
<tr>
<td>• Protocol Deviation</td>
</tr>
<tr>
<td>At the time of occurrence or notification of event</td>
</tr>
<tr>
<td><strong>Subject Termination</strong></td>
</tr>
<tr>
<td>• Subject Termination</td>
</tr>
<tr>
<td>When a subject is deemed to be no longer available for follow-up evaluation for any reason or when the subject completes the study</td>
</tr>
<tr>
<td><strong>Death</strong></td>
</tr>
<tr>
<td>• Adverse Event</td>
</tr>
<tr>
<td>• Death</td>
</tr>
<tr>
<td>• Subject Termination</td>
</tr>
<tr>
<td>At the time of occurrence or notification of event</td>
</tr>
</tbody>
</table>
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
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
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.
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
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 as:

Additional populations will be used to confirm the results of the ITT population.
11.2 Randomization and Stratification

Subjects will be randomized per 1:1 ratio to test (Portico) vs. control (CAV) group according to a computer-generated randomization scheme. Randomization will be stratified by each clinical site, then by risk cohort (high risk vs. extreme risk), and vascular access method (transfemoral vs. alternative access). The purpose of using the stratified randomization is to ensure balance of the treatment groups with respect to each clinical site and each of four strata (high risk TF, high risk AA, extreme risk TF, and extreme risk AA). Permutated blocks will be used within each stratum to achieve balance and block sizes will not be revealed to sites.

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. There were 8 subjects randomized but not treated in the trial when the trial was paused; these subjects will be excluded in the primary analysis and will be replaced with 8 additional randomized subjects. The primary analysis will be performed based on combined high and extreme risk cohort with pooled access data. The primary analysis will be conducted on a dataset locked after all enrolled subjects have had their one-year study visit (except those withdrawn or lost-to-follow-up before one year).
The study hypotheses are:

**Null hypothesis**: The probability of a subject experiencing a primary effectiveness endpoint event at one year for the test group is inferior to the probability in the control group.

H₀: p_{test} > p_{control} + Δ_{p1}

**Alternative hypothesis**: The probability of a subject experiencing a primary effectiveness endpoint event at one year for the Portico test group is not inferior to the probability in the control group by more than Δ_{p1}.

Hₐ: p_{test} < p_{control} + Δ_{p1}

Where p_{test} is the probability of a subject experiencing a primary effectiveness endpoint event by one year in the Portico test group, p_{control} is the probability of a subject experiencing a primary effectiveness endpoint event by one year in the control group, and Δ_{p1}, the non-inferiority margin for the primary effectiveness endpoint, is set at 8%.

p_{test} and p_{control} will be estimated as 1-year Kaplan-Meier event rates. The hypothesis will be tested at the one-sided 5% level of significance, i.e., the upper bound of the one-sided 95% confidence interval for p_{test} - p_{control} must be entirely less than Δ_{p1}.

Non-inferiority margin

The selection of the non-inferiority margin is based upon clinically acceptable outcomes. It has been demonstrated that inoperable subjects with severe AS had a one-year mortality rate of 50%. Based on the data from the PARTNER trial for subjects who cannot undergo SAVR, the TAVR treated subjects had 31% mortality rate, therefore choosing a Delta (Δ) that is 30% of this rate will preserve more than half of 19% treatment effect. On the other hand, a non-inferiority margin of 7.5% was used for PARTNER A (high risk subjects), which is 31% of the one year mortality rate 24.2% for the High risk cohort for the TAVR group.

In a review of recent data on commercially available TAVR cases within the TVT registry, the event rate for death or major stroke was reported to be 25%. A non-inferiority margin of 8% represents 32% of the one year event rate.

Hypothesis Test

The hypothesis test will be performed by calculating the 95% one-sided upper confidence limit for the difference of (p_{test} - p_{control}), using Kaplan-Meier estimates for the event rates and standard errors. This analysis will be performed on all patients, combining data from the high risk cohort and extreme risk cohort. If the upper confidence limit for the difference is less than 0.08, the Portico test group will be determined to be non-inferior to the control group. The standard error of the test statistic P_{test} - P_{control} is defined as SE = sqrt(SE(P_{test})² + SE(P_{control})²), where SE(P_{test}) and SE(P_{control}) are Greenwood standard errors for the Kaplan-Meier estimates.

If non-inferiority is demonstrated, a reflex test for superiority will be performed to determine if the Portico test group is superior to the control group. If the upper bound
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.

The study hypotheses are:

Null hypothesis: \( \Pr_{\text{test}} \geq \Pr_{\text{control}} \)

Alternative hypothesis: \( \Pr_{\text{test}} < \Pr_{\text{control}} + \Delta \)

where \( \Pr_{\text{test}} \) is the probability of a subject experiencing a primary safety endpoint event by 30 days in the Portico test group, \( \Pr_{\text{control}} \) is the probability of a subject experiencing a primary safety endpoint event in the control group, and \( \Delta \) is the non-inferiority margin for the primary safety endpoint, set at 8.5%. The event rates, \( \Pr_{\text{test}} \) and \( \Pr_{\text{control}} \), will be estimated as 30-day Kaplan-Meier event rates. The hypothesis will be tested at the one-sided 5% level of significance, i.e., the upper bound of the one-sided 95% confidence interval for \( \Pr_{\text{test}} - \Pr_{\text{control}} \) must be entirely less than \( \Delta \).
choosing a Delta (Δ) that is 30% of this rate will preserve more than half of 19% treatment effect. On the other hand, a non-inferiority margin of 7.5% was used for PARTNER A (high risk subjects), which is 31% of the one-year mortality rate 24.2% for the High risk cohort for TAVR group. A conservative value of 30% of the rate in the control group is chosen for the non-inferiority margin in each of the high risk and extreme risk groups:

The expected \( \lambda \) control rate for the high-risk group is 27.59%, therefore \( \Delta p^2 = 0.083 \) (0.2759*0.30).

The expected \( \lambda \) control rate for the extreme-risk group is 43.69%, therefore \( \Delta p^2 = 0.131 \) (0.4369*0.30).

The expected \( \lambda \) control rate for combined high-risk and extreme-risk group by enrolling 80% high risk subjects and 20% extreme risk subjects is 30.81%, therefore \( \Delta p^2 = 0.092 \) (0.3081*0.30).

Therefore a conservative value of 8.5% is chosen as the non-inferiority margin for the primary safety endpoint for the combined high and extreme risk cohort.

Hypothesis Test

The hypothesis test will be performed by calculating a 95% one-sided upper confidence limit for the difference of \( \hat{\lambda}_{\text{test}} - \hat{\lambda}_{\text{control}} \), using the Kaplan-Meier estimates for the event rates and standard errors. This analysis is performed on all patients, combing data from the high risk cohort and extreme risk cohort. If the upper confidence limit for the difference is less than 0.085, the Portico test group will be determined to be non-inferior to the control group.

The standard error of the test statistic \( L_{\text{test}} - L_{\text{control}} \) is defined as:

\[
\text{SE} = \sqrt{\text{SE}(L_{\text{test}})^2 + \text{SE}(L_{\text{control}})^2},
\]

where \( \text{SE}(L_{\text{test}}) \) and \( \text{SE}(L_{\text{control}}) \) are Greenwood standard errors for the Kaplan-Meier estimates.

If non-inferiority is demonstrated, a reflex test for superiority will be performed to determine if the Portico test group is superior to the control group. If the upper bound of the two-sided 95% CI for \( \hat{\lambda}_{\text{test}} - \hat{\lambda}_{\text{control}} \) is entirely < 0, superiority will be claimed.

The hypotheses of superiority test are:

\( H_0: \hat{\lambda}_{\text{test}} - \hat{\lambda}_{\text{control}} \geq 0 \)
\( H_a: \hat{\lambda}_{\text{test}} - \hat{\lambda}_{\text{control}} < 0 \)

11.4 Sample Size Calculations
The control groups will be composed of subjects who receive an approved control transcatheter heart valve. The estimated primary endpoints event rates for the control group of each of the cohorts have been derived as follows:

The efficacy assessment included composite event rate of all-cause mortality or disabling stroke for the valve procedure at 1-year for high risk and extreme risk patients. The mean cumulative rates derived from all included studies are presented in Table 2 in section 2.1.

The safety data of TAVI/TAVR procedures are composite rate of all-cause mortality, disabling stroke, life-threatening bleeding, acute kidney injury requiring dialysis or major vascular complications at 30 days. The mean cumulative rates from all included studies are presented in Table 3 in section 2.1.

The subject selection process and criteria will result in a population in the Portico Test groups comparable to those enrolled in the control groups. SJM believes that performing the TAVR procedure using the Portico device will result in event rates similar to the control groups. Therefore, for hypothesis and sample size assumptions, the primary endpoint event rates for the Portico Test group are assumed to be the same as the primary endpoints event rates for each cohort's control group.

11.4.1 Sample Size for the Primary Effectiveness Endpoint

The operating characteristics of the statistical test for the primary effectiveness endpoint are calculated by simulating 10,000 trials for a given sample size using custom-written software in the R software package. The expected proportion of subjects with a primary effectiveness endpoint event in the control and Portico test groups are 22.9% for high risk group and 29.6% for extreme risk group per Table 2. The expected proportion of subjects with primary effectiveness endpoint event in control and Portico test group for the combined cohort of 80% high risk subjects and 20% extreme risk subjects are each 24.24%. This event rate assumption is consistent with data reported on commercially available TAVR within the TVT registry. As TAVR is currently indicated in the United States for extreme risk or high risk, the TVT registry is representative of patients to be studied in the PORTICO pivotal IDE trial. More than half of patients within the TVT registry have undergone transfemoral access and overall the rate of death or disabling stroke at 1 year is reported to be 26%, with transfemoral access providing...
11.4.2 Sample Size for the Primary Safety Endpoint

Using the above estimated event rates and an 8.5% non-inferiority margin, a sample size of 750 will provide 80% power at the 5% significance level to demonstrate non-inferiority of the Portico test group to the control group for the primary safety endpoint.

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.

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
• 6-minute walk at one year

Non-inferiority tests will be performed for each endpoint.

Specifically, null and alternative hypotheses for each endpoint are:

• Severe aortic regurgitation at one year (higher proportion is worse)

\[ H_0: \theta_{\text{test}, 1} \geq \theta_{\text{control}, 1} + 0.04 \]
\[ H_a: \theta_{\text{test}, 1} < \theta_{\text{control}, 1} + 0.04 \]

Where \( \theta_{\text{test}, 1} \) and \( \theta_{\text{control}, 1} \) are the proportions of subjects with severe aortic regurgitation at 1 year in the Portico test and control groups, respectively. The test statistic is based on the Farrington-Manning method of testing non-inferiority of proportions.

• KCCQ at one year (higher mean better)

\[ H_0: \theta_{\text{test}, 2} \leq \theta_{\text{control}, 2} - 10 \]
\[ H_a: \theta_{\text{test}, 2} > \theta_{\text{control}, 2} - 10 \]

Where \( \theta_{\text{test}, 2} \) and \( \theta_{\text{control}, 2} \) are the KCCQ scores at 1 year in the Portico test and control groups, respectively. The test statistic is based on a two-sample t-test.

• Moderate or severe aortic regurgitation at one year (higher proportion is worse)

\[ H_0: \theta_{\text{test}, 3} \geq \theta_{\text{control}, 3} + 0.06 \]
\[ H_a: \theta_{\text{test}, 3} < \theta_{\text{control}, 3} + 0.06 \]

Where \( \theta_{\text{test}, 3} \) and \( \theta_{\text{control}, 3} \) are the proportions of patients with moderate or severe aortic regurgitation at 1 year in the Portico test and control groups, respectively. The test statistic is based on the Farrington-Manning method of testing non-inferiority of proportions.

• 6-minute walk distance at one year (higher mean better)

\[ H_0: \theta_{\text{test}, 4} \leq \theta_{\text{control}, 4} - 36 \]
\[ H_a: \theta_{\text{test}, 4} > \theta_{\text{control}, 4} - 36 \]

Where \( \theta_{\text{test}, 4} \) and \( \theta_{\text{control}, 4} \) are the mean 6-minute walk distance at 1 year in the Portico test and control groups, respectively. The test statistic is based on a two-sample t-test.

The non-inferiority margins for the 1-year severe aortic regurgitation endpoint is 4%, for the 1-year KCCQ score is 10 points, for the 1-year moderate or severe aortic regurgitation is 6%, and for the 1-year 6-minute walk is 36m.
11.6 Multiplicity Adjustment

Multiplicity adjustment will apply to hypothesis testing for the superiority tests of primary endpoints and four non-inferiority tests of secondary endpoints (severe AR, KCCQ, moderate or severe AR, and 6-minute walk).

If non-inferiority test of either primary endpoint fails to achieve statistical significance, superiority tests of primary endpoints and non-inferiority test of secondary endpoints will not be performed.

If the primary endpoints of non-inferiority of effectiveness and safety are met, a sequential gate keeping strategy will be used in this study to ensure strong control of study-wise type I error for testing secondary endpoints and superiority of primary endpoint 43, 44, 47. In the case that non-inferiority tests of both primary endpoints are demonstrated, the secondary endpoints of non-inferiority and primary endpoints of superiority tests will be performed subsequently according to the following pre-specified hierarchical order.

The tests for the secondary endpoints will be conducted at one-sided tests at the 5% alpha level. The superiority tests of the primary endpoints (tests 3 and 4 below) will be conducted as one-sided test at the 2.5% alpha level:

1. Non-inferiority tests for severe AR at one year and KCCQ score at one year. Both tests have to be met at the 5% significance level in order to claim non-inferiority of the Portico test group to the control group on each of these endpoints.

2. If the above two secondary endpoints are met, non-inferiority tests for moderate or severe AR and 6-minute walk at one year will be performed next. Both tests have to be met at the 5% significance level in order to claim non-inferiority of the Portico test group to the control group on each of these secondary endpoints.

3. Finally, if the above endpoints met, superiority tests for the primary safety endpoint and effectiveness endpoint at one year will be performed. Both tests have to be met at the 2.5% significance level in order to claim superiority of each primary endpoint.

Hypothesis testing will stop at the first failed test.

11.7 Additional Analysis

11.7.1 Subgroup Analysis: Sex/gender

For the primary safety and effectiveness endpoints and secondary endpoints (aortic regurgitation, KCCQ score at one year, 6-minute walk at one year) tests will be performed to identify the interaction by treatment group and with gender. If the p-value statistic associated with the interaction is below 0.05, then interaction will be considered statistically significant and further analysis will be conducted on other key...
11.7.2 Additional Analyses of Primary Effectiveness Endpoint

11.7.2.1 Subgroup Analyses: Risk Status

The primary effectiveness endpoint at one year will be summarized separately for the high-risk cohort and the extreme risk cohort. The one-sided 95% confidence interval for the difference in 1-year event rates will be calculated.

11.7.2.2 Analysis Comparing Portico with each Control device

Separate analyses will be performed to compare St Jude Medical’s Portico TAVR device to each company’s device in the control group that is used in the trial for primary effectiveness endpoint at one year. The one-sided 95% confidence interval for the difference in 1-year event rates will be calculated.

In addition, hazard ratios as well as 12-month risk differences will be calculated with two-sided 95% confidence intervals overall between devices and within each risk cohort.

11.7.3 Additional Analyses of Primary Safety Endpoint

11.7.3.1 Subgroup Analysis: Risk Status

The primary endpoint and each individual component of the primary safety composite endpoint at 30 days will be summarized separately for the high-risk cohort and the extreme risk cohort. The one-sided 95% confidence interval for the difference in 30-day event rates will be calculated.

11.7.3.2 Analysis Comparing Portico with each Control device

Separate analyses will be performed to compare St Jude Medical’s Portico TAVR device to each company’s device in the control group that is used in the trial for primary safety endpoint at 30 days. The one-sided 95% confidence interval for the difference in 1-year event rates will be calculated.

In addition, hazard ratios as well as 30-day risk differences will be calculated with two-sided 95% confidence intervals overall between devices and within each risk cohort.

11.7.3.3 Augmented Analysis of Primary Safety Endpoint including FlexNav Study Data

Augmented analysis of the primary safety endpoint will be performed by combining the data for randomized Portico test group subjects with data from the FlexNav study, and data from up to 50 subjects enrolled in a prospective, multi-center single-arm FlexNav EU CE Mark study. The combined dataset of Portico subjects will be summarized for the primary safety endpoint and each individual component of the primary safety composite
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.
11.10 Statistical Methods and Analysis (FlexNav Study, Registries and CAP)

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
• 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.
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:

St. Jude Medical
Attn: Global Clinical Affairs, PORTICO Clinical Study
5050 Nathan Lane North
Plymouth, MN 55442 USA
Tel +651.756.5400

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
• 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

13.3 Investigator Responsibilities
13.4 Reports

Table 12 includes details on required reporting obligations.
<table>
<thead>
<tr>
<th>Event Type</th>
<th>Responsible Party</th>
<th>Submission To</th>
<th>Timeframe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unanticipated Adverse Device Effect (UADE), Serious Adverse Event (SAE)</td>
<td>Principal Investigator, SJM</td>
<td>SJM and IRB</td>
<td>Within 3 calendar days from becoming aware of the event.</td>
</tr>
<tr>
<td>Device deficiencies</td>
<td>Principal Investigator, SJM</td>
<td>SJM and IRB (If applicable)</td>
<td>Within 3 calendar days from becoming aware of the event.</td>
</tr>
<tr>
<td>Failure to obtain informed consent</td>
<td>Principal Investigator</td>
<td>SJM, IRB</td>
<td>Within 5 working days</td>
</tr>
<tr>
<td>Withdrawal of IRB Approval</td>
<td>Principal Investigator</td>
<td>SJM</td>
<td>Within 5 working days</td>
</tr>
<tr>
<td>Protocol deviation to protect the life or physical well-being of a subject in an emergency</td>
<td>Principal Investigator</td>
<td>IRB and Abbott</td>
<td>Within 5 working days after the emergency occurred</td>
</tr>
<tr>
<td>Annual Report</td>
<td>Principal Investigator</td>
<td>IRB and Abbott</td>
<td>Without unjustified delay, annually upon IRB approval date</td>
</tr>
<tr>
<td>Annual Progress Report</td>
<td>SJM</td>
<td>Principal Investigator, IRB and FDA</td>
<td>Annually, on approval date of IDE study</td>
</tr>
<tr>
<td>Sub-study (Appendix S)</td>
<td>SJM</td>
<td>FDA</td>
<td>After every fifty (50) randomized subjects complete 30-Day imaging (MSCT or TEE), analyzed by the Core Lab</td>
</tr>
<tr>
<td>Final Report</td>
<td>SJM</td>
<td>Principal Investigator, IRB and FDA</td>
<td>After a minimum of 200 randomized subjects complete both 30-Day and 6-Month imaging (MSCT or TEE), analyzed by the Core Lab</td>
</tr>
<tr>
<td>Final</td>
<td>SJM</td>
<td>Principal Investigator, IRB and Abbott</td>
<td>Within 6 calendar months following the completion or termination of the study</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Within 3 calendar months following the completion or termination of the study at the study site</td>
</tr>
</tbody>
</table>
13.5 Records

Records to be maintained by the Principal Investigator in a designated study file include, but are not limited to:

- Investigation plan and all amendments
- Signed Study Agreement and all amendments
- Report of Prior Investigations (ROPI)
- IRB approval letters, including a copy of the approved informed consent form, progress reports, AE reports
- IRB Registration Number
- List of IRB voting members (optional)
- Insurance certificate
- All correspondence relating to the conduct of this study between the site, sponsor and IRB
- Signed CVs and professional licenses (if applicable)
- Training records relevant to conduct of the Clinical Investigation
- Site personnel signatures and documentation regarding the Principal Investigator's delegation of responsibilities
- Site Visit Log
- Blank copies of each version of CRFs
- Documentation of all approved changes made to informed consent form
- Documentation of FDA approval and communication
- CIP/device related training records for all applicable study personnel
- Investigational device inventory information including the date, quantity, and unique identifiers for all devices shipped and received, identification of all subjects in whom the device was used, and final disposition of all devices received
- Enrollment Log including all procedurally excluded subjects
- Financial Disclosure documentation for the Principal Investigator and all Co-Investigators.

The following records must be maintained by the Principal Investigator for each subject enrolled:

- Completed CRFs
- Subject Identification Log
- Source documentation for SAEs and AEs
- Signed and dated informed consent forms
- Complete medical records including procedure reports, lab reports, source documents
- Records pertaining to a subject's death during the study (if applicable)

13.6 Record Retention

Subject study records, correspondence files, all supporting study documentation, and reports must remain on file at the study site for a minimum of two (2) years, or longer.
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.
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.
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.
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.

ThePORTICO 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.

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

13.15 Compliance

It is the responsibility of SJM to promptly secure compliance from any study site that is not complying with the requirements of this study. If a monitor is unable to secure compliance, the SJM Project Manager must be notified immediately. The Project Manager will work directly with the monitor and site to implement a compliance action plan. If the site does not complete the activities outlined in the compliance action plan, or if the noncompliance is considered significant and may affect the scientific soundness of the study or safety of the subjects, SJM may terminate the Investigator’s participation in the study.

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
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

In conjunction with the clinical study, the costs and benefits of treatment will be evaluated through an economic and quality of life analysis. Medical resource use, cost- and health-related quality of life within the trial period will be compared between treatment groups. If the Portico device is found to be safe and effective, its long-term cost-effectiveness will be assessed. The economic and quality of life analysis will be fully integrated into the clinical trial, with a common informed consent form and collection of subject reported resource use in the case report form.

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).

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.
13.20.2 Site Activation

Before a site is activated and allowed to enroll subjects, the following documents, at a minimum, must be received by SJM:

• copy of FDA letter of approval
• copy of IRB letter of approval, along with a copy of the approved informed consent form
• fully Executed Study Agreement
• current Curriculum Vitae (signed and dated) of the Principal Investigator

14 Sponsor Contact Information

To contact the Sponsor regarding the PORTICO Clinical Study:
St. Jude Medical (now Abbott)
Attn: Global Clinical Affairs, PORTICO Clinical Study
5050 Nathan Lane North
Plymouth, MN 55442 USA
Tel 651.756.5400
Bibliography


33. Manoharan G 2012 (Oct) Prospective, Multicenter Evaluation of the Portico Transcatheter Aortic Valve: Acute Results and 1-year Outcomes, TCT, Miami FL


40. Linke A. The ADVANCE TAVR registry. TCT 2012; October 22, 2012; Miami, FL.


# 16 APPENDICES

## Appendix A: Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWT</td>
<td>Six Minute Walk Test</td>
</tr>
<tr>
<td>AA</td>
<td>Alternative Access</td>
</tr>
<tr>
<td>ACC</td>
<td>American College of Cardiology</td>
</tr>
<tr>
<td>ACT</td>
<td>Activated Clotting Time</td>
</tr>
<tr>
<td>ADE</td>
<td>Adverse Device Effect</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>AF</td>
<td>Atrial Fibrillation</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>ARB</td>
<td>Angiotensin Receptor Blocker</td>
</tr>
<tr>
<td>AS</td>
<td>Aortic Stenosis</td>
</tr>
<tr>
<td>AV</td>
<td>Aortic Valve</td>
</tr>
<tr>
<td>AVA</td>
<td>Aortic Valve Area</td>
</tr>
<tr>
<td>AVR</td>
<td>Aortic Valve Replacement</td>
</tr>
<tr>
<td>BARC</td>
<td>Bleeding Academic Research Consortium</td>
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<tr>
<td>BNP</td>
<td>B-type Natriuretic Peptide</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary Artery Disease</td>
</tr>
<tr>
<td>CAP</td>
<td>Continued Access Protocol</td>
</tr>
<tr>
<td>CAV</td>
<td>FDA Approved and Commercially Available Transcatheter Valve</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete Blood Count</td>
</tr>
<tr>
<td>CCS</td>
<td>Canadian Cardiovascular Society</td>
</tr>
<tr>
<td>CE</td>
<td>Conformité Européene (European Conformity)</td>
</tr>
<tr>
<td>CEC</td>
<td>Clinical Events Committee</td>
</tr>
<tr>
<td>CIP</td>
<td>Clinical Investigation Plan</td>
</tr>
<tr>
<td>CMS</td>
<td>Centers for Medicare &amp; Medicaid Services</td>
</tr>
<tr>
<td>CPB</td>
<td>Cardiopulmonary Bypass</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
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<tr>
<td>CV</td>
<td>Curriculum Vitae</td>
</tr>
<tr>
<td>CVA</td>
<td>Cerebral Vascular Accident</td>
</tr>
<tr>
<td>DSMB</td>
<td>Data Safety Monitoring Board</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>Echo</td>
<td>Echocardiography</td>
</tr>
<tr>
<td>eDC</td>
<td>Electronic Data Capture</td>
</tr>
<tr>
<td>EEA</td>
<td>European Economic Area</td>
</tr>
<tr>
<td>EF</td>
<td>Ejection Fraction</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Term</td>
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<td>--------------</td>
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</tr>
<tr>
<td>EOA</td>
<td>Effective Orifice Area</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GI</td>
<td>Gastro Intestinal</td>
</tr>
<tr>
<td>HOCM</td>
<td>Hypertrophic cardiomyopathy with or without obstruction</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>IDE</td>
<td>Investigational Device Exemption</td>
</tr>
<tr>
<td>IFU</td>
<td>Instructions For Use</td>
</tr>
<tr>
<td>INR</td>
<td>International Normalized Ratio</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>ITT</td>
<td>Intent To Treat</td>
</tr>
<tr>
<td>KCCQ</td>
<td>Kansas City Cardiomyopathy Questionnaire</td>
</tr>
<tr>
<td>Kg</td>
<td>Kilogram</td>
</tr>
<tr>
<td>LBBB</td>
<td>Left Bundle Branch Block</td>
</tr>
<tr>
<td>LV</td>
<td>Left Ventricular</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left Ventricular Ejection Fraction</td>
</tr>
<tr>
<td>MAC</td>
<td>Mitral Annular Calcification</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial Infarction</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini-mental state examination</td>
</tr>
<tr>
<td>MR</td>
<td>Mitral Regurgitation</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>mRS</td>
<td>Modified Rankin Scale</td>
</tr>
<tr>
<td>MSCT</td>
<td>Multi-Slice Computed Tomography</td>
</tr>
<tr>
<td>NCD</td>
<td>National Coverage Determination</td>
</tr>
<tr>
<td>NIHSS</td>
<td>NIH Stroke Scale</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
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<tr>
<td>PA</td>
<td>Pulmonary Artery</td>
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<tr>
<td>PCI</td>
<td>Percutaneous Coronary Intervention</td>
</tr>
<tr>
<td>PCWP</td>
<td>Pulmonary Capillary Wedge Pressure</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>PAVR</td>
<td>Percutaneous Aortic Valve Replacement</td>
</tr>
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<td>PMA</td>
<td>Premarket Approval</td>
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<tr>
<td>PVD</td>
<td>Peripheral Vascular Disease</td>
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<tr>
<td>PVL</td>
<td>Paravalvular Leak</td>
</tr>
<tr>
<td>RA</td>
<td>Right Atrium</td>
</tr>
<tr>
<td>RV</td>
<td>Right Ventricular</td>
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<tr>
<td>SADE</td>
<td>Serious Adverse Device Effect</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Term</td>
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<td>--------------</td>
<td>-------------------------------------------</td>
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<tr>
<td>SAV</td>
<td>Surgical Aortic Valve</td>
</tr>
<tr>
<td>SAVR</td>
<td>Surgical Aortic Valve Replacement</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SJM</td>
<td>St. Jude Medical, Cardiovascular Division</td>
</tr>
<tr>
<td>SSC</td>
<td>Subject Selection Committee</td>
</tr>
<tr>
<td>STS</td>
<td>Society of Thoracic Surgeons</td>
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<tr>
<td>TA</td>
<td>Trans Apical</td>
</tr>
<tr>
<td>TAV</td>
<td>Transcatheter Aortic Valve</td>
</tr>
<tr>
<td>TAVI</td>
<td>Transcatheter Aortic Valve Implantation</td>
</tr>
<tr>
<td>TAVR</td>
<td>Transcatheter Aortic Valve Replacement</td>
</tr>
<tr>
<td>TEE</td>
<td>Transesophageal Echocardiogram (same as TOE)</td>
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<td>TF</td>
<td>Trans Femoral</td>
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<tr>
<td>TIA</td>
<td>Transient Ischemia Attack</td>
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<tr>
<td>TAo</td>
<td>Transaortic</td>
</tr>
<tr>
<td>TTE</td>
<td>Transthoracic Echocardiogram</td>
</tr>
<tr>
<td>UADE</td>
<td>Unanticipated Adverse Device Effect</td>
</tr>
<tr>
<td>US</td>
<td>United States (same as USA)</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America (same as US)</td>
</tr>
<tr>
<td>VARC 2</td>
<td>Valve Academic Research Consortium 2</td>
</tr>
<tr>
<td>VIV</td>
<td>Valve in Valve</td>
</tr>
<tr>
<td>WBC</td>
<td>White Blood Cell</td>
</tr>
<tr>
<td>WMA</td>
<td>World Medical Association</td>
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</table>
Appendix B: Synopsis (Pivotal IDE)

Study Title: Portico™ Re-sheathable Transcatheter Aortic Valve System US IDE Trial (PORTICO)

Study Number: 1203

Study Device: Portico™ Transcatheter Heart Valve and the Portico Delivery Systems

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

Primary Endpoints:
- Effectiveness endpoint: the composite endpoint of all-cause mortality or disabling stroke at one year.

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 
   - 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
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
7. Aortic insufficiency greater than trace at 30 days, 6 months, one year, and two years
8. Reintervention to treat aortic insufficiency at one year and two 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 at 30 days, 6 months, and one year

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

The pivotal IDE trial includes a randomized cohort, three nested registries (Roll-in, Valve-in-Valve and Portico Extreme Risk (now closed to enrollment)) and a separate FlexNav study arm (under Protocol version L).

For the randomized cohort, approximately 758 subjects will be enrolled from up to 70 investigational sites globally. Data from the randomized cohort and the FlexNav study will be used to support a PMA application for approval of the Portico™ Transcatheter Aortic Heart Valve and FlexNav™ Delivery System in the United States. Data of subjects enrolled in the registries will not be included in the randomized population nor the primary data analysis; however, the data will be analyzed and presented separately.

Sponsor:
St. Jude Medical (now Abbott)
Attn: Global Clinical Affairs, PORTICO Clinical Study
5050 Nathan Lane North
Plymouth, MN 55442 USA
Tel 651.756.5400

National Principal Investigator:
Greg Fontana, MD

Investigators:
Raj Makkar, MD
Appendix C: Definitions

<table>
<thead>
<tr>
<th>Source</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular Mortality (VARC 2)</strong></td>
<td>Any one of the following criteria:</td>
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<tr>
<td></td>
<td>• Death due to proximate cardiac cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure)</td>
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<tr>
<td></td>
<td>• Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease</td>
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<tr>
<td></td>
<td>• All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure</td>
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<tr>
<td></td>
<td>• All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related adverse events</td>
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<tr>
<td></td>
<td>• Sudden or unwitnessed death</td>
</tr>
<tr>
<td></td>
<td>• Death of unknown cause</td>
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<tr>
<td><strong>Myocardial Infarction (VARC 2)</strong></td>
<td><strong>Peri-procedural MI (less than or equal to (≤) 72 h after the index procedure)</strong></td>
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<tr>
<td></td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>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 (&gt;99th percentile), a further increase of at least 50% post-procedure is required AND the peak value must exceed the previously stated limit.</td>
</tr>
<tr>
<td></td>
<td><strong>Spontaneous MI (greater than (&gt;) 72 h after the index procedure)</strong></td>
</tr>
<tr>
<td></td>
<td>Any one of the following criteria:</td>
</tr>
<tr>
<td></td>
<td>• 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:</td>
</tr>
<tr>
<td></td>
<td>o Symptoms of ischaemia</td>
</tr>
<tr>
<td></td>
<td>o ECG changes indicative of new ischemia [new ST-T changes or new Left Bundle Branch Block (LBBB)]</td>
</tr>
<tr>
<td></td>
<td>o New pathological Q waves in at least two contiguous leads</td>
</tr>
<tr>
<td></td>
<td>o Imaging evidence of new loss of viable myocardium or new wall motion abnormality</td>
</tr>
<tr>
<td></td>
<td>• 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.</td>
</tr>
<tr>
<td></td>
<td>• Pathological findings of an acute myocardial infarction.</td>
</tr>
<tr>
<td><strong>Stroke (FDA/VARC 2)</strong></td>
<td>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)</td>
</tr>
<tr>
<td></td>
<td><strong>1. Definitions:</strong></td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
</tbody>
</table>
### Source Definition

#### Subclassifications of stroke:
- **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.
- **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):
- **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
- **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

#### 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.

#### 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.

#### Encephalopathy:
Altered mental state (e.g., seizures, delirium, confusion, hallucinations, dementia, coma, psychiatric episode, etc.).

#### 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)

#### Stage 1
Change in serum creatinine (up to 48 h) compared with baseline
<table>
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<th>Source</th>
<th>Definition</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>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 &lt;0.5 ml/kg per hour for &gt; 6 but &lt; 12 hours</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Increase in serum creatinine to 200% to 299% (2.0 to 2.99 X increase compared with baseline) or Urine output &lt;0.5 ml/kg per hour for &gt; 12 but &lt; 24 hours</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Increase in serum creatinine to greater than or equal to (≥) 300% (&gt;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 &lt; 0.3 ml/kg per hour for &gt; 24 hours or anuria for &gt; 12 hours. Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.</td>
</tr>
</tbody>
</table>

### Vascular Access Site and Access-Related Complications (VARC 2)

#### Major vascular complications
- Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm or
- Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) leading to death, life-threatening or major bleeding*, visceral ischaemia or neurological impairment or
- Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage or
- The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischaemia or neurological impairment or
- Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram or
- Surgery for access site-related nerve injury or
- Permanent access site-related nerve injury

#### Minor vascular complications
- Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysms, hematomas, percutaneous closure device failure) not leading to death, life-threatening or major bleeding*, visceral 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)
<table>
<thead>
<tr>
<th>Source</th>
<th>Definition</th>
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</thead>
</table>
| 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) |

<table>
<thead>
<tr>
<th>Prosthetic Valve Stenosis Criteria (VARC 2)</th>
<th>Parameter</th>
<th>Normal</th>
<th>Mild Stenosis</th>
<th>Moderate/severe Stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>In conditions of normal or near normal stroke volume (50–70 ml). (VARC 2)</td>
<td>Peak velocity (m/s)</td>
<td>less than (&lt;) 3</td>
<td>3–4</td>
<td>greater than (&gt;4)</td>
</tr>
<tr>
<td>Mean gradient (mm Hg)</td>
<td>less than (&lt;) 20</td>
<td>20–40</td>
<td>greater than (&gt;40)</td>
<td></td>
</tr>
<tr>
<td>Doppler velocity index</td>
<td>greater than or equal to (≥) 0.35</td>
<td>0.35–0.25</td>
<td>less than (&lt;) 0.25</td>
<td></td>
</tr>
<tr>
<td>Effective orifice area (cm²)</td>
<td>greater than (&gt;1) 1.1</td>
<td>1.1–0.8</td>
<td>less than (&lt;) 0.8</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prosthetic Valve Regurgitation Criteria (VARC 2)</th>
<th>Diastolic flow reversal in the descending aorta (semi-quantitative parameters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diastolic flow reversal in the descending aorta PW Doppler</td>
<td>Absent or brief early diastolic</td>
</tr>
</tbody>
</table>

* Effective orifice area (EOA) used in this protocol is 1.0 cm² for Portico valve of 23mm diameter.
<table>
<thead>
<tr>
<th>Source</th>
<th>Definition</th>
<th>less than (&lt;) 10%</th>
<th>10–29%</th>
<th>greater than or equal (≥) 30%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Circumferential extent of paraprosthetic AR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Doppler parameters (quantitative)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regurgitant volume (ml/beat)</td>
<td>less than (&lt;) 30%</td>
<td>30–59%</td>
<td></td>
<td>greater than or equal (≥) 60%</td>
</tr>
<tr>
<td>Regurgitant fraction</td>
<td>less than (&lt;) 30%</td>
<td>30–49%</td>
<td></td>
<td>greater than or equal (≥) 50%</td>
</tr>
<tr>
<td>EROA (cm²)</td>
<td>0.10 cm²</td>
<td>0.10-0.29 cm²</td>
<td>≥0.30 cm²</td>
<td></td>
</tr>
</tbody>
</table>
Appendix D: Surgical Risk Assessment Tools

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

2. Euro SCORE II (http://euroscore.org/calc.html)
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
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.
Appendix 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:**

<table>
<thead>
<tr>
<th>Excellent</th>
<th>Very good</th>
<th>Good</th>
<th>Fair</th>
<th>Poor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Much better now than one year ago</th>
<th>Somewhat better now than one year ago</th>
<th>About the same as one year ago</th>
<th>Somewhat worse now than one year ago</th>
<th>Much worse now than one year ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

<table>
<thead>
<tr>
<th>Activity</th>
<th>Yes, limited a lot</th>
<th>Yes, limited a little</th>
<th>No, not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Lifting or carrying groceries</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Climbing several flights of stairs</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Climbing one flight of stairs</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Bending, kneeling, or stooping</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Walking more than a mile</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Walking several hundred yards</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Walking one hundred yards</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>Bathing or dressing yourself</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>
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?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
</table>

- Cut down on the amount of time you spent on work or other activities
- Accomplished less than you would like
- Were limited in the kind of work or other activities
- Had difficulty performing the work or other activities (for example, it took extra effort)

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)?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
</table>

- Cut down on the amount of time you spent on work or other activities
- Accomplished less than you would like
- Did work or other activities less carefully than usual
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

<table>
<thead>
<tr>
<th>Not at all</th>
<th>Slightly</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>None</th>
<th>Very mild</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Very severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Not at all</th>
<th>A little bit</th>
<th>Moderately</th>
<th>Quite a bit</th>
<th>Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
</tbody>
</table>
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

- Did you feel full of life? .................................. □ 1 .................................. □ 3 .................................. □ 5  
- Have you been very nervous? .................................. □ 1 .................................. □ 3 .................................. □ 5  
- Have you felt so down in the dumps that nothing could cheer you up? .................................. □ 1 .................................. □ 3 .................................. □ 5  
- Have you felt calm and peaceful? .................................. □ 1 .................................. □ 3 .................................. □ 5  
- Did you have a lot of energy? .................................. □ 1 .................................. □ 3 .................................. □ 5  
- Have you felt downhearted and depressed? .................................. □ 1 .................................. □ 3 .................................. □ 5  
- Did you feel worn out? .................................. □ 1 .................................. □ 3 .................................. □ 5  
- Have you been happy? .................................. □ 1 .................................. □ 3 .................................. □ 5  
- Did you feel tired? .................................. □ 1 .................................. □ 3 .................................. □ 5  

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

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
</tbody>
</table>
11. How TRUE or FALSE is each of the following statements for you?

<table>
<thead>
<tr>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Don’t know</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
</tbody>
</table>

- I seem to get sick a little easier than other people... □ 1 .......... □ 2 .......... □ 3 .......... □ 4 .......... □ 5
- I am as healthy as anybody I know... □ 1 .......... □ 2 .......... □ 3 .......... □ 4 .......... □ 5
- I expect my health to get worse... □ 1 .......... □ 2 .......... □ 3 .......... □ 4 .......... □ 5
- My health is excellent... □ 1 .......... □ 2 .......... □ 3 .......... □ 4 .......... □ 5

Thank you for completing these questions!
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

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

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

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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?

<table>
<thead>
<tr>
<th>Every morning</th>
<th>3 or more times a week, but not every day</th>
<th>1-2 times a week</th>
<th>Less than once a week</th>
<th>Never over the past 2 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

It has been...

<table>
<thead>
<tr>
<th>Extremely bothersome</th>
<th>Quite a bit bothersome</th>
<th>Moderately bothersome</th>
<th>Slightly bothersome</th>
<th>Not at all bothersome</th>
<th>I’ve had no swelling</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Several times per day</th>
<th>At least once a day</th>
<th>3 or more times per week but not every day</th>
<th>1-2 times per week</th>
<th>Less than once a week</th>
<th>Never over the past 2 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

It has been...

<table>
<thead>
<tr>
<th>Extremely bothersome</th>
<th>Quite a bit bothersome</th>
<th>Moderately bothersome</th>
<th>Slightly bothersome</th>
<th>Not at all bothersome</th>
<th>I’ve had no fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Several times per day</th>
<th>At least once a day</th>
<th>3 or more times per week but not every day</th>
<th>1-2 times per week</th>
<th>Less than once a week</th>
<th>Never over the past 2 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 □
14. Over the past 2 weeks, how often have you felt discouraged or down in the dumbs 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

<table>
<thead>
<tr>
<th>Activity</th>
<th>Severely limited</th>
<th>Limited quite a bit</th>
<th>Moderately limited</th>
<th>Slightly limited</th>
<th>Did not limit at all</th>
<th>Does not apply or did not do for other reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hobbies, recreational activities</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Working or doing household chores</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Visiting family or friends out of your home</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Intimate relationships with loved ones</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>
Appendix H: Mini-Mental State Examination (MMSE-2)

**Standard Version**

**Blue Form**

**Instructions:** Words in boldface type should be read aloud clearly and slowly to the examinee. Items in parentheses 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.

**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.]

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MILK</td>
<td>0 1</td>
</tr>
<tr>
<td>SENSIBLE</td>
<td>0 1</td>
</tr>
<tr>
<td>BEFORE</td>
<td>0 1</td>
</tr>
</tbody>
</table>

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? What is the season? What is the month of the year? What is the day of the week? What is the date?

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1</td>
</tr>
<tr>
<td></td>
<td>0 1</td>
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<td>0 1</td>
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<td>0 1</td>
</tr>
<tr>
<td></td>
<td>0 1</td>
</tr>
</tbody>
</table>

**ORIENTATION TO PLACE**

Where are we now? What is the state (or province)?

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1</td>
</tr>
</tbody>
</table>

county (or city/town)?

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1</td>
</tr>
</tbody>
</table>

city/town (or part of city/neighborhood)?

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1</td>
</tr>
</tbody>
</table>

building (name or type)?

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1</td>
</tr>
</tbody>
</table>

floor of the building (room number or address)?

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1</td>
</tr>
</tbody>
</table>

*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.]

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MILK</td>
<td>0 1</td>
</tr>
<tr>
<td>SENSIBLE</td>
<td>0 1</td>
</tr>
<tr>
<td>BEFORE</td>
<td>0 1</td>
</tr>
</tbody>
</table>

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.
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.

<table>
<thead>
<tr>
<th>Question</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>What is 100 take away 7?</td>
<td>0</td>
</tr>
<tr>
<td>If needed, say: Keep going.</td>
<td>1</td>
</tr>
<tr>
<td>If needed, say: Keep going.</td>
<td>1</td>
</tr>
<tr>
<td>If needed, say: Keep going.</td>
<td>1</td>
</tr>
<tr>
<td>If needed, say: Keep going.</td>
<td>1</td>
</tr>
</tbody>
</table>

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     |
- What is this? [Point to ear.]                                         | 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.                               | 1     |

COMPREHENSION
- Listen carefully because I am going to ask you to do something. Show me 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.

<table>
<thead>
<tr>
<th>Correct response</th>
<th>Observed response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

READING
- [Show examinee the word stimulus page.] Please do what this says to do.
  - CLOSE YOUR EYES                                                      | 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.

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 7-sided figure.

MMSE-2:BV
- Total raw score
  - (10 max. points)
Sample

CLOSE YOUR EYES
Sample
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
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

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

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__________  Grasp 3__________

Average_____________
15 Foot Walk  _______________ seconds

<table>
<thead>
<tr>
<th></th>
<th>Cutoff for grip strength (Kg) criterion for frailty</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men</strong></td>
<td></td>
</tr>
<tr>
<td>BMI ≤ 24</td>
<td>≤ 29</td>
</tr>
<tr>
<td>BMI 24.1-26</td>
<td>≤ 30</td>
</tr>
<tr>
<td>BMI 26.1-28</td>
<td>≤ 30</td>
</tr>
<tr>
<td>BMI &gt; 28</td>
<td>≤ 32</td>
</tr>
<tr>
<td><strong>Women</strong></td>
<td></td>
</tr>
<tr>
<td>BMI ≤ 23</td>
<td>≤ 17</td>
</tr>
<tr>
<td>BMI 23.1-26</td>
<td>≤ 17.3</td>
</tr>
<tr>
<td>BMI 26.1-29</td>
<td>≤ 18</td>
</tr>
<tr>
<td>BMI &gt; 29</td>
<td>≤ 21</td>
</tr>
</tbody>
</table>

(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.
Appendix L: Explant, Return, and Analysis of Valve

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

Clinical Study Sites' Responsibilities for Explant and Return of Device:

SJM requests that all valves that are explanted or recovered be returned to SJM as follows:

➢ Contact the SJM Project Manager(s) for this study as soon as it is learned that a valve will be explanted, or recovered during an autopsy. The Clinical Representative(s) will obtain a RA# (used for returning products to SJM), and then send a St. Jude Medical Product Return Kit to the site for return of the explanted valve.

➢ When possible, take in situ photographs of the valve.

➢ Remove the valve from the subject and immediately place it in the inner jar of the product return kit. (If the explant kit is not available, place the valve in any specimen jar until the product return kit arrives.)

➢ Cover the valve with a formalin solution (usual lab concentration 3-8%). If an alternate solution is used [i.e., alkaline glutaraldehyde (Cidex) at 0.5-1% concentration], please indicate the solution type and concentration on the specimen container.

➢ Secure the cap.

➢ Complete the round white label with device, subject, and surgeon information.

➢ Place the completed label on the cap of the inner jar and fold tape edges down over jar.

➢ Place the small labeled jar in the absorbent wrapping provided, and place inside the larger jar.

➢ Secure the cap.

➢ Place the outer jar into the shipping box. Tape the box closed.

➢ Write the RA#, and the name and phone number of the person responsible for shipping the valve on the return shipping label.

➢ For infectious specimens, complete the highlighted portions of the Shipper’s Declaration for Dangerous Goods form, and keep this form with the product return kit.

➢ Send the packaged valve, in situ photographs, and operative/autopsy notes via courier to the following address:

St Jude Medical (now Abbott)  
Attn: Clinical Returns  
2305 Walnut St  
Roseville, MN  
55113

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

SJM TAV valves that are explanted or recovered at autopsy and returned will, upon receipt at St. Jude Medical, Inc., be evaluated according to documented SJM procedures.
Appendix M: Instructions for Packaging and Returning Products to St. Jude Medical (now Abbott)

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

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

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

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

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

5 - Affix the address label provided to the outside of the box and return DRK to the sponsor:
   St. Jude Medical (now Abbott)
   ATTN: Clinical Returns
   2305 Walnut St
   Roseville, MN 55113
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 of 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.
• 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."
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.
### Appendix P: Barthel Index

#### THE BARTHEL INDEX

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

**TOTAL (0–100):** ___
The Barthel ADL Index: Guidelines

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

References

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

Loewen SC, Anderson BA. “Predictors of stroke outcome using objective measurement scales.”


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Maryland State Med Journal 1965;14:56-61. Used with permission.

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Provided by the Internet Stroke Center — www.strokecenter.org
Appendix Q: Patient Informed Consent

STUDY TITLE: PORTICO™ RE-SHEATHABLE TRANSCATHETER AORTIC VALVE SYSTEM US PIVOTAL IDE TRIAL (PORTICO)

Principal Investigator: <    >
Hospital: <    >
Address: <    >
Phone: <    >

Sponsor: St. Jude Medical, Cardiology Division Inc is now part of Abbott (hereinafter referred to as “Sponsor” or “St Jude Medical”)

PART 1

1. Invitation
You are being invited to take part in a research study. Before you decide, it is important for you to know why the research is being done and what it will involve. Please take time to read the following information carefully. Feel free to discuss it with others if you wish. Ask us if there is anything that is not clear or if you want more information. Take your time to decide if you wish to participate.

2. Purpose of the study
The purpose of this study is to evaluate the safety and effectiveness of the new St Jude Medical Portico Transcatheter Heart Valve and delivery systems. The study valve is made to replace your diseased aortic heart valve.

3. Why have I been invited?
You are being asked to take part in this research study because your doctors have decided that you may be a high or extreme risk candidate for aortic heart valve replacement through open heart surgery. At your request, your study doctor will notify your personal physician of your participation in this study.

4. How many people will participate?
This study will be conducted at up to seventy (70) centers globally, and will include a maximum of 758 randomized subjects (enrollment of randomized subjects ended in October 2017). Additionally, up to 100 subjects will be enrolled in a Valve-in-Valve registry and up to 200 subjects in a separate FlexNav study.

5. What is the device being tested?
The Portico Transcatheter Heart Valve is an investigational device. This means that the valve is being studied, and is not for sale in the United States. This study is collecting data on the valve and delivery system for review and approval by the Food and Drug Administration (FDA).
The Portico Transcatheter Heart Valve is a replacement heart valve that can be placed through a tube in your leg or through your chest. The valve is made of animal tissue and is on a stent, or scaffold, which holds the valve in position. The stent portion of the valve is made with Nitinol (metal with Nickel and Titanium). Picture 1 below shows the Portico valve. Picture 2 on page 6 shows the different ways the valve can be put in place.

The Portico Transcatheter Heart Valve is loaded into a delivery system which is part of the catheter used to help the study doctor place the valve in your heart. The delivery system is about as big around as your ring finger. The valve is put into the delivery system with a two-part funnel system which compresses the stent to fit inside the delivery system.

While using echocardiography and fluoroscopy (angiogram pictures) the study doctor will position the valve in your heart. After positioning the heart valve, the delivery system will slowly let the valve expand to the full size.

The Portico Transcatheter Heart Valve is designed to have the capability to be released slowly in a controlled manner, be repositioned (should the need arise), be removed completely and another attempt made, and the final position can be checked thoroughly before final valve release (with normal new valve function during the assessment).

6. Do I have to take part?

No. Your participation in this study is entirely voluntary and you are under no pressure to take part. If you decide to participate in this study, but later change your mind, you can withdraw at any time without explanation and without any loss of medical care or benefits you would otherwise have received. You can withdraw from this study without penalty, and withdrawal from this study will not jeopardize your future care or your relationship with the study doctor. If you withdraw from the study, you will be asked what the reason is for withdrawing from the study, but you do not have to answer.
If the study doctor has concerns about your participation, you will not be able to take part in the study. The study doctor can also withdraw you from the study at any time. If you do decide to take part, you will be asked to sign this consent form. By consenting to take part in this study you are agreeing that the St Jude Medical Portico valve (Picture 1) may be implanted using the delivery system.

7. What are the alternate treatments?

If you do not wish to take part in this study, your study doctor may treat your aortic valve with:

1. Medication
2. An FDA approved Transcatheter Aortic Valve Replacement (TAVR) valve and delivery system
3. Standard open heart surgery by a referral to a heart surgeon

8. How long will my participation last in this clinical study?

Your participation in this study will begin when you sign the informed consent form and for up to five years following your implant, unless it is determined that you do not meet the study eligibility criteria or you decide to stop your participation in the study. If you are randomized in the study and do not receive a TAVR valve, you will be followed through the one-year visit, as part of the primary analysis intent to treat (ITT) population, and then withdrawn from the study. If you are enrolled in a registry or the FlexNav study and do not receive a Portico valve, you will be followed for any adverse events through the 30 days post procedure and then withdrawn from the study. If you undergo study-specific testing, but are not randomized you will be followed for any adverse events for 30 days from informed consent and then withdrawn from study participation. If you undergo study-specific testing, but are not assigned to a registry or enrolled in the FlexNav study you will not be required to return for any follow-up.

You may stop your participation in this study at any time. Your participation in this study may also be stopped by St Jude Medical or by your study doctor. Reasons for ending your participation in the study by the Principal Investigator include, but are not limited to, the following:

• Study participation was not in your best interest
• You did not meet the inclusion/exclusion criteria
• You and/or family request, if applicable
• You aren't able to comply with the requirement of the study (e.g., you aren't able to attend follow-up visits)
• Death
• Your non-compliance with study requirements
• You are considered “lost to follow-up”, which occurs 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 by traceable mail
• Your participation is terminated by the Principal Investigator if it is not in your best interest to continue in the study
• Study discontinued due to St Jude Medical management decision or request from applicable governing bodies
• Investigation at site ends participation in the study

The study may be temporarily stopped or terminated, either at the local or national level, at the request of the Institutional Review Board (IRB), regulatory authorities (FDA), or St Jude Medical. St Jude Medical may stop the study if new information about the device is learned during the duration of the study to ensure patient safety.

You will be notified in writing if there are new findings or reasons for any changes to the study plan which will affect your continued participation in the study.

9. What will take place during the study?

This is a randomized research study. “Randomized” means that you will be assigned to a study group by chance, like flipping a coin. Depending on your valve size you will be randomized into one of two study groups which will determine the device you are implanted with:

• Test Group: Portico Transcatheter Heart Valve
• Control Group: FDA-approved Transcatheter Heart Valve

Note: The randomized cohort completed enrollment in October 2017.

There are also two (2) registries and a separate FlexNav study group (which uses a new delivery system) in this research study. If you are placed in a registry or the FlexNav study you will receive a Portico valve rather than be randomized.

The first registry is called a roll-in registry. You may be considered for this registry based on your order of enrollment in the study. All those placed in this registry will receive a Portico valve. The second registry is for those who have already received a replacement surgical aortic valve and require another. If you qualify for this registry, a Portico valve will be implanted inside your existing surgical valve.
The FlexNav study will evaluate the safety of the new FlexNav™ Delivery System. All those assigned to the study group will receive a Portico valve using the new delivery system. There is no change in the intended use of the new delivery system compared to the first-generation Portico Delivery System. Modifications that have been made to the new FlexNav™ Delivery System are designed to reduce the overall size of the system, improve the doctor’s ability to position the heart valve, and promote overall ease of use. These design modifications do not alter the procedure to load or deploy the Portico valve.

Before your operation:
To determine if you qualify for the study, you may have the following tests performed, depending on your clinical condition. None of these tests are considered experimental and would be part of your normal care even if you were not in the study:

• Physical Exam: your study doctor or a trained member of his or her staff will ask you about your medical history and do a basic physical exam.
• CT Scan: a test to assess the blood vessels (ascending aorta, bilateral iliac arteries) of your body.
• Chest x-ray: An x-ray will be taken to assess any abnormalities in your chest. This takes about 5 minutes to complete.
• Echocardiography (echo): a test that uses sound waves to look at how your heart is functioning.
• Electrocardiogram (ECG): a tracing of your heart’s rhythm.
• Lab work: standard blood tests.
• Frailty Index: an evaluation by your doctor used to predict your risk for medical procedures.
• NYHA Functional Classification and Angina Scale: an evaluation by your study doctor to rank the limitations in your daily activities based on shortness of breath and chest pain.
• STS Risk Score/EuroSCORE II: evaluations to measure the amount of risk surgery may pose to you.
• Pulmonary Function Test: a breathing test to check the function of your lungs.
• Coronary and Aortic Angiogram: a test to assess the blood vessels of your body.

If you do not meet all the criteria for the study, no further procedures will be performed. If you do meet all criteria for the study, and would like to participate, then you will complete the following tests prior to being randomized and scheduled for the procedure. You may not have to repeat some tests that were performed during screening. You can change your mind even after signing this form; simply let the research staff know. The baseline tests include:
Lab work: standard blood tests

Quality of Life Questionnaires (QOL): you will be asked to complete questionnaires about your general health, and symptoms that you may or may not have

Medications: you will be asked the names of medications you are taking

6 Minute Walk: you will be asked to walk for 6 minutes at your normal speed. The distance you walk and how you feel will be recorded. The purpose of this test is to measure how many feet you can walk in six minutes

Stroke Scales: scales used to measure the degree of disability or dependence in daily activities for people who have had a stroke. This will be done for this study even if you have not had a stroke

Disability Scale: an evaluation to assess your physical functions, self-care and ability to get around

Mini-Mental State Exam: you will be asked to answer questions and to perform a few tasks to assess your thinking and memory

During your procedure:
The Portico Transcatheter Heart Valve implant will be done in the hospital catheterization laboratory, a special room for these kinds of procedures. You may be given medication to make you sleepy and more comfortable during the procedure or you may be put fully asleep for the duration of the procedure.

If your blood vessels are the right size and shape the study doctor will make an incision in your groin (upper part of your leg where it connects to your hip) and insert a catheter (small tube) into the opening made. The catheter will be moved through your femoral (leg) artery (picture 2a) up to the heart and into position in the heart to allow placement of the valve.

If your leg blood vessels are too small or diseased the study valve will be implanted through your chest (picture 2b), or through blood vessels near your shoulder (picture 2c or 2d)
Different Methods for Valve Implantation

- **a)** transfemoral
- **b)** transaortic
- **c)** left subclavian
- **d)** left axillary (courtesy of Rodés-Cabau, J. Nat. Rev. Cardiol. 9, 15–29 (2012))

The study doctor will use various special imaging methods such as angiographic pictures (x-ray picture of the coronary arteries) to check the position of the catheter and valve. Once the catheter and valve are in the correct position, the study doctor will slide the valve out of the catheter and it will unpack and expand to form a replacement aortic valve.

With the replacement valve in place, the study doctor will use echo and angiographic pictures to check that the valve is working correctly. When the study doctor has confirmed placement, the catheter will be removed and you will be taken to the recovery area.

Following the procedure, if you had the valve placed through your leg, you will have pressure applied to the groin area and will be required to lay flat for a specified amount of time. If you had the valve placed through your chest, your doctor will determine your limitations.

If the study doctor was unable to place the valve in your heart, you may need open heart surgery to replace the valve using standard surgical methods.
During the procedure, a representative of St Jude Medical may be in the procedure room to provide technical support on the device for your doctor. After your operation, you will be visited by the study doctor. The study doctor will be looking to see whether you have any complications from the procedure. Before you are discharged from the hospital the following will be done:

- **Physical Exam**: your study doctor or a trained member of his/her staff will ask you about your medical history and do a basic physical exam
- **Echocardiography**: a test that uses sound waves to look at how your heart is functioning. This test will be completed after the procedure or before you are discharged from the hospital.
- **Lab work**: standard blood tests
- **Medications**: you will be asked for the name of the medications you are taking
- **ECG**: tracing of your heart rhythm
- **Stroke Scale**: scales used to measure the degree of disability or dependence in daily activities for people who have had a stroke. This will be done for this study even if you have not had a stroke.
- **Assessment of changes in health status**: you will be asked if there are any changes in your health status since you have had your heart valve replaced. Your health status assessment will continue throughout the course of your participation in this study.
- **Disability Scale**: an evaluation to assess your physical functions, self-care and ability to get around
- **Angina Scale**: an evaluation by your study doctor to rank the limitations in your daily activities based on shortness of breath and chest pain

Follow-up visits

After the procedure, you will return to the study doctor's office for follow-up visits at 30 days, 6 months, and 12 months (one year) and yearly through five years after the procedure. At these visits the following will be done:

- **Physical Exam**: your study doctor or a trained member of his/her staff will ask you about your medical history and do a basic physical exam
- **ECG**: tracing of your heart rhythm
- **Echocardiography**: a test that uses sound waves to look at how your heart is functioning.
- **QOL**: you will be asked to complete questionnaires about how you are feeling
- **Medications**: you will be asked the names of medications you are taking
- **6 Minute Walk**: you will be asked to walk for 6 minutes at your normal speed. The distance you walk and how you feel will be recorded. The purpose of this...
If you are one of the first approximately 500 subjects enrolled, you will have the following test performed at your 30-Day and 6-month follow-up visits:

- **Multi-Slice Computed Tomography (MSCT) Scan:** a sophisticated x-ray machine that utilizes a liquid dye to produce sharp, detailed 3-D images of the heart and vessels. If your doctor decides you are not a good candidate for the MSCT Scan, a Transesophageal Echocardiogram (TEE) test will be performed instead: a type of echo test which provides a close look at the heart's valves and chambers, without interference from the ribs or lungs. Your doctor will inform you if you are part of this group undergoing the additional scans (Note: Participation in this group is now closed).

If you have a suspected stroke or other neurological event, the following will be done at a visit 90 days after the event:

- **Neurological assessment:** an examination of how your brain functions to help determine if you may have had a stroke
- **Stroke Scale:** scales used to measure the degree of disability or dependence in daily activities for people who have had a stroke.
Health Economic Analysis

The Sponsor is also conducting a health economic analysis. The Health Economic Analysis will evaluate the costs and benefits of treatment. This information is being collected so we can understand the cost effects of the treatment in the PORTICO study.

For the purpose of this Health Economic Analysis, information about your reported resource use of hospital care will be collected. Medical resource use, cost and health-related quality of life within the trial period will be compared between study subject groups.

Radiation exposure

This study may involve radiation exposure from a CT or fluoroscopy. As part of everyday living, everyone is exposed to a small amount of background radiation. Background radiation comes from space and naturally-occurring radioactive minerals.

The angiography procedure uses x-ray radiation to guide the examination. The amount of radiation you are exposed to during this procedure will depend on the complexity of the procedure, but will range from the equivalent of 3 to 12 years of exposure to the natural background radiation to which we are all exposed. In this research you will not be exposed to any additional radiation during the procedure, as you will undergo the same procedure regardless of whether or not you choose to participate in this research trial.

The overall risk from this dose is considered small. A part of this radiation exposure would already be necessary for your medical care.

Potential risks and side effects of transcatheter aortic valve implantation

Possible risks and discomforts associated with the participation in this study will be similar as those associated with any routine transcatheter aortic valve implantation and related follow-up and may include, but are not limited to:

<table>
<thead>
<tr>
<th>Technical Name</th>
<th>What it means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access site complications</td>
<td>primarily relates to bruising or bleeding at the site where the delivery system was inserted</td>
</tr>
<tr>
<td>Acute coronary obstruction</td>
<td>blocking the arteries carrying blood to the heart</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>heart attack</td>
</tr>
<tr>
<td>Access site injury</td>
<td>Injury during the process of inserting valve or the valve damages other parts of the body near it</td>
</tr>
<tr>
<td>Technical Name</td>
<td>What it means</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>----------------------------------------------------</td>
</tr>
<tr>
<td>Allergic reaction to antiplatelet agents, contrast medium, anesthesia or valve components</td>
<td>reaction to some medications, x-ray dye, procedural dye, or materials used to make the valve</td>
</tr>
<tr>
<td>Anaphylactic shock/toxic reaction</td>
<td>serious allergic reaction</td>
</tr>
<tr>
<td>Annulus rupture</td>
<td>tearing of the ring tissue around the heart valve</td>
</tr>
<tr>
<td>Aortic rupture</td>
<td>tearing of the aortic valve</td>
</tr>
<tr>
<td>Ascending aortic trauma</td>
<td>damage to the largest artery in your body. The artery is the main supply from the heart.</td>
</tr>
<tr>
<td>Atrio-ventricular node block</td>
<td>a slowed heart beat due to top and bottom chambers of your heart not beating normally together</td>
</tr>
<tr>
<td>AV fistula</td>
<td>abnormal connection between an artery or vein</td>
</tr>
<tr>
<td>Bleeding</td>
<td>an episode which involves bleeding</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>irregular heart beat</td>
</tr>
<tr>
<td>Cardiovascular or vascular injury</td>
<td>injury to blood vessels, heart</td>
</tr>
<tr>
<td>Conduction system injury</td>
<td>a change in the way your heart impulses are transmitted which may require a pacemaker insertion</td>
</tr>
<tr>
<td>Death</td>
<td>Death</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>infection in the heart</td>
</tr>
<tr>
<td>Embolism: air, calcification or thrombus</td>
<td>clogging an artery or vein stopping blood flow to a body part</td>
</tr>
<tr>
<td>Exercise intolerance (weakness)</td>
<td>unable to exercise at your normal level of physical tolerance</td>
</tr>
<tr>
<td>Fever</td>
<td>elevated body temperature</td>
</tr>
<tr>
<td>Heart failure</td>
<td>heart cannot pump enough blood to the rest of the body</td>
</tr>
<tr>
<td>Hematoma</td>
<td>collection of blood outside a blood vessel</td>
</tr>
<tr>
<td>Hemodynamic compromise</td>
<td>problems with blood flow</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>break down of the blood cells</td>
</tr>
<tr>
<td>Hemolytic anemia</td>
<td>abnormal breakdown of the red blood cells in your blood</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>excessive bleeding</td>
</tr>
<tr>
<td>Hypertension</td>
<td>blood pressure is too high</td>
</tr>
<tr>
<td>Hypotension</td>
<td>blood pressure is too low</td>
</tr>
<tr>
<td>Immunological reaction</td>
<td>disorder of the immune system</td>
</tr>
<tr>
<td>Infection</td>
<td>organisms in body causing abnormal body reactions or sickness</td>
</tr>
<tr>
<td>Technical Name</td>
<td>What it means</td>
</tr>
<tr>
<td>----------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Leakage, regurgitation</td>
<td>some blood flows around the edges of the valve</td>
</tr>
<tr>
<td>Left ventricular failure/rupture</td>
<td>lower left chamber of your heart does not work correctly or tears</td>
</tr>
<tr>
<td>Left ventricular impairment (due to apical scar)</td>
<td>lower left chamber of your heart does not work correctly due to past damage</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td>not enough blood flow to the heart muscle</td>
</tr>
<tr>
<td>Mitral valve insufficiency</td>
<td>heart valve does not close properly and leaks</td>
</tr>
<tr>
<td>Multi-organ failure</td>
<td>more than one body organ does not function</td>
</tr>
<tr>
<td>Neurological changes including stroke/transient ischemic attack</td>
<td>a blood clot travels to a vessel in your brain and blocks blood flow (stroke)/blood flow to a part of the brain stops for a brief period of time (tia)</td>
</tr>
<tr>
<td>Non-structural dysfunction</td>
<td>wrong size valve, suture or tissue gets in way of valve function</td>
</tr>
<tr>
<td>Pannus</td>
<td>abormal layer of tissue</td>
</tr>
<tr>
<td>Paravalvular leak</td>
<td>some blood flows around the edges of the valve</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>bleeding into the sac around the heart</td>
</tr>
<tr>
<td>Perforation, of the myocardium or a blood vessel</td>
<td>hole in blood vessel</td>
</tr>
<tr>
<td>Potential coronary obstruction</td>
<td>Coronary artery is blocked</td>
</tr>
<tr>
<td>Renal failure</td>
<td>kidneys not functioning to normal capacity</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>poor kidney function</td>
</tr>
<tr>
<td>Respiratory failure (shortness of breath)</td>
<td>breathing difficulty requiring medical intervention</td>
</tr>
<tr>
<td>Sepsis</td>
<td>generalized overall systemic infection</td>
</tr>
<tr>
<td>Septal rupture</td>
<td>tear in the tissue which divides the heart chambers</td>
</tr>
<tr>
<td>Stenosis (high gradient)</td>
<td>a high amount of vessel narrowing</td>
</tr>
<tr>
<td>Stroke</td>
<td>a blood clot travels to a vessel in your brain and blocks blood flow</td>
</tr>
<tr>
<td>Structural valve deterioration</td>
<td>parts of valve do not work or do not work as expected</td>
</tr>
<tr>
<td>Systemic peripheral ischemia</td>
<td>inadequate blood flow</td>
</tr>
<tr>
<td>Tamponade</td>
<td>a large amount of fluid collects around the sac surrounding your heart</td>
</tr>
<tr>
<td>Valve migration or malposition</td>
<td>valve movement out of position</td>
</tr>
<tr>
<td>Valve explant</td>
<td>remove valve</td>
</tr>
<tr>
<td>Valve embolization</td>
<td>valve is not in contact with aortic annulus</td>
</tr>
<tr>
<td>Valve stenosis</td>
<td>narrowing of valve opening</td>
</tr>
</tbody>
</table>
Valve thrombosis: a blood clot is attached to or near the valve.

Ventricular failure (acute): the lower chamber of your heart is currently not functioning.

Ventricular rupture: a tear in the lower chamber of the heart.

Vessel dissection or spasm: the structure of the vessel is changed.

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

Due to the nature of the delivery methods used, TAVR procedures may be associated with an increased risk of stroke and vascular complications when compared to surgical aortic valve replacement.

A layer of thrombus (blood clot) has been seen on some TAVR valves when four-dimensional computed tomography (4D CT) scans or transesophageal echocardiograms (TEE) are used to examine the valve after implant. In several cases, this layer of thrombus has been shown to prevent valve leaflets from opening properly. The layer of thrombus may be present but not seen if a 4D CT scan or TEE is not done.

Blood thinners and anti-clot medicine can be used to treat the thrombus and may be prescribed by your study doctor even if no thrombus has been seen.

The overall risk of death from transcatheter aortic valve implantation at this hospital at 30 days is between <insert site risk>% (<>/100 to <>/100), depending on your other pre-existing illnesses.

There are additional risks for study related tests. These risks may include but are not limited to the following:

**Six minute walk test:** the possible risks from this test are that you may experience fatigue, shortness of breath, chest pain and/or leg cramps. This test is done under the...
supervision of a trained professional in a testing area where medical care is immediately available. The test will be immediately stopped if you experience chest pain, intolerable shortness of breath, leg cramps or pale appearance.

Blood sample: the risk of inserting a needle into a vein in your arm may include temporary discomfort from the needle stick. There is also a small risk of infection, bruising, swelling, bleeding or fainting. These risks are minimized by cleansing the site carefully prior to obtaining the blood sample and applying pressure to the site after the blood sample is obtained.

Echocardiogram: For a Transthoracic Echocardiogram (TTE), a lubricant (gel) is used on the skin to improve picture quality and this may feel cold. There are no known risks associated with receiving a TTE echocardiogram. There may be discomfort from the pressure of the transducer as the images are taken.

Another type of echocardiogram is called a Transesophageal Echocardiogram (TEE), which takes images by putting a scope down your throat while you are asleep. Some risks include, but are not limited to, esophageal bleeding, sore throat, and bruising. Your doctor will determine which echocardiograms are best to get the best images of your heart.

CT/MSCT and Fluoroscopy: There may be risks due to the radiation used during the CT and fluoroscopy scan. There is a risk that the contrast media/dye used during the CT/MSCT and fluoroscopy procedures could harm your kidneys or that you will have an allergic response. In either case, your doctor will be prepared to treat you with medications.

13. What are the risks for women of childbearing age?
If you are pregnant or plan to become pregnant in the duration of the study, you should discuss your participation with your study doctor. Subjects who become pregnant while taking part in the study should contact the study doctor right away. There could be other risks or discomforts to you (or to an embryo, unborn child or nursing infant if you become pregnant) that are not known at this time. You will be told in writing about any new information that may become available during your participation in the study or that may influence your decision to continue participation in this study.

14. Potential Benefits of taking part in the study
This study may not benefit you directly, but may benefit other patients with a similar condition in the future. Such future benefits to other patients may possibly include:
• Making the operation simpler by reducing the need for:
  o Open heart surgery
  o Use of the heart and lung machine
• Fewer number of days spent in the hospital
• Less risk of complications
• Allowing a faster return to your normal activity level
• Potential improvement in your heart function

15. What if something goes wrong?
Any complaint about the way you have been treated during the study, if you have any questions about your rights, or any possible harm you might suffer, talk to your study doctor or hospital patient advocate.

16. Whom should I contact if I have questions or if I am injured during the study?
During the course of this clinical study, if you have any further questions, concerns, or research related injuries as a result of your participation, please contact [add Principal Investigator contact information here].

For questions regarding your rights as a research subject, please contact the hospital ethics board (often called an IRB or Institutional Review Board) at [add IRB contact information here].

17. What will happen if I don't want to continue with the study?
You can withdraw from the study at any time. Feel free to inform the study staff of your decision to withdraw from the study even while you are being taken to the procedure room. If you decide not to participate in the study before the procedure, you will not get a St Jude Medical Portico valve.

18. What if there is a problem?
If you were to suffer harm of any kind as a direct result of this study, treatment for that injury including surgery, first aid, and emergency care will be available as applicable under Federal, State, and local law. The hospital or clinic where you received treatment will bill your insurance company for the routine costs of care available under your health care plan and you may also have to pay some costs such as co-pays or deductibles.

If you followed all study instructions and are hurt during the study as a direct result of the study device or study procedures (not part of your routine medical care), St. Jude Medical will pay for reasonable and necessary medical and hospital expenses. St. Jude Medical will not cover the cost of injuries to the extent that they are caused by your failure to follow study instructions or other negligence, or that of the hospital or study doctor, the natural progression of an underlying condition (whether diagnosed or not) or pre-existing condition, or events that would have been expected from the standard treatment using currently approved therapies for your condition.
Signing this consent form in no way limits your legal rights against the Sponsor, investigators, or anyone else, and you do not release the study doctors or participating institutions from their legal and professional responsibilities. If you have a concern about any aspect of this study, you should ask to speak to the researchers at Hospital or MD who will do his best to answer your questions.

In the event of your death, if you received a St. Jude Medical valve, your implanted valve may be removed and returned to St. Jude Medical for analysis. The study doctor will get your family's approval prior to removing the device.

19. Will my taking part in this study be kept confidential?

If you decided to take part in this research study, your participation, medical records, and personal information will be kept confidential to the extent allowed by Federal, State, and local law. However, research records and health or other source records identifying you may be inspected by the Sponsor (St Jude Medical) and its affiliated companies (located in the U.S. and other countries), representative designees of Sponsor that provide services related to the device and/or this study, the U.S. Food and Drug Administration and other government authorities (in the U.S. and other countries), and the Institutional Review Board (IRB) for the purpose of: 1) monitoring the research; 2) accurately documenting and reporting any adverse events that may occur during your participation in this study 3) satisfying any other requirements imposed by government authorities located throughout the world, including the U.S. FDA. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless otherwise permitted by law. Your regular doctor may be told of your participation in the study at your request.

You will be assigned a unique study number as a subject in this study. This number will be used on any research-related information collected about you during the course of this study, so that your identity [i.e. your name or any other information that could identify you] as a subject in this study will be kept confidential. Information that contains your identity will remain only with the study investigator and/or designate. The list that matches your name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. Please note information may not be available on ClinicalTrials.gov until the study is completed and the device is marketed.

By signing the Patient Consent Form, you are consenting to the collection, use, review, processing and disclosure of such information.
20. What will happen to the results of the study?

Once the study is complete and analyzed, the results may be submitted for publication in a scientific journal and presented at scientific conferences. Your confidentiality will be maintained and you will not be identified in any report or publication of this study. If you wish to see the results when they are published, let the researcher who obtains informed consent from you know and a copy of the results can be sent to you. The data may be used for additional medical or scientific research projects in the future and obtaining regulatory approvals for further studies about the device. Data may, if necessary for the above purposes, be communicated to the processors, regulatory authorities and Ethics Committees located in countries of the European Economic Area ("EEA"), in the United States of America ("USA"), Canada, and governmental agencies (including regulatory agencies) in other countries. Some of the non-EEA countries to which your data may be transferred may not offer an adequate level of protection of privacy of personal data.

St Jude Medical has taken security measures to ensure your personal data will be processed and used in a confidential way. Data may also be used to present reimbursement information to public and private payers to advocate changes in coverage, coding or reimbursement rates and payment policies.

21. Who is organizing and funding the study?

This study is being organized and funded by St. Jude Medical. The Hospital will receive payments from St Jude Medical for participating in this study and for providing study data.

22. What expenses may result from my participation in the study?

You or your insurance will be billed for tests that are standard of care and would be done even if you were not taking part in the study. Tests and procedures that will be done just for the study will be paid for by the sponsor. You will receive a stipend in the amount of $25 per visit to cover the cost of travel and parking for attending required research related visits. There are a total of 8 required visits (baseline, 30 day, 6 month, 12 month, 2 year, 3 year, 4 year, and 5 year).

23. Who has reviewed the study?

The study was reviewed by the hospital system and has been approved to be conducted at this hospital by the <IRB>. If you have any questions about your rights as a research subject you can contact the <IRB> at <contact information>.

24. What are my responsibilities if I am in the study?

As study participant, you are asked to follow study requirements, follow medical instructions given by your study doctor, inform your study doctor of any changes in your health, and inform your study doctor of any other medical care or drugs you are receiving (whether prescribed by a physician or bought over the counter).
AUTHORIZATION TO USE AND DISCLOSE HEALTH INFORMATION

I agree to permit {add Investigator name here} and staff members and, St. Jude Medical, the sponsor of the PORTICO clinical trial to use and disclose health information that identifies me for the purposes described below. I also agree to permit {add hospital/clinical study site information here}, my doctors, and my other health care providers to disclose health information in my medical records to the researchers, St. Jude Medical and the FDA, or other regulatory bodies for the purposes described below.

1. The health information that may be used and disclosed includes:
   • All information collected during the research as described in the Informed Consent Form; and
   • Health information in my medical records that is relevant to the research described in the Informed Consent Form.

2. The researchers may:
   • Use and share my health information to conduct the research;
   • Disclose my health information to the Sponsor of research, St. Jude Medical and its affiliated companies (located in the U.S. and other countries), representatives designees that provide services related to the device and/or this study;
   • Disclose my health information as required by law;
   • Disclose my health information to representatives of government organizations and other persons who are required to watch over the safety and effectiveness of medical products and therapies and the conduct of research; and
   • Remove from my health information my name and other information that could be used to identify me.

3. St. Jude Medical and its affiliated companies (located in the U.S. and other countries), representatives designees that provide services related to the device and/or this study may:
   • Use and share my health information to conduct the research;
   • Disclose my health information as described in the Informed Consent Form;
   • Disclose my health information as required by law;
   • Disclose my health information to representatives of government organizations and other persons who are required to watch over the safety and effectiveness of medical products and therapies and the conduct of research; and
   • Remove from my health information my name and other information that could be used to identify me.

4. Once information that could be used to identify me has been removed, the information that remains is no longer subject to this Authorization and may be
5. Once my health information has been disclosed to a third party, privacy laws may no longer protect it from further disclosure. However, the researchers and St. Jude Medical agree to protect my health information by using and disclosing it only as permitted by me in this Authorization and the Informed Consent. Also, no publication about the research will reveal my identity without my specific written permission. These limitations continue even if I revoke (take back) this Authorization.

Please note that:

- You do not have to sign this Authorization, but if you do not, you will not be allowed to participate in the research.
- You may change your mind and revoke this authorization at any time. To revoke this Authorization, you must write to {name and contact information}. However, if you revoke this Authorization, you will no longer be allowed to participate in the research. Also, if you revoke this Authorization, the information already obtained by the researchers and St. Jude Medical may be used and disclosed as permitted by the Authorization and the Informed Consent.
- While the research is in progress, you will not be allowed to see your health information that is created or collected in the course of the research. After the research is finished, however, you may see this information as described in the {add hospital/clinical study site name here}'s Notice of Information practices.
- This Authorization does not have an expiration (ending) date.
- You will be given a copy of this Authorization after you have signed it.

Thank you for considering taking part in this study.

If you decide to participate you will be asked to sign the below and will be given a copy of this form to keep.

Name of Principal Investigator: [Insert Name]
1. I confirm that I have read and understood the Informed Consent for this Portico IDE study. I have had sufficient time to think about it and I have been given the opportunity to ask questions, and have had these answered satisfactorily.

2. I understand that:
   - my participation is voluntary and that I am free to refuse to participate in this study or to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.
   - my relationship with my doctor will not be affected if I withdraw.
   - there will not be any penalty if I decide to withdraw from the study.
   - if I withdraw before the aortic valve replacement procedure, I will not get a St Jude Medical Portico valve.
   - my attendance at study visits is important to the study and I should follow the study doctors instructions.

3. I understand that:
   - my medical information, information collected during the study and study results may be looked at, used, and disclosed by responsible individuals from St. Jude Medical, a U.S. company, and its affiliates (located in the U.S. and other countries, and other people who work for St. Jude Medical to provide services related to the device and this study, regulatory authorities, the IRB and, when it is relevant to my taking part in this research. I give permission for these individuals to have access to my medical information, information collected during the study, and study results.
   - my data gathered in this study may be stored (after anonymized) in a database and may be used and disclosed by St Jude Medical.
   - my relevant personal data may be used for the purpose of this clinical study.
   - data collected from the time I sign this document until the time I withdraw from the study will be used after I withdraw.
   - I will not financially benefit from this study.
   - I may be responsible for insurance copayments.

4. I understand how to contact the research team.

5. I agree to my General Practitioner being informed of my participation in the study.

6. I understand the risks of aortic valve surgery and the risks of participating in this study and

7. I am willing to participate in this study.

Name of Participant (please print):

Signature: __________________________
Date: ____________
Time: _______________

Name of Person Obtaining Consent (please print):

Signature: __________________________
Date: ____________
Time: _______________
### Appendix R: List of Investigational Sites in the Study

This list is subject to change. SJM maintains a current list of the Investigational Sites conducting the study that is available upon request.

<table>
<thead>
<tr>
<th>Principal Investigator(s)/Address</th>
<th>Site Name</th>
<th>IRB Approval</th>
<th>IRB Chairperson/Address</th>
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</thead>
<tbody>
<tr>
<td>Paul Sorajja, MD</td>
<td>Abbott Northwestern Hospital/Minneapolis Heart Institute</td>
<td></td>
<td>Stephen Rosenfeld, M.D., M.B.A. Quorum IRB 1601 Fifth Ave. Suite 1000 Seattle, WA 98101</td>
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<tr>
<td>Ravi Ramana, DO</td>
<td>Advocate Christ Medical Center</td>
<td></td>
<td>Stephen Rosenfeld, M.D., M.B.A. Quorum IRB 1601 Fifth Ave. Suite 1000 Seattle, WA 98101</td>
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<tr>
<td>Antone Tatooles, MD</td>
<td>Albany Medical Center</td>
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<td>Lewis W. Britton III, MD Albany Medical College 47 New Scotland Avenue MC 192 Albany, NY 12208</td>
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<td>Currien MacDonald, MD Western Institutional Review Board 1019 39th Ave SE Suite 120 Puyallup, WA 98374-2115</td>
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<tr>
<td>Ramzi Khalil, MD</td>
<td>Allegheny Singer Research Institute</td>
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<tr>
<td>Alan Zajarias, MD</td>
<td>Barnes-Jewish Hospital</td>
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<td>Jonathan Green, MD Washington University School of Medicine IRB 660 South Euclid Ave. Campus Box 8089 St. Louis, MO 63110</td>
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<tr>
<td>Bassem M Chehab, MD</td>
<td>Cardiovascular Research Institute of Kansas</td>
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<td>Via Christi Hospitals Wichita, INC. Institutional Review Board 929 N. St. Francis Wichita, KS 67214</td>
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<tr>
<td>Site Name</td>
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<td>Catholic Medical Center</td>
<td>James Flynn, MD 100 McGregor Street, Manchester, NH, 03102</td>
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<td>Eleanor Dahar, Catholic Medical Center IRB 100 McGregor Street, Manchester, NH 03102</td>
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<tr>
<td>Cedars-Sinai Medical Center</td>
<td>Raj R. Makkar, MD Cedars-Sinai Medical Center 127 S. San Vicente Ave, #A3600, Los Angeles, CA 90048</td>
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<td>Stephen Lim, Cedars-Sinai Medical Center Office of Research Compliance and Quality Improvement 6500 Wilshire Blvd, Suite 1800, Los Angeles, CA 90048</td>
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<tr>
<td>Centennial Medical Center</td>
<td>John Riddick, MD, V. Sreenath Reddy, MD 2400 Patterson Street Suite 502, Nashville, TN 37203</td>
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<tr>
<td>CHI St. Luke's Health Baylor College of Medicine Medical Center</td>
<td>Joseph S. Coselli, MD, Guilherme V. Silva, MD Texas Heart Institute 6770 Bertner Avenue Suite 350, Houston, TX 77030</td>
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<td>Currien MacDonald, MD Western Institutional Review Board 1019 39th Ave SE Suite 120, Puyallup, WA 98374-2115</td>
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<tr>
<td>The Cleveland Clinic Foundation</td>
<td>Brijeshwar S Maini, MD The Cleveland Clinic Foundation 9500 Euclid Ave., Cleveland, OH 44195</td>
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<td>Alan E. Lichtin, MD The Cleveland Clinic Foundation 9500 Euclid Avenue/Wb2, Cleveland, OH 44095</td>
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<td>Delray Medical Center</td>
<td>Amar Krishnaswamy, MD, Lars Svennson, MD The Cleveland Clinic Foundation 9500 Euclid Ave., Cleveland, OH 44195</td>
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<td>Duke University Medical Center</td>
<td>Todd Kiefer, MD, Jeffery Gaca, MD Duke University Medical Center 2301 Erwin Road Box 3126, Durham, NC 27710</td>
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<td>John Fallette, MD Duke University School of Medicine Institutional Review Board 2424 Erwin Rd., Suite 405, Durham, NC 27705</td>
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<tr>
<td>East Carolina Heart Institute</td>
<td>Andy Kiser, MD East Carolina Heart Institute 115 Heart Drive, Greenville, NC 27834</td>
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<td>Wiley Nifong, MD University &amp; Medical Center (UMC) IRB 600 Moye Boulevard, Greenville, NC 27884</td>
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<td>Gerald Yong, Dr F</td>
<td>Fiona Stanley Hospital</td>
<td>X Dr Ramin Gharbi Research Ethics &amp; Governance Unit</td>
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<td>601 E. Rollins St. MB#99</td>
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| | | Harrisburg, PA 17104 |
| Royal Adelaide Hospital | X | A/Prof Andrew Thornton
| | | Chairman, Royal Adelaide Hospital
| | | Human Research Ethics Committee
| | | Level 4, Women's Health Centre
| | | Royal Adelaide Hospital
| | | North Terrace
| | | Adelaide, South Australia 5000 |
| Sanford USD Medical Center | | Currien MacDonald, MD
| | | Western Institutional Review Board
| | | 1019 39th Ave SE Suite 120
| | | Puyallup, WA 98374 |
| Scripps Green | | Ronald A. Simon, MD
| | | Scripps Office for the Protection of Research Subjects
| | | 4275 Campus Point Court CPB 200
| | | San Diego, CA 92121 |
| Sentara Norfolk General Hospital | | Currien MacDonald, MD
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| | | 1019 39th Avenue SE Suite 120
| | | Puyallup, WA 98374-2115 |
| Sparrow Clinical Research Institute | | Currien MacDonald, MD
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| St. Francis Hospital | | Mitchell Chorost MD
| | | St. Francis Institutional Review Board
| | | 100 Port Washington Blvd
| | | Roslyn, NY 11576-1348 |
| St. Luke's Hospital of Kansas City | | Justin Osborne, MA
| | | Schulman Associates IRB
| | | 4445 Lake Forest Drive Suite 300
| | | Cincinnati, OH 45242 |
| St. Vincent Hospital | | P.T. Hodgin, MD
| | | St. Vincent Institutional Review Board
| | | 8402 Harcourt Road, Suite 120
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<td>Anwar Tandar, MD</td>
<td>University of Utah</td>
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<td>Gerald Treiman, University of Utah Institutional Review Board Research Administration Bldg 75 South 2000 East Salt Lake City, UT 84112</td>
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<td>Joy Cavagnaro, PhD, DABT, RAC, Chesapeake Research Review, Inc (CCRI) 7063 Columbia Gateway Dr., Suite 110 Columbia, MD 21046</td>
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<td>Winthrop University Hospital</td>
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<td>Institutional Review Board Winthrop University Hospital 222 Station Plaza North, Suite 521 Mineola, NY 11501</td>
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Appendix S: TAVR Leaflet Motion Sub-study

Background

Worldwide Portico implants, including new enrollments for the Portico OUS clinical trials, were paused in September 2014 so that a detailed investigation could be conducted to gain better insight into a leaflet motion observation present on 4D-CT scanning during the Portico US IDE study.

As a part of the US IDE study, CT scans were being performed at 30-day post-implant for all patients to evaluate clinical stent deformations for stent stress/strain level determination as required by FDA. 4D-CT videos were generated from the original CT images at the discretion of the investigator at a clinical investigational site. While reviewing the 4D-CT video of 2 patients, the physicians noticed a leaflet motion observation. Since 4D-CT videos have not been previously validated or routinely used to visualize leaflet motion, it was not clear whether the leaflet motion observation was real. SJM determined it in the best interest of patients to pause all Portico implants (worldwide) until such time this observation and its clinical impact was better understood.

Through investigation of additional 4D-CT scan image data in combination with Trans-Esophageal Echocardiography (TEE) in the available US study population, more mobility observations were noted in Portico as well as commercially available valves. Bench testing, manufacturing reviews, core lab investigation and clinical assessments were conducted throughout this investigation and significant analysis took place.

Manufacturing related factors were ruled out as the root cause factors of leaflet motion observations.

The leaflet motion observation was determined to be caused by the presence of a layer of subclinical valve thrombus. Analysis concluded that valve thrombosis in the recess between the stent frame and the aortic surface of the leaflet was causing the observed leaflet motion observation. For patients identified with a leaflet motion observation, valve hemodynamic assessment was found to be within normal limits and patients were generally asymptomatic.

An assessment of hemodynamic data across all patients was conducted, focused on valve hemodynamic data that was collected at the time of hospital discharge and at the 30-day follow-up visit. There was no statistically significant difference in the mean aortic valve (AV) gradient or in the mean aortic valve area (AVA), between patients that did not have a valve leaflet observation (Group 1) and patients that did (Group 2), across all patients implanted with any device type.

There was no statistically significant difference in the mean AV gradient at hospital discharge and at 30-day follow up visit between Group 1 and Group 2. The AVA for patients implanted with the Portico valve did have a small, statistically significant difference at hospital discharge between Group 1 and Group 2, with no significant difference at the 30-day follow up visit.
Purpose

The purpose of this sub-study is to further assess valve leaflet motion in subjects implanted with the Portico Transcatheter Aortic Valve as well as FDA-approved commercially available valves participating in the Portico US IDE Trial.

Objectives

The objectives for this sub-study are to:

• Evaluate the incidence of the leaflet motion observation
• Evaluate the impact of the leaflet motion observation on clinical outcomes and valve hemodynamics
• Evaluate potential contributing factors for developing a leaflet motion observation

Design

This sub-study is a multi-center, prospective, blinded observational study. The first approximately 500 subjects enrolled in the Portico US IDE Trial under Clinical Investigational Plan at the time of randomization or assignment to a registry (Roll-in or Valve-in-Valve) will participate in this sub-study.

An assessment of leaflet motion will be made by an independent core lab or laboratory based on an MSCT scan (or TEE, if MSCT is medically or technically contraindicated) obtained at the 30-day follow-up visit, at which time subjects will be assigned into the following three groups:

• Group 1: Patients with normal leaflet motion
• Group 2: Patients with a leaflet motion observation
• Group 3: Patients with unknown leaflet status (imaging missing or uninterpretable)

For Groups 1 and 2, subjects and investigators will be blinded to the core laboratory assessment of leaflet motion. These subjects will undergo follow-up MSCT (or TEE, if MSCT is medically or technically contraindicated) at the 6-month follow-up visit.

Subjects in Group 3 will be exited from the sub-study, and will not undergo the 6-month MSCT (or TEE).

Sample Size

New enrollment in the sub-study will end when approximately 285 randomized subjects have been enrolled. Allowing for 30% attrition/missed scans/inadequate scan quality, a total of 200 complete sets of 30-day and 6-month scans (MSCT or TEE) will be obtained from randomized subjects. The attrition rate will be monitored and the sample size may be extended if needed to achieve 200 complete sets of 30-day and 6-month scans. The sponsor will notify sites when the enrollment target has been met.
Statistical Method and Analysis

The TAVR Leaflet Motion Sub-study is a prospective, multi-center, observational clinical study. All patients who have provided written Patient Informed Consent and have been randomized or assigned to a registry (Roll-in or Valve-in-Valve) will be considered enrolled in the sub-study until the minimum sub-study sample size has been achieved.

This section describes the statistical methods and analysis for randomized subjects unless otherwise specified. Data collected for subjects in a registry (Roll-in or Valve-in-Valve) will be summarized separately from randomized subjects using descriptive statistics.

1. General Considerations

Descriptive statistics of continuous variables will be presented by leaflet motion groups and include sample size, mean, median, standard deviation, minimum and maximum. For categorical variables, the number and percentage of subjects in each category will be presented by leaflet motion groups. All statistical analyses will be performed using SAS for Windows (version 9.3 or higher) or other widely accepted statistical or graphical software.

2. Statistical Analysis and Reporting

a. Analysis of baseline characteristics

All clinically relevant baseline variables collected in this study will be tabulated and compared between the two leaflet motion groups. Categorical variables will be tested using Chi-square test or Fisher's exact tests as appropriate and continuous variables will be tested using two sample t-test or Wilcoxon rank-sum test as appropriate.

b. Analysis of incidence of the leaflet motion observation

The data collected from this sub-study will be used to evaluate the incidence of the leaflet motion observation. The incidence of the leaflet motion observation at 30-days post-implant will be calculated overall and by each valve brand. The incidence rate will also be calculated at 6-months post-implant.

c. Analysis of clinical outcomes and valve hemodynamics

Event rates of the following clinical outcomes at 6-months (180 days) will be calculated for both leaflet motion groups:

• Stroke
• Acute myocardial infarction
• Heart failure hospitalization
• Reoperation for structural valve deterioration
• All-cause mortality
The numerator for 6-month event rate in a leaflet motion group is the number of subjects who experienced an event by 180 days. The denominator is the number of subjects in that leaflet motion group, however, subjects withdrawn (e.g., due to death, subject preference or loss to follow-up etc.) before 6 months without an event will be excluded.

Fisher's exact tests will be performed to compare the 6-month event rates between the two leaflet motion groups.

The following valve hemodynamic characteristics will be analyzed at 30-days and 6-months post implant with available hemodynamics data:

- Aortic valve (AV) mean gradient
- Aortic valve area
- Aortic valve regurgitation

Two sample t-tests or Wilcoxon rank sum tests will be performed to compare AV mean gradient and AV area at 1-month visit, 6-month visit, and changes from 1-month to 6-month visit between the two leaflet motion groups. Chi-square test or Fisher's exact test will be performed to compare AV regurgitation between the two leaflet motion groups.

Supplementary analyses of clinical outcomes and valve hemodynamics using propensity score methods may be performed as necessary to confirm similarity of the two leaflet motion groups. Propensity score method will use logistic regression on selected baseline variables to determine subject's propensity of being in one leaflet motion group versus another, and then the estimated propensity scores will be used to check balance between the leaflet motion groups. Clinical outcomes and valve hemodynamics will be compared adjusting for the propensity scores. When supplementary analyses of propensity score adjusted analyses are deemed necessary, the propensity score methodology and list of baseline variables will be pre-specified and communicated with FDA before the supplementary analyses are performed.

The following potential contributing factors of leaflet motion observation at 30 days will be analyzed:

- Antithrombotic therapy
- Baseline index of flow state (e.g., Stroke volume)
- Stent depth

Categorical contributing factors will be tested using Chi-square test or Fisher's exact tests as appropriate and continuous contributing factors will be tested using two sample t-test or Wilcoxon rank sum test as appropriate between the two leaflet motion groups.

In addition, a logistic regression model will be performed for the outcome of leaflet motion observation at 30 days including the covariates of all aforementioned contributing factors.
Leaflet motion observation incidence rates and descriptive statistics of available clinical outcomes and valve hemodynamics will be reported to FDA after 50, 100, 150, and 200 interpretable 30-day MSCT (or TEE) scans from randomized subjects have been analyzed by the Core Lab.

When 200 complete sets of 30-day and 6-month MSCT (or TEE) scans have been analyzed by the Core Lab, all statistical analyses described in this section – Statistical Analysis and Reporting – will be conducted and a final clinical report will be submitted to FDA.

Within each report, the data obtained from the Registry subjects (Roll-in and Valve-in-Valve) will be analyzed separately and summarized using descriptive statistics.

**MSCT Scan Parameters**

The CT Core Laboratory's Standard Operating Procedures provides detailed data acquisition instructions. A dual-source CT scanner or a latest generation CT scanner capable of fast gantry rotation is required. MSCT scans are to be acquired using the following requirements:

- The CT scan shall cover the entire heart and aorta to the top of the aortic arch including the brachiocephalic artery takeoff.
- Intravenous contrast at a dose of 60-100 cc is required for this assessment, at the discretion of the treating center.
- Full retrospective gating without dose attenuation is required to facilitate an acquisition throughout the cardiac cycle. A DICOM with cine 0-100% at 5-10% increments should be provided.

**TEE Scan Parameters**

The Echocardiography Core Laboratory Acquisition Protocol provides detailed instructions to standardize transesophageal echocardiogram (TEE) image acquisition. A physician or sonographer familiar with valvular heart disease and experienced in performing echocardiograms should perform each study. Prior to enrolling the first patient, the echocardiographer(s) must take part in the training material supplied for this study to insure they are familiar with the clinical protocol and the echo imaging protocol.
### Appendix T: Principal Contacts

**Portico Executive Committee**

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<tr>
<th>Interventional Cardiologists</th>
<th>Cardiovascular Surgeons</th>
<th>Neurologist</th>
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<td>Raj Makkar, M.D.</td>
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<td>David Brown, M.D.</td>
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<td>Heart Hospital Baylor, Plano, TX</td>
<td>Hospitals of the University of Pennsylvania, Philadelphia, PA</td>
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<td>Samir Kapadia, M.D.</td>
<td>William Brinkman, M.D.</td>
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<td>Hackensack University Medical Center, Hackensack, NJ</td>
<td>Washington Hospital Center, Washington, D.C.</td>
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<td>Stephen Worthley, M.D.</td>
<td>Alfredo Trento, M.D.</td>
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<td>Genesis Care, Adelaide, Australia</td>
<td>Cedars-Sinai Medical Center, Los Angeles, CA</td>
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**Sponsor**

St. Jude Medical (now Abbott), Plymouth, MN

**Data Safety Monitoring Board**

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<td>Donald Glower, M.D.</td>
<td>Stanford University, Stanford, CA</td>
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**Clinical Events Committee**

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<th>Schuyler Jones, MD (Co-Chair)</th>
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<th>Name</th>
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<td>Bradly Kolls, M.D.</td>
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<td>Joseph Dedrick Jordan, M.D., PhD</td>
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<td>Shu Lin, MD</td>
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<td>Rahul Sharma, M.D.</td>
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<td>Cedars-Sinai Heart Institute</td>
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Appendix U: NIH Stroke Scale (NIHSS)

NIH STROKE SCALE

Patient Information:

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).

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<th>Instructions</th>
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<td>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, intracranial trauma/hemorrhage. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.</td>
<td>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 stimulus to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and anoxemic.</td>
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<td>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, intracranial 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 &quot;help&quot; the patient with verbal or non-verbal cues.</td>
<td>0 = Answers both questions correctly. 1 = Answers one question correctly. 2 = Answers neither question correctly.</td>
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<td>1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-parietal 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.</td>
<td>0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.</td>
<td></td>
</tr>
<tr>
<td>2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (ouloccephalic) 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 another 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.</td>
<td>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 ouloccephalic maneuver.</td>
<td></td>
</tr>
</tbody>
</table>
NIH STROKE SCALE

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-out asymmetry, including quadrant anomaloscope, 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.

4. Facial Palsy: Ask – or use panopticon to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimul in the poorly responsive or non-comprehending patient. If facial trauma/bandages, intracranial tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.

5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palm 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 panopticon, 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.

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 6 seconds. The aphasic patient is encouraged using urgency in the voice and panopticon, 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.
### NIH Stroke Scale

**Interval:**
- [ ] Baseline
- [ ] 2 hours post treatment
- [ ] 24 hours post onset of symptoms ± 20 minutes
- [ ] 7-10 days
- [ ] 3 months
- [ ] Other __________________________

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Limb Ataxia</td>
<td>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 untenable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.</td>
<td>0 = Absent; 1 = Present in one limb; 2 = Present in two limbs.</td>
</tr>
<tr>
<td>8. Sensory</td>
<td>Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtained or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas as possible (tongue, face, trunk, etc.) 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 a 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 1-3) are automatically given a 2 on this item.</td>
<td>0 = Normal; no sensory loss; 1 = Mild-to-moderate sensory loss; patient feels pinprick is less sharp or is dulled 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</td>
</tr>
<tr>
<td>9. Best Language</td>
<td>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.</td>
<td>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 communication 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; an 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’s response; 3 = Mute, global aphasia; no usable speech or auditory comprehension</td>
</tr>
<tr>
<td>10. Dysarthria</td>
<td>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 untenable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.</td>
<td>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 mumbled</td>
</tr>
</tbody>
</table>

**UN** = Intubated or other physical barrier, explain: __________________________
NIH STROKE SCALE

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.

<table>
<thead>
<tr>
<th>0</th>
<th>No abnormality.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities.</td>
</tr>
<tr>
<td>2</td>
<td>Profound hemi-inattention or extinction to more than one modality: does not recognize own hand or orient to only one side of space.</td>
</tr>
</tbody>
</table>

Patient Identification: ____________
Pt. Date of Birth __/__/____
Hospital ______________________ (____ - ____)
Date of Exam __/__/____
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.
Appendix V: Portico Continued Access Protocol (CAP)

1. Purpose

1.1 Indications for Use

The Portico™ Transcatheter 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 IDE CAP is a prospective, multicenter, single-arm, continued access study designed to collect additional safety and clinical effectiveness data on the SJM Portico Transcatheter Heart Valve and Delivery System (Portico) following completion of enrollment in both the pivotal IDE randomized cohort and FlexNav Study. The study will also allow implanters to maintain their technical proficiency while the premarket approval (PMA) application for the Portico™ Transcatheter Aortic Heart Valve and the FlexNav™ Delivery System is under FDA review.

The Pivotal IDE trial completed enrollment of 758 randomized subjects in October 2017. Enrollment in the FlexNav study is anticipated to be completed in May 2019 and upon reaching this milestone, the CAP will be (re)initiated. IDE sites were first approved to enroll subjects in the CAP using the first-generation Portico Delivery System in October 2017 under protocol version K. However, the latest protocol revision (version L) requires enrollment of subjects in the FlexNav study to be complete before enrollment the CAP using the second-generation FlexNav™ Delivery System can resume.

Up to 1260 subjects may participate in the CAP. This sample size is based on the assumption of one enrollment per IDE center per month for 21 months, assuming 60 IDE centers in the US and Australia actively participate in the CAP study. This expected enrollment rate is based on the enrollment rate in the pivotal IDE trial over the last 12 months. The 21-month duration of the CAP is based on the 12-month follow-up requirement for the randomized cohort and a 9-month PMA review. Subjects enrolled in the CAP will be followed for a minimum of one year and up to 5 years or upon study completion (whichever is reached first). Interim safety and efficacy data on CAP subjects will be reported annually to the FDA as a part of the Portico IDE annual report until study closure.

1.3 Study Endpoints

The primary and secondary endpoints for this clinical study have been modified from that in the pivotal IDE trial to account for the design and objectives of the CAP. The primary endpoint in the CAP will focus on the early safety of the Portico valve using a composite endpoint of all-cause mortality or disabling stroke at 30 days post-implantation.
A selection of descriptive endpoints including valve performance parameters, clinical function assessments and adverse events defined according to VARC II criteria will be assessed at 30 days (and at 1 year if indicated)

Primary Endpoints

Primary Safety Endpoint: A composite of VARC 2-defined all-cause mortality or disabling stroke at 30 days.

Descriptive Endpoints

A selection of key valve performance parameters, clinical function assessments and adverse events defined according to VARC 2 criteria will be assessed:

- 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
- Life threatening bleeding requiring blood transfusion and major bleeding at 30 days from the index procedure
- Acute kidney injury at 30 days from the index procedure
- Major and minor vascular access complication rate at 30 days
- Permanent pacemaker insertion at 30 days from the index procedure
- Paravalvular Leak (PVL) at 30 days and one year
- NYHA functional classification at 30 days and one year
- Disabling stroke at 30 days and one year
- All-cause mortality at 30 days and one year
- KCCQ Quality of Life (QOL) score from baseline to 30 days and one year

2. Clinical Protocol

2.1 Background Information

The purpose of the CAP is to continue collection of safety and effectiveness data on the Portico Transcatheter Heart Valve and evaluate the learning curve while the device remains under investigational use in the United States. The CAP will also allow current IDE study implanters to maintain their technical proficiency in Portico device implantation. The CAP will commence once enrollment in the randomized cohort and FlexNav study of the pivotal IDE trial is completed. Subject selection and data collection will be similar to the pivotal IDE in order to facilitate future comparison of data with the pivotal IDE randomized cohort. All subjects enrolled in the CAP will undergo Portico valve implantation.

Roll-in patients at sites participating in the CAP will be included in the IDE roll-in registry.

All CAP subjects enrolled under version L of the protocol will be implanted using the second-generation FlexNav™ Delivery System ("FlexNav™ Delivery System").

There is no pre-specified minimum number of subjects required to be enrolled in the CAP. Enrollment will continue in the CAP until approval of the Portico™ Transcatheter Aortic Heart Valve and FlexNav™ Delivery System in the US.

2.2 Rationale

The rationale for this study is to allow current IDE study implanters to maintain their technical proficiency in Portico valve implantation. CAP data will not be included in the randomized population nor the primary data analysis; however, the data will be analyzed and presented separately and may be used to support the PMA application for the Portico™ Transcatheter Aortic Heart Valve and FlexNav™ Delivery System.

3. Name and Description of the Investigational Device

The investigational devices used in the CAP are listed above in Section 2.4 of the main protocol above. Detailed information regarding the Portico Transcatheter Heart Valve can be found in Section 3.0.

Detailed information regarding the first-generation Portico Delivery System and FlexNav™ Delivery System can be found in Sections 3.1.1 and 3.1.2.

4. Risk and Benefits of the Study Device and Clinical Study

There are no changes to the risks or benefits reported in the pivotal IDE trial for subjects participating in the CAP. Please refer to the IFU of the Portico Transcatheter Aortic Heart Valve for a description of risks and to the adverse events section in this protocol for a list of the potential adverse events.

5. Study Population – High Risk and Extreme Risk

The study population in the CAP is expected to be the same as that enrolled in the pivotal IDE trial; patients with symptomatic, severe aortic stenosis that are considered to be high or extreme risk for surgery and are eligible for TAVI via a transfemoral or alternative access route.

Although there is no stratification of patients based on risk in the CAP, the patients' risk classification (high vs extreme) will be documented and reviewed for final approval by the Subject Selection Committee. See Section 5 of the main document.

6. Inclusion/Exclusion Criteria

The inclusion/exclusion criteria for the CAP are the same as that in the pivotal IDE trial. See Sections 5.1 and 5.2 of the main protocol.
8. **Screening Process**

The screening process for the CAP is the same as the pivotal IDE trial. Although there is no randomization in the CAP, after Subject Selection Committee approval, patients assigned to the CAP will not be considered enrolled until the index procedure. Subjects who do not meet the subject selection criteria will not be scheduled for Portico valve implantation and will be exited from the study without further follow-up.

9. **Subject Assignments**

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

10. **Subject Enrollment**

CAP 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 Portico delivery system enters the subjects' body.

Subjects who are scheduled to receive a Portico valve via transfemoral access and found not to be suitable for this delivery modality (per the heart team medical decision) can receive a Portico valve using an alternate access modality and vice versa. However, this will be considered a protocol deviation unless the Subject Selection Committee provides prior approval for multiple access sites. The rationale for this decision must be documented.

11. **Study Conduct**

Table 9 summarizes the required assessments in the pivotal IDE and CAP. The primary differences between the required pivotal IDE assessments and the CAP assessments are:

- A 6 month visit is not required
- The 6MWT and SF-36 will not be required at any follow-up visit

11. **Statistical Methods and Analysis**

11.1 **Analysis Population (CAP)**

The CAP analysis population will include all subjects enrolled in the CAP in whom a Portico valve implant is attempted. A Portico implant attempt is defined as the insertion of the delivery system into the subject's body.
11.2 Statistical Analysis

The primary study endpoint at 30 days will be summarized and descriptively compared to results reported in the pivotal IDE randomized cohort and published results on CAV.

All descriptive endpoints will be summarized and presented for the entire analysis population and according to access route (transfemoral vs alternative access).
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.

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.
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 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
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. 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.

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

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.
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)
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.

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:
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.
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.

6.3 Proctoring

A Portico proctor will be required to attend a minimum of one (1) roll-in case at investigational sites that have not performed a Portico valve implant in the last 12 months. Sites that have enrolled subjects as part of the CAP (under version K of the protocol) may require a Portico proctor at the request of the Sponsor. The request by the Sponsor will be dependent on the site’s enrollment cadence and safety performance in the CAP.

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

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.
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)
9.2 Data and Safety Monitoring Board

The 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
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.
11.0 Bibliography


Principal Investigator: <    >
Hospital: <    >
Address: <    >
Phone: <    >

Sponsor: St. Jude Medical, Cardiology Division Inc. (hereinafter referred to as “Sponsor” or “St Jude Medical”)

PART 1
1. Invitation
You are being invited to take part in a research study. Before you decide, it is important for you to know why the research is being done and what it will involve. Please take time to read the following information carefully. Feel free to discuss it with others if you wish. Ask us if there is anything that is not clear or if you want more information. Take your time to decide if you wish to participate.

2. Purpose of the study
The purpose of this study is to evaluate the safety and effectiveness of the new St Jude Medical Portico Transcatheter Heart Valve and delivery systems. The study valve is made to replace your diseased aortic heart valve.

3. Why have I been invited?
You are being asked to take part in this research study because your doctors have decided that you may be a high or extreme risk candidate for aortic heart valve replacement through open heart surgery. At your request, your study doctor will notify your personal physician of your participation in this study.

4. How many people will participate?
This study will be conducted at up to seventy (70) centers globally, and will include a maximum of 1260 subjects.

5. What is the device being tested?
The Portico Transcatheter Heart Valve is an investigational device. This means that the valve is being studied, and is not for sale in the United States. This study is collecting data on the valve and delivery systems for review and approval by the Food and Drug Administration (FDA).

The Portico Transcatheter Heart Valve is a replacement heart valve that can be placed through a tube in your leg or through your chest. The valve is made of animal tissue and...
is on a stent, or scaffold, which holds the valve in position. The stent portion of the valve is made with Nitinol (metal with Nickel and Titanium). Picture 1 below shows the Portico valve. Picture 2 on page 6 shows the different ways the valve can be put in place.

The Portico Transcatheter Heart Valve is loaded into a delivery system which is part of the catheter used to help the study doctor place the valve in your heart. The delivery system is about as big around as your ring finger. The valve is put into the delivery system with a two-part funnel system which compresses the stent to fit inside the delivery system.

While using echocardiography and fluoroscopy (angiogram pictures) the study doctor will position the valve in your heart. After positioning the heart valve, the delivery system will slowly let the valve expand to the full size.

The Portico Transcatheter Heart Valve is designed to have the capability to be released slowly in a controlled manner, be repositioned (should the need arise), be removed completely and another attempt made, and the final position can be checked thoroughly before final valve release (with normal new valve function during the assessment).

6. Do I have to take part?

No. Your participation in this study is entirely voluntary and you are under no pressure to take part. If you decide to participate in this study, but later change your mind, you can withdraw at any time without explanation and without any loss of medical care or benefits you would otherwise have received. You can withdraw from this study without penalty, and withdrawal from this study will not jeopardize your future care or your relationship with the study doctor. If you withdraw from the study, you will be asked what the reason is for withdrawing from the study, but you do not have to answer.

If the study doctor has concerns about your participation, you will not be able to take part in the study. The study doctor can also withdraw you from the study at any time.
If you do decide to take part, you will be asked to sign this consent form. By consenting to take part in this study you are agreeing that the Portico valve (Picture 1) may be implanted using the delivery system.

7. What are the alternate treatments? If you do not wish to take part in this study, your study doctor may treat your aortic valve with:

1. Medication
2. An FDA approved Transcatheter Aortic Valve Replacement (TAVR) valve and delivery system
3. Standard open heart surgery by a referral to a heart surgeon

8. How long will my participation last in this clinical study? Your participation in this study will begin when you sign the informed consent form and for up to five years following your implant, unless it is determined that you do not meet the study eligibility criteria or you decide to stop your participation in the study.

If you are enrolled in the study and do not receive a TAVR valve, you will be followed for any adverse events through the 30 days post procedure and then withdrawn from the study.

If you undergo study-specific testing, but are not enrolled, you will be exited from the study without any further follow-up.

You may stop your participation in this study at any time. Your participation in this study may also be stopped by the sponsor by your study doctor.

Reasons for ending your participation in the study by the Principal Investigator include, but are not limited to, the following:

• Study participation was not in your best interest
• You did not meet the inclusion/exclusion criteria
• You and/or family request, if applicable
• You aren’t able to comply with the requirement of the study (e.g., you aren’t able to attend follow-up visits)
• Death
• Your non-compliance with study requirements
• You are considered “lost to follow-up”, which occurs 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 by traceable mail
• Your participation is terminated by the Principal Investigator if it is not in your best interest to continue in the study
• Study discontinued due to sponsor management decision or request from applicable governing bodies
• Investigational site ends participation in the study
The study may be temporarily stopped or terminated, either at the local or national level, at the request of the Institutional Review Board (IRB), regulatory authorities (FDA), or the sponsor. The sponsor may stop the study if new information about the device is learned during the duration of the study to ensure patient safety.

You will be notified in writing if there are new findings or reasons for any changes to the study plan which will affect your continued participation in the study.

9. What will take place during the study?

This is a non-randomized research study. This means you will be implanted with a Portico Transcatheter Heart Valve.

Before your operation:

To determine if you qualify for the study, you may have the following tests performed, depending on your clinical condition. None of these tests are considered experimental and would be part of your normal care even if you were not in the study:

- Physical Exam: your study doctor or a trained member of his or her staff will ask you about your medical history and do a basic physical exam
- CT Scan: a test to assess the blood vessels (ascending aorta, bilateral iliac arteries) of your body
- Chest x-ray: An x-ray will be taken to assess any abnormalities in your chest. This takes about 5 minutes to complete.
- Echocardiography (echo): a test that uses sound waves to look at how your heart is functioning
- Electrocardiogram (ECG): a tracing of your heart's rhythm
- Lab work: standard blood tests
- Frailty Index: an evaluation by your doctor used to predict your risk for medical procedures
- NYHA Functional Classification and Angina Scale: an evaluation by your study doctor to rank the limitations in your daily activities based on shortness of breath and chest pain
- STS Risk Score/EuroSCORE II: evaluations to measure the amount of risk surgery may pose to you
- Pulmonary Function Test: a breathing test to check the function of your lungs
- Coronary and Aortic Angiogram: a test to assess the blood vessels of your body

If you do not meet all the criteria for the study, no further procedures will be performed. If you do meet all criteria for the study, and would like to participate, then you will complete the following tests prior to being scheduled for the procedure. You
During your procedure:

The Portico Transcatheter Heart Valve implant will be done in the hospital catheterization laboratory, a special room for these kinds of procedures. You may be given medication to make you sleepy and more comfortable during the procedure or you may be put fully asleep for the duration of the procedure.

If your blood vessels are the right size and shape the study doctor will make an incision in your groin (upper part of your leg where it connects to your hip) and insert a catheter (small tube) into the opening made. The catheter will be moved through your femoral (leg) artery (picture 2a) up to the heart and into position in the heart to allow placement of the valve.

If your leg blood vessels are too small or diseased the study valve will be implanted through your chest (picture 2b), or through blood vessels near your shoulder (picture 2c or 2d).
Different Methods for Valve Implantation

a) transfemoral  
b) transaortic  
c) left subclavian  
d) left axillary (courtesy of Rodés-Cabau, J. Nat. Rev. Cardiol. 9, 15–29 (2012))

The study doctor will use various special imaging methods such as angiographic pictures (x-ray picture of the coronary arteries) to check the position of the catheter and valve. Once the catheter and valve are in the correct position the study doctor will slide the valve out of the catheter and it will unpack and expand to form a replacement aortic valve. With the replacement valve in place, the study doctor will use echo and angiographic pictures to check that valve is working correctly. When the study doctor has confirmed placement, the catheter will be removed and you will be taken to the recovery area.

Following the procedure, if you had the valve placed through your leg, you will have pressure applied to the groin area and will be required to lay flat for a specified amount of time. If you had the valve placed through your chest, your doctor will determine your limitations.

If the study doctor was unable to place the valve in your heart, you may need open heart surgery to replace the valve using standard surgical methods.
During the procedure, a representative from the sponsor may be in the procedure room to provide technical support on the device for your doctor.

After your operation, you will be visited by the study doctor. The study doctor will be looking to see whether you have any complications from the procedure. Before you are discharged from the hospital the following will be done:

- **Physical Exam:** your study doctor or a trained member of his/her staff will ask you about your medical history and do a basic physical exam
- **Echocardiography:** a test that uses sound waves to look at how your heart is functioning. This test will be completed after the procedure or before you are discharged from the hospital.
- **Lab work:** standard blood tests
- **Medications:** you will be asked for the name of the medications you are taking
- **ECG:** tracing of your heart rhythm
- **Stroke Scales:** scales used to measure the degree of disability or dependence in daily activities for people who have had a stroke. This will be done for this study even if you have not had a stroke
- **Assessment of changes in health status:** you will be asked if there are any changes in your health status since you have had your heart valve replaced. Your health status assessment will continue throughout the course of your participation in this study.
- **Disability Scale:** an evaluation to assess your physical functions, self-care and ability to get around
- **Angina Scale:** an evaluation by your study doctor to rank the limitations in your daily activities based on shortness of breath and chest pain

**Follow-up visits**

After the procedure, you will return to the study doctor's office for follow-up visits at 30 days, 12 months (one year) and yearly through five years after the procedure. At these visits the following will be done:

- **Physical Exam:** your study doctor or a trained member of his/her staff will ask you about your medical history and do a basic physical exam
- **ECG:** tracing of your heart rhythm
- **Echocardiography:** a test that uses sound waves to look at how your heart is functioning.
- **QOL:** you will be asked to complete questionnaires about how you are feeling
- **Medications:** you will be asked the names of medications you are taking
- **Lab Work:** standard blood tests (This will not be done at the yearly visits past one year.)
• Assessment of changes in health status: you will be asked if there are any changes in your health status since you have had your heart valve replaced. Your health status assessment will continue throughout the course of your participation in this study.

• Frailty Index: an evaluation by your doctor used to predict your risk for medical procedures (This will not be done at the yearly visits past one year.)

• Stroke Scales: scales used to measure the degree of disability or dependence in daily activities for people who have had a stroke. This will be done for this study even if you have not had a stroke.

• NYHA Functional Classification and Angina Scale: evaluations by your study doctor to rank the limitations in your daily activities based on shortness of breath and chest pain

• Mini-Mental State Exam: you will be asked to answer questions and to perform a few tasks to assess your thinking and memory (This will not be done at the annual visits past one year.)

• Disability Scale: an evaluation to assess your physical functions, self-care and ability to get around

• Angina Scale: an evaluation by your study doctor to rank the limitations in your daily activities based on shortness of breath and chest pain

If you have a suspected stroke or other neurological event, the following will be done at a visit 90 days after the event:

• Neurological assessment: an examination of how your brain functions to help determine if you may have had a stroke

• Stroke Scales: scales used to measure the degree of disability or dependence in daily activities for people who have had a stroke.

10. Health Economic Analysis

The Sponsor is also conducting a health economic analysis. The Health Economic Analysis will evaluate the costs and benefits of treatment. This information is being collected so we can understand the cost effects of the treatment in the PORTICO study. For the purpose of this Health Economic Analysis, information about your reported resource use of hospital care will be collected. Medical resource use, cost and health-related quality of life within the trial period will be compared between study subject groups.

11. Radiation exposure

This study may involve radiation exposure from a CT or fluoroscopy. As part of everyday living, everyone is exposed to a small amount of background radiation. Background radiation comes from space and naturally-occurring radioactive minerals. The angiography procedure uses x-ray radiation to guide the examination. The amount of radiation you are exposed to during this procedure will depend on the complexity of
12. Potential risks and side effects of transcatheter aortic valve implantation

<table>
<thead>
<tr>
<th>Technical Name</th>
<th>What it means</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access site complications</td>
<td>primarily relates to bruising or bleeding at the site where the delivery system was inserted.</td>
</tr>
<tr>
<td>Acute coronary obstruction</td>
<td>blocking the arteries carrying blood to the heart.</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>heart attack</td>
</tr>
<tr>
<td>Access site injury</td>
<td>Injury during the process of inserting valve or the valve damages other parts of the body near it.</td>
</tr>
<tr>
<td>Allergic reaction to antiplatelet agents, contrast medium, anesthesia or valve components</td>
<td>reaction to some medications, x-ray dye, procedural dye, or materials used to make the valve</td>
</tr>
<tr>
<td>Anaphylactic shock/toxic reaction</td>
<td>serious allergic reaction</td>
</tr>
<tr>
<td>Annulus rupture</td>
<td>tearing of the ring tissue around the heart valve.</td>
</tr>
<tr>
<td>Aortic rupture</td>
<td>tearing of the aortic valve</td>
</tr>
<tr>
<td>Ascending aortic trauma</td>
<td>damage to the largest artery in your body. The artery is the main supply from the heart.</td>
</tr>
<tr>
<td>Atrioventricular node block</td>
<td>a slowed heart beat due to top and bottom chambers of your heart not beating normally together</td>
</tr>
<tr>
<td>AV fistula</td>
<td>abnormal connection between an artery or vein</td>
</tr>
<tr>
<td>Bleeding</td>
<td>an episode which involves bleeding</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>irregular heart beat</td>
</tr>
<tr>
<td>Cardiovascular or vascular injury</td>
<td>injury to blood vessels, heart</td>
</tr>
<tr>
<td>Technical Name</td>
<td>What it means</td>
</tr>
<tr>
<td>----------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Conduction system injury</td>
<td>a change in the way your heart impulses are transmitted which may require a pacemaker insertion</td>
</tr>
<tr>
<td>Death</td>
<td>Death</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>infection in the heart</td>
</tr>
<tr>
<td>Embolism: air, calcification or thrombus</td>
<td>clogging an artery or vein stopping blood flow to a body part</td>
</tr>
<tr>
<td>Exercise intolerance (weakness)</td>
<td>unable to exercise at your normal level of physical tolerance</td>
</tr>
<tr>
<td>Fever</td>
<td>elevated body temperature</td>
</tr>
<tr>
<td>Heart failure</td>
<td>heart cannot pump enough blood to the rest of the body</td>
</tr>
<tr>
<td>Hematoma</td>
<td>collection of blood outside a blood vessel</td>
</tr>
<tr>
<td>Hemodynamic compromise</td>
<td>problems with blood flow</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>break down of the blood cells</td>
</tr>
<tr>
<td>Hemolytic anemia</td>
<td>abnormal breakdown of the red blood cells in your blood</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>excessive bleeding</td>
</tr>
<tr>
<td>Hypertension</td>
<td>blood pressure is too high</td>
</tr>
<tr>
<td>Hypotension</td>
<td>blood pressure is too low</td>
</tr>
<tr>
<td>Immunological reaction</td>
<td>disorder of the immune system</td>
</tr>
<tr>
<td>Infection</td>
<td>organisms in body causing abnormal body reactions or sickness</td>
</tr>
<tr>
<td>Leakage, regurgitation</td>
<td>some blood flows around the edges of the valve</td>
</tr>
<tr>
<td>Left ventricular failure/rupture</td>
<td>lower left chamber of your heart does not work correctly or tears</td>
</tr>
<tr>
<td>Left ventricular impairment (due to apical scar)</td>
<td>lower left chamber of your heart does not work correctly due to past damage</td>
</tr>
<tr>
<td>Myocardial ischemia</td>
<td>not enough blood flow to the heart muscle</td>
</tr>
<tr>
<td>Mitral valve insufficiency</td>
<td>heart valve does not close properly and leaks</td>
</tr>
<tr>
<td>Multi-organ failure</td>
<td>more than one body organ does not function</td>
</tr>
<tr>
<td>Neurological changes including stroke/transient ischemic attack</td>
<td>a blood clot travels to a vessel in your brain and blocks blood flow (stroke)/blood flow to a part of the brain stops for a brief period of time(tia)</td>
</tr>
<tr>
<td>Non-structural dysfunction</td>
<td>wrong size valve, suture or tissue gets in way of valve function</td>
</tr>
<tr>
<td>Pannus</td>
<td>abnormal layer of tissue</td>
</tr>
<tr>
<td>Paravalvular leak</td>
<td>some blood flows around the edges of the valve</td>
</tr>
<tr>
<td>Technical Name</td>
<td>What it means</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>bleeding into the sac around the heart</td>
</tr>
<tr>
<td>Perforation</td>
<td>hole in blood vessel</td>
</tr>
<tr>
<td>Potential coronary</td>
<td>obstruction</td>
</tr>
<tr>
<td>Renal failure</td>
<td>kidneys not functioning to normal capacity</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>poor kidney function</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>shortness of breath</td>
</tr>
<tr>
<td>Sepsis</td>
<td>generalized overall systemic infection</td>
</tr>
<tr>
<td>Septal rupture</td>
<td>tear in the tissue which divides the heart</td>
</tr>
<tr>
<td>Stenosis (high gradient)</td>
<td>a high amount of vessel narrowing</td>
</tr>
<tr>
<td>Stroke</td>
<td>a blood clot travels to a vessel in your brain and blocks blood flow</td>
</tr>
<tr>
<td>Structural valve</td>
<td>deterioration parts of valve do not work or do not work as expected</td>
</tr>
<tr>
<td>Systemic peripheral</td>
<td>ischemia inadequate blood flow</td>
</tr>
<tr>
<td>Tamponade</td>
<td>a large amount of fluid collects around the sac surrounding your heart</td>
</tr>
<tr>
<td>Valve migration or</td>
<td>malposition valve movement out of position</td>
</tr>
<tr>
<td>Valve explant</td>
<td>remove valve</td>
</tr>
<tr>
<td>Valve embolization</td>
<td>valve is not in contact with aortic annulus</td>
</tr>
<tr>
<td>Valve stenosis</td>
<td>narrowing of valve opening</td>
</tr>
<tr>
<td>Valve thrombosis</td>
<td>blood clot is attached to or near the valve</td>
</tr>
<tr>
<td>Ventricular failure</td>
<td>(acute) current lower chamber of your heart is not functioning</td>
</tr>
<tr>
<td>Ventricular rupture</td>
<td>tear in the lower chamber of the heart</td>
</tr>
<tr>
<td>Vessel dissection or</td>
<td>spasm structure of vessel is changed</td>
</tr>
</tbody>
</table>

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
- Permanent pacemaker
Due to the nature of the delivery methods used, TAVR procedures may be associated with an increased risk of stroke and vascular complications when compared to surgical aortic valve replacement.

A layer of thrombus (blood clot) has been seen on some TAVR valves when four-dimensional computed tomography (4D CT) scans or transesophageal echocardiograms (TEE) are used to examine the valve after implant. In several cases, this layer of thrombus has been shown to prevent valve leaflets from opening properly. The layer of thrombus may be present but not seen if a 4D CT scan or TEE is not done.

Blood thinners and anti-clot medicine can be used to treat the thrombus and may be prescribed by your study doctor even if no thrombus has been seen.

The overall risk of death from transcatheter aortic valve implantation at this hospital at 30 days is between <insert site risk>% (<>/100 to <>/100), depending on your other pre-existing illnesses.

There are additional risks for study related tests. These risks may include but are not limited to the following:

**Blood sample:**
- the risk of inserting a needle into a vein in your arm may include temporary discomfort from the needle stick. There is also a small risk of infection, bruising, swelling, bleeding or fainting. These risks are minimized by cleansing the site carefully prior to obtaining the blood sample and applying pressure to the site after the blood sample is obtained.

**Echocardiogram:**
- For a Transthoracic Echocardiogram (TTE), a lubricant (gel) is used on the skin to improve picture quality and this may feel cold. There are no known risks associated with receiving a TTE echocardiogram. There may be discomfort from the pressure of the transducer as the images are taken.
- Another type of echocardiogram is called a Transesophageal Echocardiogram (TEE), which takes images by putting a scope down your throat while you are asleep. Some risks include, but are not limited to, esophageal bleeding, sore throat, and bruising. Your doctor will determine which echocardiograms are best to get the best images of your heart.

**CT/MSCT and Fluoroscopy:**
- There may be risks due to the radiation used during the CT and fluoroscopy scan. There is a risk that the contrast media/dye used during the CT/MSCT and fluoroscopy procedures could harm your kidneys or that you will have an allergic response. In either case, your doctor will be prepared to treat you with medications.

13. What are the risks for women of childbearing age?
If you are pregnant or plan to become pregnant in the duration of the study, you should discuss your participation with your study doctor. Subjects who become pregnant while taking part in the study should contact the study doctor right away. There could be other risks or discomforts to you (or to an embryo, unborn child or nursing infant if you become pregnant) that are not known at this time. You will be told in writing about any new information that may become available during your participation in the study or that may influence your decision to continue participation in this study.

14. Potential Benefits of taking part in the study

This study may not benefit you directly, but may benefit other patients with a similar condition in the future. Such future benefits to other patients may possibly include:

• Making the operation simpler by reducing the need for:
  o Open heart surgery
  o Use of the heart and lung machine
• Fewer number of days spent in the hospital
• Less risk of complications
• Allowing a faster return to your normal activity level
• Potential improvement in your heart function

15. What if something goes wrong?

Any complaint about the way you have been treated during the study, if you have any questions about your rights, or any possible harm you might suffer, talk to your study doctor or hospital patient advocate.

16. Whom should I contact if I have questions or if I am injured during the study?

During the course of this clinical study, if you have any further questions, concerns, or research related injuries as a result of your participation, please contact [add Principal Investigator contact information here].

For questions regarding your rights as a research subject, please contact the hospital ethics board (often called an IRB or Institutional Review Board) at [add IRB contact information here].

17. What will happen if I don't want to carry on with the study?

You can withdraw from the study at any time. Feel free to inform the study staff of your decision to withdraw from the study even while you are being taken to the procedure room or are in the procedure room. If you decide not to participate in the study before the procedure, you will not get a Portico valve.
18. What if there is a problem?

If you were to suffer harm of any kind as a direct result of this study, treatment for that injury including surgery, first aid, and emergency care will be available as applicable under Federal, State, and local law. The hospital or clinic where you received treatment will bill your insurance company for the routine costs of care available under your health care plan and you may also have to pay some costs such as co-pays or deductibles.

If you followed all study instructions and are hurt during the study as a direct result of the study device or study procedures (not part of your routine medical care), the sponsor will pay for reasonable and necessary medical and hospital expenses.

The sponsor will not cover the cost of injuries to the extent that they are caused by your failure to follow study instructions or other negligence, or that of the hospital or study doctor, the natural progression of an underlying condition (whether diagnosed or not) or pre-existing condition, or events that would have been expected from the standard treatment using currently approved therapies for your condition.

Signing this consent form in no way limits your legal rights against the Sponsor, investigators, or anyone else, and you do not release the study doctors or participating institutions from their legal and professional responsibilities. If you have a concern about any aspect of this study, you should ask to speak to the researchers at Hospital or MD who will do his best to answer your questions.

In the event of your death, if you received a Portico valve, your implanted valve may be removed and returned to the sponsor for analysis. The study doctor will get your family's approval prior to removing the device.

19. Will my taking part in this study be kept confidential?

If you decided to take part in this research study, your participation, medical records, and personal information will be kept confidential to the extent allowed by Federal, State, and local law. However, research records and health or other source records identifying you may be inspected by the Sponsor and its affiliated companies (located in the U.S. and other countries), representative designees of Sponsor that provide services related to the device and/or this study, the U.S. Food and Drug Administration and other government authorities (in the U.S. and other countries), and the Institutional Review Board (IRB) for the purpose of: 1) monitoring the research; 2) accurately documenting and reporting any adverse events that may occur during your participation in this study; 3) satisfying any other requirements imposed by government authorities located throughout the world, including the U.S. FDA. No information or records that disclose your identity will be published without your consent, nor will any information or records that disclose your identity be removed or released without your consent unless otherwise permitted by law. Your regular doctor may be told of your participation in the study at your request.
You will be assigned a unique study number as a subject in this study. This number will be used on any research-related information collected about you during the course of this study, so that your identity [i.e. your name or any other information that could identify you] as a subject in this study will be kept confidential. Information that contains your identity will remain only with the study investigator and/or designate. The list that matches your name to the unique study number that is used on your research-related information will not be removed or released without your consent unless required by law.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time. Please note information may not be available on ClinicalTrials.gov until the study is completed and the device is marketed.

By signing the Patient Consent Form, you are consenting to the collection, use, review, processing and disclosure of such information.

20. What will happen to the results of the study?
Once the study is complete and analyzed, the results may be submitted for publication in a scientific journal and presented at scientific conferences. Your confidentiality will be maintained and you will not be identified in any report or publication of this study. If you wish to see the results when they are published, let the researcher who obtains informed consent from you know and a copy of the results can be sent to you. The data may be used for additional medical or scientific research projects in the future and obtaining regulatory approvals for further studies about the device. Data may, if necessary for the above purposes, be communicated to the processors, regulatory authorities and Ethics Committees located in countries of the European Economic Area (“EEA”), in the United States of America (“USA”), Canada, and governmental agencies (including regulatory agencies) in other countries. Some of the non-EEA countries to which your data may be transferred may not offer an adequate level of protection of privacy of personal data. St Jude Medical has taken security measures to ensure your personal data will be processed and used in a confidential way. Data may also be used to present reimbursement information to public and private payers to advocate changes in coverage, coding or reimbursement rates and payment policies.

21. Who is organizing and funding the study?
This study is being organized and funded by St. Jude Medical. The <Hospital> will receive payments from St Jude Medical for participating in this study and for providing study data.
What expenses may result from my participation in the study?

You or your insurance will be billed for tests that are standard of care and would be done even if you were not taking part in the study. Tests and procedures that will be done just for the study will be paid for by the sponsor.

You will receive a stipend in the amount of $25 per visit to cover the cost of travel and parking for attending required research related visits. There are a total of 7 required visits (baseline, 30 day, 12 month, 2 year, 3 year, 4 year, and 5 year).

Who has reviewed the study?

The study was reviewed by the hospital system and has been approved to be conducted at this hospital by the IRB.

If you have any questions about your rights as a research subject you can contact the IRB at [contact information].

What are my responsibilities if I am in the study?

As a study participant, you are asked to follow study requirements, follow medical instructions given by your study doctor, inform your study doctor of any changes in your health, and inform your study doctor of any other medical care or drugs you are receiving (whether prescribed by a physician or bought over the counter).
AUTHORIZATION TO USE AND DISCLOSE HEALTH INFORMATION

I agree to permit {add Investigator name here} and staff members and, St. Jude Medical, the sponsor of the PORTICO clinical trial to use and disclose health information that identifies me for the purposes described below. I also agree to permit {add hospital/clinical study site information here}, my doctors, and my other health care providers to disclose health information in my medical records to the researchers, Jude Medical and the FDA, or other regulatory bodies for the purposes described below.

1. The health information that may be used and disclosed includes:
   • All information collected during the research as described in the Informed Consent Form; and
   • Health information in my medical records that is relevant to the research described in the Informed Consent Form.

2. The researchers may:
   • Use and share my health information to conduct the research;
   • Disclose my health information to the Sponsor of the research, St. Jude Medical and its affiliated companies (located in the U.S. and other countries), representatives/designees that provide services related to the device and/or this study;
   • Disclose my health information as required by law;
   • Disclose my health information to representatives of government organizations and other persons who are required to watch over the safety and effectiveness of medical products and therapies and the conduct of research; and
   • Remove from my health information my name and other information that could be used to identify me.

3. St. Jude Medical and its affiliated companies (located in the U.S. and other countries), representatives/designees that provide services related to the device and/or this study may:
   • Use and share my health information to conduct the research;
   • Disclose my health information as described in the Informed Consent Form;
   • Disclose my health information as required by law;
   • Disclose my health information to representatives of government organizations and other persons who are required to watch over the safety and effectiveness of medical products and therapies and the conduct of research; and
   • Remove from my health information my name and other information that could be used to identify me.

4. Once information that could be used to identify me has been removed, the information that remains is no longer subject to this Authorization and may be
5. Once my health information has been disclosed to a third party, privacy laws may no longer protect it from further disclosure. However, the researchers and St. Jude Medical agree to protect my health information by using and disclosing it only as permitted by me in this Authorization and the Informed Consent. Also, no publication about the research will reveal my identity without my specific written permission. These limitations continue even if I revoke (take back) this Authorization.

Please note that:

• You do not have to sign this Authorization, but if you do not, you will not be allowed to participate in the research.
• You may change your mind and revoke this authorization at any time. To revoke this Authorization, you must write to {name and contact information}. However, if you revoke this Authorization, you will no longer be allowed to participate in the research. Also, if you revoke this Authorization, the information already obtained by the researchers and St. Jude Medical may be used and disclosed as permitted by the Authorization and the Informed Consent.
• While the research is in progress, you will not be allowed to see your health information that is created or collected in the course of the research. After the research is finished, however, you may see this information as described in the {add hospital/clinical study site name here}'s Notice of Information practices.
• This Authorization does not have an expiration (ending) date.
• You will be given a copy of this Authorization after you have signed it.

Thank you for considering taking part in this study.

If you decide to participate you will be asked to sign below and will be given a copy of this form to keep.

Name of Principal Investigator: [Insert Name]
1. I confirm that I have read and understood the Informed Consent for this Portico IDE study. I have had sufficient time to think about it and I have been given the opportunity to ask questions, and have had these answers satisfactorily.

2. I understand that:
   • my participation is voluntary and that I am free to refuse to participate in this study or to withdraw at any time, without giving any reason and without my medical care or legal rights being affected
   • my relationship with my doctor will not be affected if I withdraw
   • there will not be any penalty if I decide to withdraw from the study
   • if I withdraw before the aortic valve replacement procedure, I will not get a St Jude Medical Portico valve
   • my attendance at study visits is important to the study and I should follow the study doctors instructions

3. I understand that:
   • my medical information, information collected during the study and study results may be looked at, used, and disclosed by responsible individuals from St. Jude Medical, a U.S. company, and its affiliates (located in the U.S. and other countries, and other people who work for St. Jude Medical to provide services related to the device and this study, regulatory authorities, the IRB and, when it is relevant to my taking part in this research. I give permission for these individuals to have access to my medical information, information collected during the study, and study results
   • my data gathered in this study may be stored (after anonymized) in a database and may be used and disclosed by St Jude Medical
   • my relevant personal data may be used for the purpose of this clinical study
   • data collected from the time I sign this document until the time I withdraw from the study will be used after I withdraw
   • I will not financially benefit from this study
   • I may be responsible for insurance copayments

4. I understand how to contact the research team

5. I agree to my General Practitioner being informed of my participation in the study

6. I understand the risks of aortic valve surgery and the risks of participating in this study and

7. I am willing to participate in this study

Name of Participant (please print)

Signature

Date

Time____________

Name of Person Obtaining Consent (please print)

Signature

Date

Time__________