Clinical Investigational Plan

Portico Alternative Access

"Assessment of the St Jude Medical Portico Resheathable Aortic Valve System-Alternative Access"

CRD_878

Study Document No: SJM-CIP-10144

Version D

Date: 10-Oct-2017

Clinical Investigation Plan (CIP)

Sponsor

Abbott
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SITE PRINICPAL INVESTIGATOR SIGNATURE PAGE

Portico Alternative Access

Version D, 10-Oct-2017

Reference #: SJM-CIP-10144

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

Site Principal Investigator

Printed name: _____

Signature:_____

Date: _____

Steering Committee Co-Chair

SIGNATURE PAGE

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Steering Committee Co-Chair

Printed name: Prof. Axel Linke

Signature: _____

Date: 11/OCT/2017

Steering Committee Co-Chair

Printed name: Dr. Giuseppe Bruschi

Signature: _____

Date: _____

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Printed name: Prof. Axel Linke_____

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Date: _____

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Printed name: Dr. Giuseppe Bruschi_____

Signature: _____

Date: October, 10th 2017

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1.0 Synopsis

Title:	Assessment of the St. Jude Medical Portico™ Re-sheathable Aortic Valve System – Alternative Access
Acronym:	Portico Alternative Access
Purpose:	The purpose of this clinical investigation is to expand the indication of the Portico TF Delivery System and obtain approval of the Alternative Access Delivery System to place a Portico transcatheter aortic valve through an alternative access site, specifically subclavian/axillary or transaortic (TAo) in subjects with symptomatic severe native aortic stenosis who are considered high surgical risk.
Endpoints:	Primary Endpoint: The study will have a single primary safety endpoint of major vascular complications through 30 days, as defined by the Valve Academic Research Consortium[i] (VARC-2) for each access arm of the study.
	Secondary Endpoints for each access arm of the study: 1. The event rates at 30 days of the following: • All-cause mortality • Cardiovascular mortality • Disabling stroke • Non-disabling stroke • Life-threatening bleeding requiring transfusion • Acute kidney injury requiring dialysis • Composite of ○ Periprocedural encephalopathy ○ all stroke ○ all TIA 2. The event rates at 1 year of the following: • All-cause mortality • Cardiovascular mortality • Disabling stroke • Moderate and severe aortic regurgitation 3. Improvement from baseline as compared to 30 days by: • NYHA Functional Classification • Six minute walk test • Effective Orifice Area (EOA) 4. 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 ○ peak velocity <3 m/s ○ no moderate or severe prosthetic valve regurgitation In addition successful access, delivery and deployment of the valve and retrieval of the delivery system will be collected.

Design:	This is a multicenter prospective, non-randomized, 2-arm investigational study without concurrent or matched controls, designed to assess the use of the Portico TF or Alternative Access Delivery System to place a transcatheter aortic valve through an alternative access site, specifically subclavian/axillary and TAo. A minimum of 45 subjects will undergo transcatheter aortic valve replacement (independent of valve size) using the Portico TF or Alternative Access Delivery System in each study access arm (subclavian/axillary and TAo). A minimum of 45 implants will be accessed via the subclavian/axillary access site and a minimum of 45 implants will be accessed via the TAo access site. A maximum of 12 investigational sites with prior alternative access technique experience in Europe will be trained to participate in the study. Enrollment is anticipated to be completed approximately 8 months from the date of first enrollment. Data will be collected at pre-procedure, peri-procedure and at discharge as well as at 30 days, 6 months and 1 year post implantation. All active subjects will be followed for 1 year. Data from other prospective Portico clinical trials with ALT access in similar patient populations outside of Europe may be included in the analysis and support the submission for CE Mark. CE Mark will be submitted for each access route after implantation and 30 day follow up are completed. Although the study will not test a hypothesis, the primary endpoint event rate for each cohort will be presented within the context of the range of rates reported for alternative access delivery of transcatheter valves in the literature.
Devices used:	The devices to be used in this study are the Portico delivery systems which are available in two different lengths, 110 and 65cm. Both of these devices are considered investigational for alternative access use. The 110cm delivery system is already CE marked for Transfemoral access. This study will also use the CE marked Transfemoral/Alternative Access Loading systems (18 or 19F) and Portico valves available in 23, 25, 27 and 29mm sizes.
Study Population	A patient becomes a subject once he/she has been fully informed about the study, has agreed to participate, signed & dated the consent.
Inclusion/Exclusion Criteria	<u>Inclusion Criteria</u> 1. Subject has provided written informed consent prior to uploading CT scan to core lab. 2. Subject is ≥ 18 years of age or legal age in host country. 3. Subject's aortic annulus diameter meets the range indicated in the Instructions for Use as measured by multislice CT conducted within 180 days prior to the index procedure. 4. Subject has senile degenerative aortic stenosis seen by echocardiography within 90 days of index procedure as measured by one of the following:

- Mean gradient ≥ 40 mmHg
- Peak velocity ≥ 4.0 m/s
- Doppler Velocity Index < 0.25
- Aortic valve area (AVA) of < 1.0 cm^2 or indexed EOA < 0.6 cm^2/m^2.

5. Subject has symptomatic aortic stenosis as demonstrated by NYHA Functional Classification of Class II, or greater or other symptoms of aortic stenosis (e.g. syncope).
6. Subject is deemed high operable risk and preferred TAVI delivery route is alternate access (subclavian/axillary or direct aortic) per the medical opinion of the center's heart team and confirmed by SSC.

- High risk is defined as an STS mortality ≥ 8% or documented heart team agreement ≥ high risk for SAVR due to frailty or co-morbidities

Exclusion Criteria

1. Subject is unwilling or unable to comply with all study-required follow-up evaluations.
2. Subject has a documented history of a cerebral vascular accident (CVA) or transient ischemic attack (TIA) within 6 months (less than or equal to 180 days) prior to the index procedure.
3. Subject has carotid artery disease requiring intervention.
4. Subject has evidence of a myocardial infarction (MI) within 30 days prior to patient index procedure.
5. Subject has a native aortic valve that is congenitally unicuspid, bicuspid, quadricuspid or non-calcified as seen by echocardiography.
6. Subject has severe mitral valvular regurgitation.
7. Subject has severe mitral stenosis.
8. Subject has a pre-existing prosthetic cardiac device, valve, or prosthetic ring in any position.
9. Subject refuses any blood product transfusion.
10. Subject has resting left ventricular ejection fraction (LVEF) less than 20%.
11. Subject has documented, untreated symptomatic coronary artery disease (CAD) requiring revascularization.
12. Subject has had a percutaneous interventional or other invasive cardiovascular or peripheral vascular procedure less than or equal to 14 days prior to index procedure.
13. Subject has severe basal septal hypertrophy that would interfere with transcatheter aortic valve placement.

14. Subject has a history of, or is currently diagnosed with, endocarditis.
15. There is imaging evidence of intracardiac mass, thrombus, or vegetation.
16. Subject is considered hemodynamically unstable (requiring inotropic support or mechanical heart assistance).
17. Subject is in acute pulmonary edema or requiring intravenous diuretic therapy to stabilize heart failure.
18. Subject with severe pulmonary disease as determined by STS score.
19. Subject is on chronic oral steroid therapy.
20. Subject has a documented hypersensitivity or contraindication to anticoagulant or antiplatelet medication.
21. Subject has renal insufficiency as evidenced by a serum creatinine greater than 3.0 mg/dL (265.5 µmol/L) or end-stage renal disease requiring chronic dialysis.
22. Subject has morbid obesity defined as a BMI greater than or equal to 40.
23. Subject has ongoing infection or sepsis.
24. Subject has uncontrolled blood dyscrasias as defined: leukopenia (WBC<3000 mm^3), acute anemia (Hb<9 g/dL), thrombocytopenia (platelet count <50,000 cells/mm^3,).
25. Anatomy falling outside the recommended values in the IFU, unless specifically approved by the Subject Selection Committee.
26. Subject has an active peptic ulcer or has had gastrointestinal (GI) bleeding within 90 days prior to the index procedure.
27. Subject is currently participating in another investigational drug or device study, unless approved by the Sponsor.
28. Subject has/had emergency surgery for any reason within 30 days of the index procedure.
29. Subject has a life expectancy less than 1 year.
30. Subject has other medical, social or psychological conditions that, in the opinion of the site Heart Team or the Subject Selection Committee, preclude the subject from study participation.
31. Subject is diagnosed with a state of dementia which would fundamentally complicate rehabilitation from the procedure or compliance with follow-up visits.
32. Subject has a documented allergy to contrast media that cannot adequately be treated, nitinol alloys, porcine tissue, or bovine tissue.

	33. Significant aortic disease including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5cm or greater 34. Subjects with severe pulmonary hypertension and severe RV dysfunction 35. Subjects with hypertrophic cardiomyopathy Transaortic Subject Cohort Specific Exclusion Criteria 1. Subject has a chest condition (anatomical or otherwise) that prevents TAo access. 2. Subject has pre-existing patent RIMA graft that would preclude access. 3. Subject has a porcelain aorta, defined as an extensive circumferential calcification of the ascending aorta that would complicate TAo access. Subclavian/Axillary Subject Cohort Specific Exclusion Criteria 1. Subject's access vessel (subclavian/axillary) diameter will not allow for introduction of the 18/19 Fr delivery system. 2. Subject's subclavian/axillary arteries have severe calcification and/or tortuosity. 3. Subject has a history of LIMA/RIMA graft that would preclude access
Data Collection	Data will be collected pre-procedure, peri-procedure, and discharge as well as 30 days, 6 months and 1 year post implantation. A Clinical Events Committee (CEC) will adjudicate the relatedness of endpoint events with respect to the procedure, delivery system, valve and by event type according to the VARC-2 endpoint definitions document. CEC adjudications will be used when assessing and reporting study results.

2.0 Background and Justification for Clinical Study

Aortic Stenosis (AS) is currently the most common valvular disease in the Western population[1] and its prevalence tends to increase with age, being present in 4.6% of adults ≥75 years.[2] Replacement of the aortic valve remains an effective treatment of severe AS. There was a near doubling of surgical aortic valve replacements (AVRs) over a 10-year period (1995-2004)[3] and the need for AVR is projected to escalate as the population grows older due to the increase in life expectancy.[4]

The average life expectancy of patients with severe, symptomatic AS is 2-3 years from the onset of symptoms with a significant risk of sudden death.[5] Symptomatic aortic stenosis is an accepted indication for surgery, in which valve replacement can both reduce symptoms and extend life.[6] Despite this, many patients with severe aortic stenosis do not undergo surgery because of excessive risk, advanced age, or preference. Prognosis with medical management is poor[1] and prior to TAVR, percutaneous alternatives to surgery have been limited to balloon valvuloplasty with palliation that is modest and short-lived.[7,8]

Many patients with severe AS are considered high surgical risk and do not undergo AVR due to severe comorbidities. Because of the limited therapeutic options in patients deemed at high surgical risk, there was interest in the development of a less invasive method to restore valve function.

With technological advancements, an alternative to surgical AVR, known as TAVR (Transcatheter Aortic Valve Replacement) and TAVI (Transcatheter Aortic Valve Implantation) has been under active investigation and proven safe and effective by a number of groups.[9-15] This concept was first demonstrated by Andersen et al[16] 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,[17] reported the first successful human TAVI 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 for standard surgical aortic valve replacement.

The safety and effectiveness of TAVI is now confirmed with the recent published results of the randomized, controlled PARTNER trial[18], CoreValve IDE[29] which demonstrated the noninferiority of TAVI as compared to conventional AVR in high risk patients.

The first two devices commercially available were the Medtronic CoreValve™ (Medtronic Inc., Minneapolis, Minnesota), and the Edwards Sapien™ valve (Edwards Lifesciences Corporation, Irvine, CA) which received CE Mark in 2007 for transarterial implantation. In addition, the Edwards Sapien prosthesis received CE Mark for transapical implantation in December 2007. The Edwards Sapien XT™ valve (Edwards Lifesciences Corporation, Irvine, CA) received CE Mark in 2010 for transarterial and transapical implantation. In October 2011, two additional valves received CE Mark: the JenaValve™ valve (JenaValve Technology München, Germany) and the Symetis Acurate TA™ system (Symetis, Ecublens, Switzerland). Both valves are designed for a percutaneous aortic valve implantation via a transapical route.

Transcatheter aortic valve replacement was originally described through an antegrade transseptal route by Cribier and colleagues in 2002.[19] Because of the complexity of the procedure and risks associated with crossing the mitral valve, this approach has been abandoned in favor of more reproducible alternatives, primarily the transfemoral (TF) route.

Typically, TF access is the initial default strategy unless the vascular anatomy conveys a prohibitive risk due to vessel tortuosity, small caliber, or heavy calcification.

Although the TF route is the least invasive, it may not be feasible in every patient.[20] General (absolute and relative) contraindications to the TF approach include severely calcified or tortuous iliac arteries; an iliac artery diameter of < 6 mm to < 9 mm (depending on the type of device used); previous aortofemoral bypass grafts; severely angulated aorta or atherosclerotic aortic arch; transverse ascending arch (for balloon-expandable devices); and aortic aneurysm with extensive mural thrombus and coarctation of the aorta. In a recent evaluation by Kurra et. al. of 100 patients undergoing TAVR screening, 35% of patients had at least one criterion of unsuitable iliofemoral anatomy, including 27 patients with small minimal luminal diameter (<8 mm), 12 patients with severe circumferential calcification at the iliac bifurcation (>60%), and 4 with severe angulation of the iliac arteries (<90°).[21]

The decision of using one delivery approach versus another is typically based upon a multidisciplinary team's consensus, comprising the expertise of interventional cardiologists, imaging cardiologists, cardiac surgeons, and cardiac anesthetists - following a careful evaluation of the patient. Even though the experience and skills of the operators have improved and new technologies have become available since the initial TAVI experiences, patient selection remains a key element in the TAVI outcome. Selection criteria have a crucial influence on complication rates and clinical outcomes after TAVI.[22]

Subclavian/axillary and Transaortic (TAo) access have been introduced as alternative routes in patients with difficult transfemoral access for implantation of a transcatheter heart valve[23]. Compared to the TF approach, subclavian/axillary and TAo access provides a less remote access point to the aortic valve. This shorter distance also reduces bending stress on the delivery system through multiple vasculature points potentially improving steerability and placement control of the transcatheter aortic valve.

The subclavian/axillary approach is preferably performed via the left subclavian artery. Hence, a patent left internal mammary artery (LIMA) graft is a relative contraindication for TAVR from the left side. In these patients, the right subclavian artery can be used; however, it may be challenging to achieve the correct angulation of the transcatheter aortic valve during positioning. The presence of a permanent pacemaker in the left pectoral region is not an absolute contraindication.[20]

Transaortic (TAo) approach, also known as "direct aortic" access, provides proximate, direct access to the aortic annulus allowing for precise manipulation of both the delivery system and transcatheter heart valve. This is important in cases where the implantation with other approaches (e.g., TF, TA) may be difficult such as cases with a vertical valve orientation, a horizontal ascending aorta, or where the native valve is at the upper limit of the size.[20]

TAo approaches are either through a ministernotomy or through a mini-right thoracotomy. In a ministernotomy, a limited skin incision (5 cm) is made starting just below the sternal notch. A partial upper sternotomy (J-shape) is performed through the second or third right intercostal space. This exposes the upper portion of the ascending aorta for direct cannulation. A ministernotomy is preferred in obese patients, patients with an ascending aorta in the mid-line/to the left or a short ascending aorta, and in patients with poor respiratory reserve because the pleura remains intact, and it has less effect on the respiratory dynamics. This approach can also be used in patients with previous coronary artery bypass grafting and a patent LIMA graft provided that the LIMA graft is not in the mid-line and the innominate vein and aorta are not in close proximity to the sternum.[20]

The use of each of these alternate access approaches has been demonstrated to be a safe and effective means of delivering transcatheter aortic valves as evidenced by the approved products mentioned above and thus increases the number of patients who can be treated successfully and can ultimately benefit from transcatheter aortic valve replacement.

3.0 Device under Investigation

3.1 Portico TF and ALT Delivery System

The study will use the CE Marked Portico™ transcatheter valves available in 23, 25, 27, and 29mm sizes. The devices under investigation are the Portico TF (110cm) Delivery System and the Alternative Access (65cm) Delivery System which both come in 18 Fr or 19 Fr diameter. Both delivery systems are over-the-wire, (0.035”-compatible). The outer diameter of the delivery systems is 18 Fr and 19 Fr at the distal end and 13 Fr at the proximal end.

The delivery system design facilitates gradual, controlled deployment of the valve. If needed, the valve may be re-sheathed and repositioned up to 2 times, provided the valve has not been >80% deployed.

The valve is deployed annulus end first, from the distal end of the delivery system. The distal end of the delivery system includes an atraumatic radiopaque tip to guide the delivery system and facilitate visualization. The protective sheath covers and maintains the valve in the collapsed position. The protective sheath features a marker band that provides a reference point used to determine the extent of the valve deployment. The protective sheath may be advanced or retracted to facilitate valve loading and deployment. When the protective sheath is retracted, the inner shaft is exposed. The valve is loaded onto the inner shaft. Retainer tabs on the valve lock into a retainer receptacle that is mounted on the inner shaft. The inner shaft also features a radiopaque inner shaft marker band that provides a reference point used to align the valve in the native annulus.

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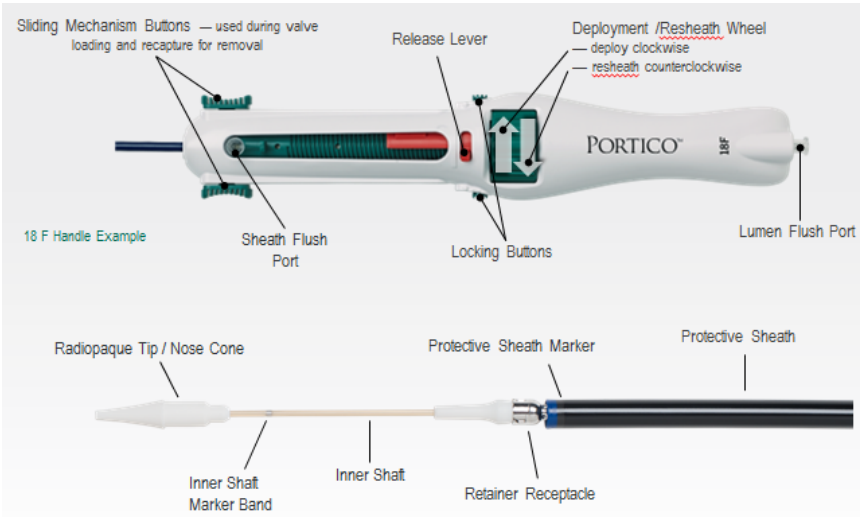

Figure 1: Portico Delivery System

Table 1: Regulatory Status of Devices

Device Component	Model/Type	Investigational or Market Released
110cm Delivery System	18F TF Delivery System	Market Released*
110cm Delivery System	19F TF Delivery System	Market Released*
65cm Delivery System	18F ALT Delivery System	Investigational
65cm Delivery System	19F ALT Delivery System	Investigational
Loading System	18F Transfemoral/Alternative Access Loading System	Market Released
Loading System	19F Transfemoral/Alternative Access Loading System	Market Released
Valve	PRT-23	Market Released
Valve	PRT-25	Market Released
Valve	PRT-27	Market Released
Valve	PRT-29	Market Released

*Will be investigational when used for alternative access delivery

3.2 Device Handling and Storage

Abbott requires all investigational products be stored, according to the labeling, in a secure area to prevent unauthorized access or use. This will prevent non-investigational use of products that are provided only for use in this study.

3.3 Device Accountability

An Abbott representative will notify the sites of activation. Investigational product shall be shipped after the site is activated and shipping authorization is complete.

The Principal Investigator or an authorized designee must maintain a device accountability log documenting the date of receipt, the identification of each investigational device (batch number, lot number or unique code), the subject identification, the date of use, the expiration date and final disposition.

Storage locations for the investigational use only labeled devices will be locked with access restricted only to Investigators and authorized research personnel.

St. Jude Medical must also maintain device accountability documenting all shipments and returns of investigational labeled devices.

4.0 Study Design

4.1 Purpose

The purpose of this clinical investigation is to expand the indication of the Portico TF Delivery System and obtain approval of the Alternative Access Delivery System to place a transcatheter aortic valve through an alternative access site, specifically subclavian/axillary or TAo in subjects with symptomatic severe native aortic stenosis who are considered high surgical risk.

4.2 Study Design and Scope

This is a multicenter prospective, non-randomized, 2-arm investigational study without concurrent or matched controls, designed to assess the use of the Portico TF or Alternative Access Delivery System to place a Portico transcatheter aortic valve through an alternative access site, specifically subclavian/axillary or TAo.

A minimum of 45 subjects will undergo transcatheter aortic valve replacement (independent of valve size) via the Portico TF or Alternative Access Delivery System in each arm. A minimum of 45 implants will be accessed via the subclavian/axillary access site arm of the study and a minimum of 45 implants will be accessed via the TAo access site arm of the study. A maximum of 12 investigational sites with prior alternative access technique experience in Europe and will be trained to participate in the study. Enrollment is anticipated to be completed approximately 8 months from the date of first enrollment. Data will be collected at pre-procedure, peri-procedure and at discharge as well as at 30 days, 6 months and 1 year post implantation. All active subjects will be followed for 1 year.

Data from other prospective clinical trials of ALT access in similar patient populations outside of Europe may be included in the analysis and support the submission for CE Mark. CE Mark will be submitted for each access route after implantation and 30 day follow up are completed.

Although the study will not test a hypothesis, the primary endpoint event rate for each cohort will be presented within the context of the range of rates reported for alternative access delivery of transcatheter valves in the literature.

4.3 End Points

4.3.1 Primary Endpoint for Each Access Arm of the Study:

The study will have a primary safety endpoint for each arm of the study which is the rate of major vascular complications through 30 days, as defined by the Valve Academic Research Consortium[ii] (VARC-2).

4.3.2 Secondary Endpoints:

The following secondary endpoints will be evaluated for each arm of the study.

1. The event rates at 30 days of the following:
   - All-cause mortality
   - Cardiovascular mortality
   - Disabling stroke
   - Non-disabling stroke
   - Life-threatening bleeding requiring transfusion
   - Acute kidney injury requiring dialysis
   - Composite of
     - periprocedural encephalopathy

- all stroke
- all TIA

2. The event rates at 1 year of the following:
   - All-cause mortality
   - Cardiovascular mortality
   - Disabling stroke
   - Moderate and severe aortic regurgitation
3. Improvement from baseline as compared to 30 days by:
   - NYHA functional classification
   - Six minute walk test
   - Effective orifice area
4. 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
     - peak velocity < 3 m/s
     - no moderate or severe prosthetic regurgitation

In addition successful access, delivery and deployment of the valve and retrieval of the delivery system will be collected.

4.4 Study Population

The subjects targeted for this study have symptomatic severe native aortic stenosis and are deemed high operable risk in the medical opinion of the center's heart team and subsequently the Subject Selection Committee (see section 7.2 for details). In the opinion of the implant team, the preferred access route for the patients enrolled in the trial should be alternate access (subclavian/axillary or direct aortic). The determination of the preferred route may take into account patient specific anatomical considerations and other risk factors as well as implanter and patient preference. To participate in this study, patients must meet all inclusion and none of the exclusion criteria for the study.

4.4.1 Inclusion Criteria

To participate in this clinical study, the subject must meet all of the following inclusion criteria:

1. Subject has provided written informed consent prior to uploading CT scan to core lab.
2. Subject is ≥ 18 years of age or legal age in host country.
3. Subject's aortic annulus diameter meets the range indicated in the Instructions for Use as measured by multislice CT conducted within 180 days prior to the index procedure.
4. Subject has senile degenerative aortic stenosis seen by echocardiography within 90 days of index procedure as measured by one of the following:
   a. Mean gradient ≥ 40 mmHg
   b. Peak velocity ≥ 4.0 m/s
   c. Doppler Velocity Index < 0.25
   d. Aortic valve area (AVA) of < 1.0 cm^2 or indexed EOA < 0.6 cm^2/m^2

5. Subject has symptomatic aortic stenosis as demonstrated by NYHA Functional Classification of Class II or greater or other symptoms of aortic stenosis (e.g. syncope)
6. Subject is deemed high operable risk and preferred TAVI delivery route is alternative access (subclavian/axillary or direct aortic) per the medical opinion of the center's heart team and confirmed by SSC
    a. High risk is defined as STS mortality ≥8% or documented heart team agreement ≥ high risk for SAVR due to frailty or co-morbidities

4.4.2 Exclusion Criteria

Subjects are not eligible for clinical study participation if they meet any of the following exclusion criteria:

1. Subject is unwilling or unable to comply with all study-required follow-up evaluations.
2. Subject has a documented history of a cerebral vascular accident (CVA) or transient ischemic attack (TIA) within 6 months (less than or equal to 180 days) prior to the index procedure.
3. Subject has carotid artery disease requiring intervention.
4. Subject has evidence of a myocardial infarction (MI) within 30 days prior to patient index procedure.
5. Subject has a native aortic valve that is congenitally unicuspid, bicuspid, quadricuspid or non-calcified as seen by echocardiography.
6. Subject has severe mitral valvular regurgitation.
7. Subject has severe mitral stenosis.
8. Subject has a pre-existing prosthetic cardiac device, valve, or prosthetic ring in any position.
9. Subject refuses any blood product transfusion.
10. Subject has resting left ventricular ejection fraction (LVEF) less than 20%.
11. Subject has documented, untreated symptomatic coronary artery disease (CAD) requiring revascularization.
12. Subject has had a percutaneous interventional or other invasive cardiovascular or peripheral vascular procedure less than or equal to 14 days prior to index procedure.
13. Subject has severe basal septal hypertrophy that would interfere with transcatheter aortic valve placement.
14. Subject has a history of, or is currently diagnosed with endocarditis.
15. There is imaging evidence of intracardiac mass, thrombus, or vegetation.
16. Subject is considered hemodynamically unstable (requiring inotropic support or mechanical heart assistance).
17. Subject is in acute pulmonary edema or requiring intravenous diuretic therapy to stabilize heart failure.
18. Subject with severe pulmonary disease as determined by STS score.
19. Subject is on chronic oral steroid therapy.
20. Subject has a documented hypersensitivity or contraindication to anticoagulant or antiplatelet medication.
21. Subject has renal insufficiency as evidenced by a serum creatinine greater than 3.0 mg/dL (265.5 µmol/L) or end-stage renal disease requiring chronic dialysis.
22. Subject has morbid obesity defined as a BMI greater than or equal to 40.
23. Subject has ongoing infection or sepsis.
24. Subject has uncontrolled blood dyscrasias as defined: leukopenia (WBC<3000 mm^3, acute anemia (Hb<9g/dL), thrombocytopenia (platelet count <50,000 cells/mm^3).

25. Anatomy falling outside the recommended values in the IFU, unless specifically approved by the Subject Selection Committee.
26. Subject has an active peptic ulcer or has had gastrointestinal (GI) bleeding within 90 days prior to the index procedure.
27. Subject is currently participating in another investigational drug or device study, unless approved by the Sponsor.
28. Subject has/had emergency surgery for any reason within 30 days of the index procedure.
29. Subject has a life expectancy less than 1 year.
30. Subject has other medical, social or psychological conditions that, in the opinion of the site Heart Team or the Subject Selection Committee, preclude the subject from study participation.
31. Subject is diagnosed with a state of dementia which would fundamentally complicate rehabilitation from the procedure or compliance with follow-up visits.
32. Subject has a documented allergy to contrast media that cannot adequately be treated, nitinol alloys, porcine tissue, or bovine tissue.
33. Significant aortic disease including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5cm or greater
34. Subjects with severe pulmonary hypertension and severe RV dysfunction
35. Subjects with hypertrophic cardiomyopathy

4.4.3 Transaortic Subject Cohort Specific Exclusion Criteria

Subjects are not eligible for participation in the TAo access arm if they meet any of the following exclusion criteria:

1. Subject has a chest condition (anatomical or otherwise) that prevents TAo access.
2. Subject has pre-existing patent RIMA graft that would preclude access.
3. Subject has a porcelain aorta, defined as an extensive circumferential calcification of the ascending aorta that would complicate TAo access.

4.4.4 Subclavian/Axillary Subject Cohort Specific Exclusion Criteria

Subjects are not eligible for participation in the subclavian/axillary access arm if they meet any of the following exclusion criteria:

1. Subject's access vessel (subclavian/axillary) diameter will not allow for introduction of the 18/19 Fr delivery system.
2. Subject's subclavian/axillary arteries have severe calcification and/or tortuosity.
3. Subject has a history of LIMA/RIMA graft that would preclude access

5.0 Procedures

5.1 Informed Consent Process

Prior to enrolling in the clinical study and conducting study-specific procedures, all subjects will be consented, as required by applicable regulations and the center's EC. Informed consent must be obtained from each subject, signed and dated by the subject and by the person obtaining the consent.

The Principal Investigator or his/her authorized designee will conduct the Informed Consent Process. This process will include a verbal discussion with the subject on all aspects of the clinical study that are relevant to the subject's decision to participate in the clinical study. The subject will be given enough time to review the consent and ask any questions regarding the study.

The subject shall be provided with the informed consent form that is written in a language that is understandable to the subject and has been approved by the center's EC. Failure to obtain informed consent from a subject prior to study enrollment should be reported to Abbott within 5 working days and to the reviewing center's EC consistent with the center's EC reporting requirements.

5.2 Subject Screening

Potential study subjects should be evaluated for study participation by site staff. This site staff evaluating the potential subject should be trained on the CIP and delegated to do so.

Subjects meeting the inclusion/exclusion criteria will be fully informed about the study and asked to participate. If the subject agrees, a duly signed and dated Patient Informed Consent will be obtained. Patients who do not meet the inclusion/exclusion criteria will not be eligible to participate in this study.

5.3 Point of Enrollment

Subjects are considered enrolled in the study from the moment the subject has provided written Patient Informed Consent.

5.4 Study Activities

Table 2.Study Activity Definitions

Study Activity Definitions	
Study Activity	**Definition**
Adverse Event Assessment	Adverse events will be documented according to definitions in Appendix D.
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.
Blood Work	Blood lab tests will be collected at each required interval. The specific lab tests are indicted in Table 4
Cardiac Rhythm Monitoring	Assessment of heart rate, QRS and dominant rhythm preprocedure and during the procedure.
Chest X-Ray	Imaging conducted at Baseline per institutional guidelines.
Coronary and Aortic Angiogram with Runoff	Angiographic imaging off aortic arch the coronary, subclavian and axillary arteries. Assessment to be conducted per institutional guidelines.
CT Scan	Assessment to be conducted per institutional guidelines.
Echocardiography	Each site is responsible for performing the echocardiogram (echo) according to the Echocardiographic protocol. Echocardiogram will be copied to CD/DVD (or other large media storage device) and provided to an Echocardiographic Core Lab for evaluation.
Electrocardiogram (ECG)	Assessment of dominant rhythm, heart rate, and QRS interval via 12-lead.

Frailty Index	Used to assess if frailty is a high risk factor for subjects. Frailty index assessment is defined in APPENDIX G: FRALITY ASSESSMENT
Informed Consent	An Ethics Committee and Sponsor-approved Informed Consent must be obtained.
Medical History	General medical history of the patient: • Previous cardiovascular operations • Coexisting cardiovascular diseases • Clinically significant peripheral vascular disease • Previous peripheral vascular operations • Other coexisting medical conditions (eg, diabetes, hypertension, kidney and lung disease, endocarditis)
Medication Assessment	Only the following medication will be collected at each specified interval: • Beta Blockers • Calcium Channel Blockers • Anticoagulants • Antiplatelet agents including Aspirin • Diuretics • ACE-Inhibitors • Angiotensin Receptor Blocker (ARBs)
Modified Rankin Stroke Scale	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, using the structured interview found in (APPENDIX H: SCALES). 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.
NIH Stroke Scale	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. The NIHSS is an 11-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 patient'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.
NYHA Classification	The New York Heart Association (NYHA) Functional Classification provides a simple way of classifying the extent of heart failure and defined in APPENDIX I : NYHA CLASSIFICATION.
Physical Assessment	At the baseline visit the following measurement must be assessed: • Age on consent date • Gender • Height The following measurements must be assessed at all visits: • Weight

	• Heart rate • Heart rhythm • Physical Assessment
Procedure Information	Procedure information must be collected including: • Pre-procedure Information • Procedure Information • Procedure Evaluation • Post-procedure Information
Procedural imaging	All imaging collected during the procedure (intra-procedure) such as the cineangiogram and/or echocardiography should be collected and provided to the Sponsor.
QoL Questionnaire	EQ-5D 3L is a standardized instrument for use as a measure of health outcomes. The process to complete this questionnaire is indicated in APPENDIX F: QUALITY OF LIFE-EQ-5D 3L.
Surgical Risk Assessment	Surgical Risk Assessment tools Consists of the 3 assessments as defined in Appendix E: Risk Calculations: • Logistic EuroSCORE • EuroSCORE II • STS Risk Score
Six Minute Walk Test	Used to quantitatively assess submaximal exercise tolerance as defined in APPENDIX J: ATS GUIDELINES FOR THE SIX MINUTE WALK TEST.

5.5 Procedures

The clinical study will be conducted in accordance with the CIP. All parties participating in the conduct of the clinical study will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately. The data collection elements required for each follow-up are summarized in Table 3 below.

Table 3: List of all study specific activities/procedures

Follow-up procedure scheme							
Study Activity Visit window [days]	**Baseline** (within 30 days)	**Procedure**	**Discharge** [+0 to 7 days]	**30-Day** [-7/+14 days]	**6-Month** [±30 days]	**1-Year** [±30 days]	**90 day visit after neuro event** [±14 days]
Informed Consent	X						
Demographics	X						
Medical History	X						
Surgical Risk Assessment	X						
Coronary and Aortic Angiogram with runoff	X ‡						
Physical Assessment	X		X	X	X	X	
Barthel Index	X		X	X		X	X
Modified Rankin Stroke Scale (mRS)	X			X		X	X
NIH Stroke Scale (NIHSS)	X		X	X		X	X
Echocardiogram	X	X§	X	X	X	X	
CT Scan	X *						
Cine angiogram		X§					
Electrocardiogram (ECG)	X		X	X	X	X	
Chest x-ray	X						
Cardiac Rhythm Monitoring		X					
Blood Work	X	X¤	X	X		X	
NYHA Classification	X			X	X	X	

Study Activity Visit window [days]	**Baseline** (within 30 days)	**Procedure**	**Discharge** [+0 to 7 days]	**30-Day** [-7/+14 days]	**6-Month** [±30 days]	**1-Year** [±30 days]	**90 day visit after neuro event** [±14 days]
Frailty Index	X			X		X	
QoL Questionnaire	X			X		X	
Six Minute Walk Test	X			X		X	
Medication Assessment	X		X	X	X	X	
Adverse Events Assessment	X	X	X	X	X	X	

‡ Coronary and aortic angio may be completed up to 120 days prior to index procedure
* CT scan may be completed up to 180 days prior to index procedure
§ All index procedure imaging must be sent to Abbott
¤ Index procedure bloodwork is tested twice (See Table 4):

5.6 Enrollment Visit

The baseline visit procedures must take place within 30 days of the index procedure. It is not necessary to repeat the coronary and aortic angiogram, if completed within 120 days of the planned index procedure. It is not necessary to repeat the CT scan (#12) if it will be completed within 180 days of the planned index procedure. The baseline visit consists of the following activities:

1. Obtain Informed Consent and Data Protection Form
2. Medical History including current diagnosis and Demographics
3. Initial Screening: Perform an initial screening to determine study eligibility
4. Chest X-Ray (CXR)
5. Surgical Risk Assessment
6. Coronary and Aortic Angiogram with runoff
7. Physical Assessment
8. Barthel Index
9. Modified Rankin Stroke Scale
10. NIH Stroke Scale
11. Echocardiogram
12. Computed Tomography (CT) Scan (required for sizing)
13. Electrocardiogram (ECG)
14. Blood work
15. New York Heart Association (NYHA) Functional Classification
16. Frailty Index Assessment
17. Quality of Life Questionnaire (QoL)
18. Six Minute Walk Test
19. Medication Assessment

5.7 Implant/Procedure

The medical team performing the study procedure will typically consist of:

- the primary cardiac surgeon at the site who will perform the TAo procedure
- the primary interventional cardiologist at the site who will perform the subclavian/axillary procedure
- second operator (cardiac surgeon or interventional cardiologist) who is recommended to be present during the procedure
- perfusionist
- anesthesiologist

At least one transcatheter aortic valve may be deployed via the physician determined alternative access pathway in every subject who has signed the Informed Consent Form, and Data Protection Form. Although not recommended, if a physician determines it is in the best interest of the subject to have a second transcatheter aortic valve placed, a subject may receive an additional transcatheter aortic valve.

The procedure visit will consist of the following activities:

5.7.1 Pre procedure Activities

1. Blood work (within 72 hours prior to index procedure, refer to Table 4)
    - Urea
    - Creatinine

2. ECG

5.7.2 Procedure Activities

1. Assess for adverse events
2. Document transcatheter aortic valve deployment information
3. Cardiac Rhythm Monitoring
   - Rhythm changes will be monitored and recorded at the following time points:
     a. Immediately post valvuloplasty (if applicable)
     b. After valve deployment and system retrieval
4. Procedural imaging (angiogram, intra-procedure echocardiography)

5.7.3 Post Procedure Activities

1. Blood work (within 48 hours post implant, refer to Table 4)
   - Creatinine
   - Urea

5.7.4 Procedural Exclusion

During the procedure, the implanting investigator may determine transcatheter aortic valve implantation using the Portico TF or ALT Delivery System is neither feasible nor in the best interest of the subject. Any subject that does not have a delivery system enter his or her body will be withdrawn from the study. Data collected on these subjects, at baseline, will consist of reason(s) for exclusion and possible adverse events. Subjects that have a Delivery System enter his or her body but no valve will be followed for 30 days to collect adverse events.

Following the procedure, the delivery and loading systems should be securely disposed of per hospital requirements for hazardous materials. If there are any concerns noted with the delivery system, loading system, or valve during the procedure, they should be reported and returned to Abbott.

5.8 Scheduled Follow-ups

5.8.1 Discharge Visit

The discharge visit will take place at the time of hospital discharge or 7 days post implant, whichever occurs first. Discharge testing maybe completed the day after procedure up until discharge or within 7 days if the subject has yet to be discharged. The discharge assessment will include:

1. Physical assessment
2. Barthel Index
3. NIH Stroke Scale
4. Echocardiography (to be performed between 24 hours and 7 days post implant)
5. ECG
6. Blood work
7. Medication assessment
8. Adverse events assessment

5.8.2 30-Day Visit

The 30-Day visit window is 30-7/+14 days after the index procedure, and will include:

1. Physical assessment
2. Barthel Index
3. Modified Rankin Stroke Scale
4. NIH Stroke Scale

5. Echocardiography
6. ECG
7. Blood work
8. NYHA Functional Classification
9. Frailty Index assessment
10. Quality of Life Questionnaire (QOL)
11. Six Minute Walk Test
12. Medication assessment
13. Adverse events assessment

5.8.3 6-Month Visit

The 6-Month (180 days) visit window is 180±30 days after the index procedure and will include:

1. Physical assessment
2. Echocardiography
3. ECG
4. NYHA Functional Classification
5. Medication assessment
6. Adverse events assessment

5.8.4 1 Year Visit

The 1 year (360 days) visit window is 360±30 days after the index procedure and will include:

1. Physical assessment
2. Modified Rankin Stroke Scale
3. NIH Stroke Scale
4. Echocardiography
5. ECG
6. Barthel Index
7. Blood work
8. NYHA Functional Classification
9. Frailty Index assessment
10. Quality of Life Questionnaire (QoL)
11. Six Minute Walk Test
12. Medication assessment
13. Adverse events assessment

5.9 Unscheduled Visit 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)[1] from the date of the neurological event. The unscheduled visit will include the following assessments:

1. Barthel Index
2. NIH Stroke Scale
3. Modified Rankin Stroke Scale

5.10 Blood Work

Subject's blood samples will be collected at the intervals indicated in Table 4

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

Table 4. Laboratory Scheme					
Lab Test	**Baseline**	**Procedure**		**Discharge**	**30 days, & 1 Year**
		Pre	**Post**		
Complete Blood Count • White Blood Cell Count • Red Blood Cell Count • Hemoglobin • Hematocrit	X			X	
Platelet count	X			X	
Urea and Creatinine	X	X*	X**	X	X
BNP ***or*** ProBNP	X			X	X
INR (if subject is on Coumadin/Warfarin)	X				
Troponin ***or*** CK, CK-MB	X				
Albumin	X				X

** Within 72 hours before index procedure*
***Within 48 hours after index procedure*

5.11 Imaging

Echocardiographic examinations will be conducted at the intervals indicated in Table 3 of this Clinical Investigation Plan. Each site is responsible for performing the echocardiogram according to the Echocardiographic Protocol.

Echocardiographic examinations will be forwarded to the Echocardiographic Core Laboratory for interpretation. It is the responsibility of each site to perform the local interpretation of the echocardiogram for clinical assessment.

The Echocardiographic Core Laboratory will not be responsible to notify the site of any abnormal findings that are identified in the echo study. The responsibility of the Echocardiographic Core Laboratory is to complete the echocardiography data collection forms and submit these to the Sponsor.

The Echocardiographic Core Laboratory will provide the study required interpretation and documentation of each echocardiogram submitted. Data obtained from the core laboratory readings will be used for study purposes only and not for clinical treatment of the subject. Abbott will use only the measurements from the Echocardiographic Core Laboratory for analysis. If the Core Laboratory determines the echocardiogram is unreadable, the site will be responsible for having the subject return for another echocardiogram.

5.12 Medications

The subject's use of the following medications will be collected at each visit:

- Beta Blockers
- Calcium Channel Blockers
- Anticoagulants
- Antiplatelet agents including Aspirin
- Diuretics
- ACE Inhibitors
- Angiotensin Receptor Blockers (ARBs)

5.13 Description of Activities Performed by Sponsor Representatives

Trained Sponsor personnel may perform certain activities to ensure compliance to the clinical investigational plan and may provide technical expertise during the implant procedure.

5.14 Subject Study Completion

When the subject's participation in the clinical study has been completed the subject will return to the medical care as per physician's recommendation.

5.15 Subject Withdrawal

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 relationship with the Investigator. Subjects will be asked to specify the reason for the termination, but have the right not to answer.

The Investigator may decide to withdraw a subject from the study at any time with reasonable rationale. The subject's future care will not be influenced 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 study.

Reasons for subject's withdrawal include, but are not limited to:

1. Subject refuses to continue participating in the study
2. Subject does not have a delivery system enter his or her body
3. Subject does not meet the inclusion/exclusion criteria and does not require additional follow-up for safety reasons.
4. Subject is deceased (cause must be documented)
5. Subject's non-compliance
6. Subject's participation is terminated by the PI or Investigator, although the subject consented, since participation is no longer medically appropriate

Every effort will be made to obtain follow-up data. Potential methods of subject tracking should be documented and may include:

- Attempting to contact the subject by multiple phone calls and letters documented at the site
- Mailing a registered letter to the subject's last known address requesting that the subject contact the site

If a subject cannot be located after at least two documented contact attempts, the patient's general practitioner shall quickly be contacted to investigate about the subjects whereabouts and its health status.

Note: If a subject misses one or more of the scheduled follow up visits (inclusive of the assigned visit windows), this will be considered as a missed visit. The subject may therefore still return for subsequent visits and will not be excluded from the study.

If a subject withdraws from the clinical study, the site will record the subject's reasons for withdrawal, on a Withdrawal CRF.

When subject withdrawal from the clinical study is due to an adverse event the subject will be followed until resolution of that adverse event or determination that the subject's condition is stable. The status of the subject's condition should be documented at the time of withdrawal.

6.0 Statistical Considerations

The following section describes the statistical methods for the clinical investigation and justification of the design.

6.1 General Statistical Methods

Baseline and procedural data will be presented using appropriate descriptive statistics. Continuous data will be summarized using descriptive statistics including mean, standard deviation, median and range. Categorical data will be summarized by the frequencies and percentages in the corresponding categories.

6.2 Endpoints

6.2.1 Primary Endpoint

The primary safety endpoint is major vascular complications through 30 days, as defined by the Valve Academic Research Consortium[iii] (VARC-2) for each access arm of the study.

6.2.1.1 Analysis Methodology

The proportion of subjects experiencing a primary safety endpoint through 30 days (less than or equal to 30 days) post implant will be estimated as the number of subjects who experience the safety endpoint divided by the total number of subjects in the analysis population (see Section 6.2.1.2). The 95% upper confidence limit for the proportion of subjects experiencing a primary safety endpoint will be calculated using the exact binomial method.

6.2.1.2 Analysis Population

All subjects who have received a Patient Information Sheet, and signed an Informed Consent Form and Data Protection Form will be considered enrolled in the study. However, the analysis population will be based on subjects who have provided signed Informed Consent Form and Data Protection Form and had the SJM TAVI delivery system enter his/her body. The anticipated dropout rate for this study population is expected to be low, as part of the selection criteria is subject compliance with all follow-up visits. Subjects that withdraw from the investigation or are lost to follow-up will not be replaced in the analysis dataset.

It is anticipated that there may be subjects who are enrolled in the study but are not included in the analysis population. There may be subjects who gave consent to participate in the study but did not satisfy the baseline inclusion exclusion criteria, these are considered screen failures. There may also be subjects who have enrolled in the study and started the procedure, but do not have the SJM TAVI delivery system enter his/her body and are procedural exclusions due to their anatomy, circumstances related to the procedure, or physician judgment; these are considered to be procedural exclusion subjects. Screen failure subjects and procedurally excluded subjects will not be part of the analysis population.

In general, data analysis will be performed based on the analysis population on a per subject basis. If more than 1 device has entered the subject's body, the data analysis may be summarized on a per device basis, as appropriate.

6.2.2 Secondary Endpoints

The following endpoints will be summarized using descriptive statistics for each access arm of the study.

Event rates at 30 days for all-cause mortality, cardiovascular mortality, disabling stroke, non-disabling stroke, life threatening bleeding requiring transfusion, and acute kidney injury requiring dialysis and composite of periprocedural encephalopathy/all stroke/and all TIA:

The count and proportion of subjects who experience each of above endpoints as adjudicated by the CEC through 30 days post implant will be summarized. Subjects in the analysis population defined in section 6.2.1.2 will be included in the analysis.

Event rates at one year for all-cause mortality, cardiovascular mortality and disabling stroke:

Kaplan-Meier survival analysis will be used to estimate the event rates of all cause mortality, cardiovascular mortality and disabling stroke at one year post implant. Subjects in the analysis population defined in section 6.2.1.2 will be included in the analysis. The index procedure (TAVI) day is considered Day 0. The time-to-event will be determined from the date of index procedure to the first occurrence of the event for subjects experiencing the event, or, for those subjects not experiencing the event, to the last date they are known to be free of the event (this usually will be the last follow-up, contact date, or death date).

Rate of moderate or severe aortic regurgitation at one year:

The count and proportion of subjects with moderate or severe aortic regurgitation at one year will be summarized.

Functional improvements in NYHA classification, 6 minute walk test and EOA will be compared at 30 days:

Changes of NYHA classification, 6 minute walk and EOA at 30 days from baseline will be summarized using descriptive statistics.

Acute device success:

The count and proportion of subjects with acute device success (see Section 4.3.2) will be summarized.

6.3 Sample Size

The sample size of 45 subjects for each access route is based on the desire to estimate the rate of 30-day vascular complication with a sufficient degree of precision. The rate of major vascular complications at 30 days in Portico TF EU study was 5.9%. The rate of major vascular complications reported for other TAVI valves at 30 days in a weighted meta-analysis of 3,519 patients from 16 studies ranged from 5.0% to 23.3%[24]. The same meta-analysis calculated a major vascular complication pooled estimate 30-day rate of 11.9% (95% CI 8.6%-16.4%[24]). Assuming an event rate of 5.9%, with 45 subjects, the exact 90% CI is (1.45%, 15.32%). Therefore, a sample size of 45 will result in the 90% confidence interval half-width of 9.42% and the 95% upper confidence limit is within the range reported in the literature

To ensure enrollment balance, each investigational center cannot enroll more than 50% of sample size (23) of each access arm without the prior written approval of the Sponsor.

6.4 Justification of Clinical Investigation Design

The Portico valve has demonstrated safety and favorable clinical results via TF access in the TF EU Portico Trial (n=222). The study will evaluate the safety of alternative access for the approved Portico transcatheter aortic and includes a primary safety endpoint of major vascular complications at 30 days. This endpoint is appropriate because vascular access is the only new aspect being investigated in this study and 30-days has been established by VARC2 as the appropriate time period to assess early safety events such as major vascular complications[25].

Numerous studies have demonstrated that vascular complication rates at 30 days with ALT access are similar to that of the TF approach[26-27] and that survival at 1 and 2 years is similar between the subclavian and the TF approach[28]. The sample size of 45 subjects is adequate to ensure that the rate of the primary endpoint, major vascular complications at 30 days, is consistent with the rate for Portico valves delivered by TF access as well as with rates reported in the literature.

6.5 Timing of Analysis

CE Mark will be submitted for each access route. The analyses for CE Mark report will be conducted separately for each access route on datasets locked after 45 subjects in each access route have had the 30-day study visit (excepting deaths, withdrawals and loss-to-follow-up before 30 days) or crossed the 30-day visit window without a visit (missed visit).

6.6 Success Criteria

The study has one primary endpoint without formal hypothesis. The primary endpoint result will be compared with data reported in the literature and is expected to fall within the range of 5-23.3[24]% (pooled estimate 11.9% and CI 8.6%-16.4%).

6.7 Interim Analysis

No interim analyses are planned for this study.

6.8 Statistical Criteria for Termination

There are no statistical criteria for termination of this study.

6.9 Deviations from Statistical Plan

If any deviations from the original statistical plan occur, such deviations will be documented in the clinical study report or statistical report containing the analysis results.

7.0 Study Committees

7.1 Clinical Event Committee (CEC)

An independent CEC will be established for the trial. The primary function, responsibilities and membership will be described in detail in a CEC charter.

7.2 Subject Selection Committee

The Subject Selection Committee will consist of cardiac surgeons and interventionalists who will be responsible for ensuring subject eligibility for implant according to the protocol. After study

Informed Consent Form and Data Protection Form are obtained and study eligibility is confirmed, subject data will be reviewed by the Subject Selection Committee prior to the implant procedure to confirm, risk assessment, echo and CT measurements. CT Imaging, will be reviewed to ensure acceptable annular measurements for the Portico Transcatheter Heart Valve.

The Subject Selection Committee's decision on whether to include the subject in the study must be documented and communicated to the enrolling site by the Sponsor. If the Subject Selection Committee considers the subject ineligible for implant, the subject will be withdrawn from the study and the reason for exclusion documented.

The membership and process is further defined in the Subject Selection Committee Charter.

8.0 Risks and Benefits of the Clinical Study

8.1 Anticipated Clinical 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. In addition, these or additional benefits may occur to future subjects through experience gained in this clinical study.

8.2 Anticipated Adverse Events and Adverse Device Effects

Anticipated adverse events associated with any transcatheter aortic valve placement may include, but are not limited to:

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:

- Transfusion
- Conversion to open surgical procedure
- Reoperation or re-intervention
- Emergent balloon valvuloplasty
- Emergent percutaneous coronary intervention (PCI)
- Emergent surgery (i.e., coronary artery bypass, heart valve replacement)
- Explantation of the valve

- Permanent Disability
- Death
- Permanent Pacemaker implantation
- Valve in valve implantation

There are no known interactions of the Portico TF or ALT Delivery System with concomitant medical treatment.

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

There may be additional risks that are unknown at this time and risks that are unanticipated. Further study related tests which are not standard of care for a TAVI procedure have added risks which may include:

Six minute walk test: the possible risks from this test are that the subject 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 the subject experiences chest pain, intolerable shortness of breath, leg cramps or pale appearance.

Blood work: the risk of inserting a needle into a vein in the subjects 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: 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 an echocardiogram there may be discomfort from the pressure of the transducer as the images are taken.

8.3 Residual Risks Associated with the Device Under Investigation

An analysis of the risks associated with the design of the TF and ALT Delivery systems have been performed.

The benefit of using a transcatheter aortic valve via alternative access in high-risk and/or inoperable patients outweighs the residual risks associated with TAVI treatment. The inoperable patient population is at an increased risk of death despite maximal medical therapy. In clinical practice, at least 30% of the high-risk patient population with severe aortic stenosis does not undergo surgery,[1-3] so TAVI provides a less invasive treatment option, with similar outcomes to surgery.[4]

The unique features of the TF and ALT Delivery systems include the ability to resheath, reposition, and redeploy to allow for optimal placement at the implant location prior to full deployment. These design features may reduce the risk of adverse events related to misplacement and adjustments made post implant.

Abbott's final opinion is that the residual risks associated with the TF and ALT Delivery systems are outweighed by the potential benefit for use in patients with an increased risk of death despite maximal medical therapy.

9.0 Requirements for Investigator Records and Reports

9.1 Deviations from CIP

A deviation is defined as an event where the clinical investigator, site personnel, Sponsor or Sponsor representative did not conduct the clinical study according to the Clinical Investigational Plan, EC requirements or the Investigator Agreement.

Deviations from the CIP should be avoided, except in cases where the investigator determines that adhering to the CIP might expose the subject to unreasonable risks.

Regulations require that the PI maintain accurate, complete, and current records, including documents showing the date of and reason for every deviation from the Clinical Investigational Plan. Relevant information for each deviation will be documented on a Deviation Case Report Form. The site will submit the CRF to Abbott.

Regulations require Investigators obtain approval from Abbott and the EC [as required] before initiating changes in or deviations from the protocol, except when necessary to protect the life or physical well-being of a subject in an emergency. Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Sponsor and the EC. Such deviations shall be documented and reported to the Sponsor and the EC as soon as possible, but no later than 5 working days.

Prior approval must be requested when the PI anticipates, contemplates, or makes a conscious decision to depart from the CIP, except when unforeseen circumstances are beyond the Investigator's control (e.g. a subject who fails to attend a scheduled follow-up visit, a subject is too ill to perform a CIP-required test, etc.). All deviations, including those beyond the Investigator's control, must be reported on a CRF.

To obtain approval, the Principal Investigator may call or email and discuss the potential deviation with Abbott or designee prior to initiating any changes.
All deviations must be reported to appropriate regulatory authorities in specified timelines (if appropriate).

9.2 Safety Reporting

Safety surveillance and safety reporting for this study are both performed by the Investigator (per the local country requirements) and starts as soon as the subject is enrolled in this study (date of signature of the informed consent). German requirements are outlined in Appendix M. Safety surveillance and safety reporting will continue until the last investigational visit has been performed, the subject is deceased, the subject/investigator concludes his participation into the study or the subject/investigator withdraws the subject from the study, except as otherwise specified in the CIP.

All reportable adverse event data including deaths and device deficiency data will be collected throughout the clinical study and will be reported to the Sponsor through the EDC system. The Investigator will record all reportable adverse events and device deficiencies on the appropriate case report forms.

Records relating to the subject's subsequent medical course must be maintained and submitted (as applicable) to the Sponsor until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained. Adverse events will be monitored until they are adequately resolved, the subject is withdrawn, or completes the study. The status of the subject's condition should be documented at each visit.

The Investigator will report the event to the EC per their reporting requirements.

Reportable events to Sponsor are:
1. Endpoint VARC-2 events
   - Death
   - Vascular complications
   - Stroke/TIA
   - Life threatening bleeding requiring transfusion
   - Acute kidney injury requiring dialysis
2. All Adverse Device Effects
3. All Serious Adverse Events (whether or not the event is considered device or procedure related)
4. Device deficiencies, that could have led to a serious adverse device effect
   - if either suitable action had not been taken
   - if intervention had not been made or
   - if circumstances had been less fortunate

Non-serious adverse events documentation and reporting are limited to cardiovascular and neurovascular events; they all have to be reported regardless of their relationship with the device or the procedure. All above events will be reported to the Sponsor, as soon as possible, but no later than 72 hours of first learning of the event.

The Sponsor will ensure that all events and device deficiencies are reported to the relevant authorities as per regulations.

The following information should be collected for each event:
1. Date AE occurred
2. Date the center, Investigator, became aware of the event
3. Main symptoms of the event
4. Treatment
5. Seriousness
6. Relationship to device and/or procedure
7. Status

Additional information may be requested, when required, by the Sponsor in order to support the reporting of AEs to regulatory authorities.

If required by national and local laws or regulations, the Investigator must notify the EC of the AEs reported to the Sponsor.

All adverse events will be reported as per applicable regulatory requirements.

9.2.1 Subject Death

All subject deaths are to be documented and reported to the Sponsor within 72 hours after becoming aware of the event.

The subject death CRF should always be accompanied with the relevant adverse event CRF and relevant source documentation. In the event of a subject death, an autopsy should be performed whenever possible and the Portico valve explanted and returned to Abbott for evaluation. Death summaries and autopsy reports should be provided to Abbott.

9.2.2 Device Deficiency (DD)

During the trial, the Investigator will be responsible for reporting all device deficiencies. A device deficiency is defined as an inadequacy of a medical device with respect to its identity, quality,

durability, reliability, safety or performance and includes malfunctions, user errors and inadequate labeling.

If the device deficiency involves an adverse event, the Principal Investigator must complete an adverse event form including information on the device deficiency and report to the Sponsor within 5 days after becoming aware of the event. If the device deficiency does not involve an adverse event, then the Investigator must complete the device deficiency form within 5 days after becoming aware of the event

9.3 Records Retention

The Principal Investigator will maintain all clinical study documents from prior, during and (as specified) after the clinical study on file at the site for a minimum of 15 years after the termination of this study, or longer as per local laws, or when it is no longer needed to support a marketing application, whichever is later.

The PI must contact the Sponsor prior to destroying or archiving off-site any records and reports pertaining to this study to ensure that they no longer need to be retained on-site.

All original subject files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the site, the Investigator will notify the Sponsor.

All data and documents will be made available on request of the relevant authorities in case of an audit.

The Sponsor will archive and retain all essential clinical study documents from prior, during and (as specified) after the clinical study as per requirements.

10.0 Clinical Data Handling

Overall, the Sponsor will be responsible for the data handling. The Sponsor and/or its affiliates will be responsible for compiling and submitting all required reports to governmental agencies.

Data will be analyzed by the Sponsor and may be transferred to the Sponsor's locations outside of Europe and/or any other worldwide regulatory authority in support of a market-approval application.

Abbott respects and protects personally identifiable information that we collect or maintain. As part of our commitment, Abbott is certified to the U.S. - European Union Framework Agreement regarding human resources and subject clinical trial personal information. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data. Confidentiality of data will be observed by all parties involved at all times throughout the clinical study. All data will be secured against unauthorized access.

The Principal Investigator or institution will provide direct access to source data during and after the clinical study for monitoring, audits, EC review and regulatory authority inspections. As required, the Principal Investigator or institution will obtain permission for direct access to source documents from the subject, hospital administration and national regulatory authorities before starting the clinical study.

10.1 Data Management Plan

A detailed Data Management Plan will be established, prior to study initiation, to ensure consistency of the data. This document will include procedures used for data review, database cleaning, issuing and resolving data queries, study/database closeout, and data export for

statistical analysis. If appropriate, the DMP may be updated throughout the study duration. All revisions will be tracked and document controlled.

CRF data will be captured in a validated electronic database management system hosted by Abbott.

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

10.2 Document and Data Control

10.2.1 Traceability of documents and data

The investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the Sponsor on the CRFs and in all required reports.

10.2.2 Recording data

Source documents will be created and maintained by the investigational site team throughout the clinical study.

The data reported on the CRFs will be derived from, and be consistent with, these source documents, and any discrepancies will be explained in writing.

Required CRFs will be signed by authorized site personnel.

11.0 Monitoring

Monitoring will be conducted by trained and experienced clinical representatives according to the Abbott Clinical Monitoring standard operating procedure.

Prior to beginning the study, Abbott will contact the investigator or designee to discuss the study and data requirements during a site initiation visit.

After enrollment begins, a Abbott monitor will periodically review the subject records and associated source documents. Each actively enrolling site will be visited at least annually. During these routine visits, the investigator shall make subject and study records available to the clinical monitor for monitoring. There will be 100% source verification on all available source documentation. In case of a subject not being able to be located, the monitor will verify that adequate measures have been undertaken to contact the subject's treating General Practitioner and exchange data about the whereabouts and health status of the subject. Monitoring reports will be created for each visit.

Once all subjects have completed the study a close out visit will be completed.

It is the responsibility of Abbott as the Sponsor of the study to ensure the study is conducted, recorded, and reported according to the approved protocol, subsequent amendment(s), applicable regulations, and guidance documents and to secure compliance from each investigative site as necessary.

Investigators are required to adhere to the protocol, signed investigator agreement and any conditions required by the EC. If a site has long-standing, open monitoring findings or challenges with compliance, the monitor or study management shall consider developing a corrective and preventative action plan.

12.0 Compliance Statement

12.1 Statement of Compliance

The study will be performed in accordance with the most current versions of the World Medical Association (WMA) Declaration of Helsinki, ISO 14155 and any regional and/or national regulations and will be compliant to this International Standard and any regional and national regulations, as appropriate.

The investigator will not start enrolling subjects or requesting informed consent from any subject prior to obtaining EC approval and Competent Authority approval, if applicable, and authorization from the sponsor in writing for the study.

In case additional requirements are imposed by the EC or Competent Authority, those requirements will be followed, if appropriate. If any action is taken by an EC, and regulatory requirements with respect to the study, that information will be forwarded to Abbott.

As Sponsor, Abbott has taken up general liability insurance in accordance with the requirements of the applicable local laws. Appropriate country representative will be utilized to understand the requirements for the type of insurance that will be provided for subjects, such information will be incorporated into the informed consent, as applicable.

12.2 Regulatory Inspections

The investigator and/or delegate should contact Abbott immediately upon notification of a governmental agency inspection at the site. A clinical monitor or designee will assist the investigator and/or delegate in preparing for the audit.

An investigator who has authority to grant access will permit authorized governmental agency 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 any person acting on behalf of such a person with respect to the study, will permit authorized governmental agency employees, at reasonable times and in reasonable manner, to inspect and copy all records relating to the study.

An investigator will permit authorized governmental agency employees to inspect and copy records that identify subjects, upon notice that governmental agency 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 EC have not been submitted or are incomplete, inaccurate, false or misleading.

12.3 Repeated and Serious Non-Compliance

In the event of repeated non-compliance or a one-time serious non-compliance, as determined by the Sponsor, a Clinical Research Associate or clinical representative will attempt to secure compliance by one or more of the following actions:

- Visiting the Investigator
- Contacting the Investigator by telephone
- Contacting the Investigator in writing
- Retraining of the Investigator

If an investigator is found to be repeatedly non-compliant with the signed agreement, the CIP or any other conditions of the clinical study, the Sponsor will either secure compliance or, at its sole discretion, terminate the Investigator's participation in the clinical study.

13.0 Core Lab

Echocardiographic examinations will be forwarded to an echocardiographic core laboratory for interpretation. It is the responsibility of each site to perform the local interpretation of the echocardiogram for clinical assessment. The echocardiographic core laboratory will not be responsible to notify the site of any abnormal finding that are identified in the echo study.

The echocardiographic core laboratory will provide the study required interpretation and documentation of each echocardiogram submitted to the Sponsor. Data obtained from the core laboratory readings will be used for study purposes only and not for clinical treatment of the subject.

14.0 Suspension or Premature Termination of the Clinical Investigation

The Sponsor reserves the right to terminate the clinical investigation at any stage, with appropriate written notice to the investigators, ECs and relevant Regulatory authorities, if required.

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

If suspicion of an unacceptable risk to subjects arises during the clinical investigation in either arm of the study or when so instructed by the EC or regulatory authority, the Sponsor may suspend the clinical investigation while the risk is assessed.

Termination criteria are set based on a maximum allowable number of major vascular complications through 30 days across the two study arms. The study will continue in the arm of the study not under suspension. The Sponsor will terminate the clinical investigation if an unacceptable risk for major vascular complications through 30 days is confirmed with accumulating data as noted in the table below. The termination criterion is selected to be x events such that the probability of observing x or more events is < 0.05 assuming that the number of events follows a binomial distribution with event probability 0.119. This event probability is based on the 30-day rate of major vascular complications reported in the literature (see Section 6.3).

If the Sponsor completes an analysis of the reasons for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, the Sponsor will inform the Principal Investigators, EC, or regulatory authority, where appropriate, of the rationale, providing them with the relevant data supporting this decision. Approval from the EC or regulatory authority, where appropriate, will be obtained before the clinical investigation resumes. If subjects have been informed of the suspension, the Principal Investigator or authorized designee will inform them of the reasons for resumption.

Number enrolled (n)	Number of events (major vascular complications through 30 days) to	Probability of observing ≥ x events

	meet termination criteria (x)	
20	6	0.0251
30	8	0.0211
40	9	0.0423

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

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

14.1 Study Conclusion

The study will be concluded when:
1. All sites are closed AND
2. The final report generated by Abbott has been provided to sites or Abbott has provided formal documentation of study closure

15.0 Publication Policy

The results of the clinical study will be submitted, whether positive or negative for publication.

A 'Publication Agreement' will be signed between the Principal Investigator and the Sponsor either as a separate Publication Agreement or within the Clinical Trial Agreement.

For more information on publication guidelines, please refer to the International Committee of Medical Journal Editors (ICMJE) on www.icmje.org.

This study will be posted on ClinicalTrials.gov and results will be posted on ClinicalTrials.gov as required.

Appendix A: Abbreviations

Select or add abbreviations used

Abbreviation	Term
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
CA	Competent Authority
CEC	Clinical Events Committee
CIP	Clinical Investigational Plan
CRF	Case Report Form
DD	Device Deficiency
DMP	Data Management Plan
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMEA	Europe, Middle East, Africa
IB	Investigator Brochure
ICMJE	International Committee of Medical Journal Editors
ISO	International Organization for Standardization
MP	Monitoring Plan
NA	Not Applicable
PI	Principal Investigator
RDC	Remote Data Capture
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SJM	St. Jude Medical
USADE	Unanticipated Serious Adverse Device Effect
WMA	World Medical Association

Appendix B: CIP Revision History

Procedure for CIP Amendments

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

The acknowledgement of the amended CIP by the Steering Committee Co-chairs and the Principal Investigators will be collected on the signature pages.

EC and relevant Regulatory Authorities, if applicable, will approve all amendments to the CIP.

Revision History				
Amendment Number	Version	Date	Rationale	Details
Not Applicable	VA	22 Sep 2016	First release of CIP	NA
	VB	2 Feb 2017	Requested updates from Competent Authority	
	VB	3 Mar 2017	Requested updates from Competent Authority	
	VC (Switzerland only)	31 May 2017	Requested updates from Competent Authority	
	VC (Switzerland only)	22 Jun 2017	Requested updates from Competent Authority	

Appendix C: Bibliography

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Appendix D: Definitions

Cardiovascular Mortality **(VARC2)**	**Any 1 of the following criteria:** • Death due to proximate cardiac cause (e.g., myocardial infarction, cardiac tamponade, worsening heart failure) • Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease • All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure • All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related adverse events • Sudden or unwitnessed death • Death of unknown cause

Myocardial Infarction
 	
(VARC2)
	POST TAVI Definition (VARC2)
	Periprocedural MI (less than or equal to (≤) 72 h after the index procedure)
	New ischemic symptoms (eg, chest pain or shortness of breath), or new ischemic signs (eg, ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, or imaging evidence of new loss of viable myocardium or new wall motion abnormality),
	AND
	Elevated cardiac biomarkers within 72 h after the index procedure consisting of at least 1 sample postprocedure with a peak value exceeding 15x upper reference limit (troponin) or 5x for CK-MB. If cardiac biomarkers are increased at baseline (>99th percentile), a further increase of at least 50% postprocedure is required AND the peak value must exceed the previously stated limit.
	
	Spontaneous MI (greater than 72 h after the index procedure)
	Any 1 of the following criteria:
	• Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least 1 value above the 99th percentile URL, together with evidence of myocardial ischemia with at least 1 of the following:
	  ○ Symptoms of ischaemia
	  ○ ECG changes indicative of new ischemia [new ST-T changes or new Left Bundle Branch Block]
	  ○ New pathological Q waves in at least 2 contiguous leads
	  ○ Imaging evidence of new loss of viable myocardium or new wall motion abnormality
	• Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST-segment elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/ or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
	• Pathological findings of an acute myocardial infarction.

Stroke **(FDA/VARC2)**	This study is following the FDA's definition of Stroke per FDA's Current Thinking Regarding Neurological Assessments for Transcatheter aortic valve Trials (Revised: 25 Aug 2011).

	1. Definitions: a. Stroke: Stroke is an acute symptomatic episode of neurological dysfunction attributed to a vascular cause. 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 VARC2 Definitions): Severity i. Disabling (Major): an mRS score of 2 or more at 90 days and an increase of at least 1 mRS category from an individual's prestroke baseline ii. Non-disabling (Minor): an mRS score of <2 at 90 days or 1 that does not result in an increase of at least 1 mRS category from an individual's prestroke baseline b. Cerebral Infarction: Evidence of brain cell death from imaging studies or pathological examination. If there are clinical symptoms, then it is a stroke; otherwise, it is an asymptomatic cerebral infarction. c. Transient Ischemic Attack (TIA): A transient (less than 24 hrs) episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction. No evidence of infarction if imaging performed. d. Encephalopathy: Altered mental state (e.g., seizures, delirium, confusion, hallucinations, dementia, coma, psychiatric episode). e. Intracranial Hemorrhage: Collection of blood between the brain and skull. Subcategorized as epidural, subdural, and subarachnoid bleeds.
Bleeding **(VARC2)**	**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 2 or 3 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 **<u>Minor bleeding (BARC type 2 or 3a, depending on the severity)</u>** • Any bleeding worthy of clinical mention (eg, access site hematoma) that does not qualify as life-threatening, disabling, or major
Acute Kidney Injury *(AKIN Classification)* **(VARC2)**	Change in serum creatinine (up to 48 h) compared with baseline **<u>Stage 1</u>** Increase in serum creatinine to 150% to 199% (1.5 to 1.99 X increase compared with baseline) or increase of greater than or equal to 0.3 mg/dL (26.4 mmol/L) or Urine output <0.5 mL/kg per hour for >6 but <12 hours **<u>Stage 2</u>** Increase in serum creatinine to 200% to 299% (2.0 to 2.99 X increase compared with baseline) or Urine output <0.5 mL/kg per hour for >12 but <24 hours **<u>Stage 3</u>** Increase in serum creatinine to greater than or equal to 300% (3 X increase compared with baseline) or serum creatinine of ≥ 4.0 mg/dL (354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L)or Urine output <0.3 mL/kg per hour for ≥24 hours or anuria for ≥12 hours. *Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.*
Vascular Access Site and Access-Related Complications (VARC2)	**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, arteriovenous 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, arteriovenous fistula, pseudoaneuysms, hematomas, percutaneous closure device failure) ***not leading to*** death, life-threatening or major bleeding*, visceral ischaemia or neurological impairment or

	• Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage or • Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication or • Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft) or **Percutaneous closure device failure** Failure of a closure device to achieve haemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)
Acute Device Success (VARC)	Acute device success is defined as a subject who achieves a) successful vascular access, delivery and deployment of the device and successful retrieval of the delivery system, b) correct position of the device in the proper anatomical location, c) intended performance of the prosthetic heart valve, and d) only 1 valve implanted in the proper anatomical location. 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.

Prosthetic Valve Stenosis Criteria ***In conditions of normal or near normal stroke volume (50–70 ml).*** **(VARC2)**	**Parameter**	**Normal**	**Mild Stenosis**	**Moderate/severe Stenosis**
	Peak velocity (m/s)	less than 3	3–4	greater than 4
	Mean gradient (mm Hg)	less than 20	20–40	greater than 40
	Doppler velocity index	greater than or equal to 0.35	0.35–0.25	less than 0.25
	Effective orifice area (cm^2)	greater than 1.1*	1.1–0.8	less than 0.80

Prosthetic Valve Regurgitation Criteria (Central and Paravalvular)	**Parameter**	**Mild**	**Moderate**	**Severe**
	Valve structure and motion	Usually normal	Usually abnormal	Usually abnormal
	Left ventricular size	Normal	Normal/mildly dilated	Dilated
	Doppler parameters ***(qualitative or semiquantitative)***			

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

(VARC2)	*Jet width in central jets (% LVO diameter): color*	Narrow (less than or equal to 25%)	Intermediate (26%–64%)	Large (greater than or equal to 65%)
	Jet density: CW Doppler	Incomplete or faint	Dense	Dense
	Jet deceleration rate (PHT, ms): CW Doppler	Slow (greater than 500)	Variable (200–500)	Steep (less than 200)
	LV outflow vs. pulmonary flow: PW Doppler	Slightly increased	Intermediate	Greatly increased
	Diastolic flow reversal in the descending aorta (semi-quantitative parameters)			
	PW Doppler	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic
	Circumferential extent of paraprosthetic AR	less than 10%	10–29%	greater than or equal 30%
	Doppler parameters *(quantitative)*			
	Regurgitant volume (ml/beat)	less than 30%	30–59%	greater than or equal 60%
	Regurgitant fraction	less than 30%	30–49%	greater than or equal 50%

Non-study Specific Definitions

Adverse Event (AE)
Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device under study.

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

Serious Adverse Event (SAE)
An adverse event that led to:
1. Death
2. A serious deterioration in the health of the subject, that either resulted in:
   - A life-threatening illness or injury OR

- A permanent impairment to a body structure or a body function OR
- An in-patient or prolonged hospitalization OR
- A medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function OR
- Fetal distress, fetal death or a congenital abnormality or birth defect

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

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

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

This definition includes any event resulting from the use error or from intentional misuse of the investigational medical device.

Serious Adverse Device Effect (SADE)
Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Unanticipated Serious Adverse Device Effect (USADE)
A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Device Deficiency (DD)
A Device Deficiency is defined as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors and inadequate labeling

Appendix E: Risk Calculations

This clinical study requires the use of 3 surgical risk assessment tools:

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

Appendix F: 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 (*eg, 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	❑

Appendix G: Frality 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 3 evaluations:

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

Katz Index of Independence in Activities of Daily Living Activities

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

Grip strength *Subjects elbow should be at a 90 degree angle without arm supported or resting on table or against chest wall. Each grasp should be completed with the dynamometer in the dominant hand.*
Grasp 1_____ Grasp 2_____ Grasp3_____

Average Grip Strength_____

15 Foot/4.9m Walk

This examination should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The walking course must be 15 Feet/4.9m in length. The time to walk this distance is to be recorded.

_____seconds

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

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

(Appendix, Fried et al)

Appendix H: Scales

These assessments must be completed by a rater who has a current certificate that demonstrates completion of an accredited training program for this stroke scale. Certifications can be completed using the following link: http://StJudeMedical.trainingcampus.net

Modified Rankin Scale (mRS)

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

The purpose of the mRS is to record whether the patient is severely, moderately, or slightly disabled and 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)

Score	Description
5	• Severe disability • Someone needs to be available at all times; • Care may be provided by either a trained or an untrained caregiver *Question: Does the person require constant care*?
4	• Moderately severe disability • Need for assistance with some basic activities of daily living, but does not require constant care *Question: Is assistance essential for eating, using the toilet, daily hygiene, or walking?*
3	• Moderate disability • Need for assistance with some instrumental activities of daily living but not basic activities of daily living. *Question: Is assistance essential for preparing a simple meal, doing household chores, looking after money, shopping, or traveling locally?*
2	• Slight disability; • Limitations in participation in usual social roles • Independent for activities of daily living. *Questions: Has there been a change in the person's ability to work or look after others if these were roles before stroke? Has there been a change in the person's ability to participate in previous social and leisure activities? Has the person had problems with relationships or become isolated?*
1	• No significant disability • Symptoms present but no other limitations. *Question: Does the person have difficulty reading or writing, difficulty speaking or finding the right word, problems with balance or coordination, visual problems, numbness (face, arms, legs, hands, feet), loss of movement (face, arms, legs, hands, feet), difficulty with swallowing, or other symptom resulting from stroke*?
0	• No symptoms at all

	• No limitations and no symptoms

National Institute of Health Stroke Scale (NIHSS)

The National Institutes of Health Stroke Scale (NIHSS) is a systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit. The NIHSS was developed in 1983 by NIH-sponsored stroke research neurologists.

NIHSS Administration Process
The NIHSS items are to be administered in the designated order. This helps to maintain the tool's reliability or reproducibility and validity. Performance in each category is to be recorded after each subscale exam. Examiners should not go back and change any scores and the examiner must always score the patient's first attempt. Some patients may later correct an error, but scores should not be changed. Examiners are to follow the directions provided for each exam technique. Scores recorded 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 (ie, repeated requests to patient to make a special effort).

NIHSS Item Instructions & Scale Definitions
The first group of items on the NIHSS is intended to assess wakefulness or level of consciousness (LOC). A decrease in a patient's LOC can indicate deterioration in clinical status. The pathophysiology for this decline can be metabolic (hypoxia, systemic organ failure, toxins, infections or ischemia), structural (injury or compression of the brainstem, as a result of direct mass lesions, such as intracranial hematomas or secondary mass volume such as cerebral edema), or a combination of the two.

1a. Level of Consciousness
This is an evaluation of the overall impression of alertness. The examiner assesses the patient's response to random verbal stimuli. The Investigator must chose a response if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.

Scale Definition:
0 = Alert; keenly responsive.
1 = Not alert; but arousable by minor stimulation to obey, answer, or respond.
2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped.)
3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid and areflexic.

1b. LOC Questions
The patient is asked the month and his/her age. The answer must be correct — there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier, or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.

Scale Definition
0 = Answers both questions correctly.
1 = Answers one question correctly.
2 = Answers neither question correctly.

1c. LOC Commands
This evaluates the patient's ability to follow one-step commands. The patients is asked to open and close his or her eyes and then to grip and release the non-paretic hand. The examiner may substitute another simple 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 the command, the task should be demonstrated to the patient and the result scored. Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands and only the first attempt is scored.

Scale Definition
0 = Performs both tasks correctly.
1 = Performs one task correctly.
2 = Performs neither task correctly.

The second and third items of the NIHSS are intended to evaluate a stroke patient's vision. Visual field cues and impaired eye movements are frequently demonstrated by patients with acute stroke.

2. Best Gaze
This item evaluates extraocular movements. Abnormal findings can indicate pathophysiology involving the frontal lobe, brainstem, cerebellar or vestibular dysfunction or generalized dysfunction of the cerebral cortex.

Only horizontal eye movements are tested, however these can be voluntary or reflexive. If the patient is alert and able to follow commands, the evaluator will ask the patient to follow his or her fingers with his or her eyes from left of midline to right of midline while keeping the head still. A patient with pre-existing blindness can be asked verbally to move the eyes to the right, left, up and down. If the patient does not understand or attend to command, gaze can be assessed by establishing eye contact and then moving one's face to the right and left of midline. If the patient is unresponsive, this item can be scored using the oculocephalic reflex (dolls eyes maneuver.) This technique requires the rapid rotation of the patient's head side to side with the eyelids held open and observing for movement in the direction opposite to the head turn.

Scale Definition
0 = Normal. Able to move both eyes left to right across midline.
1 = Partial gaze palsy. Gaze is abnormal in one or both eyes, but forced deviation, or total gaze paresis is not present. Able to move one or both eyes, but may not be able to cross midline.
2 = Forced deviation. Total gaze paresis is not overcome by the oculocephalic maneuver.

3. Best Visual.
This item is a visual field assessment. Abnormalities here usually arise from damage of the optic radiations or occipital lobes. This item tests the upper and lower quadrants of vision by confrontation exam. The examiner positions himself or herself opposite the patient's face. The

patient is then asked (while looking at the examiners nose) to count the fingers of the examiner as they are introduced in the patient's visual field quadrants. Patients can be encouraged as appropriate. Stroke patients who are unable to understand these instructions can be evaluated by response to moving fingers displayed by confrontation. These patients will often look in the direction of moving fingers displayed by the assessor in the four quadrants without comprehension of the examination. Such patients can also be tested by visual threat. This is done by introducing a striking hand threat into the patient's visual fields. A blink response implies that vision is intact. If there is unilateral blindness or enucleation, the test is completed for the functioning eye.

Scale Definition

0 = No visual loss.

1 = Partial hemianopia. Includes loss in only one quadrant.

2 = Complete hemianopia. Loss of vision in both top and bottom quadrants on the right or left side of a patient's visual field.

3 = Bilateral hemianopia. Blindness of any cause, including cortical blindness, or if visual loss is noted on both right and left sides of the visual fields.

The next several items of the NIHSS are intended to assess voluntary movement of the stroke patient.

4. Facial Palsy.

This item evaluates symmetry or equality of facial movement. Facial asymmetry is often seen even in minor strokes and can be the first clue to the presence of swallowing difficulties or dysphasia. The examiner asks the patient or gestures for the patient to show his or her teeth, raise eyebrows and squeeze eyes closed. In poorly responsive patients or patients who are unable to follow commands or gestures, painful stimuli can be introduced by a sterna rub and a grimace can be evaluated. If facial trauma/bandages orotracheal tape, or other physical barriers obscure the face, these should be removed to the extent possible. Pathologic findings on this item indicate a lower motor neuron lesion of ipsilateral cranial nerve VII. Bilateral findings can indicate brainstem lesions.

Scale Definition

0 = Normal. Symmetrical movements.

1 = Minor paralysis. Flattened nasolabial fold, asymmetry on smiling.

2 = Partial paralysis. Total or near-total paralysis of lower face.

3 = Complete paralysis of one or both sides of face. Absence of movement in the upper and lower face.

5. Motor Arm. (a. Left Arm, b. Right Arm)

This item evaluates symmetry of voluntary movement in both upper extremities. The arms are evaluated one at a time by instructing or demonstrating to the patient to lift his or her arm up (palm up) to a 90 degree angle (45 degrees if lying down.) and holding it up for a count of 10. Gestures or pantomime may be used to gain cooperation of the aphasic or confused stroke patient but noxious stimuli should not be used. The score is determined by the patient's ability to resist gravity. After one extremity is scored, the process is repeated and scored for the opposite extremity. The non-paretic arm is tested first. Only in cases of amputation or joint fusion at the shoulder should an examiner record a score of untestable (UN) and clearly write the reason for this choice.

Scale Definition

0 = No drift. Limb holds 90 (or 45) degrees for a full 10 seconds.

1 = Drift. Limb holds 90 (or 45) degrees, but then drifts down before full 10 seconds; does not hit bed or other support.
2 = Some effort against gravity. Limb cannot get to or maintain 90 (or 45) degrees, drifts down to bed, but has some effort against gravity.
3 = No effort against gravity. Limb falls.
4 = No movements. Flaccid extremities with no effort noted.

6. Motor Leg. (a. Left Leg, b. Right Leg)
This item is evaluated similarly to item 5. Each lower extremity is evaluated separately, beginning with the non-paretic leg. Patients should always be in supine position. The leg is lifted or elevated to 30 degrees off the bed and held for a count of five seconds. The aphasic patient can be encouraged using urgency in the voice or pantomime, but again, no noxious stimuli should be used for this item. Only in the case of amputation or joint fusion at the hip should the examiner record a score of untestable and clearly write the reason for this choice.

Scale Definition
0 = No drift. Leg holds 30 degree position for full five seconds.
1 = Drift. Leg falls by the end of the five second period, but does not hit bed.
2 = Some effort against gravity. Leg falls to bed by five seconds, but has some effort against gravity.
3 = No effort against gravity. Leg falls to bed immediately.
4 = No movement. Flaccid extremities with no effort noted.

7. Limb Ataxia.
This is used to evaluate the stroke patient's coordination of movements which may indicate a unilateral cerebellar lesion. A weakened extremity can appear poorly coordinated when evaluating ataxia, but item 7 is scored as present only if the ataxia or poorly controlled movements are out of proportion to the extremity weakness noted in items 5 or 6. Each limb is evaluated and scored separately with the patient's eyes open. The exam technique is finger to nose or heel to shin testing. The examiner instructs the patient to touch his or her finger to touch the examiner's finger, then to repeatedly touch their nose and retouch the examiner's finger. This is done for each upper extremity and scored. If the patient cannot understand the command or is unable to move his arm, ataxia is scored as absent. Lower extremity ataxia is evaluated by instructing the patient to lift his or her leg and slide the heel of his or her foot down the opposite shin, and repeat the motion at least twice. Only in the case of amputation or joint fusion should the examiner record a score as untestable and the reason should be noted. In case of blindness, test by having the patient touch own nose from extended arm position.

Scale Definition
0 = Absent.
1 = Present in one limb.
2 = Present in two limbs.

8. Sensory.
Sensory and perceptual deficits are common in stroke patients and need to be carefully evaluated to ensure patient safety. Abnormal findings or sensory loss usually indicate lesions or dysfunction involving the contralateral thalamus or parietal lobe cortex. Tactile sensation is tested by sensation or grimace to pin prick or withdrawal to noxious stimulus for the obtunded or aphasic patient. The body areas that should be tested include at least the face, arms (not hands) legs (not feet) and trunk. The ability to sense pin prick from the left to right side is tested

for normal or abnormal feelings, whether it “feels different” from the opposite side. The patient is asked, “Do you feel the pin?” and “Does it feel the same on both sides?” A score of two should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuperous or aphasic patients will therefore probably score 1 or 0. The patient with brainstem stroke with bilateral sensory loss will score 2. If the patient does not respond and is quadriplegic, score 2. Patients in a coma (item 1a = 3) automatically score 2 on this item

Scale Definition

0 = Normal. No sensory loss.

1 = Mild to moderate sensory loss. Patient feels pin prick is less sharp or is dull on the affected side or there is a loss of superficial pain with pin prick, but patient is aware of being touched.

2 = Severe to total sensory loss. Patient is not aware of being touched on the face, arm and leg.

9. Best Language.

Language deficits are known to be common in stroke patients. Disturbances in speech and communication most commonly indicate lesions involving the Brocha’s Area, Wernicke’s Area or the frontal, parietal, or parieto-occipital areas of the left hemisphere. The primary language center is located in the left cerebral hemisphere in most people. A small number of people will have language function centered in the right hemisphere. A great deal of information about comprehension will be obtained in the preceding sections of the examination. The NIHSS uses a standardized set of visual stimuli (pictures, sentences, word list, appendix A) that are shown to the patient, and the patient is instructed to describe the picture, name the objects, read the sentences or say the words. Accommodations for patients with limited vision or education can be made my eliciting enough verbal feedback to introduce stimuli to determine the scoring described below. The examiner may ask the patient to identify common objects placed in the hand or repeat and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a = 3) will score 3 on this item. The examiner must chose a score for the patient with stupor or limited cooperation, but a score of 3 should only be used if the patient is mute and follows no one-step commands.

Scale Definition

0 = No aphasia. Normal fluent speech.

1 = Mild to moderate aphasia. Some obvious loss of fluency or facility of comprehension without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials, examiner can identify picture or naming card content from patient’s response.

2 = Severe aphasia. All communication is through fragmentary expression; great need for inference, questioning and guessing by the listener. Often limited to one-word answers. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response.

3 = Mute. Global aphasia. No usable speech or auditory comprehension.

10. Dysarthria.

This item assesses the quality of the stroke patient’s speech. This exam is done by having the patient read a list of words (Appendix A) or having the patient repeat single words. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. The examiner should record this item as untestable only if the patient in intubated or has other

physical barriers to producing speech and the reason should be clearly recorded. The NIH recommends that the examiner not tell the patient why he or she is being tested.

Scale Definition

0 = Normal

1= Mild to moderate dysarthria. Patient slurs at least some words and at worst, can be understood with some difficulty.

2 = Severe dysarthria. Patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia or is mute.

11. Extinction and Inattention (formerly neglect).

This item primarily evaluates the contralateral parietal lobe cortex. A stroke patient's ability to perceive needs to be evaluated, documented and incorporated into the plan of care as early as possible. The recognition of visual, tactile, special or personal inattention deficits can help prevent patient falls, one of the most common complications after stroke. This item is last on the stroke scale because it requires the examiner to consider information obtained during prior sections of the scale. Sensory information may be sufficient to score a patient, but in situations where abnormalities are not clear, double simultaneous stimulation (DSS) is recommended. To perform tactile DSS testing the patient is first asked to close his or her eyes. The examiner then introduces touch stimuli alternatively from the left to right side. The patient is asked to discriminate which arm or leg is being touched. After a consistent response is produced, the examiner introduces tactile stimulation to both sides at once. The normal individual can identify sensation on both sides. A stroke patient without sensory impairment on individual limb testing may have difficulty with DSS and extinguish or neglect the weaker sensory information on the affected side. Thus, he or she will only feel simultaneous information on the "good" side. If a patient is aphasic but appears to attend to both sides, the score is normal. The concept of DSS is also applicable to visual fields testing and, in cooperative patients, testing of hearing.

Scale Definition

0 = Normal

1 = Visual, tactile, auditory, special or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities.

2 = Profound hemi-inattention or extinction to more than one modality. Patient does not recognize own hand or orients to only one side of space.

Scoring and Outcomes

Upon completion of all items, the examiner compiles the patient's score. Total scores on the NIHSS range from 0 to 42, with higher values reflecting more severe cerebral infarcts. The level of stroke severity as measured by the NIH stroke scale scoring system is further stratified as follows:

- 0= no stroke
- 1-4= minor stroke
- 5-15= moderate stroke
- 15-20= moderate/severe stroke
- 21-42= severe stroke

Appendix I : NYHA Classification

Class I	Patient has cardiac disease but without resulting limitations of ordinary physical activity. Ordinary physical activity (eg, 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 2 blocks or climbing more than 1 flight of stairs results in limiting symptoms (eg, 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 (eg, walking 1 to 2 level blocks or climbing 1 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 J: ATS Guidelines for the Six Minute Walk Test

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

SAFETY ISSUES

1. Testing should be performed in a location where a rapid, appropriate response to an emergency is possible. The appropriate location of a crash cart should be determined by the physician supervising the facility.
2. Supplies that must be available include oxygen, sublingual nitroglycerine, aspirin, and albuterol (metered dose inhaler or nebulizer). A telephone or other means should be in place to enable a call for help.
3. The technician should be certified in cardiopulmonary resuscitation with a minimum of Basic Life Support by an American Health Association–approved cardiopulmonary resuscitation course. Advanced cardiac life support certification is desirable. Training, experience, and certification in related health care fields (registered nurse, registered respiratory therapist, certified pulmonary function technician, etc.) are also desirable. A certified individual should be readily available to respond if needed.
4. Physicians are not required to be present during all tests. The physician ordering the test or a supervising laboratory physician may decide whether physician attendance at a specific test is required.
5. If a patient is on chronic oxygen therapy, oxygen should be given at their standard rate or as directed by a physician or a protocol.

Reasons for immediately stopping a 6MWT include the following: (*1*) chest pain, (*2*) intolerable dyspnea, (*3*) leg cramps, (*4*) staggering, (*5*) diaphoresis, and (*6*) pale or ashen appearance.

Technicians must be trained to recognize these problems and the appropriate responses. If a test is stopped for any of these reasons, the patient should sit or lie supine as appropriate depending on the severity or the event and the technician's assessment of the severity of the event and the risk of syncope. The following should be obtained based on the judgment of the technician: blood pressure, pulse rate, oxygen saturation, and a physician evaluation. Oxygen should be administered as appropriate.

CONTRAINDICATIONS
Absolute contraindications for the 6MWT include the following: unstable angina during the previous month and myocardial infarction during the previous month. Relative contraindications include a resting heart rate of more than 120, a systolic blood pressure of more than 180 mm Hg, and a diastolic blood pressure of more than 100 mm Hg.

Patients with any of these findings should be referred to the physician ordering or supervising the test for individual clinical assessment and a decision about the conduct of the test. The results from a resting electrocardiogram done during the previous 6 months should also be reviewed before testing. Stable exertional angina is not an absolute contraindication for a 6MWT, but patients with these symptoms should perform the test after using their antiangina medication, and rescue nitrate medication should be readily available. A deviation from the Clinical Investigation Plan will need to be collected if the subject is unable to complete this test.

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

PROCEDURE

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

PATIENT PREPARATION
- Comfortable clothing should be worn.
- Appropriate shoes for walking should be worn.
- Patients should use their usual walking aids during the test (cane, walker, etc.).
- The patient's usual medical regimen should be continued.
- A light meal is acceptable before early morning or early afternoon tests.
- Patients should not have exercised vigorously within 2 hours of beginning the test.
- 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. Have the patient stand and rate their baseline dyspnea and overall fatigue using the Borg scale.
2. 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.

Post-test
Record the postwalk Borg dyspnea and fatigue levels and ask this:
"What, if anything, kept you from walking farther?"

1. Record the number of laps from the counter (or tick marks on the worksheet).
2. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.
   Congratulate the patient on good effort and offer a drink of water.

Appendix K : Sample Informed Consent

The consent template will be kept under a separate cover and is available upon request.

Appendix L : Case Report Forms

The case report forms will be kept under a separate cover and are available upon request.

Appendix M. German Handling of Serious Adverse Events

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

1. Definition of SAE according to §2, Section 5 MPSV:
   Serious Adverse Event: any untoward event occurring within a clinical investigation requiring authorization, which directly or indirectly led to, or which might have led or could lead to death or a serious deterioration in the health of the patient, a user or other person, without taking into account whether the event was caused by the medical device.
2. Notification of SAEs:

   - As soon as the investigator becomes aware of an SAE during the course of a study, the sponsor (SJM) must be informed immediately, and in no case later than 72 hours after becoming aware.
   - The sponsor (SJM) also has the obligation to inform the BfArM of all SAEs according to following table.

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

			Annex 3.1 complication rate Please send to MPSAE@bfarm.de Please observe our notes on completing the SAE summary evaluation

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

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

  Example: CRD_878_EU0284_01_160203 for an event which occurred on 3 February for Patient 1 in center EU0284 within the Study CRD_878.
- The German Quarterly Report Template is available on the BfArM Homepage: http://www.bfarm.de/SharedDocs/Formulare/EN/MedicalDevices/sae_template.html
  Table Complication Rates http://www.bfarm.de/SharedDocs/Formulare/EN/MedicalDevices/sae_complication_rates.html
  Instructions for completing the quarterly assessment form for serious adverse events http://www.bfarm.de/SharedDocs/Formulare/EN/MedicalDevices/sae_template_notes.html

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

3. Responsibility of the investigators:

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

4. Responsibilities of the monitor (Abbott):

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

5. Responsibilities of the sponsor

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

6. Responsibilities of the sponsor in Germany

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

7. Notification of SAEs in other countries

SAEs are also reported to following countries

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

[i] Kappetein AP, Head SJ, Genereux P, et al. Updated Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation: The Valve Academic Research Consortium-2 Consensus Document. J Am Coll Cardiol 2012;60:1438-1454.
[ii] Kappetein AP, Head SJ, Genereux P, et al. Updated Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation: The Valve Academic Research Consortium-2 Consensus Document. J Am Coll Cardiol 2012;60:1438-1454.
[iii] Kappetein AP, Head SJ, Genereux P, et al. Updated Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation: The Valve Academic Research Consortium-2 Consensus Document. J Am Coll Cardiol 2012;60:1438-1454.