ACURATE IDE: Transcatheter Replacement of Stenotic Aortic Valve through Implantation of ACURATE in Subjects InDicatEd for TAVR

ACURATE IDE
S2408
CLINICAL INVESTIGATION PLAN
National Clinical Trial Identification Number: NCT03735667

Sponsor:	Boston Scientific Corporation 300 Boston Scientific Way Marlborough, MA 01752 USA European Authorized Representative Boston Scientific International S.A. Le Val Saint-Quentin 2 rue René Caudron, 78960 Voisins le Bretonneux, France Australian Representative Boston Scientific Pty. Ltd. Building 1, Level 6 191 O'Riordan Street Mascot, NSW 2020, Australia

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Original Release: 12-Oct-2018

Current Version: 20-Jan-2023

Revision History

Revision Number	Release Date	Template Version	Reason for Change
A*	12-Oct-2018	90702637 Rev/Ver AJ	Not Applicable
B	10-Jan-2019	90702637 Rev/Ver AJ	See **Table 26.1-1**
C*	21-May-2019	90702637 Rev/Ver AL	
D	31-Jul-2019	90702637 Rev/Ver AL	
E*	08-Jan-2020	90702637 Rev/Ver AL	
F*	11-Feb-2020	90702637 Rev/Ver AL	
G*	25-Feb-2020	90702637 Rev/Ver AL	
H	06-Mar-2020	90702637 Rev/Ver AL	
I	22-Apr-2020	90702637 Rev/Ver AL	
J	18-Nov-2020	90702637 Rev/Ver AO	
K	23-Mar-2021	90702637 Rev/Ver AO	
L	08-Sep-2022	90702637 Rev/Ver AQ	
M	20-Jan-2023	90702637 Rev/Ver AQ	

*Boston Scientific Corporation internal update only; Versions A, C, E, F, and G were not implemented or distributed to clinical centers.

2. Protocol Synopsis

<table>
<tr><th colspan="2">ACURATE IDE: Transcatheter Replacement of Stenotic Aortic Valve through Implantation of ACURATE in Subjects InDicatEd for TAVR</th></tr>
<tr><td>Study Objective(s)</td><td>To evaluate safety and effectiveness of the ACURATE Transfemoral Aortic Valve System for transcatheter aortic valve replacement (TAVR) in subjects with severe native aortic stenosis who are indicated for TAVR.</td></tr>
<tr><td>Planned Indication(s) for Use</td><td>The ACURATE Transfemoral Aortic Valve System is intended to improve aortic valve function in subjects with severe native aortic stenosis who are indicated for TAVR.</td></tr>
<tr><td>Test Device and Sizes</td><td>
<table>
<tr><th colspan="2">ACURATE Transfemoral Aortic Valve System (ACURATE)</th></tr>
<tr><th>Device Name/Size</th><th>Description</th></tr>
<tr><td>ACURATE neo2™ Aortic Valve
Valve size:
- S (small)
- M (medium)
- L (large)
with 23mm, 25mm, and 27mm nominal diameter at waist level, respectively</td><td>Includes 3 main components:
- A three-leaflet porcine pericardial bioprosthetic aortic valve;
- A self-expandable Nitinol stent;
- A double porcine pericardium skirt sutured on the inner and outer surface of the stent to prevent paravalvular leaks.
Introduced via the iliofemoral artery.</td></tr>
<tr><td>ACURATE neo2™ Transfemoral Delivery System
The delivery system is compatible with the S, M, and L valve sizes.</td><td>Allows positioning and delivery of the transcatheter valve via iliofemoral access.</td></tr>
<tr><td>ACURATE Prime™ Aortic Valve XL*
Valve size:
- XL (extra-large)
with 29mm nominal diameter at waist level</td><td>Includes 3 main components:
- A three-leaflet porcine pericardial bioprosthetic aortic valve.
- A self-expandable Nitinol stent.
- A double porcine pericardium skirt sutured on the inner and outer surface of the stent to prevent paravalvular leaks.
Introduced via the iliofemoral artery.</td></tr>
<tr><td>ACURATE Prime™ Transfemoral Delivery System XL*</td><td>Allows positioning and delivery of the transcatheter XL valve via iliofemoral access.</td></tr>
</table>
</td></tr>
</table>

ACURATE IDE: Transcatheter Replacement of Stenotic Aortic Valve through Implantation of ACURATE in Subjects InDicatEd for TAVR	
	<table><tr><td>ACURATE *Prime*™ Loading Kit XL*</td><td>Allows loading of the XL valve onto the delivery system.</td></tr><tr><td colspan="2">* ACURATE *Prime* XL is only available in the United States.</td></tr></table>
Control Device and Sizes	In the Main Randomized Cohort and in the Extended Durability Study (see study cohorts described below), subjects assigned to the control arm will receive a commercially available balloon-expandable SAPIEN 3™ Transcatheter Heart Valve or future iteration (SAPIEN 3; Edwards Lifesciences LLC, Irvine, CA, USA) or a commercially available self-expanding CoreValve® Transcatheter Aortic Valve Replacement System, CoreValve® Evolut™ R Recapturable TAVR System, EVOLUT™ PRO System, or future iteration (CoreValve; Medtronic, Inc., Dublin, Ireland) TAVR device that is introduced via the femoral artery using conventional catheterization techniques. **Note 1:** Every subject in the Main Randomized Cohort and the Extended Durability Study must be deemed treatable with an available size of both the test (ACURATE) device and the control device.
Study Design	ACURATE IDE is a prospective, multicenter trial designed to evaluate the safety and effectiveness of the ACURATE Transfemoral Aortic Valve System for TAVR in subjects who have severe native aortic stenosis and are indicated for TAVR. Study cohorts include the following: • **Main Randomized Cohort:** A prospective, multicenter, 1:1 randomized controlled trial (RCT; ACURATE versus Control [commercially available SAPIEN 3 or CoreValve] TAVR device). Randomization will be stratified by center and by intended control device. • **Roll-In Cohort:** A non-randomized Roll-In phase with the test device. Centers that do not have implantation experience with the ACURATE *neo*™ Aortic Bioprosthesis (transfemoral delivery; Boston Scientific Corporation, Marlborough, MA, USA) will perform at least 2 Roll-In cases with ACURATE *neo2* before commencing treatment in the randomized cohort. Centers with prior experience with ACURATE are not required to do Roll-In cases. Data from Roll-In subjects will be summarized separately from the randomized cohort and will not be included in the primary endpoint analysis.

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	• **4D CT Imaging Substudy:** Selected centers with the ability to perform high quality 4D computed tomography (CT) scans will include subjects from the Main Randomized Cohort in a 4D CT Imaging Substudy to assess the prevalence of reduced leaflet mobility and hypoattenuated leaflet thickening (HALT) and the relationship, if any, to clinical events. Subjects will be randomized to test (ACURATE) and control device. • **ACURATE *Prime*™ XL Nested Registry:** A non-randomized, nested registry cohort of subjects who will receive the ACURATE *Prime*™ Transfemoral Aortic Valve System XL (ACURATE *Prime* XL Nested Registry). Participating centers will be a subset of United States centers that have enrolled subjects in ACURATE IDE. Data from subjects in this nested registry will be summarized separately from the other cohorts. • **ACURATE Extended Durability Study:** An additional 1:1 randomized study (ACURATE versus Control [commercially available SAPIEN 3 or CoreValve] TAVR device) including only subjects considered to be at low surgical risk. Subjects will receive ACURATE *neo2* (S, M, or L valve sizes) or ACURATE *Prime* XL. Randomization will be stratified by center and by intended control device. Low-risk subjects receiving ACURATE *neo2* will be enrolled in the Extended Durability Study only after enrollment of the Main Randomized Cohort is completed. Enrollment of low-risk subjects with ACURATE *Prime* XL will start after enrollment in both the Main Randomized Cohort and the ACURATE *Prime* XL Nested Registry is completed. Data from subjects in the Extended Durability Study will be summarized separately from other cohorts. **Note:** Centers must complete the roll-in phase of the study, if applicable, before participating in the ACURATE Extended Durability Study. • **ACURATE Continued Access Study (CAS):** An additional cohort of subjects receiving ACURATE *neo2* (S, M, and L valve sizes) or ACURATE *Prime* XL. Enrollment of subjects with ACURATE *neo2* will start after enrollment of the ACURATE IDE Main Randomized Cohort is completed. Enrollment of subjects with ACURATE *Prime* XL will start after enrollment in both the Main Randomized Cohort and the ACURATE *Prime* XL Nested Registry is completed. Subjects at all surgical risks may be

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enrolled in ACURATE CAS, but low-risk subjects will be considered for enrollment only after enrollment in the Extended Durability Study is completed. Data from subjects in the ACURATE CAS will be summarized separately from other cohorts and will be used to further assess performance and safety.
Note: Centers must complete the roll-in phase of the study, if applicable, before participating in ACURATE CAS.

The devices and risk levels for the ACURATE IDE cohorts are summarized in the table below.

Devices and Risk Levels for ACURATE IDE Cohorts

Device	Cohort				
	Roll-In	**Main RCT**	***Prime* XL Nested Registry**	**Extended Durability[1]**	**Continued Access Study[1]**
ACURATE *neo2* (S, M, L)	All risks	All risks	N/A	Low risk	All risks[2]
ACURATE *Prime* (XL)	N/A	N/A	All risks	Low risk[3]	All risks[2,3]

Note 1: Enrollment of subjects in the Extended Durability cohort and the CAS cohort will begin after completion of enrollment in the Main RCT.

Note 2: Enrollment of low-surgical-risk subjects in the CAS cohort will begin after completion of enrollment the Extended Durability cohort.

Note 3: Enrollment of subjects receiving ACURATE *Prime* XL in the Extended Durability and CAS cohorts will begin after enrollment completion in both the Main RCT and *Prime* XL Nested Registry.

Abbreviations: CAS=Continued Access Study; N/A=not applicable; RCT=randomized controlled trial

The ACURATE IDE study will be conducted in accordance with 21 CFR Parts 11, 50, and 54; the relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP); the International Standard ISO 14155 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice; ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country/state/local laws and regulations. The study shall not begin until the required approval/favorable opinion from the Institutional Review Board/Research Ethics Board/Human Research Ethics Committee/ Independent Ethics Committee (IRB/REB/HREC/IEC) and/or

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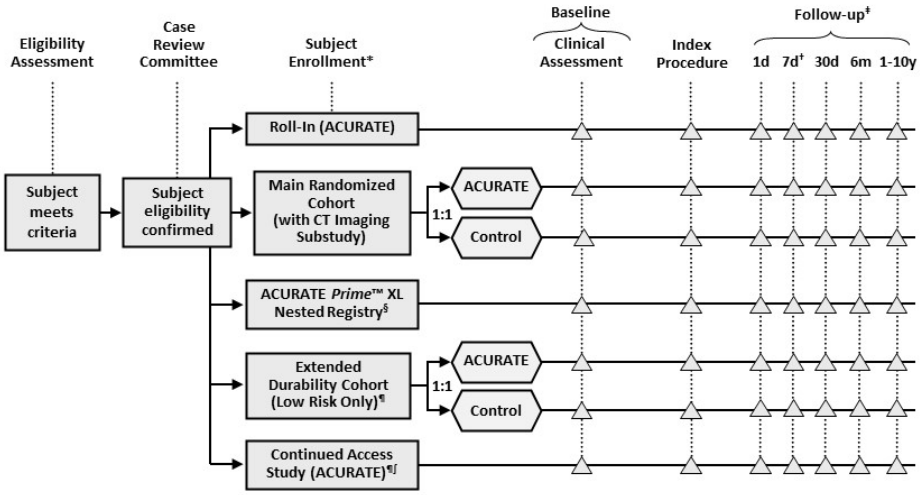
	regulatory authority has been obtained, if appropriate. The study design is summarized in the figure below.  * Randomized subjects are considered enrolled upon randomization; roll-in, ACURATE *Prime* XL Nested Registry, and Continued Access Study subjects are considered enrolled when an attempt is made to insert the ACURATE Transfemoral Aortic Valve System into the femoral artery. † Discharge or 7 days, whichever comes first ‡ Includes clinic/in-person visit or telehealth visit (https://telehealth.HHS.gov) at 30 days, 6 months, and years 1 – 5, 7 & 10; telephone follow-up at years 6, 8 & 9. For subjects in the CT Imaging Substudy, the visits at 30 days and 1 year must be done in the clinic (or in-hospital). Enrolled subjects who do not have a study device implanted will be assessed through 1-year post procedure for safety. § Includes subjects who receive the ACURATE *Prime*™ XL device. ¶ Includes subjects who receive the ACURATE *neo2*™ (S, M, L) device (after conclusion of enrollment in the Main Randomized Cohort) or ACURATE *Prime*™ XL device (after conclusion of XL Nested Registry enrollment). ∫ Low-risk subjects will be considered for enrollment in the Continued Access Study after enrollment is completed in the Extended Durability Study. **ACURATE IDE Study Design Overview**
Planned Number of Subjects and Planned Number of Investigational Centers/ Countries	Subjects will be enrolled at up to 85 centers in the United States, Canada, Australia, and Europe. In total, there will be up to 2820 subjects enrolled in ACURATE IDE across the various cohorts. It is expected that >80% of enrolled subjects will be from the United States. The number of subjects intended for each cohort is shown in the table below. To achieve sufficient distribution of lower risk subjects in the Main Randomized Cohort, there will be ≥ 30% intermediate-risk randomized subjects and ≥ 35% low-risk randomized subjects enrolled. The ACURATE *Prime* XL Nested Registry and the ACURATE Continued Access Study will enroll subjects at all surgical risks. Only low-risk subjects will be enrolled in the ACURATE Extended Durability Cohort.

Cohort	**Number of Subjects**
Main Randomized Cohort	1500*
Roll-In Cohort	Up to 170

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<tr><td></td><td>
<table>
<tr><td>ACURATE Prime XL Nested Registry</td><td>50‡</td></tr>
<tr><td>ACURATE Extended Durability Study</td><td>A minimum of 100†</td></tr>
<tr><td>ACURATE Continued Access Study (CAS)</td><td>Up to 1000§</td></tr>
<tr><td colspan="2">* A subset of subjects (minimum of 200) in the Main Randomized Cohort will also be enrolled in the 4D CT Imaging Substudy.
‡ Subjects will be enrolled at up to 20 centers in the United States.
† Only low-risk subjects will be included in the Extended Durability Study.
§ Low-risk subjects will be considered for enrollment in ACURATE CAS after enrollment is completed in the Extended Durability Study.</td></tr>
</table>
</td></tr>
<tr><td>Primary Endpoint</td><td>Composite of all-cause mortality, all stroke, and rehospitalization† at 1 year.

† Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV); per VARC-2 definition</td></tr>
<tr><td>Additional Measurements</td><td>This section describes required assessments to be performed in the ACURATE IDE study.
Additional measurements based on the VARC[a] endpoints and definitions will be collected peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, 6 months, and annually through 10 years post index procedure, unless otherwise specified below.
• Safety endpoints adjudicated by an independent Clinical Events Committee (CEC):
- Mortality: all-cause, cardiovascular, and non-cardiovascular
- Stroke: disabling and non-disabling
- Myocardial infarction (MI): periprocedural (≤72 hours post index procedure) and spontaneous (>72 hours post index procedure)
- Bleeding: life-threatening (or disabling) and major (through 5 years)
- Acute kidney injury (≤7 days post index procedure): based on the AKIN System Stage 3 (including renal replacement therapy) or Stage 2
- Major vascular complication (through 5 years)
- Repeat procedure for valve-related dysfunction (surgical or interventional therapy)</td></tr>
</table>

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	- Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV) - New permanent pacemaker implantation resulting from new or worsened conduction disturbances - New onset of atrial fibrillation or atrial flutter - Coronary obstruction: periprocedural (≤72 hours post index procedure) - Ventricular septal perforation: periprocedural (≤72 hours post index procedure) - Mitral apparatus damage: periprocedural (≤72 hours post index procedure) - Cardiac tamponade: periprocedural (≤72 hours post index procedure) - Valve migration - Valve embolization - Ectopic valve deployment - Transcatheter aortic valve (TAV)-in-TAV deployment - Prosthetic aortic valve thrombosis - Prosthetic aortic valve endocarditis • Device performance endpoints peri- and post-procedure: - Successful vascular access, delivery and deployment of the study valve, and successful retrieval of the delivery system - Grade of aortic valve regurgitation: paravalvular, central, and combined • Device success, assessed at procedure and defined as absence of procedural mortality, correct positioning of a single valve into the proper anatomical location, and intended performance of the study device (indexed effective orifice area [iEOA] >0.85 cm^2/m^2 for BMI <30 kg/m^2 and iEOA >0.70 cm^2/m^2 for BMI ≥30 kg/m^2 plus either a mean aortic valve gradient <20 mmHg or a peak velocity <3m/sec, and no moderate or severe prosthetic valve aortic regurgitation) • Additional indications of prosthetic aortic valve performance as measured by transthoracic echocardiography (TTE; see **Note 2** and **Note 3** below) and assessed by an independent core laboratory,

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	including EOA, mean and peak aortic gradients, peak aortic velocity, and grade of aortic regurgitation • Functional status as evaluated by New York Heart Association (NYHA) classification (see **Note 3** below) • Neurological status (see **Note 4** below) as determined by the following: - National Institutes of Health Stroke Scale (NIHSS) conducted by a neurology professional or certified personnel at discharge and 1 year - Modified Rankin Scale (mRS) conducted by a neurology professional or certified personnel at discharge and all follow-up visits (see **Note 4** below) - Neurological physical exam conducted by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner in all subjects where stroke is suspected • Health status as evaluated by Kansas City Cardiomyopathy and SF-12 Quality of Life questionnaires at baseline, 1 month, and 1 and 5 years. • For subjects in the CT Imaging Substudy, assessments using 4D CT at 30 days and 1 year will be done as listed below. Data will be evaluated by an independent CT core laboratory. - Assessment of leaflet mobility - Assessment of hypoattenuated leaflet thickening (HALT) - Assessment of leaflet thrombosis **Note 2:** At least 1 post-procedural echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest study performed will be used for analysis. **Note 3:** Echocardiography and NYHA assessment are not required in years 6, 8, and 9 (telephone follow-up only). **Note 4:** The mRS is required at all follow-up visits up to 5 years. For subjects diagnosed with a stroke, a neurological physical exam, mRS, and NIHSS must be performed after the event; mRS must also be administered at 90±14 days following a stroke; the simplified mRS questionnaire may be used for this follow-up assessment.

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	a: Leon M, *et al. J Am Coll Cardiol.* 2011;57:253–69 Kappetein AP, *et al*. *J Am Coll Cardiol*. 2012;60:1438–54 Alu M, et al. An introduction to "VARC-3: a focused update." Presented at *SHDS*, Chicago 2018.
Method of Assigning Patients to Treatment	**Main Randomized Cohort:** A computer generated list of random treatment allocations (randomization schedule) will be used to assign subjects to treatment in a 1:1 ratio of ACURATE to Control. A subset of subjects in the randomized cohort will also be enrolled in the 4D CT Imaging Substudy. **Roll-In Cohort:** For centers that do not have implantation experience with the ACURATE *neo*™ Aortic Bioprosthesis (transfemoral delivery) at least 2 Roll-In subjects will be treated before commencing treatment in the randomized cohort. Centers with prior experience with ACURATE are not required to do Roll-In cases. For the Main Randomized Cohort and the Roll-In Cohort, subjects will have a documented aortic annulus size of ≥21mm and ≤27mm based on pre-procedure diagnostic imaging. **ACURATE *Prime* XL Nested Registry:** Subjects will have a documented aortic annulus size of ≥26.5 mm and ≤29 mm based on pre-procedure diagnostic imaging. **ACURATE Extended Durability Study:** A computer generated list of random treatment allocations (randomization schedule) will be used to assign subjects to treatment in a 1:1 ratio of ACURATE to Control. Only subjects considered to be at low surgical risk will be included in the Extended Durability Study. Randomization will be stratified by center and by intended control device. Subjects will receive ACURATE *neo2* (S, M, or L valve sizes) or ACURATE *Prime* XL. Subjects with a documented aortic annulus size of ≥20.5mm and ≤27 mm may be enrolled in the Extended Durability Study after enrollment is concluded in the Main Randomized Cohort. Subjects with a documented aortic annulus size of ≥26.5mm and ≤29mm may be enrolled in the Extended Durability Study after enrollment is concluded in both the Main Randomized Cohort and the ACURATE Prime XL Nested Registry. **Note:** Centers must complete the roll-in phase of the study, if applicable, before participating in the ACURATE Extended Durability Study.

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	ACURATE Continued Access Study (CAS): Subjects will receive ACURATE *neo2* (S, M, or L valve sizes) or ACURATE *Prime* XL. Subjects with a documented aortic annulus size of ≥20.5mm and ≤27mm may be enrolled in ACURATE CAS after enrollment is concluded in the Main Randomized Cohort. Subjects with a documented aortic annulus size of ≥26.5mm and ≤29mm may be enrolled in ACURATE CAS after enrollment is concluded in both the Main Randomized Cohort and the ACURATE *Prime* XL Nested Registry. Subjects at all surgical risk levels may be enrolled in ACURATE CAS but low-risk subjects will be considered for enrollment only after enrollment is completed in the Extended Durability Study. **Note:** Centers must complete the roll-in phase of the study, if applicable, before participating in ACURATE CAS.
Follow-up Schedule	All subjects implanted with a test or control device will be assessed at baseline, peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, 6 months, 1 year, and then annually for up to 10 years post-procedure. Subjects who are enrolled but not implanted with a test or control device at the time of the procedure will be followed for safety through 1 year. The visits at 30 days, 6 months, 1−5 years, 7 years, and 10 years are to be an office/clinical/in-person or telehealth (https/telehealth.HHS.gov) visit (see **Note 5** below) but may be done in-hospital should the subject be admitted at the time. Telephone follow-up is allowed at 6, 8, and 9 years. Procedures at each scheduled visit are described above under "Additional Measurements." **Note 5:** For subjects in the CT Imaging Substudy, the visits at 30 days and 1 year must be done in the clinic (or in-hospital).
Study Duration	Subjects implanted with a test or control device will be followed for 10 years after the index procedure. Enrollment is expected to be completed in approximately 62 months; therefore, the total study duration is estimated to be approximately 16 years.
Participant Duration	The study duration for each subject is expected to be approximately 10 years.

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Adjunctive Pharmacologic Therapy	**Anticoagulant Therapy** Anticoagulant therapy (e.g., unfractionated heparin) per local standard of care must be administered during the implant procedure, with a recommended target activated clotting time of ≥250 seconds during the index procedure. **Anti-Platelet Therapy** Per US society guidelines[b], antiplatelet therapy is recommended after TAVR to decrease the risk of thrombotic or thromboembolic complications if there are no contraindications to these medications. ACURATE IDE study subjects must receive antiplatelet therapy (aspirin and/or a $P2Y_{12}$ inhibitor) for at least 1 month following valve implant (see below for recommended doses). It should be noted, however, that recent clinical evidence points to increased bleeding risk post TAVR among subjects receiving dual antiplatelet therapy or antiplatelet therapy plus anti-coagulation (among subjects indicated for anti-coagulation)[c]. Aspirin A loading dose of aspirin (recommended dose of 75–325 mg) is recommended for subjects who have not been on aspirin therapy for ≥72 hours at the time of the index procedure. The loading dose should be administered prior to the implant procedure. Subjects who have been taking aspirin daily for ≥72 hours at the time of the index procedure do not require a loading dose. After the valve implant procedure, the recommended aspirin dose is ≥75 mg daily. It is recommended that daily aspirin be given indefinitely as per local standard of care. $P2Y_{12}$ Inhibitor A loading dose of a $P2Y_{12}$ inhibitor (recommended dose of ≥300 mg for clopidogrel, 60 mg for prasugrel, 180 mg for ticagrelor) is recommended for subjects who have not been on $P2Y_{12}$ therapy for ≥72 hours at the time of the index procedure. The loading dose should be administered prior to the implant procedure. After the valve implant procedure, a $P2Y_{12}$ inhibitor and/or aspirin is required for at least 1 month. **Note 6:** Anti-platelet therapy dosing and the type of $P2Y_{12}$ inhibitor used should be according to the local standard of care. **Note 7:** If a subject requires chronic anticoagulation, either a $P2Y_{12}$ inhibitor or aspirin is recommended prior to and after the implant procedure in addition to the anticoagulant therapy (but both aspirin and

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	a $P2Y_{12}$ inhibitor are not recommended). After the implant procedure, the subject should be treated with an oral anticoagulant and either a $P2Y_{12}$ inhibitor or aspirin for at least 1 month. **Note 8:** Subjects who are expected to undergo chronic anticoagulation therapy after the TAVR procedure are not eligible to be included in the 4D CT Imaging Substudy (see Additional Exclusion Criteria below). b: Otto CM, et al. *J Am Coll Cardiol.* 2021;77:e25-e197 c: Nijenhuis VJ, et al. N Engl J Med 2020;382:1696–1707 Brouwer J, et al. N Engl J Med 2020;383:1447–1457
Inclusion Criteria	IC1. Subject has documented severe symptomatic native aortic stenosis defined as follows: aortic valve area (AVA) ≤1.0 cm^2 (or AVA index ≤0.6 cm^2/m^2) AND a mean pressure gradient ≥40 mmHg, OR maximal aortic valve velocity ≥4.0 m/s, OR Doppler velocity index ≤0.25 as measured by echocardiography and/or invasive hemodynamics. **Note 9:** In cases of low flow, low gradient aortic stenosis with left ventricular dysfunction (ejection fraction <50%), dobutamine can be used to assess the grade of aortic stenosis (maximum dobutamine dose of 20 mcg/kg/min recommended)[b]; the subject may be enrolled if echocardiographic criteria are met with this augmentation. IC2. Subject has a documented aortic annulus size of ≥20.5 mm and ≤29 mm based on the center's assessment of pre-procedure diagnostic imaging (and confirmed by the Case Review Committee [CRC]) and, for the Main Randomized Cohort and Extended Durability Study, is deemed treatable with an available size of both test and control device. IC3. For subjects with symptomatic aortic valve stenosis per IC1 definition above, functional status is NYHA Functional Class ≥ II. IC4. Heart team (which must include an experienced cardiac interventionalist and an experienced cardiac surgeon) agrees that the subject is indicated for TAVR, is likely to benefit from valve replacement, and TAVR is appropriate. IC5. Subject (or legal representative) understands the study requirements and the treatment procedures and provides written informed consent.

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	IC6. Subject, family member, and/or legal representative agree(s) and subject is capable of returning to the study hospital for all required scheduled follow up visits. IC7. Subject is expected to be able to take the protocol-required adjunctive pharmacologic therapy. b: Otto CM, et al. *J Am Coll Cardiol.* 2021;77:e25-e197
Exclusion Criteria	Vulnerable subjects (ISO 14155) will not be enrolled in ACURATE IDE. EC1. Subject has a unicuspid or bicuspid aortic valve. EC2. Subject has had an acute myocardial infarction within 30 days prior to the index procedure (defined as Q-wave MI or non–Q-wave MI with total CK elevation ≥ twice normal in the presence of CK-MB elevation and/or troponin elevation). EC3. Subject has had a cerebrovascular accident or transient ischemic attack clinically confirmed by a neurologist or neuroimaging within the past 6 months prior to study enrollment. EC4. Subject is on renal replacement therapy or has eGFR <20. EC5. Subject has a pre-existing prosthetic aortic or mitral valve. EC6. Subject has severe (4+) aortic, tricuspid, or mitral regurgitation. EC7. Subject has moderate or severe mitral stenosis (mitral valve area ≤1.5 cm^2 and diastolic pressure half-time ≥150 ms, Stage C or D[b]). EC8. Subject has a need for emergency surgery for any reason. EC9. Subject has a history of endocarditis within 6 months of index procedure or evidence of an active systemic infection or sepsis. EC10. Subject has echocardiographic evidence of new intra-cardiac vegetation or intraventricular or paravalvular thrombus requiring intervention. EC11. Subject has platelet count <50,000 cells/mm^3 or >700,000 cells/mm^3, or white blood cell count <1,000 cells/mm^3. EC12. Subject has had a gastrointestinal bleed requiring hospitalization or transfusion within the past 3 months or has other clinically significant bleeding diathesis or coagulopathy that would

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	preclude treatment with required antiplatelet regimen or will refuse transfusions. EC13. Subject has known hypersensitivity to contrast agents that cannot be adequately pre-medicated or has known hypersensitivity to the protocol required medications (aspirin, all $P2Y_{12}$ inhibitors, heparin), or to the individual components of the test or control valve (nickel, titanium, stainless steel, platinum, iridium or polyethylene terephthalate [PET]). EC14. Subject has a life expectancy of less than 12 months due to non-cardiac, comorbid conditions based on the assessment of the investigator at the time of enrollment. EC15. Subject has hypertrophic cardiomyopathy. EC16. Subject has any therapeutic invasive cardiac or vascular procedure within 30 days prior to the index procedure (except for balloon aortic valvuloplasty, pacemaker implantation, or implantable cardioverter defibrillator implantation, which are allowed). EC17. Subject has untreated coronary artery disease, which in the opinion of the treating physician is clinically significant and requires revascularization. EC18. Subject has severe left ventricular dysfunction with ejection fraction <20%. EC19. Subject is in cardiogenic shock or has hemodynamic instability requiring inotropic support or mechanical support devices. EC20. Subject has arterial access that is not acceptable for the study device (test or control) delivery systems as defined in the device (test or control) Directions For Use. EC21. Subject has either of the following: • Severe vascular disease that would preclude safe access (e.g., aneurysm with thrombus that cannot be crossed safely; marked tortuosity; significant narrowing of the abdominal aorta; severe unfolding of the thoracic aorta; or thick, protruding, ulcerated atheroma in the aortic arch), OR • Severe/eccentric calcification of the aortic annulus that would prevent safe implantation of the TAVR prosthesis.

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	EC22. Subject has current problems with substance abuse (e.g., alcohol, etc.) that may interfere with the subject's participation in this study. EC23. Subject is participating in another investigational drug or device study that has not reached its primary endpoint or subject intends to participate in another investigational device clinical trial within 12 months after index procedure. EC24. Subject has untreated conduction system disorder (e.g., Type II second degree atrioventricular block) that in the opinion of the treating physician is clinically significant and requires a pacemaker implantation. Enrollment is permissible after permanent pacemaker implantation. EC25. Subject has severe incapacitating dementia. b: Otto CM, et al. *J Am Coll Cardiol.* 2021;77:e25-e197
Additional Exclusion Criteria	Additional exclusion criteria apply to subjects considered for enrollment in the CT Imaging Substudy as listed below. AEC1. Subject has eGFR <30 mL/min (chronic kidney disease stage IV or stage V). AEC2. Subject has atrial fibrillation that cannot be rate controlled to ventricular response rate < 60 bpm. AEC3. Subject is expected to undergo chronic anticoagulation therapy after the index procedure. **Note 10:** Subjects treated with short-term anticoagulation post procedure can be included in the CT Imaging Substudy; in these subjects the 30-day imaging will be performed 30 days after discontinuation of anticoagulation.
Statistical Methods	
Analysis Sets	Analysis sets for the ACURATE IDE Main Randomized Cohort and the Extended Durability Study are listed below. Subjects in the Main Randomized Cohort and the Extended Durability Study are considered enrolled in the study upon randomization. - Intention-To-Treat (ITT): This population includes all subjects who sign an Informed Consent Form, are enrolled in the trial, and are randomized, whether or not an assigned study device is implanted.

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	- Implanted: This population includes all subjects who sign an Informed Consent Form, are enrolled in the trial, and are implanted with the assigned (control versus test), randomized study device. **Note 11:** For the Main Randomized Cohort and Extended Durability Study, if a subject receives 2 different valve types from 2 different manufacturers, the subject will be excluded from the Implanted analysis. Among the Roll-In, ACURATE *Prime* XL, and Continued Access Study cohorts, for the ITT analysis, all subjects who sign an Informed Consent Form and are enrolled in the study will be included in the analysis sample, regardless of whether the test device was implanted. The Implanted analysis set will include all subjects who sign an Informed Consent Form and are implanted with an ACURATE valve. For these single-arm cohorts, the subject is considered enrolled in the trial when there is an attempt made to insert the ACURATE Transfemoral Aortic Valve System into the subject's femoral artery.
Primary Endpoint Statistical Hypothesis	In the Main Randomized Cohort, the primary endpoint (composite of all-cause mortality, all stroke, and rehospitalization at 1 year) rate for the ACURATE group is non-inferior to that for the Control group.
Statistical Test Method for the Primary Endpoint	For the Main Randomized Cohort, the statistical hypothesis is that the primary endpoint rate for ACURATE is non-inferior to the rate for Control: H_0: $PE_{\_ACURATE}$ minus $PE_{\_Control} \geq \Delta$ (Inferior) H_1: $PE_{\_ACURATE}$ minus $PE_{\_Control} < \Delta$ (Non-inferior) where $PE_{\_ACURATE}$ and $PE_{\_Control}$ correspond to the primary endpoint rates for the ACURATE group (test) and the Control group, respectively, and Δ is the non-inferiority margin. The primary analysis set for the primary endpoint is the ITT analysis set. This endpoint will also be analyzed for the implanted analysis set. A Bayesian analysis[d] will be performed to estimate the treatment difference between ACURATE and Control through posterior probability. Details are shown below. d: Popma JJ, et al. N Engl J Med 2019;380:1706-15 Reardon MJ, et al. N Engl J Med 2017;376:1321-31

ACURATE IDE: Transcatheter Replacement of Stenotic Aortic Valve through Implantation of ACURATE in Subjects InDicatEd for TAVR	
Sample Size Parameters for the Primary Endpoint	Although the primary endpoint analysis is performed using the Bayesian method, the sample size calculation for the randomized cohort (see **Note 12** below) is based on a standard non-inferiority two-sample test approach. The sample size calculation for the primary endpoint is based on the following assumptions. • Expected rate for both arms = 22.3% (based on weighted average of TAVR data[e]; see **Note 13** below) • Non-inferiority margin (Δ) = 8.0% (36% relative to the expected rate) • Test significance level (α) = 0.025 (1-sided) (see **Note 14** below) • Test (ACURATE): Control ratio = 1:1 • Power (1 minus ß) > 90% • Expected rate of attrition = 5% • Total sample size = 1500 (750 per group) • Number of evaluable subjects per group = 712 • Analyses: One administrative, one formal interim, one final (see **Note 15** below) **Note 12:** The Pocock-type method[f] is used during sample size calculations. The statistical software EAST® 6.5 is used for the sample size calculations. **Note 13:** The estimated proportions of subjects by operative risk level is 10% extreme risk, 25% high risk, 30% intermediate risk, and 35% low risk. **Note 14:** A statistically equivalent posterior probability threshold for the Bayesian analysis is empirically chosen through extensive simulations and is pre-specified in the Statistical Analysis Plan (SAP). **Note 15:** The administrative interim analysis will be conducted when the first 350 subjects in the Main Randomized Cohort have completed 1-year follow-up. The formal interim analysis will be carried out after enrollment in the Main Randomized Cohort is completed. This formal interim analysis will be conducted on the full N=1500 subject cohort of the Main Randomized Cohort after the first 1050 subjects in the Main Randomized Cohort have completed 1-year follow-up. The piecewise exponential model[g] based on outcomes among these subjects will be used to predict the 1-year results by treatment group for the remaining enrolled subjects. The Bayesian method will be used to perform the hypothesis testing on the combined data sets. A final analysis for the

ACURATE IDE: Transcatheter Replacement of Stenotic Aortic Valve through Implantation of ACURATE in Subjects InDicatEd for TAVR	
	primary endpoint will be performed on all subjects with completed 1-year data if non-inferiority cannot be claimed at the formal interim analysis (see Success Criteria below). e: Adams DH, et al. N Engl J Med 2014;370:1790-8 Mack MJ, et al. N Engl J Med 2019;380:1695-705 Popma JJ, et al. J Am Coll Cardiol 2014;63:1972-81 Popma JJ, et al. N Engl J Med 2019;380:1706-15 Reardon MJ, et al. N Engl J Med 2017;376:1321-31 Smith CR, et al. N Engl J Med 2011;364:2187-98 Thourani VH, et al. Lancet 2016;387:2218-25 Waksman R, et al. J Am Coll Cardiol Intv 2019;12:901–7 Webb JG, et al. J Am Coll Cardiol Intv 2015;8:1797-806 Medtronic CoreValve System PMA P130021/S002: FDA Summary of Safety and Effectiveness Data f: Lan KKG and DeMets DL. Biometrika 1983;70:659–63 g: Popma JJ, et al. N Engl J Med 2019;380:1706-15
Success Criteria for the Primary Endpoint	The Bayesian method is used to test the non-inferiority hypothesis of the primary endpoint on the Main Randomized Cohort. To establish that the ACURATE device is non-inferior to the Control, the results will need to meet the following equation: $Pr(H_1 \mid Data) > \xi$ where • $Pr(H_1 \mid Data)$ is the posterior probability of H_1 given the observed data at either the interim or the final analysis; • H_1 is the alternative hypothesis for non-inferiority: $PE_{\_ACURATE}$ minus $PE_{\_Control} < \Delta$; • ξ is a prespecified threshold, which is empirically chosen through extensive simulations using the Bayesian approach for the non-inferiority tests. If non-inferiority has been declared at the formal interim analysis, the non-inferiority test will not be performed at the final analysis. If non-inferiority cannot be declared at this interim analysis, the non-inferiority test will be performed at the final analysis for all subjects using the Bayesian method with the same pre-specified threshold. The study will not stop for futility at the interim analysis. The detailed study operating characteristics and simulation results will be provided in the SAP.

ACURATE IDE: Transcatheter Replacement of Stenotic Aortic Valve through Implantation of ACURATE in Subjects InDicatEd for TAVR	
ACURATE *Prime* XL Nested Registry Statistical Hypothesis	Mean aortic valve pressure gradient at 30 days post implant procedure is less than a performance goal (PG): H_0: $Gradient_{30D} \geq PG$ H_1: $Gradient_{30D} < PG$ where $Gradient_{30D}$ is the 30-day mean aortic valve pressure gradient for the ACURATE *Prime* XL valve and PG is 15 mmHg.
Statistical Test Method for the ACURATE *Prime* XL Nested Registry	A one-sample *t*-test will be used to test the one-sided hypothesis at a significance level of 2.5%.
Sample Size Parameters for the ACURATE *Prime* XL Nested Registry	• Expected 30-day mean pressure gradient from ACURATE *Prime* XL = 10 mmHg[h] • Expected standard deviation = 7 mmHg • PG = 15 mmHg • Test significance level (α) = 0.025 (1-sided) • Power > 90% • Evaluable number of subjects = Minimum of 40 subjects • Expected rate of attrition = 20% (8 subjects) • Planned enrollment of 50 subjects • The analysis population for the hypothesis testing will be the subject population implanted with the ACURATE *Prime* XL valve. h: Based on Boston Scientific data on file and published data for large-annulus CoreValve devices: Tang GHL, et al. Am J Cardiol 2019;124:1091-8 Kalogeras K, et al. Catheter Cardiovasc Interv 2019;93:685-91 Ussia GP, et al. EuroIntervention 2015;10:e1-e8
Success Criteria for the ACURATE *Prime* XL Nested Registry	If the *P* value from the one-sample *t*-test is < 0.025, the ACURATE *Prime* XL valve will be concluded to have a 30-day mean aortic valve pressure gradient < 15 mmHg. This corresponds to the one-sided upper 2.5% confidence bound of the observed 30-day mean aortic valve pressure gradient being < 15 mmHg.

ACURATE IDE: Transcatheter Replacement of Stenotic Aortic Valve through Implantation of ACURATE in Subjects InDicatEd for TAVR	
Statistics Summary	Data will be summarized separately for each cohort. In addition to the hypothesis tests listed above, descriptive statistics will be used. Full methods will be described in the Statistical Analysis Plan.

3. Table of Contents

3.1. *Table of Figures*

3.2. *Table of Tables*

4. Introduction

This protocol specifies procedures and contains information relevant to the clinical evaluation of the ACURATE™ Transfemoral Aortic Valve System, which is a transcatheter aortic valve implantation/replacement (TAVI/TAVR) device designed and manufactured by Boston Scientific Corporation, Marlborough, MA, USA.

4.1. *Background*

4.1.1. Aortic Stenosis

The incidence of aortic stenosis (AS), which most commonly occurs in the very elderly, is increasing due to the aging of the world-wide population and the lack of drug therapies to prevent, halt, or effectively slow the stenotic process[1-3]. It is estimated that nearly 5% of elderly ≥75 years of age have AS and its prevalence is expected to increase due to an aging population[2,3]. Aortic stenosis is associated with high rates of death and complications after the appearance of symptoms[2,3].

Many patients with severe and symptomatic aortic stenosis are successfully treated with surgical aortic valve replacement (SAVR), which can reduce symptoms and improve survival[2-5]. However, up to one-third of patients with severe AS are not treated with SAVR because of their comorbidities and consequent perioperative risk[6-8]. With standard medical therapy, mortality after 1 year among these patients may be as high as 50%[2,3,8]. Percutaneous transluminal aortic valvuloplasty, which was introduced as an alternative to SAVR in elderly and/or high-risk surgical patients, can provide symptomatic relief and/or temporary improvement but does not provide definitive treatment in patients with severe calcific AS[3,5]. It is also associated with relatively high mortality and complication rates[3,9]. As described below in Section **4.1.2**, transcatheter aortic valve implantation/replacement provides another alternative to SAVR in select patients[4,5,10].

4.1.2. Transcatheter Aortic Valve Implantation/Replacement

There are several approaches to TAVR, including transfemoral (TF), transapical (TA), transaortic (TAo), transaxillary/subclavian, transcarotid, and transcaval[2,11]. Patients generally undergo a joint interdisciplinary screening process, including comprehensive multimodality imaging[12-15], prior to procedure recommendation. Because of the limitations of existing surgical risk scores, center heart teams also consider other co-morbidities and patient frailty to fully characterize risk[16].

The use of TAVR has produced significant reductions in mortality and repeat hospitalization compared to medical therapy[8,17,18]. In selected patients considered to be at high surgical risk, TAVR has resulted in similar[19-21] or lower[22-24] mortality when compared to SAVR. Continuous procedural refinements and device improvements have aimed to widen application to lower risk patients[25,26] and randomized controlled trials (RCT) have shown similar outcomes among intermediate-risk and low-risk surgical patients treated with TAVR or SAVR[27-30]. Meta-analyses have also shown similar long-term survival after TAVR

compared to SAVR[31,32]. Currently, TAVR is approved for use in AS patients considered inoperable or at low to high surgical risk and expert consensus documents have outlined TAVR patient selection criteria[4,5,11,33].

Table 4.1-1 summarizes outcomes at 30 days and 1 year from some TAVR studies that enrolled subjects similar to those planned for this study.

Table 4.1-1: TAVR Outcomes at 30 Days and 1 Year – Transfemoral Access

Study	Device/N	All-cause Death	Disabling / Major Stroke	Major VC	LT Bleeding	AKI	PPM
30-Day Outcomes – Randomized Studies							
PARTNER 1A[a] (2011)[19]	SAPIEN / 244[†]	3.3	2.9	14.0	9.5[b]	2.5[c]	3.7
PARTNER 2A[d] (2016)[27]	SAPIEN XT / 775*	3.0	2.3	8.5	6.7	0.5[e]	8.1
PARTNER 2B[f] (2015)[34]	SAPIEN XT / 284[†] SAPIEN / 276[†]	3.5 5.1	3.2 3.0	9.5 15.2	7.8 12.4	15.4[g] 16.8[g]	6.8 5.9
PARTNER 3[f] (2019)[29]	SAPIEN 3 / 496[#]	0.4	0.0	2.2	1.2	0.4[h]	6.5
CoreValve High Risk[i] (2014)[22]	CoreValve / 390[†]	3.3	3.9	5.9	13.6	6.0[g]	19.8
NOTION[j] (2015)[35]	CoreValve / 142[‡]	2.1	1.4[k]	5.6	11.3[l]	0.7[h]	34.1
SURTAVI[m] (2017)[28]	CoreValve / 864*	2.2	1.2	6.0	12.2	1.7[h]	25.9
CoreValve Low Risk[i](2019)[30]	CoreValve, Evolut R, Evolut PRO / 725[#]	0.5	0.5	3.8	2.4	0.9[h]	17.4
CHOICE[f] (2014)[36]	SAPIEN XT / 121[†] CoreValve / 117[†]	4.1 5.1	2.5 2.6	9.9 11.1	8.3[b] 12.0[b]	4.1[e] 9.4[e]	17.3 37.6
REPRISE III[f] (2018)[37]	Lotus Valve[n] / 607[†] CoreValve[n] / 305[†]	2.5 2.3	2.0 3.3	7.0 5.3	8.0 5.0	2.5[h] 3.6[h]	29.1 15.8
PORTICO IDE[o] (2020)[38]	Portico / 381[†] Commercial / 369[†]	3.5 1.9	1.6 1.1	9.6 6.3	5.9 3.8	1.9[e] 1.1[e]	27.7 11.6
30-Day Outcomes – Single-Arm Studies							
PARTNER NRCA[f] (2014)[39]	SAPIEN / 1023[†]	4.3	2.4	8.0	6.8[b]	1.6[e]	–
SAPIEN 3[p] (2016)[40]	SAPIEN 3 / 953* SAPIEN 3 / 491[†]	1.1 1.6	0.7 0.8	6.3 5.5	3.6 5.5	0.8[h] 1.2[h]	10.5 13.5
CoreValve Extreme Risk[q] (2014)[41]	CoreValve / 489[†]	8.4	2.3	8.2	12.7	11.8	21.6
Evolut R First in Man[r] (2015)[42]	Evolut R / 60[†]	0.0	0.0[k]	8.3	5.0	1.7[h]	9.8
CoreValve – Large Annuli[s] (2015)[43]	CoreValve 31mm / 76[†]	2.6	0.0[k]	6.6	2.6[t]	1.3[h]	23.7
EVOLUT R US Study[u](2017)[44]	Evolut R / 241[†]	2.5	3.3	7.5	7.1	1.2[h]	16.4

Table 4.1-1: TAVR Outcomes at 30 Days and 1 Year – Transfemoral Access

Study	Device/N	All-cause Death	Disabling / Major Stroke	Major VC	LT Bleeding	AKI	PPM
PORTICO Pre-CE Mark Study[f] (2018)[45]	Portico / 222[†]	3.6	3.2	7.3	3.6	1.4[e]	13.6
LRT Trial[f] (2019)[46]	SAPIEN 3 or CoreValve[v] / 200[#]	0.0	0.0	3.0	3.0[l]	0.0[e]	6.5
UK & Ireland Implanters' Registry[w] (2019)[47]	Evolut 34mm / 217[*]	3.2	3.7[k]	2.3	0.9	0.9[h]	15.7[x]
EVOLUT R – Large Annuli[y] (2019)[48]	Evolut 34mm / 35[†] CoreValve 31mm / 71[†]	0.0 8.5	0.0[k] 1.4[k]	0.0 4.2	2.9[z] 19.6[z]	0.0[e] 5.3[e]	5.7 26.8
TVT Registry – Large Annulus[y,aa] (2019)[49]	Evolut R 34 / 1813[‡] CoreValve 31 / 1813[‡]	1.9 2.2	2.2[k] 2.0[k]	0.3 0.5	4.6[l] 6.6[l]	– –	15.2[bb] 23.3[bb]
1-Year Outcomes – Randomized Studies							
PARTNER 1A[a] (2011)[19]	SAPIEN / 244[†]	22.2	3.8	14.4	16.2[b]	5.1[c]	5.5
PARTNER 2A[d] (2016)[27]	SAPIEN XT / 775*	10.0	4.3	8.8	11.1	2.2[e]	9.6
PARTNER 2B[f] (2015)[34]	SAPIEN XT / 284[†] SAPIEN / 276[†]	22.3 23.3	4.8 5.5	10.3 16.1	14.1 19.9	31.0[e] 31.3[e]	8.1 8.0
PARTNER 3[f] (2019)[29]	SAPIEN 3 / 496[#]	1.0	0.2	2.8	2.8	–	7.3
CoreValve High Risk[i] (2014)[22]	CoreValve / 390[†]	14.2	5.8	6.2	16.6	6.0[g]	22.3
NOTION[j] (2015)[35]	CoreValve / 142[‡]	4.9	2.9[k]	–	–	–	38.0
SURTAVI[m] (2017)[28]	CoreValve / 864*	6.7	2.2	–	–	–	–
CoreValve Low Risk[i] (2019)[30]	CoreValve, Evolut R, Evolut PRO / 725[#]	2.4	0.8	3.8	3.2	0.9[h]	19.4
CHOICE[f] (2015)[50]	SAPIEN XT / 121[†] CoreValve / 117[†]	17.4 12.8	5.8 3.4	11.6 12.0	14.0[b] 12.8[b]	– –	23.4 38.0
REPRISE III[f] (2018)[37]	Lotus Valve[n] / 607[†] CoreValve[n] / 305[†]	11.9 13.5	3.6 7.1	7.7 6.1	9.9 9.8	2.6[h] 3.7[h]	34.2 18.5
PORTICO IDE[o] (2020)[38]	Portico / 381[†] Commercial / 369[†]	14.3 12.0	1.6 2.9	–	–	–	–
1-Year Outcomes – Single-Arm Studies							
PARTNER NRCA[f] (2014)[39]	SAPIEN / 1023[†]	19.0	3.6	8.4	12.9[b]	3.6[e]	–
CoreValve Extreme Risk[q] (2014)[41]	CoreValve / 489[†]	24.3	4.3	8.4	17.6	11.8	26.2

Table 4.1-1: TAVR Outcomes at 30 Days and 1 Year – Transfemoral Access

Study	Device/N	All-cause Death	Disabling / Major Stroke	Major VC	LT Bleeding	AKI	PPM
SAPIEN 3[cc] (2016)[51]	SAPIEN 3 / 925*	6.5	1.7	–	–	–	12.4
PORTICO Pre-CE Mark Study[f] (2018)[45]	Portico / 222†	13.8	5.8	8.8	5.2	3.0	14.7
LRT Trial[f] (2019)[46]	SAPIEN 3 or CoreValve[v] / 200#	3.0	0.0	–	–	–	7.3

Data are presented as %; N is the number of subjects with transfemoral/iliofemoral access unless indicated otherwise; † = high/extreme surgical risk; * = intermediate surgical risk; # = low surgical risk; ‡ = all risk.
The SAPIEN™, SAPIEN XT™, and SAPIEN 3™ Transcatheter Heart Valve Systems are manufactured by Edwards Lifesciences, Irvine, CA, USA. The CoreValve®, CoreValve Evolut™ R, and CoreValve Evolut™ PRO Transcatheter Aortic Valve Systems are manufactured by Medtronic Corp, Dublin, Ireland. The PORTICO™ Transcatheter Aortic Heart Valve Implantation System is manufactured by Abbott Structural Heart, St. Paul, MN, USA. The Lotus™ Valve System is manufactured by Boston Scientific Corporation, Marlborough, MA, USA.

a: 70% TF and 30% TA
b: Major bleeding
c: Renal replacement therapy
d: 76% TF and 24% TA
e: AKIN Stage 3 (including renal replacement therapy)
f: 100% TF
g: Modified RIFLE classification per VARC 1
h: AKIN Stage 2 or 3
i: 83% TF and 17% TAo/SC for CoreValve High Risk; 99% TF and 1% Tao/SC for CoreValve Low Risk
j: 97% TF and 3% SC
k: All stroke
l: Life-threatening and major
m: 94% TF, 4% TAo, and 2% SC
n: Outcomes are for the implanted analysis sets: N=601 Lotus; N=303 CoreValve (153 CoreValve and 144 Evolut R)
o: Portico: 94% TF, 4% TAo, 2% SC; Commercial (includes SAPIEN [1%], XT [7%], SAPIEN 3 [57%], CoreValve [4%], Evolut R [25%], Evolut PRO [6%]): 95% TF, 3% Tao, 1% SC, <1% TA
p: 87% TF and 13% TA/TAo (intermediate and high risk)
q: 99% TF (1% not implanted)
r: 98% TF and 2% TAo
s: 95% TF and 5% TAx
t: Includes patients who experienced pericardial tamponade
u: 90% TF and 10% other
v: 88% SAPIEN 3 and 12% CoreValve (CoreValve, Evolut R, or Evolut PRO)
w: 91.2% TF, 7.4% SC, 1.4% TAo
x: Excludes patients with PPM at baseline
y: Outcomes at discharge/in-hospital
z: All bleeding
aa: Matched cohorts; CoreValve: 93.3% TF, 4.0% SC, 2.2% TAo and 94.7% extreme/high risk, 5.3% intermediate/low risk; Evolut R: 93.2% TF, 4.1% SC, 1.1% TAo and 78.6% extreme/high risk, 21.4% intermediate/low risk
bb: PPM or implantable defibrillator
cc: 88% TF and 12% TA/TAo

Abbreviations: AKI=acute kidney injury; LT=life threatening; PPM=permanent pacemaker; PVR=paravalvular regurgitation; SC=subclavian; TA=transapical; TAo=trans-aortic; TAVR=transcatheter aortic valve replacement; TAx=transaxillary; TF=transfemoral/iliofemoral; VARC=Valve Academic Research Consortium; VC=vascular complications

Infrequent but significant complications that potentially impact long-term outcomes may limit the utility of TAVR[52]. Suboptimal valve deployment can result in embolization, the need for a second device, or coronary occlusion[53]. Valve malposition requiring a second TAVR valve at the initial procedure has been associated with increased procedural risk[54]. Placement in a heavily calcified native valve can produce an incomplete seal between the bioprosthetic valve and aortic annulus, resulting in paravalvular regurgitation (PVR), which in turn has been associated with increased mortality[55-57]. Iterative improvements in TAVR devices and periprocedural technique have reduced but not eliminated PVR[44,51,58]. The need for permanent pacemaker (PPM) implantation is another limitation of TAVR[59-63].

Newer-generation devices have aimed to address these limitations[64]. The ACURATE TA™ Aortic Bioprosthesis (Symetis SA, Ecublens, Switzerland) is a self-expandable nitinol TAVR stent housing a porcine bioprosthesis and placed in a supra-annular position via transapical delivery[65]. The device was designed to allow easy and intuitive implantation (single operator). The ACURATE *neo*™ Aortic Bioprosthesis was subsequently developed for transfemoral (TF) use with the ACURATE *neo*™ TF Delivery System. ACURATE *neo* has a pericardial skirt on the interior and exterior of the stent body which serves to limit PVR[65].

4.2. *Study Rationale*

The ACURATE device potentially provides a number of performance and safety features beyond that of earlier TAVR devices. These include easy and intuitive delivery and valve implantation and a valve design intended to overcome high rates of post-interventional PPM implantation. The iterative ACURATE *neo* TF Aortic Bioprosthesis has a pericardial skirt on the interior and exterior of the stent body which serves to limit PVR. The subsequent ACURATE *neo2* and ACURATE *Prime* Transfemoral Valve Systems were designed with improvements in the pericardial skirt and the delivery system.

The anticipated risks and benefits known at the time this protocol was written and associated with the ACURATE Transfemoral Aortic Valve System and with participation in this clinical investigation are summarized in the Investigator Brochure (IB) and in Section **18** of this document. The conclusion of the risk-benefit analysis demonstrates that the known risks associated with the procedure, and specifically the use of the ACURATE Transfemoral Aortic Valve System, have been mitigated to acceptable limits. It was also concluded that the aforementioned design features may improve procedural safety and longer-term clinical outcomes. The available Sponsor-provided training program and proctorship for physicians (Section **16.4.2**) further mitigates risk. The result is a procedure with residual subject risk comparable to that of currently available transcatheter aortic valves and potential benefit compared with other alternatives.

It is therefore determined that:

- All applicable risks have been addressed through appropriate testing and any residual risks are acceptable when weighed against the potential benefits to the subject.
- The potential benefits of the use of the device out-weigh the risks.

Note: The term "ACURATE" is used generically and includes various iterations of the device.

5. Device Description

The study devices are intended to improve aortic valve function for subjects with severe native aortic stenosis who are indicated for TAVR. Every subject in the randomized cohort must be deemed treatable with an available size of both the test and the control device. The control device in the planned size must be approved for treatment of the subject and commercially available at the investigational center where the implant procedure is being performed.

5.1. *ACURATE Transfemoral Aortic Valve System (Test)*

The investigational device (ACURATE Transfemoral Aortic Valve System [ACURATE]) is designed by Boston Scientific Corporation, Marlborough, MA, USA. It is composed of separately packaged components as listed below.

- A single use aortic valve, the ACURATE *neo2*™ Aortic Valve (valve sizes S, M, and L) or the ACURATE *Prime*™ Aortic Valve (valve size XL)
- A single use transfemoral delivery system, the ACURATE *neo2*™ Transfemoral Delivery System (for use with valve sizes S, M, and L) or the ACURATE *Prime* Transfemoral Delivery System (for use with valve size XL)

  Note: The single use ACURATE *neo2*™ Loading Kit is packaged with the ACURATE *neo2*™ Transfemoral Delivery System.
- A single use loading kit, ACURATE *Prime*™ Loading Kit XL (to allow loading of the XL valve onto the delivery system)

Valves are manufactured in Belo Horizonte, Brazil. Delivery systems and loading kits are manufactured in Ecublens, Switzerland and/or Galway, Ireland. All components are investigational and are labeled as such. The device components are described briefly below. Additional information is provided in the ACURATE *neo2* and ACURATE *Prime* Clinical Directions/Instructions for Use (DFU/IFU) and the IB.

Note: Throughout this document DFU and IFU are used interchangeably.

5.1.1. ACURATE *neo2*™ Aortic Valve and ACURATE *Prime*™ Aortic Valve XL

The ACURATE *neo2* Aortic Valve is an iteration of the CE Mark-approved ACURATE *neo*™ Aortic Bioprosthesis (Boston Scientific Corporation, Marlborough, MA, USA). The ACURATE *Prime* Aortic Valve XL is an iteration of the CE Mark-approved ACURATE *neo2* Aortic Valve. There are 3 valve sizes of ACURATE *neo2* (Small, Medium, and Large) and 1 valve size of ACURATE *Prime* (Extra Large). **Table 5.1-1** shows the sizing chart used for the ACURATE IDE Roll-In Cohort, Main Randomized Cohort, and ACURATE *Prime* XL Nested Registry. **Table 5.1-2** shows the sizing chart for the Extended

Durability Study and the Continued Access Study. Please see Section **7.1** below for study cohort descriptions.

Note: ACURATE *Prime*™ XL is only available in the United States.

Table 5.1-1: ACURATE *neo2* and ACURATE *Prime* Aortic Valve Size Chart – Main Randomized Cohort, Roll-In Cohort and ACURATE *Prime* XL Nested Registry

Size[a]	Nominal Diameter at Waist Level	Aortic Annulus Size
Small (S)	23 mm	21 mm ≤ native annulus diameter ≤ 23 mm
Medium (M)	25 mm	23 mm < native annulus diameter ≤ 25 mm
Large (L)	27 mm	25 mm < native annulus diameter ≤ 27 mm
Extra Large (XL)[b]	29 mm	26.5 mm < native annulus diameter ≤ 29 mm

a: ACURATE *neo2*™ available in sizes S, M, L and ACURATE *Prime*™ available in size XL
b: ACURATE *Prime*™ XL is only available in the United States.

Table 5.1-2: ACURATE *neo2* and ACURATE *Prime* Aortic Valve Size Chart – Extended Durability Study and Continued Access Study

Size[a]	Nominal Diameter at Waist Level	Aortic Annulus Size
Small (S)	23 mm	20.5 mm ≤ native annulus diameter ≤ 23 mm
Medium (M)	25 mm	22.5 mm < native annulus diameter ≤ 25 mm
Large (L)	27 mm	24.5 mm < native annulus diameter ≤ 27mm
Extra Large (XL)[b]	29 mm	26.5 mm < native annulus diameter ≤ 29 mm

a: ACURATE *neo2*™ available in sizes S, M, L and ACURATE *Prime*™ available in size XL
b: ACURATE *Prime*™ XL is only available in the United States.

The valves are shown in **Figure 5.1-1** (ACURATE *neo2* Aortic Valve in Panel A and ACURATE *Prime* Aortic Valve XL in Panel B). Each valve consists of three porcine pericardial tissue leaflets, a self-expandable nitinol stent acting as an anchoring structure within the native aortic annulus for the porcine pericardium valve that is sutured onto it, and a double porcine pericardium skirt sutured on the inner and outer surface of the stent to minimize PVR. The valve is deployed from top to bottom, unsheathing first the upper crown, then the stabilization arches. The valve is designed so that in the final step the lower crown can be deployed to anchor the device with minimal protrusion into the left ventricular outflow tract. The top-down implantation technique provides predictable positioning and hemodynamic stability. The ACURATE *neo2* design iteration includes an advanced sealing technology intended to limit further the extent of PVR. The ACURATE *Prime* Aortic Valve XL iteration allows easier removal of a fully loaded valve and has optimized radial force with the addition of connected links. The valve is intended as a permanently implanted device.

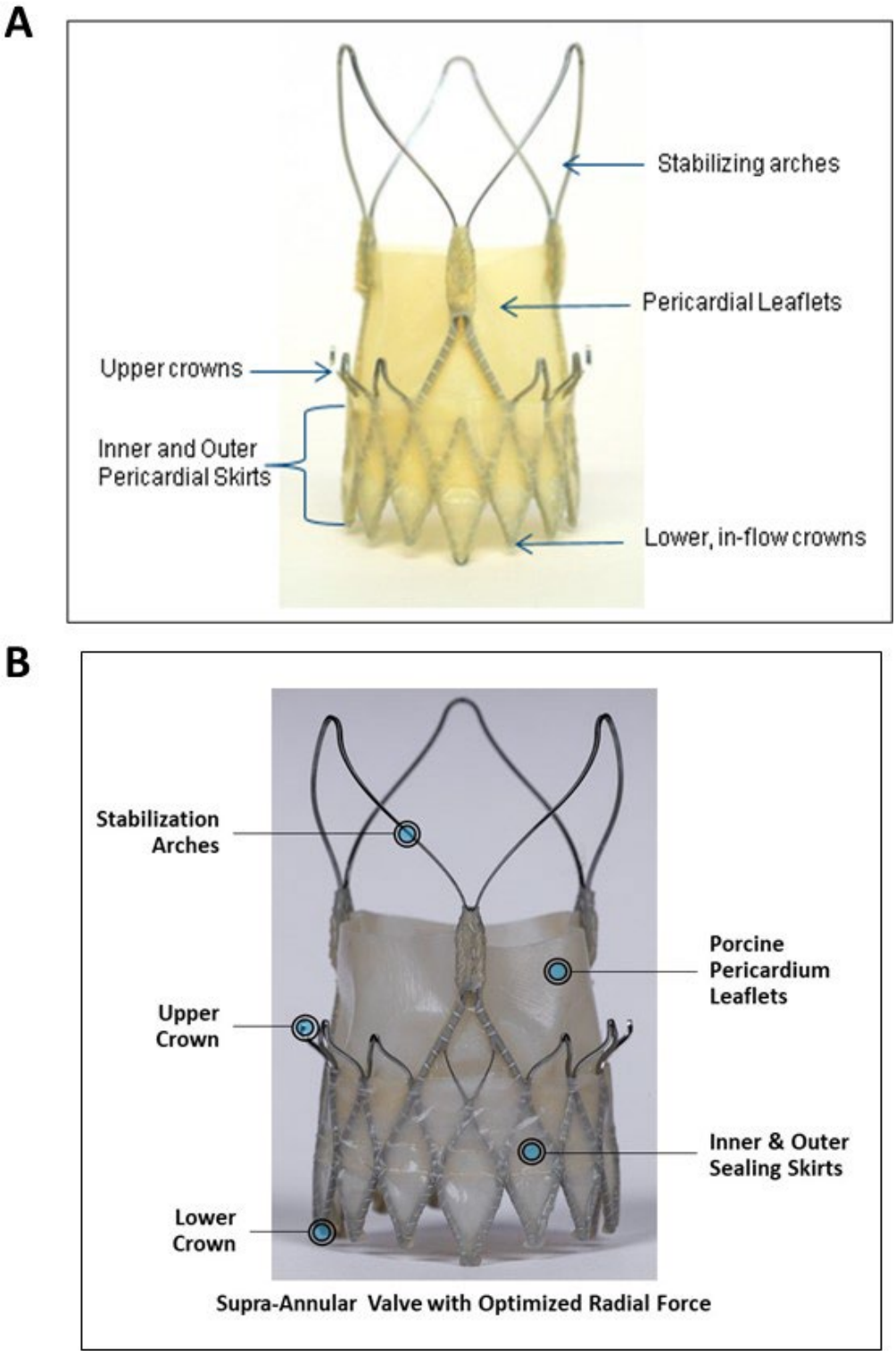


Figure 5.1-1: ACURATE Aortic Valve

A: ACURATE *neo2* Aortic Valve; B: ACURATE *Prime* Aortic Valve XL

5.1.2. ACURATE *neo2* Transfemoral Delivery System and ACURATE *Prime* Transfemoral Delivery System XL

The ACURATE *neo2* Transfemoral Delivery System and ACURATE *Prime* Transfemoral Delivery System XL are transfemoral delivery systems for the guidance and placement of the valve implant.

ACURATE *neo2* is a slightly modified version of the CE Mark-approved ACURATE TF™ Transfemoral Delivery System (Boston Scientific Corporation, Marlborough, MA, USA). **Figure 5.1-2** shows an overview of the system and **Figure 5.1-3** shows a close-up of the distal end. An insertion aid shown in **Figure 5.1-4** facilitates insertion of the delivery system into a compatible introducer sheath (see Section **5.1.3** below). The ACURATE *neo2* Aortic Valve is loaded onto the delivery system prior to use.

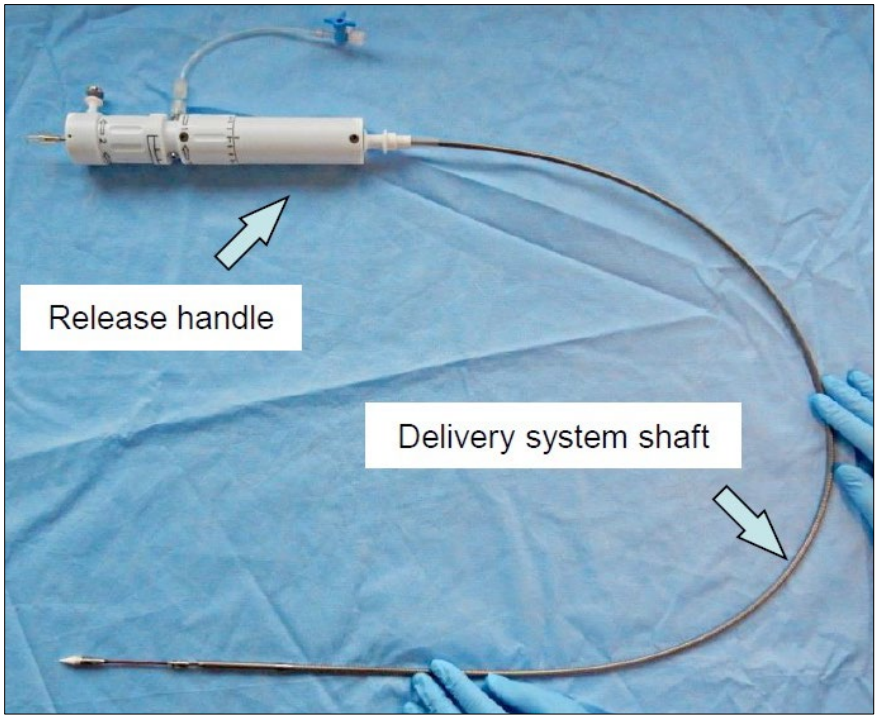


Figure 5.1-2: ACURATE *neo2* Transfemoral Delivery System – Overview

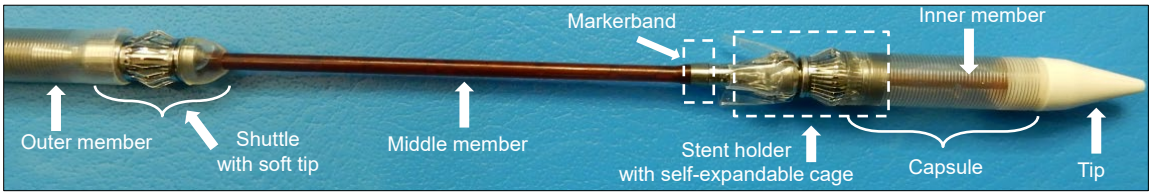


Figure 5.1-3: ACURATE *neo2* Transfemoral Delivery System – Distal End

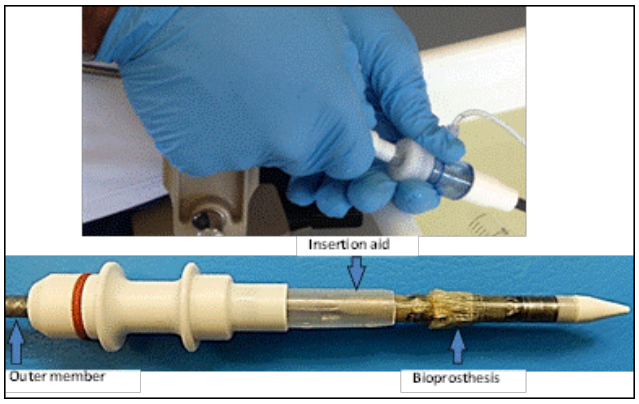


Figure 5.1-4: Insertion Aid Positioned over the Delivery System

The ACURATE *Prime* Transfemoral Delivery System XL is a slightly modified version of the ACURATE *neo2* Transfemoral Delivery System. The system is compatible with the 14F iSLEEVE introducer (see Section **5.1.3** below) and has a new distal release mechanism to allow quicker final valve release and improved valve detachment. **Figure 5.1-5** shows an overview of the system and **Figure 5.1-6** shows a close-up of the distal end. Prior to use, the ACURATE *Prime* Aortic Valve XL is loaded onto the delivery system with the investigational ACURATE *Prime* Loading Kit XL.

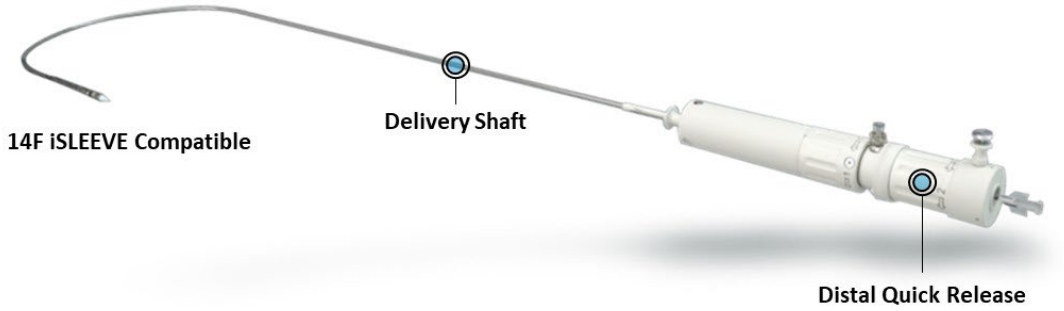


Figure 5.1-5: ACURATE *Prime*™ Transfemoral Delivery System XL – Overview

Figure 5.1-6: ACURATE *Prime*™ Transfemoral Delivery System XL – Distal End with Loaded ACURATE *Prime*™ Aortic Valve XL

The delivery systems are single-use catheters. Please see Section **10.7.2.2** for additional information on preparing and using the investigational devices. Please see Section **5.1.3** regarding the recommended introducer set.

Only BSC authorized and trained personnel may load the ACURATE Aortic Valve.

5.1.3. Introducer Set

The commercially available 14F iSLEEVE™ Introducer Set (iSLEEVE; Boston Scientific Corporation, Marlborough, MA, USA) shall be used as an accessory to the ACURATE *neo2* Transfemoral Aortic Valve System and the ACURATE *Prime* Transfemoral Aortic Valve System during the procedure. The iSLEEVE is composed of a dilator and an introducer sheath manufactured with materials commonly used in medical devices having contact with circulating blood. It has a hydrophilic coating that upon activation increases the lubricity of the surface to aid in delivery. The sheath component of the iSLEEVE is expandable, which allows for transient sheath expansion during delivery system introduction. The 14F iSLEEVE is suitable for use in subjects with femoral vascular access ≥5.5 mm.

Note: In countries where the iSLEEVE is approved, the commercial device will be used. It will be considered an investigational device in countries where it is not approved.

5.2. *Control Device*

The control device is a commercially available balloon-expandable SAPIEN 3™ Transcatheter Heart Valve or future iteration (SAPIEN 3; Edwards Lifesciences LLC, Irvine, CA, USA) or a commercially available self-expanding CoreValve® Transcatheter Aortic Valve Replacement System, CoreValve® Evolut™ R Recapturable TAVR System, EVOLUT™ PRO System, or future iteration (CoreValve; Medtronic, Inc., Dublin, Ireland) TAVR device that is introduced via the femoral artery using conventional catheterization techniques and is approved for risk profiles included in this study. The associated DFUs should be consulted to determine the appropriate control valve sizes required to treat subjects with a native annulus diameter range between 20.5mm and 29mm.

Note: Every subject in the Main Randomized Cohort and the Extended Durability Study must be deemed treatable with an available size of both the test (ACURATE) device and the control device. The control device in the planned size must be approved for treatment of the subject (e.g., if a subject to be treated is considered to be at intermediate surgical risk, then the planned control device must be approved for use in intermediate-risk subjects). The control device in the planned size must be commercially available at the investigative center where the implant procedure is being performed.

5.3. *Device Labeling*

5.3.1. Test Device

The study Manual of Operations includes the DFU/IFU for the ACURATE *neo2* Valve, ACURATE *neo2* Transfemoral Delivery System, ACURATE *Prime* Aortic Valve,

ACURATE *Prime* Transfemoral Delivery System, and ACURATE *Prime* Loading Kit. Study devices are labeled on the top and one side (one label wraps around the top and side) of the outer carton and on the sterile pouch. Packaging will include peelable, self-adhesive labels for each unit shipped. The labeling will include the following information.

- Product Name
- Unique Identifier or Lot Number/Serial Number
- Expiration (use by) date (labeled as month/year, device not to be used after the last day of the indicated month)

The following statement appears on the label.

Caution: Investigational Device. Limited by United States law to investigational use. Exclusively for Clinical Investigations.

In addition, the following statement appears on the product labeling.

Investigational Device. To be Used by Qualified Investigators only.

5.3.2. Control Device

Information is provided in the DFU/IFU supplied with the commercially available TAVR devices used as the control device in this study.

6. Study Objectives and Endpoints

6.1. *Study Objectives*

The objective of the ACURATE IDE clinical study is to evaluate safety and effectiveness of the ACURATE Transfemoral Aortic Valve System for TAVR in subjects with severe native aortic stenosis who are indicated for transcatheter aortic valve replacement.

6.2. *Study Endpoints*

Outcomes in the randomized cohorts of the ACURATE IDE trial (Main Randomized Cohort and Extended Durability Study) will be assessed on an intention-to-treat (ITT) basis and an implanted basis. The ITT analysis populations of the ACURATE IDE randomized cohorts include subjects who sign an Informed Consent Form (see Section **20**), are enrolled in the trial (see Section **9.1** for point of enrollment), and are randomized, whether or not an assigned study device is implanted. The implanted analysis populations of the ACURATE IDE randomized cohorts include ITT subjects who are implanted with the assigned (test versus control), randomized study device. For the implanted randomized cohort analysis sets, if a subject receives 2 different valve types from 2 different manufacturers, the subject will be excluded from the implanted analysis.

Among the Roll-In, ACURATE *Prime* XL, and CAS cohorts of ACURATE IDE, all subjects who sign the IRB-approved study ICF and are enrolled in the trial will be included in the

analysis sample, regardless of whether the study device was implanted. Endpoint definitions can be found in **Table 25.2-1**.

6.3. *Primary Endpoint*

The primary endpoint is a composite of all-cause mortality, all stroke, and rehospitalization at 1 year. The primary analysis set for the primary endpoint for the Main Randomized Cohort is the ITT analysis set.

Note: For the primary endpoint, rehospitalization includes hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV); per VARC-2 definition.

6.4. *Additional Measurements*

This section describes required assessments to be performed in the ACURATE IDE trial.

Additional measurements based on the VARC endpoints and definitions[66-68] (see ***Note 1*** below) will be collected peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, 6 months, and annually up to 10 years post index procedure, unless otherwise specified below.

- Safety endpoints adjudicated by an independent Clinical Events Committee (CEC; Section **21.1.1**):
  - Mortality: all-cause, cardiovascular, and non-cardiovascular
  - Stroke: disabling and non-disabling
  - Myocardial infarction (MI): periprocedural (≤72 hours post index procedure) and spontaneous (>72 hours post index procedure)
  - Bleeding: life-threatening (or disabling) and major (through 5 years)
  - Acute kidney injury (AKI; ≤7 days post index procedure): based on the AKIN System[69,70] Stage 3 (including renal replacement therapy) or Stage 2
  - Major vascular complications (through 5 years)
  - Repeat procedure for valve-related dysfunction (surgical or interventional therapy)
  - Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV)
  - New permanent pacemaker implantation resulting from new or worsened conduction disturbances (definitions in **Table 25.2-1**)
  - New onset of atrial fibrillation or atrial flutter
  - Coronary obstruction: periprocedural (≤72 hours post index procedure)
  - Ventricular septal perforation: periprocedural (≤72 hours post index procedure)
  - Mitral apparatus damage: periprocedural (≤72 hours post index procedure)
  - Cardiac tamponade: periprocedural (≤72 hours post index procedure)
  - Valve migration

  - Valve embolization
  - Ectopic valve deployment
  - Transcatheter aortic valve (TAV)-in-TAV deployment
  - Prosthetic aortic valve thrombosis
  - Prosthetic aortic valve endocarditis
- Device performance endpoints peri- and post-procedure:
  - Successful vascular access, delivery and deployment of the study valve and successful retrieval of the delivery system
  - Grade of aortic valve regurgitation: paravalvular, central and combined
- Device success, defined as absence of procedural mortality, correct positioning of a single transcatheter valve in the proper anatomical location, and intended performance of the study device (indexed effective orifice area [iEOA] >0.85 cm^2/m^2 for BMI <30 kg/m^2 and iEOA >0.70 cm^2/m^2 for BMI ≥30 kg/m^2 plus either a mean aortic valve gradient <20 mm Hg or a peak velocity < 3m/sec, and no moderate or severe prosthetic valve aortic regurgitation)
- Additional indications of prosthetic aortic valve performance as measured by transthoracic echocardiography (TTE; see ***Note 2*** and ***Note 3*** below) and assessed by an independent core laboratory, including EOA, mean and peak aortic gradients, peak aortic velocity, and grade of aortic regurgitation
- Functional status as evaluated by New York Heart Association (NYHA) classification (see ***Note 3*** below)
- Neurological status (see ***Note 4*** below) as determined by the following:
  - National Institutes of Health Stroke Scale (NIHSS) conducted by a neurology professional or certified personnel at discharge and 1 year
  - Modified Rankin Scale (mRS) conducted by a neurology professional or certified personnel at discharge and all follow-up visits up to 5 years
  - Neurological physical exam conducted by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner in all subjects where stroke is suspected
- Health status as evaluated by Kansas City Cardiomyopathy[71] and SF-12[72] Quality of Life (QOL) questionnaires at baseline, 1 month, 1 year, and 5 years.
- For subjects in the 4D CT Imaging Substudy, assessments using 4D CT at 30 days and 1 year will be done as listed below (see ***Note 5*** below).
  - Assessment of leaflet mobility
  - Assessment of hypoattenuated leaflet thickening (HALT[73])
  - Assessment of leaflet thrombosis

Note 1: The most current VARC definitions and endpoints available at the beginning of the trial were used.

Note 2: In ACURATE IDE, at least 1 post-procedural echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest study performed will be used for analysis.

Note 3: Echocardiography and NYHA assessment are not required in years 6, 8, and 9 (telephone follow-up only).

Note 4: **Table 6.4-1** summarizes actions required for subjects with a neurological event in ACURATE IDE.

Table 6.4-1: Neurological Events in ACURATE IDE

Subject Status	Action
Subjects who receive a study device (test or control) and are diagnosed with a stroke	A neurological physical exam (conducted by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner), NIHSS assessment (conducted by a neurology professional or certified personnel), and mRS (conducted by a neurology professional or certified personnel) must be performed after the event. Additionally, mRS must be administered at 90±14 days after a stroke (see **Table 10.1-1**). The simplified mRS questionnaire may be used for the follow-up assessment.
Subjects who receive a study device (test or control) and are diagnosed with a transient ischemic attack	mRS must be performed after the event.
- Subjects with an attempted procedure but no implanted study device (test or control) who experience a neurological event within the first 1 year after the index procedure - Randomized subjects with no index procedure who experience a neurological event within the first 1 year after randomization	mRS must be performed after the event; mRS must also be administered at 90±14 days after a stroke and the results must be reported to the Sponsor.

Abbreviations: mRS=modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale

Note 5: Images will be read in a standard fashion for cardiac and non-cardiac findings by the clinical center CT imaging specialist. Clinical guidelines support anticoagulation with warfarin or another vitamin K inhibitor as a Class I recommendation for patients with established valve thrombosis[4,5]. However, there is no established guidance for pharmaceutical management of subclinical leaflet thrombosis. If deterioration of subject health due to suspected thrombosis occurs, the clinical center may request an unblinding of the Core Laboratory findings.

6.5. *Overview of Objectives and Endpoints*

Table 6.5-1 provides an overview of the aforementioned study objectives and endpoints and a justification for the specific endpoints.

Table 6.5-1: Overview of Objectives and Endpoints

Objective	Endpoint	Rationale for Endpoint
Primary Safety and Effectiveness		
Determine safety and effectiveness of the valve implant	1-Year Composite: mortality, all stroke, and rehospitalization	Assess the long-term benefit (1 year) in a large elderly population receiving ACURATE *neo2*; assessments recommended by VARC[66,67]. Events are adjudicated by an independent CEC.
Additional Measurements of Safety and Effectiveness		
Evaluate safety of the valve implant and the procedure	Safety measures at discharge, 30 days, 6 months, and annually up to 10 years post index procedure	Safety assessments recommended by VARC[66,67] for this elderly population. Events are adjudicated by an independent CEC.
Evaluate effectiveness of the valve implant	Effectiveness measures at discharge, 30 days, 6 months, and annually up to 10 years post index procedure	Effectiveness assessments recommended by VARC[66,67] for this elderly population. Events are adjudicated by an independent CEC.

Abbreviations: CEC=Clinical Events Committee; VARC=Valve Academic Research Consortium

7. Study Design

ACURATE IDE is a prospective, multicenter trial designed to evaluate the safety and effectiveness of the ACURATE Transfemoral Aortic Valve System (ACURATE) for TAVR in subjects with severe native aortic stenosis who are indicated for transcatheter aortic valve replacement.

7.1. *Scale and Duration*

Subjects will be enrolled at up to 85 centers in the United States, Canada, Australia, and Europe. There will be up to 2820 subjects total in ACURATE IDE. It is expected that >80% of enrolled subjects will be from the United States. To achieve sufficient distribution of lower risk subjects in the Main Randomized Cohort, there will be ≥ 30% intermediate risk randomized subjects and ≥ 35% low risk randomized subjects enrolled (please see definition of operative risk in Section **25.2**).

The ACURATE IDE study cohorts include the following.

- **Main Randomized Cohort:** A prospective, multicenter, 1:1 randomized controlled trial (RCT; ACURATE versus a commercially available balloon-expandable SAPIEN 3™ Transcatheter Heart Valve or future iteration [SAPIEN 3; Edwards Lifesciences LLC, Irvine, CA, USA] or a commercially available self-expanding CoreValve® Transcatheter Aortic Valve Replacement System, CoreValve® Evolut™ R Recapturable TAVR System, EVOLUT™ PRO System, or future iteration [CoreValve; Medtronic, Inc., Dublin, Ireland]). There will be 1500 subjects in the RCT.
- **Roll-In Cohort:** A non-randomized Roll-In phase with the test device. Centers that do not have implantation experience with the ACURATE *neo*™ bioprosthesis

(transfemoral delivery) will perform at least 2 Roll-In cases with ACURATE *neo2* before commencing treatment in the Main Randomized Cohort (up to 170 Roll-In subjects in total). Centers with prior experience with ACURATE are not required to do Roll-In cases. Data from Roll-In subjects will be summarized separately from the Main Randomized Cohort and will not be included in the primary endpoint analysis.

- **4D CT Imaging Substudy:** Select centers with the ability to perform high quality 4D computed tomography (CT) scans will include subjects (minimum of 200) from the Main Randomized Cohort in a 4D CT Imaging Substudy to assess the prevalence of reduced leaflet mobility and hypoattenuated leaflet thickening (HALT)[73] and the relationship, if any, to clinical events. Centers should ask all eligible subjects to consider participation in the substudy.
- **ACURATE *Prime*™ XL Nested Registry:** A non-randomized, nested registry cohort of subjects who will receive the ACURATE *Prime*™ Transfemoral Aortic Valve System XL (ACURATE *Prime* XL Nested Registry). Participating centers will be a subset of United States centers that have enrolled subjects in ACURATE IDE. Data from subjects in this nested registry will be summarized separately from the randomized, Roll-In, and Continued Access Study cohorts. There will be 50 subjects at up to 20 centers in the United States enrolled in this registry.
- **ACURATE Extended Durability Study:** An additional 1:1 randomized study (ACURATE versus Control [commercially available SAPIEN 3 or CoreValve] TAVR device) including only subjects considered to be at low surgical risk. Subjects will receive ACURATE *neo2* (S, M, or L valve sizes) or ACURATE *Prime* XL. Randomization will be stratified by center and by intended control device. Low-risk subjects receiving ACURATE *neo2* will be enrolled in the Extended Durability Study only after enrollment of the Main Randomized Cohort is completed. Enrollment of low-risk subjects with ACURATE *Prime* XL will start after enrollment in both the Main Randomized Cohort and the ACURATE *Prime* XL Nested Registry is completed. Data from subjects in the Extended Durability Study will be summarized separately from other cohorts.
  Note: Centers must complete the roll-in phase of the study, if applicable, before participating in ACURATE Extended Durability Study.
- **ACURATE Continued Access Study (CAS):** An additional cohort of subjects receiving ACURATE *neo2* (S, M, and L valve sizes) or ACURATE *Prime* XL. Enrollment of subjects with ACURATE *neo2* will start after enrollment of the ACURATE IDE Main Randomized Cohort is completed. Enrollment of subjects with ACURATE *Prime* XL will start after enrollment in both the Main Randomized Cohort and the ACURATE *Prime* XL Nested Registry is completed. Subjects at all surgical risks may be enrolled in ACURATE CAS, but low-risk subjects will be considered for enrollment only after enrollment in the Extended Durability Study is completed. Data from subjects in ACURATE CAS will be summarized separately from other cohorts and will be used to further assess performance and safety.

Note: Centers must complete the roll-in phase of the study, if applicable, before participating in ACURATE CAS.

The devices to be used and the subject risk levels for the ACURATE IDE cohorts are summarized below in **Table 7.1-1**.

Table 7.1-1: Devices and Risk Levels for ACURATE IDE Cohorts

Device	Cohort				
	Roll-In	**Main RCT**	***Prime* XL Nested Registry**	**Extended Durability[1]**	**Continued Access Study[1]**
ACURATE *neo2* (S, M, L)	All risks	All risks	N/A	Low risk	All risks[2]
ACURATE *Prime* (XL)	N/A	N/A	All risks	Low risk[3]	All risks[2,3]

Note 1: Enrollment of subjects in the Extended Durability cohort and the CAS cohort will begin after completion of enrollment in the Main RCT.

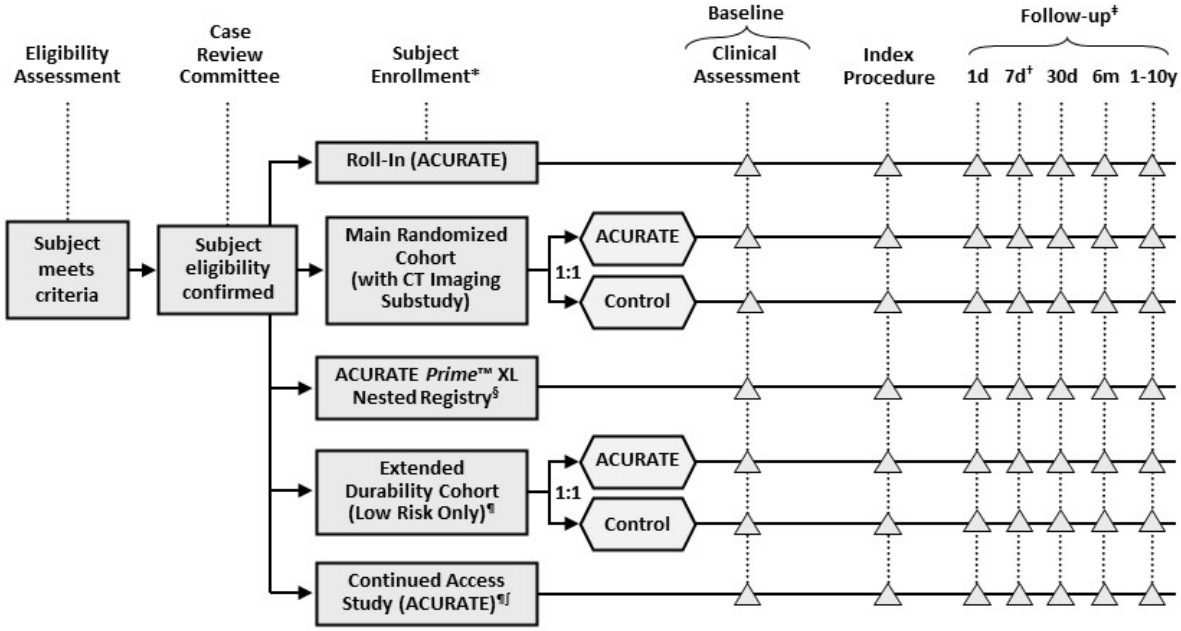
Note 2: Enrollment of low-surgical-risk subjects in the CAS cohort will begin after completion of enrollment the Extended Durability cohort.

Note 3: Enrollment of subjects receiving ACURATE *Prime* XL in the Extended Durability and CAS cohorts will begin after enrollment completion in both the Main RCT and *Prime* XL Nested Registry.

Abbreviations: CAS=Continued Access Study; N/A=not applicable; RCT=randomized controlled trial

All subjects implanted will be followed at baseline, peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, 6 months, and then annually for up to 10 years post-procedure. Enrollment is expected to be completed in approximately 62 months; therefore, the total study duration is estimated to be approximately 16 years. The study duration for each subject is expected to be approximately 10 years. Implanted subjects participating in the 4D CT Imaging Substudy will undergo additional 4D CT assessment at 30 days and 1 year. Enrolled subjects who do not have a study device implanted will be assessed through 1-year post-procedure for safety/adverse events.

The study design is summarized below in **Figure 7.1-1**. As noted above, enrollment in the Extended Durability Study will commence for low-risk subjects receiving ACURATE *neo2* after enrollment of the Main Randomized Cohort is completed. Enrollment of low-risk subjects receiving ACURATE *neo2* in ACURATE CAS will begin after enrollment in the Extended Durability Study is completed. Enrollment of low-risk subjects with ACURATE *Prime* XL will start after enrollment in both the Main Randomized Cohort and the ACURATE *Prime* XL Nested Registry is completed.



* Randomized subjects are considered enrolled upon randomization; roll-in, ACURATE *Prime* XL Nested Registry, and Continued Access Study subjects are considered enrolled when an attempt is made to insert the ACURATE Transfemoral Aortic Valve System into the femoral artery.

† Discharge or 7 days, whichever comes first

‡ Includes clinic/in-person visit or telehealth visit (https://telehealth.HHS.gov) at 30 days, 6 months, and years 1 – 5, 7 & 10; telephone follow-up at years 6, 8 & 9. For subjects in the CT Imaging Substudy, the visits at 30 days and 1 year must be done in the clinic (or in-hospital). Enrolled subjects who do not have a study device implanted will be assessed through 1-year post procedure for safety.

§ Includes subjects who receive the ACURATE *Prime*™ XL device.

¶ Includes subjects who receive the ACURATE *neo2*™ (S, M, L) device (after conclusion of enrollment in the Main Randomized Cohort) or ACURATE *Prime*™ XL device (after conclusion of XL Nested Registry enrollment).

∫ Low-risk subjects will be considered for enrollment in the Continued Access Study after enrollment is completed in the Extended Durability Study.

Figure 7.1-1: ACURATE IDE Study Design

The ACURATE IDE study will be conducted in accordance with 21 CFR Parts 11, 50, and 54; the relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP); the International Standard ISO 14155 Clinical Investigation of Medical Devices for Human Subjects–Good Clinical Practice; ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country/state/local laws and regulations. The study shall not begin until the required approval/favorable opinion from the Institutional Review Board/Research Ethics Board/Human Research Ethics Committee/ Independent Ethics Committee (IRB/REB/HREC/IEC) and/or regulatory authority has been obtained, if appropriate. See Section **10** below for additional information on study design and data collection.

The ACURATE IDE study is registered at ClinicalTrials.gov (NCT03735667).

7.2. *Treatment Assignment*

Screening materials from eligible subjects who provide written informed consent and who are identified by the investigators as having met all the inclusion and none of the exclusion criteria (see below **Table 8.2-1** and **Table 8.3-1**, respectively) will be reviewed by a Case

Review Committee (CRC; see Section **21.2**) to assess and confirm suitability of subjects for enrollment.

For the randomized cohorts (Main Randomized Cohort and Extended Durability Cohort), eligible subjects will be randomized in a 1:1 allocation to receive either the test device (ACURATE; see Section **5.1**) or a control device (SAPIEN 3 or CoreValve; see Section **5.2**). The randomization schedules will be computer-generated, using a pseudo-random number generator. Randomization will be stratified by center and by intended control device. All randomized subjects will have unique identification numbers. Random permuted blocks will be employed to ensure approximate balance of treatment allocation within each stratum. Instructions on randomization are provided in the Manual of Operations. Subjects should be randomized within 7 calendar days of CRC approval. Subjects should be treated within 14 calendar days after randomization. Because this is an unblinded study design, physician operators will not be blinded with respect to valve type implanted.

Subjects in the non-randomized ACURATE *Prime* XL Nested Registry cohort will all receive ACURATE *Prime*™ Transfemoral Aortic Valve System XL valves. Subjects in the non-randomized ACURATE CAS will receive ACURATE *neo2* (S, M or L) or ACURATE *Prime* XL valves.

Note 1: Centers that do not have implantation experience with the ACURATE *neo*™ bioprosthesis (transfemoral delivery) will perform at least 2 non-randomized Roll-In cases before commencing treatment in the Main Randomized Cohort. Centers with prior ACURATE *neo*™ experience may do Roll-In cases but are not required to do so. All Roll-In subjects will have unique identification numbers.

Note 2: Subjects in the Roll-In cohort (Section **9.1.1**) and Main Randomized Cohort (Section **9.1.2**) will have a documented aortic annulus size of ≥21mm and ≤27mm based on pre-procedure diagnostic imaging (see **Table 5.1-1**). Subjects in the ACURATE *Prime* XL Nested Registry (Section **9.1.3**) will have a documented aortic annulus size of ≥26.5mm and ≤29mm based on pre-procedure diagnostic imaging (see **Table 5.1-1**). Subjects in the Extended Durability Study (Section **9.1.4**) and the Continued Access Study (Section **9.1.5**) will have a documented aortic annulus size of ≥20.5mm and ≤29mm based on pre-procedure diagnostic imaging (see **Table 5.1-2**).

7.2.1. Treatment and Control

Treatment and control devices are described briefly in **Table 7.2-1**. Please see Section **5** for the investigational device matrix and additional device information.

Table 7.2-1: Treatment and Control Devices

Treatment	Device Name	Device Description
Test Device ACURATE	ACURATE *neo2*™ Aortic Valve Valve size: - S (small) - M (medium) - L (Large)	Valve (additional information in Section **5.1.1**) Includes 3 main components: - A three-leaflet porcine pericardial bioprosthetic aortic valve; - A self-expandable Nitinol stent;

Table 7.2-1: Treatment and Control Devices

Treatment	Device Name	Device Description
	Nominal diameter at waist level is 23mm, 25mm, and 27mm for the small, medium, and large valve diameters, respectively. ACURATE *Prime*™ Aortic Valve XL Valve size: - XL (extra-large) Nominal diameter is 29mm at waist level. ACURATE *neo2*™ Transfemoral Delivery System The delivery system is compatible with the S, M, and L valve sizes. ACURATE *Prime*™ Transfemoral Delivery System XL The delivery system is compatible with the XL valve size. ACURATE *Prime*™ Loading Kit XL	- A double porcine pericardium skirt sutured on the inner and outer surface of the stent to prevent paravalvular leaks. Introduced via the iliofemoral artery. Delivery System (additional information in Section **5.1.2**) Allows positioning and delivery of the transcatheter valve via iliofemoral access. Allows loading of the XL valve onto the compatible delivery system.
Control Device SAPIEN 3*; CoreValve*	Commercial TAVR device introduced via the femoral artery	Balloon-expandable SAPIEN 3 or self-expanding CoreValve TAVR device (see descriptions in Section **5.2**) that is commercially available in the applicable region.

Note: Every subject in the randomized cohort must be deemed treatable with an available size of both the test device and the control device. The control device in the planned size must be approved for treatment of the subject (i.e., if a subject to be treated is considered intermediate surgical risk, then the planned control device must be approved for use in intermediate-risk subjects). The control device in the planned size must be commercially available at the investigative center where the implant procedure is being performed.

* Or future iteration

Abbreviation: TAVR=transcatheter aortic valve replacement

7.3. *Justification for the Study Design*

There will be up to 2820 subjects total in ACURATE IDE. In order to support the stated objectives of this study (see Section **6.1**) while also limiting the potential exposure of study subjects to risk, up to 170 subjects will be enrolled in the Roll-In phase of this study (centers without implantation experience with the ACURATE *neo*™ bioprosthesis [transfemoral delivery] are required to do 2 Roll-In cases each), 1500 subjects will be randomized and enrolled in the Main Randomized Cohort, 50 subjects will be enrolled in the ACURATE *Prime* XL Nested Registry at a subset of U.S. centers, a minimum of 100 subjects will be randomized in the Extended Durability Study, and up to 1000 subjects will be enrolled in the ACURATE Continued Access Study. Up to 85 centers in the United States, Canada, Australia, and Europe will participate in the study. Safety and effectiveness results will be reported on all enrolled subjects (see Section **19** for information on safety reporting). Selected centers with the ability to perform high quality 4D CT scans will include subjects

from the Main Randomized Cohort in a 4D CT Imaging Substudy to assess the prevalence of reduced leaflet mobility and HALT[73] and their relationship, if any, to clinical events. In addition to the risk-benefit analysis noted in Section **4.2** (see also Section **18**), ongoing dynamic data safety monitoring will be performed throughout the trial to minimize risk to subjects (see Section **21.1**). All implanted subjects will be followed for up to 10 years post index procedure. To achieve sufficient distribution of lower risk subjects, there will be ≥ 30% intermediate risk and ≥ 35% low risk subjects enrolled in the Main Randomized Cohort. Per society guidelines[4,5] antiplatelet therapy with aspirin and/or a $P2Y_{12}$ inhibitor is recommended after TAVR to decrease the risk of thrombotic or thromboembolic complications if there are no contraindications to these medications.

8. Subject Selection

8.1. *Study Population and Eligibility*

Inclusion and Exclusion criteria are listed below in Section **8.2** and Section **8.3**, respectively.

8.2. *Inclusion Criteria*

Subjects who meet all criteria in **Table 8.2-1** may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section **8.3**) is met. Centers participating in the 4D CT Imaging Substudy must have the ability to perform high quality 4D CT scans; subjects in this substudy must meet none of the additional exclusion criteria listed in **Table 8.3-2**.

Table 8.2-1: ACURATE IDE Inclusion Criteria

IC1.	Subject has documented severe symptomatic native aortic stenosis defined as follows: aortic valve area (AVA) ≤1.0 cm^2 (or AVA index ≤0.6 cm^2/m^2) AND a mean pressure gradient ≥40 mmHg, OR maximal aortic valve velocity ≥4.0 m/s, OR Doppler velocity index ≤0.25 as measured by echocardiography and/or invasive hemodynamics[76]. ***Note:*** In cases of low flow, low gradient aortic stenosis with left ventricular dysfunction (ejection fraction <50%), dobutamine can be used to assess the grade of aortic stenosis (maximum dobutamine dose of 20 mcg/kg/min recommended)[76]; the subject may be enrolled if echocardiographic criteria are met with this augmentation.
IC2.	Subject has a documented aortic annulus size of ≥20.5 mm and ≤29 mm based on the center's assessment of pre-procedure diagnostic imaging (and confirmed by the Case Review Committee [CRC]) and, for the Main Randomized Cohort and Extended Durability Study, is deemed treatable with an available size of both test and control device.
IC3.	For subjects with symptomatic aortic valve stenosis per IC1 definition above, functional status is NYHA Functional Class ≥ II.
IC4.	Heart team (which must include an experienced cardiac interventionalist and an experienced cardiac surgeon) agrees that the subject is indicated for TAVR, is likely to benefit from valve replacement, and TAVR is appropriate.
IC5.	Subject (or legal representative) understands the study requirements and the treatment procedures and provides written informed consent.

Table 8.2-1: ACURATE IDE Inclusion Criteria

IC6.	Subject, family member, and/or legal representative agree(s) and subject is capable of returning to the study hospital for all required scheduled follow up visits.
IC7.	Subject is expected to be able to take the protocol-required adjunctive pharmacologic therapy.

Abbreviations: AVA=aortic valve area; CRC=Case Review Committee; NYHA=New York Heart Association; STS=Society of Thoracic Surgeons; TAVR=transcatheter aortic valve replacement

8.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (**Table 8.3-1**) cannot be included in this clinical study or will be excluded from this clinical study. No vulnerable populations will be enrolled in this study. See Section **25.2** for the definition of a vulnerable subject.

Table 8.3-1: ACURATE IDE Exclusion Criteria

EC1.	Subject has a unicuspid or bicuspid aortic valve.
EC2.	Subject has had an acute myocardial infarction within 30 days prior to the index procedure (defined as Q-wave MI or non–Q-wave MI with total CK elevation ≥ twice normal in the presence of CK-MB elevation and/or troponin elevation).
EC3.	Subject has had a cerebrovascular accident or transient ischemic attack clinically confirmed by a neurologist or neuroimaging within the past 6 months prior to study enrollment.
EC4.	Subject is on renal replacement therapy or has eGFR <20.
EC5.	Subject has a pre-existing prosthetic aortic or mitral valve.
EC6.	Subject has severe (4+) aortic, tricuspid, or mitral regurgitation.
EC7.	Subject has moderate or severe mitral stenosis (mitral valve area ≤1.5 cm^2 and diastolic pressure half-time ≥150 ms, Stage C or D[4]).
EC8.	Subject has a need for emergency surgery for any reason.
EC9.	Subject has a history of endocarditis within 6 months of index procedure or evidence of an active systemic infection or sepsis.
EC10.	Subject has echocardiographic evidence of new intra-cardiac vegetation or intraventricular or paravalvular thrombus requiring intervention.
EC11.	Subject has platelet count <50,000 cells/mm^3 or >700,000 cells/mm^3, or white blood cell count <1,000 cells/mm^3.
EC12.	Subject has had a gastrointestinal bleed requiring hospitalization or transfusion within the past 3 months or has other clinically significant bleeding diathesis or coagulopathy that would preclude treatment with required antiplatelet regimen or will refuse transfusions.
EC13.	Subject has known hypersensitivity to contrast agents that cannot be adequately pre-medicated or has known hypersensitivity to the protocol required medications (aspirin, all $P2Y_{12}$ inhibitors, heparin), or to the individual components of the test or control valve (nickel, titanium, stainless steel, platinum, iridium or polyethylene terephthalate [PET]).
EC14.	Subject has a life expectancy of less than 12 months due to non-cardiac, comorbid conditions based on the assessment of the investigator at the time of enrollment.

Table 8.3-1: ACURATE IDE Exclusion Criteria

EC15.	Subject has hypertrophic cardiomyopathy.
EC16.	Subject has any therapeutic invasive cardiac or vascular procedure within 30 days prior to the index procedure (except for balloon aortic valvuloplasty, pacemaker implantation, or implantable cardioverter defibrillator implantation, which are allowed).
EC17.	Subject has untreated coronary artery disease, which in the opinion of the treating physician is clinically significant and requires revascularization.
EC18.	Subject has severe left ventricular dysfunction with ejection fraction <20%.
EC19.	Subject is in cardiogenic shock or has hemodynamic instability requiring inotropic support or mechanical support devices.
EC20.	Subject has arterial access that is not acceptable for the study device (test or control) delivery systems as defined in the device (test or control) Directions For Use.
EC21.	Subject has either of the following: • Severe vascular disease that would preclude safe access (e.g., aneurysm with thrombus that cannot be crossed safely; marked tortuosity; significant narrowing of the abdominal aorta; severe unfolding of the thoracic aorta; or thick, protruding, ulcerated atheroma in the aortic arch), OR • Severe/eccentric calcification of the aortic annulus that would prevent safe implantation of the TAVR prosthesis.
EC22.	Subject has current problems with substance abuse (e.g., alcohol, etc.) that may interfere with the subject's participation in this study.
EC23.	Subject is participating in another investigational drug or device study that has not reached its primary endpoint or subject intends to participate in another investigational device clinical trial within 12 months after index procedure.
EC24.	Subject has untreated conduction system disorder (e.g., Type II second degree atrioventricular block) that in the opinion of the treating physician is clinically significant and requires a pacemaker implantation. Enrollment is permissible after permanent pacemaker implantation.
EC25.	Subject has severe incapacitating dementia.

Abbreviations: CK=creatine kinase; MI=myocardial infarction; TAVR=transcatheter aortic valve replacement

Additional exclusion criteria apply to subjects considered for enrollment in the 4D CT Imaging Substudy as listed below in **Table 8.3-2**.

Table 8.3-2: ACURATE IDE Additional Exclusion Criteria for the 4D CT Imaging Substudy

AEC1.	Subject has eGFR <30 mL/min (chronic kidney disease stage IV or stage V).
AEC2.	Subject has atrial fibrillation that cannot be rate controlled to ventricular response rate < 60 bpm.
AEC3.	Subject is expected to undergo chronic anticoagulation therapy after the index procedure. ***Note:*** Subjects treated with short-term anticoagulation post procedure can be included in the 4D CT Imaging Substudy; in these subjects the 30-day imaging will be performed 30 days after discontinuation of anticoagulation.

Abbreviations: CT=computed tomography; eGFR=estimated glomerular filtration rate

9. Subject Accountability

9.1. *Point of Enrollment*

9.1.1. Roll-In Subjects

There will be a non-randomized Roll-In phase with only the test device. Centers that do not have previous implantation experience with the ACURATE *neo*™ bioprosthesis (transfemoral delivery) will perform at least 2 Roll-In cases before commencing treatment in the Main Randomized Cohort; centers with prior experience with ACURATE *neo* are not required to do Roll-In cases. For this Roll-In phase, subjects confirmed eligible for the study by the CRC (see Section **21.2**) and who provided written informed consent (see Section **20**) are considered enrolled in the study as soon as an attempt is made to insert the test device into the subject's femoral artery.

9.1.2. Main Randomized Cohort Subjects

For the Main Randomized Cohort, subjects confirmed eligible for the study by the CRC (see Section **21.2**) and who provided written informed consent (see Section **20**) are considered enrolled in the study upon randomization.

9.1.3. ACURATE *Prime*™ XL Nested Registry Subjects

For the ACURATE *Prime* XL Nested Registry, subjects confirmed eligible for the study by the CRC (see Section **21.2**) and who provided written informed consent (see Section **20**) are considered enrolled in the study as soon as an attempt is made to insert the test device into the subject's femoral artery.

9.1.4. ACURATE Extended Durability Study Subjects

Subjects confirmed eligible for the ACURATE Extended Durability Study by the CRC (see Section **21.2**) and who provided written informed consent (see Section **20**) are considered enrolled in the study upon randomization.

9.1.5. ACURATE Continued Access Study Subjects

For the ACURATE Continued Access Study, subjects confirmed eligible for the study by the CRC (see Section **21.2**) and who provided written informed consent (see Section **20**) are considered enrolled in the study as soon as an attempt is made to insert the test device into the subject's femoral artery.

9.2. *Discontinuation of Study Intervention*

If a test device (ACURATE valve) is explanted during conventional scheduled or emergent surgical valve replacement or during an autopsy, if possible, the explanted valve should be assessed by the independent histopathology core laboratory for macroscopic and microscopic

analyses. Please refer to the study Manual of Operations for recommendations on the explant procedure and shipment of the explanted valve.

If a control device is explanted during conventional scheduled or emergent surgical valve replacement or during an autopsy, please follow the directions in the associated DFU/IFU.

Information on the explant procedure must be documented in source notes and captured in the Explant Form of the eCRF. If a study valve is surgically explanted, the subject will be followed for safety (no protocol-required echocardiography, electrocardiography or QOL assessment) through end of study.

9.3. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study) shall be accounted for and documented. If a subject withdraws from the clinical investigation the reason(s) shall be reported. Reasons for withdrawal include but are not limited to physician discretion, subject choice to withdraw consent, or death. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.

While all efforts will be made to minimize attrition, subjects may withdraw from the study at any time, with or without reason, and without prejudice to further treatment. Withdrawn subjects will not undergo any additional study follow-up, nor will they be replaced. The investigator may discontinue a subject from participation in the study if the investigator feels that the subject can no longer fully comply with the requirements of the study or if any of the study procedures are deemed potentially harmful to the subject. Data that have already been collected on withdrawn subjects will be retained and may be used for analysis, unless local regulations apply. No new data will be collected after subject withdrawal.

All applicable case report forms up to the point of subject withdrawal and an "End of Study" form for the subject must be completed. If the withdrawal is due to investigator discretion, the investigator should follow-up with the subject per standard of care.

9.4. *Lost to Follow-Up*

All subjects implanted will be followed for up to 10 years post-procedure. Enrolled subjects who do not have a study device implanted will be assessed through 1-year post procedure for safety/adverse events but do not need to have protocol-required echocardiography. A subject will be considered "lost to follow-up" and terminated from the study when ***all*** criteria listed below have been met.

- Failure to complete 2 consecutive visits without due cause (beginning with the 6-month and 1-year visits, i.e., subjects should not be considered lost to follow-up prior to the 1-year follow-up visit), AND
- Documentation of 3 unsuccessful attempts, one of which must be in written communication, by the Investigator or his/her designee to contact the subject or next of kin, AND

- Notification from the Investigator to Sponsor reporting subject as lost to follow-up.

9.5. *End-of-Study Definition*

This clinical trial will be considered completed when subjects are no longer being examined or the last subject's last study visit as outlined in the data collection schedule (**Table 10.1-1**) has occurred. All subjects who receive a test or control device will be evaluated at discharge or 7 days (whichever comes first), 30 days, 6 months, and annually up to 10 years post index procedure. Visits at 30 days, 6 months, 1–5 years, 7 years and 10 years are office/clinical/in-person or telehealth visits. Telephone follow-up is allowed at 6, 8, and 9 years. A subject's participation in the study will be considered complete after the 10-year visit. For subjects who do not receive a test or control device, participation in the study will be considered complete after the 1-year visit.

10. Study Methods

10.1. *Data Collection*

This section indicates the data needed to fulfill the objectives of this clinical study. Boston Scientific Corporation considers data collected from clinical trial subjects to be personal data (see definitions of different data categories in **Table 25.2-1**) and compliance with privacy and data protection laws and regulations (for example, the General Data Protection Regulation [GDPR]) to be critically important. Data collection for this clinical study has been carefully considered to comply with data privacy laws.

The data collection schedule is shown in **Table 10.1-1** and in **Figure 10.1-1**. Additional information, including recommended post-procedure medical therapy, is provided in Section **10.2** through Section **10.11**. The methods are based on Valve Academic Research Consortium (VARC) metrics[66,67] and guideline recommendations[4,5].

All subjects who receive a study valve (test or control) will be evaluated at discharge or 7 days (whichever comes first), 30 days, 6 months, 1 year, and then annually through 10 years post index procedure. Office/clinical/in-person or telehealth (https/telehealth.hhs.gov) follow-up visits are scheduled for appointed times after the date of the index procedure through 5 years and at 7 and 10 years. Telephone follow-up is allowed at 6, 8, and 9 years. It is important that this schedule be maintained as closely as possible for all subjects. Boston Scientific Corporation recognizes that subjects may not be able to return for all scheduled visits at precisely the date required and, therefore, a period in which each visit is allowed is indicated in **Table 10.1-1**. Visits/telephone follow-up not completed will be considered missed and recorded as protocol deviations and will be reviewed as such by the Sponsor or designee on a regular basis in accordance with applicable standard operating procedures. Visits/telephone follow-up completed outside these windows will be recorded as protocol deviations. Each follow-up must be performed as noted in **Table 10.1-1**.

Note: All required ECG measurements and transthoracic echocardiography measurements must be done for all subjects who have a transcatheter valve implanted in the aortic position

during the index procedure, even if the associated follow-up assessment is carried out via telehealth.

All follow-up dates will be calculated from the date of the (attempted) index procedure (or from date of randomization in randomized subjects where no implant is attempted). Subjects who are enrolled but do not receive a study valve (test or control) will be followed for 1 year to assess for safety but do not need to have protocol required echocardiography, electrocardiography, or QOL assessments. If a study valve is surgically explanted, the subject will be followed for safety (no protocol required echocardiography, electrocardiography, or QOL assessments) through end of study.

Table 10.1-1: Data Collection Schedule for ACURATE IDE

Assessment	Screening[a]	Baseline	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[b] (±7 Days) Office/ Telehealth Visit	6 Months[b] (±30 Days) Office/ Telehealth Visit	1 Year[b] (±30 Days) Office/ Telehealth Visit	2–5 Years[b] [Annual] (±45 Days) Office/ Telehealth Visit	7 and 10 Years[b] (±60 Days) Office/ Telehealth Visit	6, 8, and 9 Years[b] (±60 Days) Telephone
Signed Informed Consent Form[c]	X	–	–	–	–	–	–	–	–	–	–
Demographics and medical history, including cardiac, neurological, renal and peripheral disease	X	–	–	–	–	–	–	–	–	–	–
NYHA Classification	X	–	–	–	X	X	X	X	X	X	–
NIHSS[d]	–	X	–	–	X	–	–	X	–	–	–
Modified Rankin Scale[d]	–	X	–	–	X	X	X	X	X	–	–
12-lead ECG	–	X	–	X	X	X	X	X	–	–	–
Laboratory tests[e]	–	X	–	X	–	–	–	–	–	–	–
Risk assessments[f]	X	–	–	–	–	–	–	–	–	–	–
Frailty, disability and comorbidity[g]	X	–	–	–	–	–	–	–	–	–	–
Antiplatelet and anticoagulant (if applicable) medications	X	–	X	–	X	X	X	X	X	X	X
Other CV medications	X	–	–	–	–	–	–	–	–	–	–
TTE[h]	X	–	–	–	X	X	X	X	X	X	–
TEE[i]	–	–	O	–	–	–	–	–	–	–	–
Coronary angiogram/CT coronary angiogram[j]	X	–	–	–	–	–	–	–	–	–	–
CT angiogram of aortic structure[k]	X	–	–	–	–		–	–	–	–	–
CT angiogram of iliofemoral system[l]	X	–	–	–	–	–	–	–	–	–	–
QOL surveys[m]	–	X	–	–	–	X	–	X	X[n]	–	–

Table 10.1-1: Data Collection Schedule for ACURATE IDE

Assessment	Screening[a]	Baseline	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[b] (±7 Days) Office/ Telehealth Visit	6 Months[b] (±30 Days) Office/ Telehealth Visit	1 Year[b] (±30 Days) Office/ Telehealth Visit	2–5 Years[b] [Annual] (±45 Days) Office/ Telehealth Visit	7 and 10 Years[b] (±60 Days) Office/ Telehealth Visit	6, 8, and 9 Years[b] (±60 Days) Telephone
Procedural cine-angiography with post-deployment aortogram[o]	–	–	X	–	–	–	–	–	–	–	–
Balloon aortic valvuloplasty[p]	–	–	X/O	–	–	–	–	–	–	–	–
AE and ADE assessments[q]	–	–	X	X	X	X	X	X	–	–	–
Device deficiencies, SAE, SADE, UADE and CEC event assessments[r]	–	–	X	X	X	X	X	X	X	X	X
4D CT imaging of prosthetic valve[s]	–	–	–	–	–	X	–	X	–	–	–

Note: X = required; O = optional; – = not required; follow-up should be done by study personnel or as noted below. Visits at 30 days, 6 months, 1–5 years, 7 years and 10 years are office/clinical/in-person or telehealth visits; all required ECG measurements and TTE measurements must be done for all subjects who have a transcatheter valve implanted in the aortic position during the index procedure, even if the associated follow-up assessment is carried out via telehealth.

a: Screening materials for CRC review should be submitted electronically at least 5 days in advance of CRC review.

b: All follow-up dates will be calculated from the date of the (attempted) index procedure (or from date of randomization for randomized subjects where no implant is attempted). Where indicated, visits must be an office/clinical/in-person visit but may be done in-hospital should the subject be admitted at the time. Subjects who are enrolled but do not receive a study device (test or control) will be followed for 1 year to assess for safety but do not need to have protocol required TTE, ECG or QOL assessments.

c: Study-specific consent includes screening consent to perform required assessments beyond standard of care that will be evaluated by the CRC to confirm subject eligibility. If the study Informed Consent Form is modified during the course of the study, study subjects will be re-consented as necessary.

d: NIHSS and mRS must be performed by a neurology professional or certified personnel (external certification for NIHSS; internal or external certification for mRS). The NIHSS and mRS assessors should be independent (not involved with the care of study subjects). In addition to the assessments noted in the table, there are additional requirements for administering NIHSS/mRS/neurological physical exams in subjects where stroke is suspected. A neurological physical exam conducted by an independent neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner must be performed in all subjects where stroke is suspected. For subjects diagnosed with a neurological event, mRS and NIHSS must be performed after the event; mRS must also be administered at 90±14 days after a stroke. If a subject who has not received a study device (investigational or control) experiences a neurological event within the first 1 year after the index procedure, mRS must be performed on that subject after the event; mRS must also be administered at 90±14 days after a stroke and the results must be reported to the Sponsor.

e: Laboratory tests at baseline include CBC with platelets, albumin, serum creatinine, and cardiac enzymes. Cardiac enzymes (CK is required, CK-MB or troponin if CK is elevated) must be collected twice at intervals per standard of care within 6–24 hours post-procedure. Acute kidney injury should be assessed through discharge/7 days based on the AKIN system.

f: Consists of STS PROM score, euroSCORE II, and heart team assessment including an in-person evaluation by a center cardiac surgeon that must be confirmed by the CRC (which must include an experienced cardiac surgeon).

Table 10.1-1: Data Collection Schedule for ACURATE IDE

Assessment	Screening[a]	Baseline	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[b] (±7 Days) Office/ Telehealth Visit	6 Months[b] (±30 Days) Office/ Telehealth Visit	1 Year[b] (±30 Days) Office/ Telehealth Visit	2–5 Years[b] [Annual] (±45 Days) Office/ Telehealth Visit	7 and 10 Years[b] (±60 Days) Office/ Telehealth Visit	6, 8, and 9 Years[b] (±60 Days) Telephone

g: Frailty, disability, and comorbidity risk assessments must be captured at screening: height, weight, strength and balance (use of wheelchair, gait speed to walk 5 meters, number of falls in the past 6 months, maximal grip strength), and activities of daily living (Katz Index).

h: Transthoracic echocardiogram is required for all subjects who have a study valve implanted in the aortic position. This includes assessment of EOA, peak and mean aortic valve pressure gradients, peak aortic velocity, aortic regurgitation assessment, and LVEF. Screening TTE must be performed within 90 days prior to CRC approval. At least 1 echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest study performed will be used for analysis. All TTEs must be performed according to the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). If a subject does not receive a study valve, then no follow-up TTE is required.
Note: In cases of low flow, low gradient aortic stenosis with left ventricular dysfunction (ejection fraction <50%), dobutamine can be used to assess the grade of aortic stenosis; the subject may be enrolled if echocardiographic criteria are met with this augmentation. In cases where a subject who has met the echocardiographic criteria for enrollment receives BAV prior to the index procedure and subsequently no longer meets the study's aortic valve pressure gradient or EOA criteria, the subject may still be enrolled based on the pre-BAV echocardiographic data. In such cases, the most recent echocardiogram done prior to the index procedure (even if after BAV) must be submitted to the echocardiography core laboratory to be included in the baseline data.

i: TEE can be performed at the discretion of the operator.

j: A coronary angiogram/CT coronary angiogram must be performed within 365 days prior to CRC approval. If there is concern regarding the current extent of coronary artery disease or aortic stenosis, the CRC may recommend a repeat study closer to the time of enrollment.

k: A CT angiogram of the aortic complex must be performed within 180 days prior to CRC approval (and should be performed within 90 days if possible) to evaluate the aortic valve anatomy and aortic root dimensions for device sizing. CT angiogram must be performed according to the CT/Angiography Core Laboratory procedure guidelines (see study Manual of Operations). It must be sent to the core laboratory for detailed measurements and analyses in advance of the CRC review where results will be assessed to confirm subject's eligibility.

l: An assessment of the iliofemoral system must be performed within 180 days prior to CRC approval (and should be performed within 90 days if possible). A CT angiogram of the iliofemoral system should be performed for complete visualization of the iliac and femoral arteries to assess for dimensions, tortuosity, and calcification. The CT angiogram should be performed per the procedure guidelines (see study Manual of Operations) and sent to the CT core laboratory with the screening CT angiogram of the aortic structure. An iliofemoral invasive angiogram may be substituted for the iliofemoral CT angiogram.

m: Includes the Kansas City Cardiomyopathy and SF-12 QOL questionnaires. Baseline QOLs must be performed within 30 days prior to the index procedure.

n: QOL survey at 5 years.

o: Procedural cine-angiogram including the baseline images of the aortic complex and the final post-deployment aortogram of the ascending aorta must be performed and sent to the CT/Angiography core laboratory for analysis.

p: Balloon aortic valvuloplasty following standard techniques must be performed with an appropriately sized valvuloplasty balloon before test device implantation; BAV may be performed before control device implantation, but planned use should be reviewed by the CRC.

q: In subjects who receive a study device, AEs and ADEs will be monitored and collected from the time of enrollment through 12-month follow-up. For subjects who do not receive a study device, AEs will be monitored through 12-month follow-up.

r: Information on device deficiencies for the test device will be monitored and reported to Boston Scientific. Information on all SAEs, SADEs, UADEs, and CEC events will be monitored and reported to Boston Scientific for enrolled subjects from the time of enrollment through 5 years. After 5 years, serious adverse event assessment (includes SAE, SADE, UADE, and relevant VARC events to be adjudicated by the CEC [see ***Note*** below]) for test and control device(s) and device deficiencies assessment for test device(s) with associated treatment will be monitored and reported to Boston Scientific for enrolled subjects through termination of the study (or until a subject exits the study). For subjects who are enrolled

Table 10.1-1: Data Collection Schedule for ACURATE IDE

Assessment	Screening[a]	Baseline	Procedure	Within 1 Day Post-procedure	Prior to Discharge or 7 Days Post-Procedure	30 Days[b] (±7 Days) Office/ Telehealth Visit	6 Months[b] (±30 Days) Office/ Telehealth Visit	1 Year[b] (±30 Days) Office/ Telehealth Visit	2–5 Years[b] [Annual] (±45 Days) Office/ Telehealth Visit	7 and 10 Years[b] (±60 Days) Office/ Telehealth Visit	6, 8, and 9 Years[b] (±60 Days) Telephone

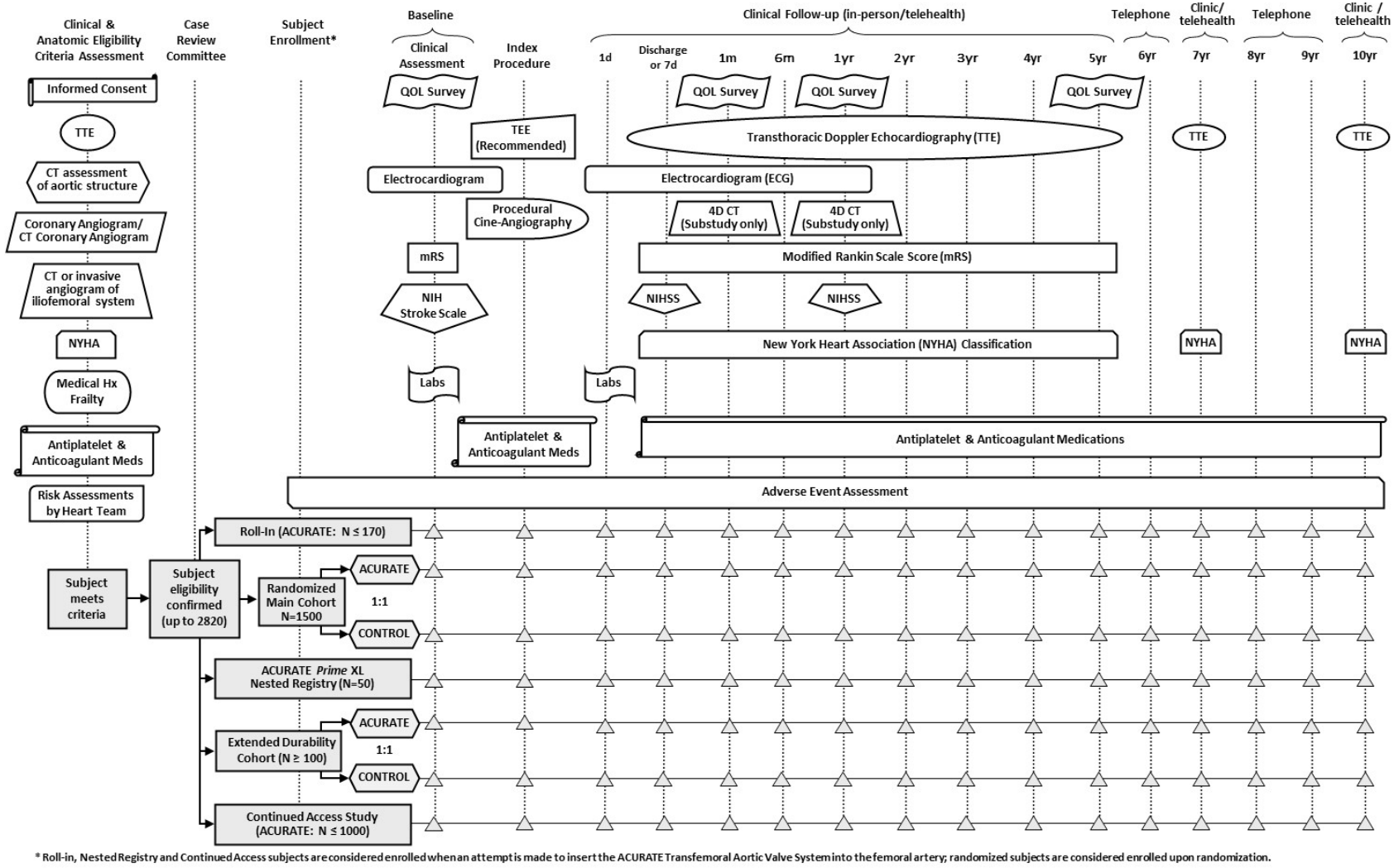
with an attempted procedure but no implanted study valve (test or control), the aforementioned events will be monitored through 1-year post-index procedure. For randomized subjects with no index procedure, the aforementioned events will be monitored through 1-year post randomization. Please refer to Section **19.1** for a list of CEC events and **Table 25.2-1** for definitions of these events, which specify data required for CEC adjudication. Complaint reporting of any device deficiencies for any commercially available products used should be carried out using the manufacturer's processes.

***Note*:** Relevant VARC events after 5 years to be adjudicated by the CEC include the following: mortality, stroke, spontaneous myocardial infarction, acute kidney injury, repeat procedure for valve-related dysfunction, hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA III or IV), new pacemaker, new onset atrial fibrillation or atrial flutter, prosthetic aortic valve malpositioning (valve migration, valve embolization, or ectopic valve deployment), TAV-in-TAV, prosthetic aortic valve thrombosis and endocarditis.

s: This applies to subjects in the 4D CT Imaging Substudy. Please refer to the CT Core Laboratory procedure guidelines (see study Manual of Operations). Results must be sent to the CT Core Laboratory (see Section 13.3.2).

Note: For subjects in the CT Imaging Substudy, the visits at 30 days and 1 year must be done in the clinic (or in-hospital).

Abbreviations: AE=adverse event; ADE=adverse device effect; AKIN=Acute Kidney Injury Network; BAV=balloon aortic valvuloplasty; CBC=complete blood count; CEC=Clinical Events Committee; CK-MB=creatine kinase-myoglobin band; CRC=Case Review Committee; CT=computed tomography; CV=cardiovascular; ECG=electrocardiogram; EOA=effective orifice area; mRS=modified Rankin Scale; NIHSS=National Institutes of Health Stroke Scale; NYHA=New York Heart Association; QOL=Quality of Life; SAE=serious adverse event; SADE=serious adverse device effect; STS=Society of Thoracic Surgery; TEE=transesophageal Doppler echocardiography; TTE=transthoracic Doppler echocardiography; UADE=unanticipated adverse device effect



* Roll-in, Nested Registry and Continued Access subjects are considered enrolled when an attempt is made to insert the ACURATE Transfemoral Aortic Valve System into the femoral artery; randomized subjects are considered enrolled upon randomization.

Figure 10.1-1: Data Collection Schedule for ACURATE IDE

See **Table 10.1-1** for additional information.

10.2. *Study Candidate Screening*

Subjects will be evaluated for eligibility by the center heart team (which must include an experienced cardiac interventionalist and an experienced cardiac surgeon). The heart team should consider the Society of Thoracic Surgeons (STS) score as well as other factors including frailty, prior surgical history, malignancy or radiation therapy, pulmonary disease, renal disease, liver disease, neuromuscular disease, orthopedic disease, chest deformity, and aortic calcification. Eligible subjects will have agreement from the heart team that the subject is indicated for TAVR (see **Table 8.2-1** for inclusion criteria; see definition of operative risk in **Table 25.2-1**). Risk of operative mortality and morbidity is to be assessed via an in-person evaluation by a center cardiac surgeon and must be confirmed by the CRC (which must include an experienced cardiac surgeon). The heart team must also agree that the subject is likely to benefit from valve replacement.

Screening assessments are detailed in Section **10.4** below. Clinical assessment and evaluation, collected tests and images (e.g., echocardiography, computerized tomography [CT], angiography) performed in preparation for TAVR, and planned use of balloon aortic valvuloplasty (BAV) will be reviewed by the CRC (see Section **7.2** and Section **21.2**). Informed consent will be obtained before any study-specific screening procedures in advance of TAVR that go beyond standard of care. The CRC will be comprised of experienced cardiac surgeons, experienced interventional cardiologists, and Sponsor staff proficient with the ACURATE Transfemoral Aortic Valve System and will confirm subject eligibility for enrollment.

10.2.1. Strategies for Recruitment and Retention

The ACURATE IDE study will include subjects presenting with documented severe native aortic valve stenosis who are indicated for TAVR (Section **8.2**). It is estimated that nearly 5% of elderly ≥75 years of age have aortic stenosis and its prevalence is expected to increase due to an aging population[2,3]. Because aortic stenosis most commonly occurs in the very elderly, women are well represented in TAVR trials. Traditionally underrepresented populations are expected to be included in the subject population as allowed by governing law/national regulation; as the very elderly will represent the majority of subjects enrolled in the trial, efforts to maximize retention are by definition targeted to traditionally under-represented groups. The inclusion and exclusion criteria are not expected to have a negative effect on recruitment or retention of said populations. In the United States, the subjects eligible for inclusion in this study are likely to be Medicare patients due to their expected age and the results of this study are likely to be highly generalizable to a Medicare population.

All efforts will be made to minimize attrition (see Section **9.4**). Investigators are encouraged to enroll subjects who are willing to comply with the follow-up requirements of the study. If a visit is missed, the center should attempt to contact the subject to reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule.

10.3. *Subject Informed Consent*

Informed consent (see Section **20**) must be obtained from a potential subject prior to conducting any preoperative assessments that are not part of the local routine preparation and evaluation of a subject for TAVR, even if the subject's eligibility has not yet been completely determined.

The Investigator/designee, who has been trained on the protocol, will explain the nature and scope of the study, potential risks and benefits of participation, and answer questions for the subject. If the subject agrees to participate, the Institutional Review Board (IRB)/Research Ethics Board (REB)/Human Research Ethics Committee (HREC)/Independent Ethics Committee (IEC)-approved Informed Consent Form (ICF) must be signed and personally dated by the subject or his/her legally authorized representative at the time of consent. The Investigator/designee must also sign and date the ICF at the time of consent and prior to subject enrollment. Any additional persons required by the center's IRB/REB/HREC/IEC to sign the ICF must also comply. Study personnel should explain to the subject that even if the subject agrees to participate in the study and signs the ICF, the heart team and/or the CRC may determine that the subject is not a suitable candidate for the study and/or TAVR procedure.

If during preoperative evaluations, the subject is found not to be eligible for inclusion in the study, the subject should be notified. Reason for ineligibility will be accounted for as "screening failure" and will be documented as such in the eCRF screening module. If the subject has signed the ICF but is found not eligible for inclusion in the study prior to or during the procedure, the subject should receive the appropriate treatment as identified by the clinical investigator. Information regarding the screening failure will be captured on the screening module and the subject will be included in the "screening cohort" accountability.

Note: Centers may use remote consent as allowed by institutional policy and the center's IRB/REB/HREC/IEC.

10.4. *Screening Assessments*

Results from the screening tests and procedures listed below (including planned control device if subject is randomized to the control arm and planned use of BAV with the control device during the index procedure) must be submitted to the CRC (see Section **21.2**) for evaluation to confirm a subject's eligibility for the study. Screening assessment documentation should be provided via electronic upload at least 5 days in advance of a scheduled CRC review or at least 5 days in advance of the planned procedure date. It is expected that CRC reviews will take place at least weekly or as needed to ensure timely review and confirmation of subject eligibility. For the randomized cohort, a subject should be randomized after CRC approval and within 7 calendar days of CRC approval.

Centers will be trained on the screening process as detailed in the ACURATE IDE Training Plan (see Section **16.4.2**). Specific data points will be collected in the ACURATE IDE electronic Case Report Forms (eCRFs) as shown below.

- Clinical assessments
  - Demographics including age and gender
  - Medical history (general medical; cardiac [including previous cardiac surgery]; neurological, renal [including creatinine] and peripheral disease; and other medical conditions)
  - Physical examination including weight and height
  - NYHA classification
  - Current antiplatelet and other cardiovascular medications
  - Planned use of BAV (i.e., predilation)
  - Risk assessments: Society of Thoracic Surgeons (STS) score, euroSCORE II, heart team assessment including an in-person evaluation by a center cardiac surgeon and any frailty assessments (detailed in next bullet). In the United States, CMS currently requires independent evaluation by 1 cardiac surgeon for reimbursement.
- Frailty, disability, and comorbidity assessments (collected prospectively)[74,75]
  - Body Mass Index from the physical exam
  - Strength and balance
    - Use of wheelchair
    - Gait speed as measured by a stopwatch for a subject to walk 5 meters (3 measures averaged)[75-77]
    - Number of falls in the past 6 months
    - Maximal grip strength (kg) in the dominant hand (3 measures averaged), using a hand-held dynamometer[78]
  - Activities of daily living: Katz Index[74,79] is based on an evaluation of the functional independence or dependence of a subject in bathing, dressing, going to toilet, transferring, continence, and feeding. A point is assigned for independence in each of the 6 functions, and 0 points if there is any dependence in these 6 categories.
- Imaging assessments
  - Within 90 days prior to CRC approval, TTE (2-D, M-Mode, and color) must be carried out. The evaluation should include assessment of effective orifice area (EOA), peak and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, left ventricular ejection fraction (LVEF), left ventricular end-diastolic and end-systolic diameter, tricuspid regurgitation (TR) jet velocity, and left atrial (LA) volume. The TTE must be performed according to the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). For enrolled subjects, the TTE must be provided to the echocardiography core laboratory for independent analyses. In cases of low flow/low gradient aortic stenosis with left ventricular dysfunction (ejection fraction <50%), dobutamine can be used to assess the grade of aortic stenosis (maximum dobutamine dose of 20 mcg/kg/min recommended)[4]; the subject may be enrolled if echocardiographic criteria are met with this augmentation. In cases where a subject

who has met the echocardiographic criteria for enrollment receives BAV prior to the index procedure and subsequently no longer meets the ACURATE IDE aortic valve pressure gradient or EOA criteria, the subject may still be enrolled based on the pre-BAV echocardiographic data. In such cases, the most recent echocardiogram done prior to the index procedure (even if after BAV) must be submitted to the echocardiography core laboratory to be included in the baseline data.

- A coronary angiogram/CT coronary angiogram must be performed within 365 days prior to CRC approval. If there is concern regarding the current extent of coronary artery disease or aortic stenosis, the CRC may recommend a repeat study closer to the time of enrollment. An aortogram and hemodynamics including simultaneous ascending aorta and left ventricle pressure measurements should be performed.
- A CT angiogram of the aortic complex must be performed 180 days prior to CRC approval (and should be performed within 90 days if possible) to evaluate the aortic valve anatomy and aortic root dimensions to determine eligibility and device sizing. It must meet the CT/Angiography Core Laboratory procedure guidelines (see study Manual of Operations) and be provided in advance to the core laboratory for detailed measurements and independent analyses, which will be reviewed by the CRC to confirm a subject's eligibility.
- An assessment of the iliofemoral system must be performed within 180 days prior to CRC approval (and should be performed within 90 days if possible). A CT angiogram of the iliofemoral system should be performed for complete visualization of the iliac and femoral arteries to assess for dimensions, tortuosity, and calcification. The CT angiogram of the iliofemoral system should be performed per the procedure guidelines (see study Manual of Operations) and provided to the CT/Angiography Core Laboratory with the screening CT angiogram of the aortic structure for independent measurements and review by the CRC to confirm a subject's eligibility. An iliofemoral invasive angiogram may be substituted for the iliofemoral CT angiogram.

10.5. *Baseline Assessments*

The following assessments must be completed within 30 days prior to the index procedure, unless otherwise specified below. The ACURATE IDE electronic CRFs identify the specific data points to be collected.

- Confirmation of CRC approval date
- NIH Stroke Scale (NIHSS), which must be performed by a neurology professional or certified personnel (external certification); NIHSS assessors should be independent (not involved with the care of study subjects)
- Modified Rankin Scale (mRS) score, which must be performed by a neurology professional or certified personnel (external or internal certification); mRS assessors should be independent (not involved with the care of study subjects)

- 12-lead electrocardiogram (ECG)
- Laboratory tests
  - Complete blood count (CBC) with platelets
  - Albumin
  - Serum creatinine
  - Cardiac enzymes (creatine kinase [CK] is required, CKMB or troponin if CK is elevated)
- Quality Of Life (QOL) Surveys: Kansas City Cardiomyopathy[71] and SF-12[72] QOL Questionnaires

Note: In cases where a subject who has met the echocardiographic criteria for enrollment receives BAV prior to the index procedure and subsequently no longer meets the ACURATE IDE aortic valve pressure gradient or EOA criteria, the subject may still be enrolled based on the pre-BAV echocardiographic data. In such cases, the most recent echocardiogram done prior to the index procedure (even if after BAV) must be submitted to the echocardiography core laboratory to be included in the baseline data.

10.6. *Pre-procedure Medications*

Pre-procedure medications are listed below.

- Antiplatelet therapy (aspirin plus a $P2Y_{12}$ inhibitor) is recommended prior to valve implantation.
  - Aspirin: A loading dose of aspirin (recommended dose of 75–325 mg) is recommended for subjects who have not been on aspirin therapy for ≥72 hours at the time of the index procedure. The loading dose should be administered prior to the implant procedure. Subjects who have been taking aspirin daily for ≥72 hours at the time of the index procedure do not require a loading dose.
  - $P2Y_{12}$ Inhibitor: A loading dose of a $P2Y_{12}$ inhibitor (recommended dose of ≥300 mg for clopidogrel, 60 mg for prasugrel, 180 mg for ticagrelor) is recommended for subjects who have not been on $P2Y_{12}$ therapy for ≥72 hours at the time of the index procedure. The loading dose should be administered prior to the implant procedure.

    Note: If a subject is treated with anticoagulation, either a $P2Y_{12}$ inhibitor or aspirin is recommended prior to the implant procedure, but not both.
- Anticoagulant therapy (e.g., unfractionated heparin) must be administered per local standard of care during the implant procedure, with a recommended target activated clotting time (ACT) of ≥250 seconds during the implantation procedure.
- Prophylactic antibiotic therapy should be given according to local practice. The choice of antibiotic drug is left to the investigator's discretion.

10.7. *Index Procedure*

The TAVR procedures will be performed at centers and by operators trained in implanting both the control and test devices. The preparation of both valves will be conducted by experienced and certified personnel. In the United States, CMS coverage criteria currently require that cardiac surgeon and interventional cardiologist members of the heart team participate in the technical aspects of the index procedure.

The preparation of the subject for the procedure will be performed following standard techniques. Balloon aortic valvuloplasty following standard techniques must be performed with an appropriately sized valvuloplasty balloon before test device implantation; BAV is optional for the control device and at the discretion of the physician.

Transfemoral access must be attempted for all subjects (assessment of the iliofemoral system prior to subject enrollment must indicate that transfemoral access is considered appropriate). If the transfemoral approach is unsuccessful, the operator will decide the best alternative approach to treat the subject.

10.7.1. Control Cohort

The DFU/IFU associated with the control device should be followed. A balloon valvuloplasty on the existing valve following standard techniques may be performed with an appropriately sized valvuloplasty balloon before control device implantation. A final post-deployment aortogram of the ascending aorta must be performed and forwarded to the computed tomography/angiography core laboratory with the procedural cine-angiogram for analysis.

Labels from devices used during the procedure (e.g., transcatheter heart valve, introducer, etc.) should be retained so that they can be included in the appropriate source documents and reported in the eCRFs. During the procedure, designated center study personnel must capture necessary information on acute device/delivery system performance and procedure. The following information will be collected during the procedure.

- Date of procedure
- Success of each attempted valve implant
- Specifics of device(s) used (such as size and model)
- Time of puncture (at site of TAVR sheath) and time of vascular closure for TAVR sheath (introducer insertion and removal time)
- Descriptive information on balloon valvuloplasty, if performed (e.g., size of balloon, number of balloon inflations)
- Any devices used and adjunctive procedures performed during the implant procedure
- Valve catheter insertion and removal time
- Descriptive information on valve implantation procedure

- Adverse event (AE) assessment and associated treatment (including AE, serious adverse event [SAE], serious adverse device effect [SADE], unanticipated adverse device effect [UADE], adverse device effect [ADE] and Clinical Events Committee [CEC] events; see Section **19.1**)

Note: For subjects randomized to the Control group who do not receive the intended Control valve, the valve type actually implanted must be recorded.

10.7.2. ACURATE Transfemoral Aortic Valve System (Test) Cohort

The DFUs/IFUs for the ACURATE Transfemoral Aortic Valve System should be followed. The commercially available 14F iSLEEVE introducer sheath (see Section **5.1.3**) shall be prepared and placed in the subject's femoral artery as per the introducer DFU/IFU. .

10.7.2.1. Valvuloplasty

Following standard techniques and using an appropriately sized valvuloplasty balloon, BAV must be performed on the existing valve before implantation of the ACURATE valve. Careful attention should be paid to the position of the guidewire throughout the BAV procedure. Prior to introduction of the ACURATE Transfemoral Aortic Valve System, the subject's hemodynamic status must be assessed (12-lead ECG is not required).

Information on the BAV, including number of inflations, should be documented in the source data and will be captured in the eCRFs.

10.7.2.2. Preparing and Using the ACURATE Transfemoral Aortic Valve System

All operators must comply with the appropriate DFU/IFU and must be adequately trained and certified by BSC personnel in accordance with the training plan before performing the procedure (see Section **16.4.2** for additional information on training). Guidelines provided by the Sponsor for valve size selection should be followed.

The ACURATE Transfemoral Aortic Valve System (valve plus transfemoral delivery system) must be prepared in accordance with the appropriate DFU/IFU and other training material (see Section **16.4.2**). Device preparation should only be performed by certified persons who have completed applicable training with the ACURATE Transfemoral Aortic Valve System (Section **16.4.2)**.

Prior to insertion of the ACURATE Transfemoral Aortic Valve System catheter into the introducer, the recommended target ACT (≥250 seconds) should be confirmed, with additional boluses of heparin administered if needed.

The appropriate DFU/IFU should be followed. The procedure is briefly summarized below for the ACURATE *neo2*™ Transfemoral Aortic Valve System. A similar procedure is used for preparation of the ACURATE *Prime* Aortic Valve XL; please see the corresponding DFU/IFU and other training material provided by BSC. All steps described below shall be performed under fluoroscopic control and with optional transesophageal echocardiography guidance.

1) The ACURATE *neo2* valve is loaded onto the ACURATE *neo2* delivery catheter following the DFU/IFU. A compatible introducer sheath is placed in the femoral artery and the ACURATE *neo2* delivery catheter with the ACURATE *neo2* valve is introduced transfemorally over a 0.035 in (0.89 mm) guidewire, maintaining proper guidewire positioning across the existing valve and into the ventricle.
2) The delivery system with valve is carefully advanced through the aorta and the aortic arch and is preliminarily positioned with the distal tip across the calcified native aortic valve through the ascending aorta (see **Figure 10.7-1**, Position 1).
3) The first rotating knob is turned counterclockwise, retracting the outer member of the delivery system containing the ACURATE *neo2* valve; the upper crown and stabilization arches are deployed and contact the ascending aorta (**Figure 10.7-1**, Position 2). This orients the system towards the longitudinal direction of the aorta (**Figure 10.7-1**, Position 3). The upper crown should be positioned slightly above the aortic annular plane. An optional episode of rapid ventricular pacing may facilitate the final confirmation of the optimal positioning.
4) The second rotating knob is turned, which advances the capsule, and the ACURATE *neo2* valve detaches from the delivery system leaving the lower crown fully expanded. The diabolo shape of the two anchoring crowns facilitates conformation to the calcified annulus and results in stable positioning (**Figure 10.7-1**, Position 4).
5) The tip and capsule of the delivery system are carefully retracted through the functioning valve.
6) After withdrawing through the valve, the delivery system is retracted into the descending aorta and the capsule over the stent holder is closed by turning the second rotating knob. The system is pulled out of the body.
7) A final post-deployment aortogram of the ascending aorta must be performed and forwarded to the core laboratory with the procedural cine-angiogram for analysis.
8) The introducer is then removed.
9) The femoral access is closed according to standard practice.

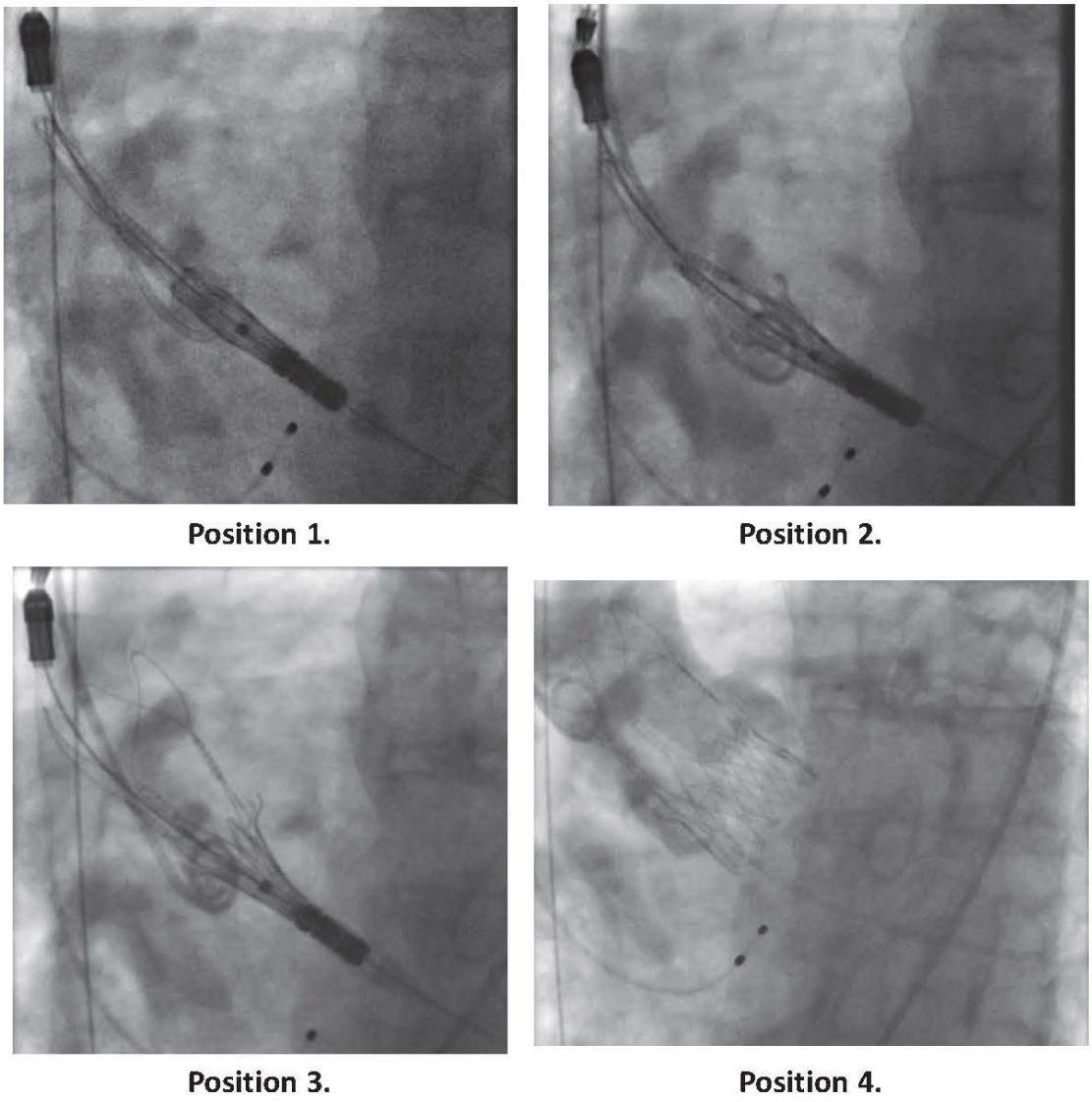


Figure 10.7-1: Valve Implantation Procedure

Position 1: Delivery system is placed through the native valve. **Position 2:** The upper anchoring crown is deployed. **Position 3:** The stabilization arches are deployed, and partial release is achieved. **Position 4:** The lower anchoring crown is deployed, and final release is achieved.
Note: This example shows the ACURATE *neo2* valve.

Labels from the devices used during the procedure (e.g., valve, introducer, etc.) should be retained so that they can be included in the appropriate source documents and reported in the eCRFs.

During the procedure, designated center study personnel must capture necessary information on acute device/delivery system performance and procedure. The following information will be collected during the procedure.

- Date of procedure
- Device size (Small, Medium, Large, or Extra Large)
- Time of puncture (at site of TAVR sheath) and time of vascular closure for TAVR sheath (introducer insertion and removal time)
- Descriptive information on balloon valvuloplasty (e.g., size of balloon, number of balloon inflations)
- Any devices used and adjunctive procedures performed during the implant procedure
- ACURATE Transfemoral Aortic Valve System catheter insertion and removal time
- Descriptive information on the valve implantation procedure
- Adverse event assessment and associated treatment (including AE, SAE, SADE, UADE, ADE, and CEC events; see Section **19**)
- Device deficiencies assessment for the ACURATE Transfemoral Aortic Valve System

Note: All ACURATE transfemoral aortic valve implantation procedures will be performed with the support/presence of trained BSC personnel.

10.8. *Post Index Procedure*

The following are to be performed post-procedure.

- Per society guidelines[4,5] antiplatelet therapy is recommended to reduce the risk of thrombotic or thromboembolic complications if there are no contraindications to these medications. Subjects must be treated with antiplatelet therapy (aspirin and/or a $P2Y_{12}$ inhibitor) for at least 1 month following valve implantation. Extended dual antiplatelet therapy may be administered per physician choice. It should be noted, however, that recent clinical evidence points to increased bleeding risk post TAVR among subjects receiving dual antiplatelet therapy or antiplatelet therapy plus anti-coagulation (among subjects indicated for anti-coagulation)[80,81].
    - After the valve implant procedure, aspirin (recommended dose of ≥75 mg daily) and/or a $P2Y_{12}$ inhibitor must be given for at least 1 month. It is recommended that daily aspirin be given indefinitely thereafter as per local standard of care. Aspirin dose may be adjusted to the closest approximation based on local tablet formulation availability. The $P2Y_{12}$ inhibitor choice and dosing should be per local standard of care.
    - If a subject is treated with anticoagulation, either a $P2Y_{12}$ inhibitor or aspirin is recommended after the implant procedure in addition to the anticoagulant therapy (but treatment with both aspirin and a $P2Y_{12}$ inhibitor after the implant procedure is not recommended). The subject should be treated with an oral anticoagulant (OAC) and either a $P2Y_{12}$ inhibitor or aspirin for at least 1 month. After 1 month, subjects requiring chronic anticoagulation may be treated at the discretion of the treating physician.

- Prophylactic antibiotic regimen should be completed per local practice.
- Additional medications may be used at the investigator's discretion.
- It is recommended that the subject's heart rhythm be monitored using telemetry for at least 48 hours after the index procedure.
- 12-lead ECG must be completed within 24 hours post-procedure.
- Cardiac enzymes (CK is required, CK-MB or troponin if CK is elevated) must be collected twice at intervals per standard of care within 6–24 hours post-procedure.

10.9. *Prior to Discharge or 7 Days Post-Procedure (Whichever Comes First)*

Subjects must be evaluated prior to discharge or 7 days post-procedure (whichever comes first) based on the assessments below. The ACURATE IDE eCRFs identify the specific data points to be collected.

- Weight
- NYHA classification
- NIHSS, which must be performed by a neurology professional or certified personnel (external certification); NIHSS assessors should be independent (not involved with the care of study subjects).
- Modified Rankin Scale score, which must be performed by a neurology professional or certified personnel (external or internal certification); mRS assessors should be independent (not involved with the care of study subjects).
- 12-lead ECG
- TTE, including assessment of EOA, peak and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity and LA volume, per the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). All TTEs for enrolled subjects must be provided to the echocardiography core laboratory for independent analyses.

  Note: For all subjects who have a valve implanted in the aortic position during the index procedure at least 1 echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest study performed will be used for analysis. Subjects who do not receive a study valve during the index procedure are not required to have follow-up TTE.
- Current antiplatelet and anticoagulant (if applicable) medications
- Complete adverse event (AE, SAE, SADE, UADE, ADE, and CEC events) assessment for test and control devices and device deficiencies assessment for the test device, with associated treatment.

10.10. *Follow-up*

All subjects implanted with a study valve (test or control) will be evaluated per the schedule in **Table 10.1-1**. Subjects who are enrolled and have an attempted procedure but do not receive a study valve (test or control) will be assessed through 1-year post index procedure for safety/adverse events but do not need to have protocol required echocardiography. Randomized subjects who do not have an attempted index procedure will be assessed through 1-year post randomization but do not need to have protocol required echocardiography. Subjects who receive a surgical valve will be followed through the end of the study but do not need to have protocol required echocardiography. Data from the required tests and images as well as medical assessments will be recorded in source documentation and captured in the eCRFs. The determination of specified study endpoints and measurements such as valve function and CEC events will require data from images and tests as outlined in the event definitions (**Table 25.2-1**).

If study personnel learn of a subject's hospitalization outside the study center, the center should make every effort to obtain copies of reports or results based on tests (e.g., echocardiogram) and/or procedures performed on the study subject.

Note 1: A subject who has received a study valve should not be enrolled in a clinical trial of an investigational drug/device/treatment until the subject has reached the ACURATE IDE primary endpoint (1 year).

Note 2: Where indicated in **Table 10.1-1**, the follow-up visits must be conducted in-person or as telehealth visits. If an in-person/telehealth assessment cannot be performed, follow-up by telephone call should be attempted. The subject or the subject's physician should provide rationale for why the subject cannot comply with the follow-up in-person/telehealth assessment.

10.10.1. 30-Day Follow-up (30±7 Days)

All enrolled subjects must be evaluated 30 (±7) days after the index procedure in person or via telehealth. During the 30-day follow-up visit, the following assessments must be completed. The ACURATE IDE eCRFs identify the specific data points to be collected.

- Weight
- NYHA classification
- Modified Rankin Scale score, which must be performed by a neurology professional or certified personnel (external or internal certification); mRS assessors should be independent (not involved with the care of study subjects).
- 12-lead ECG

  Note 1: A 12-lead ECG must be obtained for all subjects, even if the associated follow-up assessment is carried out via telehealth.
- Current antiplatelet, anticoagulant (if applicable) medications

- TTE including assessment of EOA, peak and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity and LA volume. TTE must be performed per the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). All TTEs for enrolled subjects must be provided to the echocardiography core laboratory for independent analyses.

  Note 2: TTE must be done for all subjects who have a transcatheter valve implanted in the aortic position during the index procedure, even if the associated follow-up assessment is carried out via telehealth. Enrolled subjects who have an attempted procedure but do not receive a transcatheter valve are not required to have follow-up TTE.

- Quality of Life Surveys: Kansas City Cardiomyopathy and SF-12 Quality of Life Questionnaires

- Complete adverse event (AE, SAE, SADE, UADE, ADE and CEC events) assessment for test and control devices and device deficiencies assessment for test device(s), with associated treatment

- For subjects enrolled in the CT Imaging Substudy, assessment of prosthetic valve leaflet mobility using 4D CT must be performed per the CT Core Laboratory (Section 13.3.2) procedure guidelines (see study Manual of Operations). All 4D CT scans for subjects enrolled in the CT Imaging Substudy must be sent to the CT Core Laboratory for independent analyses.

  Note 3: Images will be read in a standard fashion for cardiac and non-cardiac findings by the clinical center CT imaging specialist. Clinical guidelines support anticoagulation with warfarin or another vitamin K inhibitor as a Class I recommendation for patients with established valve thrombosis[4,5]. However, there is no established guidance for pharmaceutical management of subclinical leaflet thrombosis. If deterioration of subject health due to suspected thrombosis occurs, the clinical center may request an unblinding of the Core Laboratory findings.

10.10.2. 6-Month Follow-up (180±30 Days)

All enrolled subjects must be evaluated 180 (±30) days after the index procedure in person or via telehealth. During the 6-month follow-up visit, the following assessments must be completed. The ACURATE IDE eCRFs identify the specific data points to be collected.

- Weight
- NYHA classification
- Modified Rankin Scale score, which must be performed by a neurology professional or certified personnel (external or internal certification); mRS assessors should be independent (not involved with the care of study subjects).
- 12-lead ECG

Note 1: A 12-lead ECG must be obtained for all subjects, even if the associated follow-up assessment is carried out via telehealth.

- Current antiplatelet, anticoagulant (if applicable) medications
- TTE including assessment of EOA, peak and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity and LA volume. TTE must be performed per the Echocardiography Core Laboratory procedure guidelines (see study Manual of Operations). All TTEs for enrolled subjects must be provided to the echocardiography core laboratory for independent analyses.

  Note 2: TTE must be done for all subjects who have a transcatheter valve implanted in the aortic position during the index procedure, even if the associated follow-up assessment is carried out via telehealth. Subjects who do not receive a transcatheter valve during the index procedure are not required to have follow-up TTE.
- Complete adverse event (AE, SAE, SADE, UADE, ADE and CEC events) assessment for test and control devices and device deficiencies assessment for test device(s), with associated treatment

10.10.3. 1-Year Follow-up (365±30 Days)

All enrolled subjects must be evaluated 365 (±30) days after the index procedure in person or via telehealth. During the 1-year follow-up visit, the following assessments must be completed. The ACURATE IDE eCRFs identify the specific data points to be collected.

- Weight
- NYHA classification
- Modified Rankin Scale score, which must be performed by a neurology professional or certified personnel (external or internal certification); mRS assessors should be independent (not involved with the care of study subjects).
- NIHSS, which must be performed by a neurology professional or certified personnel (external certification); NIHSS assessors should be independent (not involved with the care of study subjects).
- 12-lead ECG

  Note 1: A 12-lead ECG must be obtained for all subjects, even if the associated follow-up assessment is carried out via telehealth.
- Current antiplatelet, anticoagulant (if applicable) medications
- TTE including assessment of EOA, peak and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity and LA volume. TTE must be performed per the Echocardiography Core Laboratory procedure guidelines (see study

Manual of Operations). All TTEs for enrolled subjects must be provided to the echocardiography core laboratory for independent analyses.

Note 2: TTE must be done for all subjects who have a transcatheter valve implanted in the aortic position during the index procedure, even if the associated follow-up assessment is carried out via telehealth. Subjects who do not receive a transcatheter valve during the index procedure are not required to have follow-up TTE.

- Quality of Life Surveys: Kansas City Cardiomyopathy and SF-12 Quality of Life Questionnaires
- Complete adverse event (AE, SAE, SADE, UADE, ADE and CEC events) assessment for test and control devices and device deficiencies assessment for test device(s), with associated treatment
- For subjects enrolled in the CT Imaging Substudy, assessment of prosthetic valve leaflet mobility using 4D CT must be performed per the CT Core Laboratory procedure guidelines (see study Manual of Operations). The 4D CT scans done for the CT Imaging Substudy must be sent to the CT Core Laboratory for independent analyses.

  Note 3: Images will be read in a standard fashion for cardiac and non-cardiac findings by the clinical center CT imaging specialist. Clinical guidelines support anticoagulation with warfarin or another vitamin K inhibitor as a Class I recommendation for patients with established valve thrombosis[4,5]. However, there is no established guidance for pharmaceutical management of subclinical leaflet thrombosis. If deterioration of subject health due to suspected thrombosis occurs, the clinical center may request an unblinding of the Core Laboratory findings.

10.10.4. Annual Follow-up (±45 Days) to 5 Years

All implanted subjects must be evaluated in person or by telehealth visit at 2, 3, 4, and 5 years after the index procedure, with a window of ±45 days. During the annual follow-up, the following assessments must be completed. The ACURATE IDE eCRFs identify the specific data points to be collected.

- Weight
- NYHA classification
- Modified Rankin Scale score, which must be performed by a neurology professional or certified personnel (external or internal certification); mRS assessors should be independent (not involved with the care of study subjects).
- Current antiplatelet, anticoagulant (if applicable)
- TTE, including assessment of EOA, peak and mean aortic valve gradient pressure, aortic regurgitation assessment, mitral regurgitation, LVEF, left ventricular end-diastolic and end-systolic diameter, TR jet velocity, and LA volume, per the Echocardiography Core Laboratory procedure guidelines. All TTEs must be forwarded to the core laboratory for independent analyses.

Note: TTE must be done for all subjects who have a transcatheter valve implanted in the aortic position during the index procedure, even if the associated follow-up assessment is carried out via telehealth. Subjects who do not receive a transcatheter valve during the index procedure are not required to have follow-up TTE.

- Complete serious adverse event (SAE, SADE, UADE, and CEC events) assessment for test and control devices and device deficiencies assessment for test device(s) with associated treatment.
- Quality of Life Surveys: Kansas City Cardiomyopathy and SF-12 Quality of Life Questionnaires at 5 years

10.10.5. Follow-up (±60 Days) at 7 and 10 Years

All implanted subjects must be evaluated in person or via telehealth at 7 and 10 years after the index procedure, with a window of ±60 days. The following assessments must be completed. The ACURATE IDE eCRFs identify the specific data points to be collected.

- NYHA classification
- Current antiplatelet, anticoagulant (if applicable)
- TTE, including assessment of effective orifice area, peak and mean aortic valve gradient pressure, aortic regurgitation assessment, peak aortic velocity, and LVEF per the Echocardiography Core Laboratory procedure guidelines. All TTEs must be forwarded to the core laboratory for independent analyses.

  Note 1: TTE must be done for all subjects who have a transcatheter valve implanted in the aortic position during the index procedure, even if the associated follow-up assessment is carried out via telehealth.
- Serious adverse event (SAE, SADE, UADE, and relevant VARC events to be adjudicated by the CEC) assessment for test and control devices and device deficiencies assessment for test device(s) with associated treatment.

  Note 2: Relevant VARC events to be adjudicated by the CEC include the following: mortality, stroke, spontaneous myocardial infarction, acute kidney injury, repeat procedure for valve-related dysfunction, hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA III or IV), new pacemaker, new onset atrial fibrillation or atrial flutter, prosthetic aortic valve malpositioning (valve migration, valve embolization, or ectopic valve deployment), TAV-in-TAV, prosthetic aortic valve thrombosis and endocarditis.

10.10.6. Follow-up (±60 Days) at 6, 8 and 9 Years

All implanted subjects must be evaluated at 6, 8, and 9 years after the index procedure, with a window of ±60 days. This evaluation may be conducted by telephone. The following assessments must be completed. The ACURATE IDE eCRFs identify the specific data points to be collected.

- Current antiplatelet, anticoagulant (if applicable)
- Serious adverse event (SAE, SADE, UADE, and relevant VARC events to be adjudicated by the CEC) assessment for test and control devices and device deficiencies assessment for test device(s) with associated treatment. Please see Section **10.10.5** for a list of relevant VARC events.

10.11. *Study Completion*

All subjects who receive a test or control device will be evaluated at discharge or 7 days (whichever comes first), 30 days, 6 months, and then annually up to 10 years post index procedure. Visits in the first 5 years and at 7 and 10 years are office/in-person/telehealth visits. Evaluations may be conducted by telephone at 6, 8 and 9 years. A subject's participation in the study will be considered complete after the 10-year visit. For subjects who do not receive a test or control device, participation in the study will be considered complete after the 1-year visit. Any ongoing adverse events after study completion should be managed per standard of care.

Data are collected at each office/in-person/telehealth visit per the data collection schedule in **Table 10.1-1**.

10.12. *Source Documents*

It is preferable that original source documents, when available, are maintained at the investigative center. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. Source documentation includes but is not limited to those items noted in **Table 10.12-1**.

Table 10.12-1: Source Documentation Requirements

Requirement	Disposition
Printed, optical, or electronic document containing source data. Examples may include but are not limited to: hospital records, laboratory notes, device accountability records, photographic negatives, radiographs, records kept at the investigation center, at the laboratories and at the medico-technical departments involved in the clinical investigation.	Retain at center.

Note: Please see **Table 25.2-1** for definitions of "source data" and "source document."

10.13. *Local Laboratory/Vendor Documentation*

Appropriate certifications and documentation records are required to be maintained at the investigative center for local laboratory/vendor work.

11. Statistical Considerations

Full methods are described in the Statistical Analysis Plan.

11.1. *Endpoints*

The randomized data from the Main Randomized Cohort of the ACURATE IDE trial will be used for primary endpoint analysis.

Data will be summarized separately for subjects in the ACURATE IDE Roll-In cohort (up to 170 subjects). Descriptive statistics will be used to summarize these Roll-In cohort data and no statistical inference will be made.

Data will be summarized separately for the specific statistical hypothesis associated with the ACURATE *Prime*™ XL Nested Registry. Descriptive statistics also will be used to summarize data from subjects in the single-arm ACURATE *Prime* XL cohort.

Data will be summarized separately for subjects in the ACURATE Extended Durability Study. Descriptive statistics will be used to summarize these data and no statistical inference will be made.

Data will be summarized separately for subjects in the single-arm ACURATE Continued Access Study. Descriptive statistics will be used to summarize these data and no statistical inference will be made.

Event definitions can be found in **Table 25.2-1**.

11.1.1. Primary Endpoint

The primary endpoint is the composite of all-cause mortality, all stroke, and rehospitalization at 1 year. The events in this endpoint will be adjudicated by an independent CEC (see Section **21.1.1**).

Note 1: For the primary endpoint, rehospitalization is hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV); per VARC-2 definition

11.1.1.1. Statistical Hypothesis for the Primary Endpoint – Main Randomized Cohort

For the Main Randomized Cohort, the statistical hypothesis is that the primary endpoint (composite of all-cause mortality, all stroke, and rehospitalization at 1 year) rate for the ACURATE (test) group is non-inferior to that for the Control group.

The null and alternative hypotheses for the primary endpoint are as follows:

H_0: $PE_{\_ACURATE}$ minus $PE_{\_Control} \geq \Delta$ (Inferior)

H_1: $PE_{\_ACURATE}$ minus $PE_{\_Control} < \Delta$ (Non-inferior)

where $PE_{\_ACURATE}$ and $PE_{\_Control}$ correspond to the primary endpoint rates for the ACURATE and the Control group, respectively, and Δ is the non-inferiority margin.

The primary analysis set for the primary endpoint is the ITT analysis set. This endpoint will also be analyzed for the implanted analysis set (see Section **11.2.1** for definitions of analysis sets).

A Bayesian analysis[28,30] will be performed to estimate the treatment difference between ACURATE and Control through posterior probability. Additional information is provided below.

11.1.1.2. Sample Size Parameters for the Primary Endpoint – Main Randomized Cohort

Although the primary endpoint analysis is performed using the Bayesian method, the sample size calculation for the randomized cohort (see ***Note 2*** below) is based on a standard non-inferiority two-sample test approach. The sample size calculation for the primary endpoint is based on the following assumptions.

- Expected rate for both arms = 22.3% (based on a weighted average of TAVR data[19,22,28-30,34,41,46,51,82]; see ***Note 3*** below)
- Non-inferiority margin (Δ) = 8.0% (36% relative to expected rate)
- Test significance level (α) = 0.025 (1-sided) (see **Note 4** below)
- Test (ACURATE): Control ratio = 1:1
- Power (1 minus ß) > 90%
- Expected rate of attrition = 5%
- Total sample size = 1500 (750 per group)
- Number of evaluable subjects per group = 712
- Analyses: One administrative, one formal interim, one final (see ***Note 5*** and ***Note* 6** below)

Note 2: The Pocock-type method[83] is used for sample size calculations. The statistical software EAST® 6.5[84] is used for the sample size calculations.

Note 3: The estimated proportions of subjects in the Main Randomized Cohort by operative risk level are 10% extreme risk, 25% high risk, 30% intermediate risk, and 35% low risk.

Note 4: A statistically equivalent posterior probability threshold for the Bayesian analysis is empirically chosen through extensive simulations and is pre-specified in the Statistical Analysis Plan (SAP).

Note 5: The administrative interim analysis will be conducted when the first 350 Main Randomized Cohort subjects have completed 1-year follow-up. The formal interim analysis will be carried out after enrollment in the Main Randomized Cohort is completed. This formal interim analysis will be conducted on the full N=1500 subject cohort of the Main Randomized Cohort after the first 1050 subjects in the Main Randomized Cohort have completed 1-year follow-up. The piecewise exponential model[30] based on outcomes among these subjects will be used to predict the 1-year results by treatment group for the remaining enrolled subjects. The Bayesian method will be used to perform the hypothesis testing on the combined data sets. A final analysis will be performed on all subjects with completed 1-year data if non-inferiority cannot be claimed at the formal interim analysis (see Section **11.1.1.3**).

Note 6: Analyses of the Extended Durability Study and the ACURATE CAS are not expected to occur when the formal interim analysis is performed on the Main Randomized Cohort. See Section **11.1.2** below for information on analyses associated with the ACURATE *Prime* XL cohort.

11.1.1.3. Success Criteria for the Primary Endpoint – Main Randomized Cohort

The Bayesian method is used to test the non-inferiority hypothesis of the primary endpoint. To establish that the ACURATE device is non-inferior to the Control, the results will need to meet the following equation:

$$Pr(H_1 \mid Data) > \xi$$

where

- $Pr(H_1 \mid Data)$ is the posterior probability of H_1 given the observed data at either the interim or the final analysis;
- H_1 is the alternative hypothesis for non-inferiority: $PE_{\_ACURATE}$ minus $PE_{\_Control} < \Delta$;
- ξ is a prespecified threshold, which is empirically chosen through extensive simulations using the Bayesian approach for the non-inferiority tests.

If non-inferiority has been declared at the formal interim analysis, the non-inferiority test will not be performed at the final analysis. If non-inferiority cannot be declared at this interim analysis, the non-inferiority test will be performed at the final analysis for all subjects using the Bayesian method with the same pre-specified threshold. The study will not stop for futility at the interim analysis.

The detailed study operating characteristics and simulation results will be provided in the SAP.

11.1.1.4. Statistical Methods – Primary Endpoint – Main Randomized Cohort

All subjects who are enrolled and randomized will be eligible for evaluation. Any events or hospitalizations occurring after enrollment but prior to the index procedure should be entered in the electronic data capture system.

Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measure. Sensitivity analyses (e.g., tipping-point analysis) will be performed to assess the impact of subjects with inadequate follow-up (i.e., missing data) on the primary endpoint and to assess the robustness of the conclusion of the primary analysis. A sensitivity analysis of the primary endpoint, including events occurring after enrollment but prior to the index procedure, will be performed. Statistical models that account for censored data will be employed in appropriate circumstances (e.g., for time-to-event outcomes). Suspected invalid data will be queried and corrected in the database prior to statistical analysis. Additional information may be found in the SAP. Please also see Section **9.4**, Section **10.1**, and Section **10.2.1** regarding data collection and missing data.

11.1.2. ACURATE *Prime* XL Nested Registry Statistical Assessment

The statistical assessment for the ACURATE *Prime* XL Nested Registry is summarized in the sections below. Additional information may be found in the SAP.

11.1.2.1. Statistical Hypothesis – ACURATE *Prime* XL Nested Registry

The statistical hypothesis is that the mean aortic valve pressure gradient at 30 days post implant procedure is less than a performance goal (PG):

H_0: $Gradient_{30D} \geq PG$

H_1: $Gradient_{30D} < PG$

where $Gradient_{30D}$ is the 30-day mean aortic valve pressure gradient for the ACURATE *Prime* XL valve and PG is 15 mmHg.

A one-sample *t*-test will be used to test the one-sided hypothesis at a significance level of 2.5%.

11.1.2.2. Sample Size Parameters for the ACURATE *Prime* XL Nested Registry

The sample size calculation is based on the following assumptions.

- Expected 30-day mean pressure gradient from ACURATE *Prime* XL = 10 mmHg
- Expected standard deviation = 7 mmHg
- PG = 15 mmHg
- Test significance level (α) = 0.025 (1-sided)
- Power > 90%
- Evaluable number of subjects = Minimum of 40 subjects
- Expected rate of attrition = 20% (8 subjects)
- Planned enrollment of 50 subjects
- The analysis population for the hypothesis testing will be the subject population implanted with the ACURATE *Prime* XL valve.

Note: The expected mean gradient is based on Boston Scientific data on file and published data for large-annulus CoreValve devices[43,48,49].

11.1.2.3. Success Criteria for the ACURATE *Prime* XL Nested Registry

If the *P* value from the one-sample *t*-test is < 0.025, the ACURATE *Prime* XL valve will be concluded to have a 30-day mean aortic valve pressure gradient < 15 mmHg. This corresponds to the one-sided upper 2.5% confidence bound of the observed 30-day mean aortic valve pressure gradient being < 15 mmHg.

11.1.3. Baseline Comparability

Baseline data will be summarized by treatment group for the randomized subjects (Main Randomized Cohort and Extended Durability Study) and separately for the Roll-In, ACURATE *Prime* XL Nested Registry, and CAS subjects. Subject demographics, clinical and neurological history, risk factors, and pre-procedure characteristics will be summarized using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and frequency tables or proportions for discrete variables. Treatments for the randomized subjects will be compared with a chi-square or Fisher exact test for discrete variables and a Student *t*-test for continuous variables. Procedural characteristics will be summarized similarly. No formal statistical testing will be done for the Roll-In, Extended Durability, or CAS subjects. Please see Section **11.1.2** regarding statistical testing for the ACURATE *Prime* XL Nested Registry.

11.1.4. Post-procedure Measurements

Post-procedure information will be collected at regularly scheduled follow-up examinations as detailed in the clinical study schedule (**Table 10.1-1**) and will be summarized using descriptive statistics for continuous variables (e.g., mean, standard deviation, n, minimum, maximum) and frequency tables or proportions for discrete variables. Estimates will be reported by treatment group and, for randomized subjects (Main Randomized Cohort and Extended Durability Study), differences between treatment groups and their 95% confidence intervals will be presented. Treatments for the randomized subjects will be compared with the chi-square or Fisher exact test for discrete variables and the Student t-test for continuous variables. No inferences are planned on the additional measurements and, therefore, alpha-adjustments for multiple comparisons will not be used. The Kaplan-Meier product-limit method will be used to estimate rates for time-to-event endpoints and treatment groups will be compared using the Log-rank and Wilcoxon tests. Adverse event and SAE rates will be reported. No formal statistical testing will be done for the Roll-In, Extended Durability Study, or ACURATE CAS subjects. Please see Section **11.1.1.1** and Section **11.1.2**, respectively, regarding statistical testing for the Main Randomized Cohort and the ACURATE *Prime* XL Nested Registry.

11.2. *General Statistical Methods*

All statistical analyses will be performed using the SAS System software, version 9.2 or later (Copyright© 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved).

All statistical analyses will be conducted according to applicable Standard Operating Procedures, Work Instructions, and the study-specific SAP.

11.2.1. Analysis Sets

The primary endpoint and additional measurements will be analyzed on an ITT and an implanted basis.

Subjects in the randomized cohorts (Main Randomized Cohort and Extended Durability Study) are considered enrolled in the study upon randomization. Among the randomized cohorts, for ITT analyses, all subjects who sign the IRB/REB/HREC/ IEC-approved study ICF (see Section **10.3**), are enrolled in the trial, and are randomized will be included in the analysis, whether or not an assigned study valve (ACURATE or Control) was implanted. For implanted analyses, ITT subjects who had the assigned (Test versus Control), randomized study valve implanted will be included in the analysis. For the implanted randomized cohort analysis sets, if a subject receives 2 different valve types from 2 different manufacturers, the subject will be excluded from the implanted analysis.

With the Roll-In, ACURATE *Prime*™ XL Nested Registry, and ACURATE CAS cohorts, the subject is considered enrolled in the trial when there is an attempt made to insert the ACURATE Transfemoral Aortic Valve System into the subject's femoral artery. For ITT analyses, all subjects who sign the IRB/REB/HREC/IEC-approved study ICF and are enrolled in the trial will be included in the analysis sample, regardless of whether the study device was implanted. The implanted population includes all subjects who sign an ICF and are implanted with an ACURATE valve.

For the Main Randomized Cohort, the primary endpoint will be analyzed for the ITT and implanted analysis sets. The primary analysis for the primary endpoint will be based on the ITT analysis set.

11.2.2. Control of Systematic Error/Bias

All subjects who have met the inclusion/exclusion criteria, received a positive recommendation from the CRC, and signed the Informed Consent Form will be eligible for enrollment in the study. The center heart team's assessment of TTE measurements before device placement will contribute to the determination of subject eligibility for the study.

To control for inter-observer variability, data from independent core laboratories (see Section **13.3**) will be used for analysis. These include an echocardiography core laboratory and a CT/Angiography core laboratory to assess all data using standard techniques. Clinical endpoints will also be adjudicated by an independent CEC (Section **21.1.1**).

11.2.3. Number of Subjects Per Investigative Center

The number of subjects enrolled per investigational center should not exceed 180 without prior authorization by the sponsor.

11.2.4. Randomization Scheme

For the Main Randomized Cohort and Extended Durability Study, a computer-generated list of random treatment allocations (i.e., a randomization schedule) will be used to assign subjects in the ACURATE IDE trial to treatment in a 1:1 ratio of ACURATE to Control. Randomization will be stratified by center and by intended control device. Additional information is provided in the study Manual of Operations.

11.2.5. Reporting Events

For all subjects in the ACURATE IDE Roll-In, ACURATE *Prime*™ XL Nested Registry, and ACURATE CAS cohorts, all events that occur from the time of enrollment will be reported. For all subjects in the ACURATE IDE randomized cohorts (Main Randomized Cohort and Extended Durability Study), events from the time of randomization onward will be reported.

For randomized subjects who do not have an attempted procedure, events from the date of randomization to 1-year post-randomization will be reported. For subjects who are enrolled and have an attempted procedure but do not receive a study valve, events from the index procedure to 1-year post procedure will be reported.

For time-based clinical events, the cut-off for events for 30-day endpoints will be 30 days, for 6-month endpoints it will be 180 days, for 1-year endpoints it will be 365 days, and for endpoints at 2–10 years it will be 365 days times the number of years. For events at discharge or 7 days post-procedure, the cut-off for events will be the earlier of the date of discharge or 7 days post-procedure for each subject.

11.3. *Data Analyses*

Baseline and outcome variables will be summarized using descriptive statistics for continuous variables (mean, standard deviation, number of observations, minimum and maximum) and discrete variables (percentage and count/sample). See Section **11.1** for a discussion on analysis of the primary endpoint and additional measurements.

11.3.1. Other Measurements

Other measurements not driven by statistical hypotheses are listed in Section **6.4**.

11.3.2. Interim/Administrative Analyses

There will be 2 interim analyses as described in the SAP. The administrative interim analysis will be conducted when the first 350 subjects in the Main Randomized Cohort have completed 1-year follow-up visits. The formal interim analysis will be carried out after enrollment in the Main Randomized Cohort is completed (see ***Note 1*** below). This formal interim analysis will be conducted on all (N=1500) Main Randomized Cohort subjects after the first 1050 Main Randomized Cohort subjects have completed 1-year follow-up. The piecewise exponential model[30] based on outcomes among these subjects will be used to predict the 1-year results by treatment group for the remaining enrolled subjects. The Bayesian method will be used to perform the hypothesis testing on the combined data sets. A final analysis will be performed on all subjects in the Main Randomized Cohort with completed 1-year data if non-inferiority cannot be claimed at the formal interim analysis (see Section **11.1.1.3**). Additional information may be found in the SAP.

A Data Monitoring Committee (DMC; Section **21.1.2**) will monitor safety events. The DMC reports will be generated according to the DMC charter.

Note 1: Analyses of the Extended Durability Study and the ACURATE CAS are not expected to occur when the formal interim analysis is performed on the Main Randomized Cohort. See Section **11.1.2** for information on analyses associated with the ACURATE *Prime* XL cohort.

11.3.3. Subgroup Analyses for Main Randomized Cohort Subjects

Primary and pre-specified additional endpoints will be summarized for the following subgroups of the Main Randomized Cohort as described in the SAP.

- Gender (male and female)
- Valve type (ACURATE *neo2*, SAPIEN, CoreValve)
- Age (< 75 years and ≥ 75 years)
- Any race and ethnicity category with >100 enrolled subjects as described in the SAP
- Valve size (Small, Medium, Large)
- Operative risk (low, intermediate, high/extreme)

Treatment groups will also be compared in the age, race, and gender subgroup analyses. No adjustments for multiple comparisons will be made. Additional analyses may be performed as appropriate.

In the 4D CT Imaging Substudy, computed tomography data will be analyzed after 200 subjects have reached 1-year follow-up.

11.3.4. Justification of Pooling

Analyses for the primary endpoint in the Main Randomized Cohort will be presented using data pooled across study centers. Poolability analyses across study centers will be performed for the primary endpoint. The differences of treatment effects on the primary endpoint across study centers will be examined using the interaction term from logistic regression models. Please see the SAP for additional information.

11.3.5. Multivariable Analyses

Univariate and multivariate analyses will be performed to assess the effect of potential predictors on the primary endpoint in the Main Randomized Cohort as described in the SAP.

11.3.6. Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended SAP approved before performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

12. Health Economics Outcomes

A formal health economics analysis may be completed as part of this trial, provided meaningful clinical results are obtained. This will take into consideration any differences in mortality, event rates, quality of life, and resource utilization. Quality of life will be evaluated by the Kansas City Cardiomyopathy[71] and SF-12[72] questionnaires at baseline, 1 month, 1 year, and 5 years. These inputs may be used in any health economics analysis performed.

13. Data Management

13.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system. Only personnel trained and authorized will have access to the system.

The clinical database will reside on a production server hosted by Medidata EDC System (New York, NY, USA). All changes made to the clinical data will be captured in an electronic audit trail and made available for review by the Sponsor or its representative. The associated RAVE software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the Sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the Medidata EDC system and will be issued to the center for appropriate response. Center staff will be responsible for resolving all queries in the database.

All access to the clinical database will be changed to “Read Only” after all data are either “Hard Locked” or “Entry Locked.” Once acceptance of the final study report or finalization of publications (as applicable) is received, final database storage and archiving activities can begin. When all closeout activities are completed, a request to the BSC Information Technology department is submitted to have the database locked or decommissioned and all database access revoked.

13.2. *Data Retention*

The Principal Investigator or his/her designee or Investigational center will maintain all essential study documents and source documentation that support the data collected on the

study subjects in compliance with applicable regulatory requirements. Documents must be retained for at least 2 years after the last approval of a marketing application or until at least 2 years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with BSC or in compliance with other local regulations.

The Principal Investigator or his/her designee will take measures to prevent accidental or premature destruction of these documents. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Centers are required to inform BSC in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

13.3. *Core Laboratories*

13.3.1. Echocardiography Core Laboratory

An independent core laboratory will review echocardiography images from all centers and every subject enrolled in this study for qualitative and quantitative analysis. These analyses will minimize bias and inconsistencies by providing an independent interpretation of all measurements using standard techniques. The TTE procedure guideline is provided by the core laboratory in the study Manual of Operations.

13.3.2. CT and Angiography Core Laboratory

An independent core laboratory will centrally assess all of the CT and angiography data in this study to reduce variability. These analyses will minimize bias and inconsistencies by providing an independent interpretation of all measurements using standard techniques. Procedure guidelines are provided by the core laboratory in the study Manual of Operations. Data from subjects in the 4D CT Imaging Substudy will also be evaluated by the independent CT core laboratory; procedure guidelines for 4D CT scanning are provided by the core laboratory in the Manual of Operations.

13.3.3. Histopathology Core Laboratory

If an ACURATE valve (test device) is explanted during conventional scheduled or emergent surgical valve replacement or during an autopsy, please refer to the study Manual of Operations for recommendations on the explant procedure and shipment of the explanted valve for assessment by an independent histopathology laboratory.

14. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the

Sponsor and the reviewing IRB/REB/HREC/IEC of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using the EDC CRF. Centers may also be required to report deviations to the IRB/REB/HREC/IEC, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including IRB/REB/HREC/IEC notification, center re-training, or center discontinuation/termination) will be put into place by the Sponsor.

The sponsor will not approve protocol waivers.

15. Device Accountability

15.1. *Device Accountability for Products Labelled Investigational*

The investigational devices shall be securely maintained, controlled, and used only in this clinical study. Additionally, study personnel must follow the instructions related to the storage of the test device as noted in the corresponding clinical DFU/IFU. An electronic interactive response technology (IRT) will be used for investigational device management and accountability during the study.

The Sponsor or designee shall keep records to document the physical location of all investigational devices from shipment of the investigational devices from BSC or a designated facility to the investigation centers until return or disposal. The IRT will be used to document reception of the investigational device at a center. Records shall be kept by authorized center study personnel to document the physical location and conditions of storage of all investigational devices. Centers must not dispose of any investigational devices for any reason at the center unless instructed to do so by BSC. Any investigational device that is disposed of at the center must be documented appropriately. Centers must document the reasons for any discrepancy noted in device accountability.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return, transfer, and disposal of the investigational devices, which shall include the following.

- Date of receipt at the center
- Identification of each investigational device (unique identifier or lot number/batch number/serial number, valve size)
- Expiry date, as applicable
- Date of use

- Subject identification
- Date on which the investigational device was explanted from subject/returned, if applicable
- Date of return and quantity of all investigational devices, as applicable.

Note: Written procedures may be required by national regulations.

Once the Investigator and center are notified in writing by BSC that subject enrollment is complete, all unused investigational devices must be returned to BSC or its designee.

15.2. *Device Accountability for the Control Device*

Appropriate information on the control device size and model will be collected.

16. Compliance

16.1. *Statement of Compliance*

This clinical investigation is financed by the study sponsor. Before the investigational site can be "Authorized to Enroll," the investigational site must enter into a Clinical Study Agreement with the sponsor that details the financing of the study as well as the rights and obligations of the investigational site and the investigator.

This study will be conducted in accordance with 21 CFR 814.20 Parts 11, 50, 54 56, 812, 813; the relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP) or the International Standard ISO 14155: Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice; ethical principles that have their origins in the Declaration of Helsinki; and applicable individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the IRB/REB/HREC/IEC and/or regulatory authority has been obtained, if appropriate. Also, the study shall not begin prior to issuance of the center Authorization to Screen, as provided by the Sponsor. Any additional requirements imposed by the IRB/REB/ HREC/IEC or regulatory authority shall be followed, if appropriate.

16.2. *Investigator Responsibilities*

The Principal Investigator of an investigational center is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan/protocol, ISO 14155 or ICH/GCP, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/REB/HREC/IEC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Investigator Brochure Signature Page and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the center team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Complete training requirements associated with the Control device(s).
- Complete all ACURATE Transfemoral Aortic Valve System (investigational device) training requirements as detailed in the ACURATE IDE Training Plan (Section **16.4.2**).
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency.
- Report to BSC, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE.
- Report to the IRB/REB/HREC/IEC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by applicable laws or regulations or this protocol or by the IRB/REB/HREC/IEC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Maintain the device accountability records and control of the investigational device, ensuring that the investigational device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the Sponsor and Sponsor representatives to perform monitoring and auditing activities and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB/REB/HREC/IEC when performing auditing activities.

- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/REB/HREC/IEC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the ICF.
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation (e.g., implant card), together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation center team and facilities exist and are maintained and documented during the clinical investigation.
- Ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable.

All investigators will provide their qualifications and experience to assume responsibility for their delegated tasks through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.

16.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training, so the delegate is competent to perform the tasks they have been delegated, and adequate supervision of those to whom tasks are delegated. Where there is a sub-investigator at a center, the sub-investigator should not be delegated the primary

supervisory responsibility for the center. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

16.3. *Institutional Review Board/Research Ethics Board/Human Research Ethics Committee/ Independent Ethics Committee*

The investigational center will obtain the written and dated approval/favorable opinion of the Institutional Review Board/Research Ethics Board/Human Research Ethics Committee/ Independent Ethics Committee (IRB/REB/HREC/IEC) for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required.

A copy of the written IRB/REB/HREC/IEC approval of the protocol (or permission to conduct the study) and ICF, must be received by the Sponsor before recruitment of subjects into the study and shipment of investigational product. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Any amendment to the protocol will require review and approval by the IRB/REB/HREC/ IEC before the changes are implemented to the study. All changes to the ICF will be IRB/REB/HREC/IEC approved; a determination will be made regarding whether a new ICF needs to be obtained from subjects who provided consent, using a previously approved ICF. Annual IRB/REB/HREC/IEC approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IRB/REB/ HREC/IEC requirements. Copies of the study reports and the IRB/REB/HREC/IEC continuance of approval must be provided to the Sponsor.

16.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC and will be kept confidential in accordance with all applicable laws and regulations. Only authorized BSC personnel and/or a BSC representative including, but not limited to, a Contract Research Organization will have access to this information. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes, such as overseeing and improving the performance of its device, new medical research, and proposals for developing new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

16.4.1. Role of Boston Scientific Corporation Representatives

Boston Scientific personnel (including field clinical engineers) who are trained in the use of the investigational device will provide technical support to the investigator and other health care personnel (collectively HCP) as needed during ACURATE valve preparation and

implant and testing required by the protocol. Boston Scientific Corporation (BSC) is also responsible for ensuring investigators are trained on the investigational device DFU/IFU. Support may include HCP training (see Section **16.4.2** below), addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices.

In addition, BSC personnel may perform certain activities to ensure study quality. These activities may include the following.

- Observing testing or medical procedures to provide information relevant to protocol compliance
- Reviewing collected data and study documentation for completeness and accuracy

Boston Scientific personnel will not do the following.

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of the investigator.
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

16.4.2. Training with the Investigational Device

The Sponsor is responsible for providing investigators with the information and training on the investigational device they need to conduct the study properly. The Sponsor is responsible for maintaining documentation of attendance at each of the training sessions provided.

The ACURATE Healthcare Personnel (HCP) Training Plan developed for this study meets the requirements of ISO 5840-3 and includes the following elements.

- Device Description: A detailed description of all components of the device including a summary of the basic principle of operation.
- Patient Selection and Sizing: A detailed review of pre-procedural imaging techniques to aid in patient selection and sizing decisions for valve implantation.
- Step by Step Procedure: A detailed description of each step of the procedure. The training describes any warnings associated with any steps, and tips and tricks for valve implantation.
- Implantation Techniques: A detailed review of specific implantation techniques based on clinical cases.

- Device Demonstration: A live or hands-on training to simulate/practice the implantation procedure with demonstration devices or in a bench model or a robotic simulation system.
- Proctoring: The investigator and co-investigators as well as the scrub team will be proctored by an individual experienced with the ACURATE valve and TAVR on a minimum of 4 implantation procedures. These are to be performed in the investigator's institution with his/her staff. If the proctor or investigators are not satisfied that these initial proctored procedures are sufficient preparation, then subsequent proctoring sessions may be added as needed.

Note 1: The training requirements listed above apply to centers that do not have any previous experience implanting the ACURATE *neo2* valve. If the center has prior experience implanting the ACURATE *neo* bioprosthesis but does not have experience with the ACURATE *neo2* Transfemoral Aortic Valve System, the training will be modified to focus on the changes between the two. These ACURATE-experienced physicians will not be certified to the ACURATE *neo2* Transfemoral Aortic Valve System until these training requirements have been met and 2 implants with the ACURATE *neo2* Transfemoral Valve System have been completed.

Note 2: For centers that do not have implantation experience with the ACURATE *neo* bioprosthesis (transfemoral delivery), at least 2 Roll-In cases will be performed before treatment can commence in the randomized cohort. For centers that do not have any previous experience implanting the ACURATE *neo* bioprosthesis, the Roll-In subjects will be treated under the supervision of a proctor and will count towards the 4 required proctored cases. Centers with prior experience with the ACURATE bioprosthesis who are proctor-free are not required to do Roll-In cases but may do Roll-In subjects without the presence of a proctor.

Note 3: Centers will receive additional training on the ACURATE *Prime* investigational device. An experienced BSC representative will provide technical support as needed during valve preparation and implantation.

16.5. *Insurance*

Where required by local/country regulation, proof and type of insurance coverage by BSC for subjects in the study will be obtained.

17. Monitoring

Monitoring will be performed during the study according to the monitoring plan to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to

original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The sponsor will put a plan in place to document the specific monitoring requirements.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

18. Potential Risks and Benefits

Risks to clinical subjects associated with their participation in this clinical investigation, arising from the clinical procedures set out in the study protocol, have been identified from prior studies conducted by Boston Scientific Corporation and review of relevant literature, most recently from the Edwards Lifesciences' Placement of Aortic Transcatheter Valves (PARTNER) trial[8,17,19,20], the PARTNER II trial (RCT and SAPIEN 3 intermediate risk arm)[27,34,40], the PARTNER 3[29] trial, the SAPIEN 3 CE Mark study[85], the CoreValve Extreme Risk study[41], the CoreValve High Risk Study[22], the Evolut R CE Mark study[42], the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial[28], the CoreValve Low Risk trial[30], the EVOLUT R US study[44], the PORTICO Pre-CE Mark study[45], and the PORTICO IDE randomized trial/RESOLVE registry/SAVORY registry[86].

Benefits to subjects anticipated to arise from the use of the investigational device have also been identified. These clinical risks and benefits are summarized below, with an assessment of the balance of risks and benefits to subjects. Potential risks and benefits have been included in the study-specific template of the ICF provided to the study centers (see Section **20**).

18.1. *Anticipated Adverse Events and Risks Associated with Transcatheter Aortic Valve Replacement*

Adverse events (in alphabetical order) potentially associated with TAVR (including, but not limited to, standard cardiac catheterization and BAV) as well as additional risks related to the use of the investigational and control devices include but may not be limited to the risks listed in **Table 18.1-1** below. As a result of these complications, the subject may require medical, percutaneous, or surgical intervention, including re-operation and replacement of the implanted valve. Such complications can be fatal.

As the ACURATE Transfemoral Valve System is an investigational device, uncertainty remains over risks of experiencing some or all of the complications listed below. There may be risks that are unknown at this time.

Table 18.1-1: Risks Associated with Transcatheter Aortic Valve Replacement

Abnormal lab values (including anemia and electrolytes)
Abnormal pressure gradient
Allergic reaction (including to medications, anesthesia, contrast, or device materials)
Aneurysm (cardiovascular)
Angina
Arrhythmia or new conduction system injury (including need for pacemaker insertion)
Bleeding or hemorrhage (possibly requiring transfusion or intervention)
Cardiac arrest
Cardiac failure/low cardiac output
Cerebrovascular accident, stroke or transient ischemic attack
Coronary obstruction
Death
Device embolization, misplacement or migration
Emboli (including air, calcium, tissue, thrombus or device materials)
Emergency cardiac surgery
Endocarditis
Fever
Heart failure
Hematoma or lymphatic problems or other complications at the access sites
Hemodynamic instability or shock
Hemolysis and/or hemolytic anemia
Hypertension/hypotension
Infection (local and/or systemic, including septicemia)
Inflammation
Mitral valve insufficiency or injury
Myocardial infarction or ischemia
Myocardial or valvular injury (including perforation or rupture)
Nerve injury
Non-structural valve dysfunction including implant distortion, improper deployment or sizing
Pain
Pericardial effusion or cardiac tamponade
Peripheral ischemia or infarction
Permanent disability
Pleural effusion
Pulmonary edema
Radiation injury
Renal insufficiency or failure
Respiratory insufficiency or failure
Thrombosis/thromboembolism
Valve dysfunction, deterioration or failure
Valve-in-valve (need for additional valve within a valve)
Valve or device thrombosis

Table 18.1-1: Risks Associated with Transcatheter Aortic Valve Replacement

Valvular stenosis or regurgitation (central or paravalvular)
Vessel injury (including spasm, trauma, dissection, perforation, rupture, arteriovenous fistula, acute coronary occlusion, or pseudoaneurysm)
Wound healing disorders

Note: Risks are listed in alphabetical order.

18.1.1. Reduced Leaflet Motion/Leaflet Thrombosis

Reduced leaflet motion (RLM) suggestive of subclinical leaflet thrombosis, as detected by high-resolution CT, has been reported with bioprosthetic TAVR and SAVR valves[86-89]. It is less common among subjects receiving anticoagulant therapy and, in some cases, has been shown to resolve with such treatment[86-92].

Clinical signs of RLM include elevation of transvalvular gradients (as determined by echocardiography), central or peripheral thromboembolic events, and unexpected recurrence of heart failure. Computed tomography imaging is recommended to appropriately assess subjects with echocardiographic and/or clinical suspicion of leaflet thrombosis. Additional anticoagulant therapy may be indicated based on symptoms or signs and subject bleeding risk[86-92].

The subset of subjects undergoing 4D CT scans at 30 days and 1 year will be exposed to an additional radiation dose of about 20 milliSieverts (mSv) which is equivalent to about 10 years' worth of natural background radiation. The contrast dye used during the image acquisition can cause medical problems such as allergic reactions and increase the risk of worsening kidney function or failure.

18.2. *Risks Associated with the Study Device(s)*

Overall, there are no incremental risks expected with the investigational device compared to similar devices on the market.

18.3. *Risks Associated with Participation in the Clinical Study*

Risks associated with TAVR and participation in this clinical study are listed above in **Table 18.1-1**.

18.4. *Possible Interactions with Concomitant Medical Treatments*

Medications to be used in ACURATE IDE constitute standard of care for TAVR as described in society guidelines[4,5]. Please also see Section **10** for medications to be used in this study.

18.5. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

Boston Scientific Corporation will employ measures throughout the course of this investigation consistent with the best practices and lessons learned from other ongoing TAVR trials and commercial use to minimize risk for subjects choosing to participate. All efforts will be made to minimize risks by selecting centers that are experienced and skilled in TAVR procedures.

Risk mitigation will be accomplished through the following actions.

- Clearly defining the inclusion/exclusion criteria to ensure only appropriate subjects are enrolled
- Confirmation of eligible subjects by a Case Review Committee, including experienced investigators in TAVR
- Ensuring that treatment and follow-up of the subject are consistent with current medical practices
- Selection of investigators who are experienced and skilled in TAVR procedures
- Completion of training and proctorship provided by the Sponsor
- Performing all procedures in accordance with the DFU/IFU, including the preparation of the valve and delivery system
- Dynamic safety review processes, including assessment by the Data Monitoring Committee (DMC, Section **21.1.2**) and CEC (Section **21.1.1**) adjudication of specified events as recommended by VARC[66,67].

The ACURATE valve has a number of features that help minimize risk (see Section **5.1** for a description of the investigational device). The valve is released first at the top and last at the inflow; this top-down deployment allows for implantation with minimal protrusion into the left ventricular outflow tract. The upper crown opens first to provide stable positioning and supra-annular anchoring of the valve, capping the native leaflets and mitigating the risk of coronary obstruction. Subsequently, the flexible stabilization arches open to promote valve self-alignment and achieve coaxial alignment. The lower crown is then opened to anchor the device inside the annulus. The double porcine pericardium skirt sutured on the inner and outer surface of the valve stent is also designed to minimize paravalvular leakage with the ACURATE *neo2* and ACURATE *Prime*™ XL valves.

Anticoagulation medication (e.g., heparin) will be administered during the procedure to reduce the risk of embolism and stroke. Additionally, post-procedure antiplatelet therapy is recommended to minimize any risk of thrombus formation, stroke, or transient ischemic

attack. Neurological assessments (NIHSS and mRS) will be performed at each required follow-up visit to identify any change in the neurological status of the subjects as recommended by VARC[66,67].

Cardiac enzyme measurements as well as ECGs post-procedure will be performed to detect periprocedural MI.

Subjects will be carefully monitored during the procedure, hospitalization, and throughout the follow-up period. Serial echocardiograms and electrocardiograms will be used to evaluate valve and general cardiac function. Any abnormal rhythm will be assessed and, if needed, the implantation of a permanent pacemaker will be performed.

Subjects who are converted to standard surgical aortic valve replacement will be carefully monitored in a method appropriate for their surgical procedure.

Data will be monitored as they are submitted to BSC. Qualified employees of BSC, or a designee under contract, will conduct monitoring visits at the initiation of the study and at interim intervals described in the monitoring plan throughout the course of the study to evaluate protocol compliance and determine if there are any issues that could affect the safety or welfare of any subject in the study.

18.6. *Anticipated Benefits*

18.6.1. Potential Benefits to the TAVR Procedure

Transcatheter aortic valve replacement (TAVR) may offer certain advantages when compared to surgical replacement of the stenotic aortic valve. Known benefits associated with TAVR, as described in the scientific literature (see summary in Section **4.1.2** of this document and details in the IB), potentially include the following.

- Minimally invasive procedure and reduced risks related to open heart surgery
- Shorter stay in the intensive care unit and overall hospital stay
- Reduced blood loss
- More rapid recovery
- Reduced need for general anesthesia and associated risks

18.6.2. Potential Benefit Using the ACURATE Transfemoral Aortic Valve System

Potential benefits that may be associated specifically with use of the ACURATE Transfemoral Aortic Valve System compared to other TAVR systems include the following.

- Top-down implantation technique intended to compress the native calcified leaflet tissue below the upper crown, thus capturing the native leaflets in the waist of the device
- A lower crown which protrudes minimally towards the LVOT, thus reducing the chance of conduction disturbances

- Low aortic gradients due to the supra-annular positioning of the deployed valve
- Reduced incidence of paravalvular aortic regurgitation due to the sealing skirt
- Delivery system with a flexible shaft facilitating easy tracking in tortuous anatomy and a controlled 2-step deployment process

18.7. *Risk to Benefit Rationale*

Review of the aforementioned clinical benefits versus risks takes into account the known risks/benefits that have been identified in the published literature on other TAVR devices. The estimation of risk also includes clinical experience with the ACURATE Transfemoral Aortic Valve System and earlier generations of the device. When used according to the DFU/IFU, all known risks associated with the TAVR procedure and the specific use of the ACURATE Transfemoral Aortic Valve System are mitigated to acceptable limits comparable to existing TAVR devices. Specific design features of the valve may improve TAVR procedural safety. These include top-down implantation to capture the native calcified leaflets in the waist of the device and a lower crown that protrudes minimally towards the LVOT and may minimize conduction disturbances. The supra-annular positioning may result in lower aortic pressure gradients. The sealing skirt may provide long term benefit as it is designed to minimize paravalvular regurgitation, which has been associated with long term mortality in TAVR.

19. Safety Reporting

19.1. *Reportable Events by Investigational Center to Boston Scientific*

It is the responsibility of the investigator to assess and report to BSC any event that occurs in any of the following categories; reporting requirements are described below in **Table 19.4-1**.

- All serious adverse events
- All adverse events and adverse device effects (through 12 months)
- All investigational device deficiencies
- Unanticipated adverse device effects/unanticipated serious adverse device effects
- New findings/updates in relation to already reported events

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and/or device deficiency.

Any reportable event required by the protocol, experienced by the study subject after informed consent and once considered enrolled in the study, whether during or subsequent to the procedure, must be recorded in the eCRF.

Underlying diseases are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE but should only be reflected as an outcome of one (1) specific SAE (see **Table 19.2-1** for AE definitions).

In-patient hospitalization is defined as the subject being admitted to the hospital, with the following exceptions.

- A hospitalization that is uncomplicated and elective/planned (i.e., planned prior to enrollment) does not have to be reported as an SAE.
- If complications or AEs occur during an elective/planned (i.e., planned prior to enrollment) hospitalization after enrollment, the complications and AEs must be reported as AEs or SAEs if they meet the protocol-specified definitions.

For the randomized cohort, event reporting (eCRF data entry) is required beginning from the time of randomization. For the Roll-In and ACURATE *Prime* XL Nested Registry cohorts, event reporting (eCRF data entry) is required beginning from the time an attempt is made to insert the ACURATE Transfemoral Aortic Valve System into the subject's femoral artery.

Refer to Section **18** for the known risks associated with the study devices (test and control).

Based on the VARC[66,67] recommendations and definitions, the adverse events and/or safety endpoints requiring adjudication by the CEC include the following.

- Mortality: all-cause, cardiovascular, and non-cardiovascular
- Stroke: disabling and non-disabling
- Myocardial infarction (MI): periprocedural (≤72 hours post index procedure) and spontaneous (>72 hours post index procedure)
- Bleeding events: life-threatening (or disabling) and major (through 5 years)
- Acute kidney injury (≤7 days post index procedure): based on the AKIN System [69,70] Stage 3 (including renal replacement therapy) or Stage 2
- Vascular complications: major (including annular rupture; through 5 years)
- Repeat procedure for valve-related dysfunction (surgical or interventional therapy)
- Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV)
- New permanent pacemaker implantation resulting from new or worsened conduction disturbances
- New onset of atrial fibrillation or atrial flutter
- Coronary obstruction: periprocedural (≤72 hours post index procedure)

- Ventricular septal perforation: periprocedural (≤72 hours post index procedure)
- Mitral apparatus damage: periprocedural (≤72 hours post index procedure)
- Cardiac tamponade: periprocedural (≤72 hours post index procedure)
- Prosthetic aortic valve malpositioning, including valve migration, valve embolization, or ectopic valve deployment
- TAV-in-TAV deployment
- Prosthetic aortic valve thrombosis
- Prosthetic aortic valve endocarditis

Details on the CEC events and procedures are outlined in the CEC charter. Tests and images required to adjudicate these events are specified in the event definitions (see **Table 25.2-1**).

19.2. *Definitions and Classification*

Adverse event definitions are provided in **Table 19.2-1**. Administrative edits were made on the safety definitions from ISO 14155 and MEDDEV 2.7/3 for clarification purposes.

Table 19.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the investigational medical device. ***Note 1:*** This includes events related to the investigational medical device or comparator. ***Note 2:*** This definition includes events related to the procedures involved. ***Note 3:*** For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of an investigational medical device ***Note 1:*** This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. ***Note 2:*** This definition includes any event resulting from use error or intentional abnormal use of the investigational medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	***Note 1:*** This definition meets the reporting objectives and requirements of ISO 14155 and MEDDEV 2.7/3. Adverse event that: a) Led to death, b) Led to serious deterioration in the health of the subject as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient hospitalization or prolongation of existing hospitalization, or

Table 19.2-1: Safety Definitions

Term	Definition
	4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) Led to fetal distress, fetal death, or a congenital abnormality or birth defect. ***Note 2:*** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	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. ***Note****:* Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Serious Health Threat *Ref: ISO 14155*	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health of subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. ***Note 1:*** This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	An inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.
The following definitions will be used for defining hospitalization or prolongation of hospitalization for SAE classification purposes:	
Hospitalizations	Hospitalization does not include: • Emergency room visit that does not result in in-patient admission ***Note 1:*** Although an emergency room visit does not itself meet the definition for hospitalization, it may meet other serious criteria (e.g., medical or surgical intervention to prevent permanent impairment or damage) • Elective and pre-planned treatment/surgery for a pre-existing condition that is documented in the subject's record at the time of consent/enrollment

Table 19.2-1: Safety Definitions

Term	Definition
	• Admission for social reasons and/or respite care in the absence of any deterioration in the subject's general condition (e.g., subject is homeless, caregiver relief) Pre-planned, protocol-specified admission related to the clinical study (e.g., procedure required by protocol)
Prolongation of Hospitalization	In-patient admission to the hospital that is prolonged beyond the expected standard duration for the condition under treatment. ***Note 1:*** New adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criterion.

19.3. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the reportable AE/SAE to the study device and procedure. See criteria in **Table 19.3-1:**

Table 19.3-1: Criteria for Assessing Relationship of Study Device and Procedure to Adverse Event

Classification	Description
Not Related *Ref: MEDDEV 2.7/3*	Relationship to the device or procedures can be excluded when: • the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; • the event has no temporal relationship with the use of the investigational device or the procedures; • the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; • the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; • the event involves a body-site or an organ not expected to be affected by the device or procedure; • the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); • the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Table 19.3-1: Criteria for Assessing Relationship of Study Device and Procedure to Adverse Event

Classification	Description
Unlikely Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
Probably Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.
Causal Relationship *Ref: MEDDEV 2.7/3*	The serious event is associated with the investigational device or comparator or with procedures beyond reasonable doubt when: • the event is a known side effect of the product category the device belongs to or of similar devices and procedures; • the event has a temporal relationship with investigational device use/application or procedures; • the event involves a body-site or organ that - the investigational device or procedures are applied to; - the investigational device or procedures have an effect on; • the serious event follows a known response pattern to the medical device (if the response pattern is previously known); • the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); • other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; • harm to the subject is due to error in use; • the event depends on a false result given by the investigational device used for diagnosis, when applicable In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

19.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in **Table 19.4-1**.

Table 19.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline (premarket studies)** (MEDDEV 2.7/3: CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect (UADE/USADE)	Complete AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• At request of Sponsor.
Serious Adverse Event (SAE)	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• At request of Sponsor
Serious Adverse Device Effects (SADE)	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available • At Sponsor request.
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) ***Note:*** Any Investigational Device	Complete AE eCRF page with all available new and updated information.	Investigational Device: • Within 3 calendar days of first becoming aware of the event. • Reporting required through 12 months Control Device: • As required per DFU/IFU and as per local/regional regulations

Table 19.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline (premarket studies)** (MEDDEV 2.7/3: CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)
Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	Investigational Device: • At request of Sponsor
Adverse Event including Adverse Device Effects (AE/ADE)	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner (e.g., recommend within 10 business days) after becoming aware of the information • Reporting required through 12 months
	Provide all relevant source documentation (de-identified/pseudonymized) for reported event.	• At request of Sponsor

* Please note that pre-market studies are clinical studies with investigational devices or with medical devices that bear the regulatory approval and are not being used for the same approved indications.

19.5. *Device Deficiencies*

Complaint reporting of any device deficiencies for any commercially available products used should be carried out using the manufacturer's processes.

19.5.1. Boston Scientific Device Deficiencies

All device deficiencies related to the test device or future iterations will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the investigational device(s) will be provided in the study Manual of Operations. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device deficiencies should also be documented in the subject's source records.

Device deficiencies are not adverse events. However, an adverse event that results from a device deficiency would be recorded as an adverse event on the appropriate eCRF.

19.5.2. Control Device Deficiencies

Device deficiencies related to use of the control device should be reported per the DFU/IFU and per applicable local/regional requirements. If an AE results from a device deficiency or other device issue, the AE must be reported on the appropriate eCRF.

19.6. *Reporting to Regulatory Authorities / IRBs / REBs / HRECs / IECs / Investigators*

Boston Scientific Corporation will notify all participating study centers if UADEs, SAEs, SADEs, or investigational device deficiencies occur which imply a possible increase in the anticipated risk of the procedure or use of the device or if the occurrence of certain SAEs/SADEs requires changes to the protocol or the conduct of the study in order to further minimize the unanticipated risks.

Boston Scientific Corporation is responsible for reporting adverse event information to all participating Principal Investigators, IRBs/REBs/HRECs/IECs, and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the IRB/REB/HREC/IEC and regulatory authorities of UADEs and SAEs as required by local/regional regulations.

20. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, the relevant parts of ISO 14155 and the ICH guidelines for GCP, any applicable national regulations, and local Ethics Committee and/or Regulatory authority, as applicable. The ICF must be accepted by BSC or its delegate (e.g., CRO) and approved by the center's IRB/REB/HREC/IEC, or central IRB, if applicable.

Boston Scientific Corporation will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative center's IRB/REB/HREC/IEC. Any modification requires acceptance from BSC or authorized representative prior to use of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the center in obtaining a written consent translation. Translated consent forms must also have IRB/REB/ HREC/IEC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,

- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions, if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations, and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs the ICF, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the center and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Note: Centers may use remote consent as allowed by institutional policy and the center's IRB/REB/HREC/IEC.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory authority according to their requirements (e.g., the United States Food and Drug Administration [FDA] requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the Sponsor and local regulatory authorities (e.g., IRB/REB/HREC/IEC), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB/REB/HREC/IEC. The new version of the ICF must be approved by the IRB/REB/HREC/IEC. Acceptance by Boston Scientific Corporation is required if changes to the revised ICF are requested by the center's IRB/REB/HREC/IEC. The IRB/REB/HREC/IEC will determine the subject population to be re-consented.

Study personnel should explain that even if a subject agrees to participate in the study and signs an ICF, the heart team and/or the CRC may determine that the subject is not a suitable candidate for the study and/or TAVR procedure. A confidential Screening/Enrollment Log will be maintained by the center to document select information about candidates who fail to meet the general or "other specific" entry criteria.

21. Committees

21.1. *Safety Monitoring Process*

The BSC personnel from the Medical Safety and Safety Trial Operations teams review safety data as they are reported by the centers throughout the duration of the study. During scheduled monitoring activities, clinical research monitors further support this review through their review of source documents and other data information. The BSC Medical Safety and Safety Trial Operations teams includes health care providers with expertise in cardiology and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above (Section **19**).

21.1.1. Clinical Events Committee

A Clinical Events Committee (CEC) will be used in this study. A CEC is an independent group of individuals with pertinent expertise, including cardiovascular interventional therapy, cardiovascular surgery, and neurology, which reviews and adjudicates important endpoints and relevant adverse events reported by study investigators. The CEC will review a safety event dossier, which may include copies of subject source documents provided by study centers and adjudicate study endpoint related clinical events. The responsibilities, qualifications, membership, and committee procedures of the CEC are outlined in the CEC Charter.

21.1.2. Data Monitoring Committee

The DMC is responsible for the oversight review of all AEs. The DMC will include leading experts in cardiovascular interventional therapy, cardiovascular surgery, and biostatistics who are not participating in the study and who have no affiliation with BSC. During the course of the study, the DMC will review accumulating safety data to monitor the incidence of CEC events and other trends that would warrant modification or termination of the study. Responsibilities, qualifications, membership, and committee procedures are outlined in the DMC Charter.

21.2. *Case Review Committee*

A Case Review Committee (CRC) will be comprised of experienced cardiac surgeons and interventional cardiologists, including the Study Coordinating PIs, Center PIs, other Investigators, Proctors and Medical Consultants experienced in TAVR for their clinical/medical expertise, and the Sponsor for technical expertise on the ACURATE Transfemoral Aortic Valve System requirements. This committee will be responsible for the review of subject screening data to confirm eligibility given the increased surgical risk of the subject population being studied and to ensure consistency of subjects enrolled across study centers. Responsibilities, qualifications, membership, and committee procedures are outlined in the CRC Charter. Minutes are written for each CRC review session and the decisions are documented in these minutes and provided to the centers as appropriate.

21.3. *Steering Committee*

A Steering Committee consisting of Sponsor Clinical Management, the Study Coordinating PIs, cardiac surgeons, and other investigators experienced in TAVR will be convened. Responsibilities may include oversight of the overall conduct of the study with regard to protocol development, study progress, subject safety, overall data quality and integrity, as well as disseminating any study results through appropriate scientific sessions and publications. Steering Committee members may participate in the review and approval of all requests for data analysis, abstract and manuscript preparation and submission.

22. Suspension or Termination

22.1. *Premature Termination of the Study*

Boston Scientific Corporation reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or business reasons and reasons related to protection of subjects. Investigators, associated IRBs/REBs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

22.1.1. Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following.

- Suspicion of an unacceptable risk. In this case, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed.
- Instructions by the IRB/REB/HREC/IEC or regulatory authorities to suspend or terminate the clinical investigation.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development of the device.

22.2. *Termination of Study Participation by the Investigator or Withdrawal of IRB / REB / HREC / IEC Approval*

Any investigator, or associated IRB/REB/HREC/IEC or regulatory authority may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to BSC. Investigators, associated IRBs/REBs/HRECs/IECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

22.3. *Requirements for Documentation and Subject Follow-up*

In the event of premature study termination, a written statement as to why the premature termination has occurred will be provided to all participating centers by BSC. The IRB/REB/ HREC/IEC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB/REB/HREC/IEC terminates participation in the study, participating investigators, associated IRBs/REBs/HRECs/IECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by BSC.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility, detailed information on how enrolled subjects will be managed thereafter will be provided by BSC.

The Principal Investigator or his/her designee must return all study-related documents and investigational product to BSC, unless this action would jeopardize the rights, safety, or welfare of the subjects.

22.4. *Criteria for Suspending/Terminating a Study Center*

Boston Scientific Corporation reserves the right to stop the inclusion of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled for a period beyond 4 months after center initiation, or if the center has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of center participation, all study devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/REB/HREC/IEC and regulatory authorities, as applicable, will be notified. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

23. Study Registration and Results

23.1. *Study Registration*

To comply with applicable laws and regulations, the study has been registered on the publicly accessible database ClinicalTrials.gov (NCT03735667).

23.2. *Clinical Investigation Report*

Study results will be made available in accordance with the legal requirements and the recognized ethical principles, in accordance with the Boston Scientific Policy. A Clinical Investigation Report will be made available to all investigators, IRB/REB/HREC/IEC and regulatory authorities, as applicable in accordance with the Boston Scientific Policy and local

requirements. As applicable an abbreviated Clinical Investigation Report will be made available on a publicly accessible database.

23.3. *Publication Policy*

Boston Scientific Corporation requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. Boston Scientific Corporation will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific Corporation adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed.

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

The data, analytic methods, and study materials for this clinical trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (http://www.bostonscientific.com/en-US/data-sharing-requests.html).

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25. Abbreviations and Definitions

25.1. *Abbreviations*

Abbreviations are shown in **Table 25.1-1**.

Table 25.1-1: Abbreviations and Acronyms

Abbreviation/Acronym	Definition
ADE	adverse device effect
AE	adverse event
AKIN	Acute Kidney Injury Network
AR	aortic regurgitation
AS	aortic stenosis
AV	atrioventricular
AVA	aortic valve area
AVR	aortic valve replacement
BARC	Bleeding Academic Research Consortium
BAV	balloon aortic valvuloplasty
BMI	body mass index
BSA	body surface area
BSC	Boston Scientific Corporation
CAD	coronary artery disease
CBC	complete blood count
CEC	Clinical Events Committee
CK	creatine kinase
CK-MB	creatine kinase-myoglobin band, a fraction of creatine kinase
CRC	Case Review Committee
CT	computed tomography
CVA	cerebrovascular accident
DFU	Directions for Use
DVI	Doppler velocity index
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOA	effective orifice area
GCP	Good Clinical Practices

Table 25.1-1: Abbreviations and Acronyms

Abbreviation/Acronym	Definition
GDPR	General Data Protection Regulation
HCP	healthcare personnel
HREC	Human Research Ethics Committee
IB	Investigator Brochure
ICF	Informed Consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
iEOA	indexed effective orifice area
IFU	Instructions for Use
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISO	International Organization for Standardization
ITT	intention-to-treat
LBBB	left bundle branch block
LV	left ventricle
LVEF	left ventricular ejection fraction
MACCE	major adverse cardiovascular and cerebrovascular events
MI	myocardial infarction
MRI	magnetic resonance imaging
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
NYHA	New York Heart Association
OAC	oral anticoagulant
PG	performance goal
PPM	permanent pacemaker
QOL	quality of life
REB	Research Ethics Board
RLM	reduced leaflet motion
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SAVR	surgical aortic valve replacement
TAVI/TAVR	transcatheter aortic valve implantation/replacement
TEE	transesophageal Doppler echocardiography
TIA	transient ischemic attack
TTE	transthoracic Doppler echocardiography
UADE	unanticipated adverse device effect
URL	upper reference limit (defined as 99th percentile of normal reference range)
VARC	Valve Academic Research Consortium

25.2. *Definitions*

Terms are defined in **Table 25.2-1**. See **Table 25.1-1** for abbreviations.

Table 25.2-1: Definitions

Term	Definition
ACUTE KIDNEY INJURY (AKI) (AKIN System[69,70])	Change in serum creatinine (up to 7 days) compared to baseline: • Stage 1: Increase in serum creatinine to 150–199% (1.5–1.99 × increase compared with baseline) OR increase of ≥0.3 mg/dl (≥26.4 mmol/L) • Stage 2: Increase in serum creatinine to 200–299% (2.0–2.99 × increase compared with baseline) • Stage 3: Increase in serum creatinine to ≥300% (>3 × 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- Based on urine output (up to 7 days): • Stage 1: <0.5 ml/kg per hour for >6 but <12 hours • Stage 2: <0.5 ml/kg per hour for >12 but <24 hours • Stage 3: <0.3 ml/kg per hour for ≥24 hours or anuria for ≥12 hours ***Note:*** Subjects receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.
ACUTE VESSEL OCCLUSION	The state of complete luminal obstruction with no antegrade blood flow
ADVERSE EVENT (AE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	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. ***Note:*** This definition includes events related to the investigational medical device or the comparator. ***Note:*** This definition includes events related to the procedures involved. ***Note:*** For users or other persons, this definition is restricted to events related to investigational medical devices.
ADVERSE EVENT BECOME AWARE DATE	The become aware date for an adverse event that requires reporting per the protocol is the date that study personnel listed on the Delegation of Authority Log identify or are notified of the event.
ADVERSE DEVICE EFFECT (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of an investigational medical device ***Note:*** 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. ***Note:*** This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
AORTIC DISSECTION	Intimal tear resulting in blood splitting the aortic media and producing a false lumen that can progress in an antegrade or retrograde direction Aortic dissection is further classified using Stanford classification (Types A and B depending on whether ascending or descending aorta involved) or DeBakey classification (Types I, II and III) [see Figure below].

Table 25.2-1: Definitions

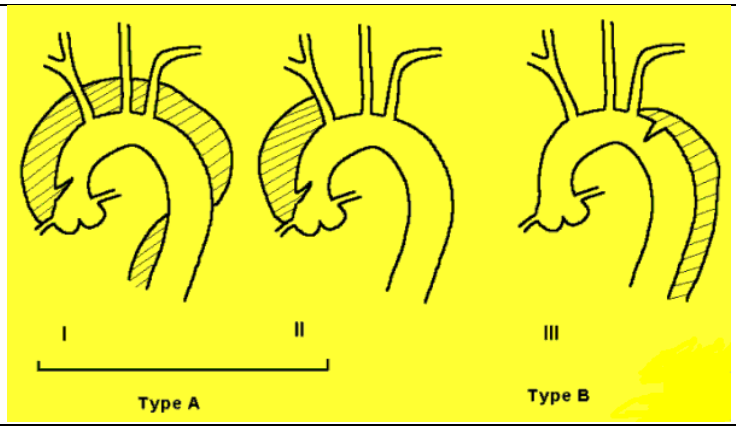
Term	Definition
	
AORTIC REGURGITATION (AR)	The leaking of the aortic valve that causes blood to flow in the reverse direction during ventricular diastole, from the aorta into the left ventricle. The echocardiographic findings in severe aortic regurgitation include the following. • An AR color jet dimension >60% of the left ventricular outflow tract diameter (may not be true if the jet is eccentric) • The pressure half-time of the regurgitant jet is <250 msec • Early termination of the mitral inflow (due to increase in LV pressure due to the AR) • Early diastolic flow reversal in the descending aorta. • Regurgitant volume >60 mL • Regurgitant fraction >55%
ARRHYTHMIA	Any variation from the normal rhythm of the heartbeat, including sinus arrhythmia, premature beat, heart block, atrial fibrillation, atrial flutter and tachycardia. Complete heart block, ventricular tachycardia and ventricular fibrillation are considered major arrhythmias. Data should be collected on any new arrhythmia resulting in hemodynamic instability or requiring therapy (therapy includes electrical/medical cardioversion or initiation of a new medication [oral anticoagulation, rhythm or rate controlling therapy]). New onset atrial fibrillation or atrial flutter (AF) is diagnosed as any arrhythmia within hospitalization that has the ECG characteristics of AF and lasts sufficiently long to be recorded on a 12-lead ECG, or at least 30 seconds on a rhythm strip. The therapeutic approach to new-onset AF (spontaneous conversion, electrical or medical cardioversion, initiation of oral anticoagulation, and rate or rhythm control medications) and any clinical consequences should be documented. ***Note:*** See also definitions for conductance disturbance and permanent pacemaker.
BLEEDING[66,67]	<u>Life-threatening or Disabling Bleeding</u> • Fatal bleeding (Bleeding Academic Research Consortium [BARC] type 5[93,94]) • Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c)

Table 25.2-1: Definitions

Term	Definition
	• Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) • Overt source of bleeding with drop in hemoglobin of ≥5 g/dL or whole blood or packed red blood cells (RBC) transfusion ≥4 units (BARC type 3b)* <u>Major Bleeding (BARC type 3a)</u> • Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0g/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 (e.g., access site hematoma) that does not qualify as life-threatening, disabling, or major * Given one unit of packed RBC typically will raise blood hemoglobin concentration by 1 g/dL, an estimated decrease in hemoglobin will be calculated.
CARDIAC DECOMPENSATION	Inability of the heart to maintain adequate circulation
CARDIAC TAMPONADE	Evidence of a new pericardial effusion associated with hemodynamic instability and clearly related to the TAVR procedure. Clinical syndrome caused by the accumulation of fluid in the pericardial space, resulting in reduced ventricular filling and subsequent hemodynamic compromise.
CARDIOGENIC SHOCK	An insufficient forward cardiac output to maintain adequate perfusion of vital organs to meet ongoing demands for oxygenation and metabolism. Cardiogenic shock is due to either inadequate left ventricular pump function (such as in congestive heart failure) or inadequate left ventricular filling (such as in cardiac tamponade). Cardiogenic shock is defined as sustained hypotension (>30 minutes) with evidence of tissue hypoperfusion including oliguria (<30 mL/h), cool extremities, cyanosis, and altered mental status.
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.
CHRONIC RENAL INSUFFICIENCY	Subject has chronic impairment of kidney function.
CLINICAL PROCEDURAL SUCCESS (IN-HOSPITAL)	Implantation of the device in the absence of death, disabling stroke, major vascular complications, and life-threatening or major bleeding
CONDUCTION DISTURBANCES[66,67]	Implant-related new or worsened cardiac conduction disturbances include new or worsened first degree atrioventricular (AV) block, second degree AV block (Mobitz I or Mobitz II), third degree AV block, incomplete right bundle branch block (RBBB), RBBB, intraventricular conduction delay, left bundle branch block (LBBB), left anterior fascicular block, or left posterior fascicular block, including block requiring permanent pacemaker implant ***Note:*** High grade AV block is considered persistent if it is present every time the underlying rhythm is checked. ***Note:*** See also definitions for arrhythmia and permanent pacemaker.
CONVERSION TO OPEN SURGERY	Conversion to open sternotomy during the TAVR procedure secondary to any procedure-related complications

Table 25.2-1: Definitions

Term	Definition
CORONARY OBSTRUCTION	Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary ostium, either by the valve prosthesis itself, the native leaflets, calcifications, or dissection, occurring during or after the TAVR procedure. Mechanical coronary artery obstruction following TAVR or surgical AVR that typically occurs during the index procedure. Possible mechanisms for mechanical coronary obstruction include the following. • Impingement of the coronary ostia by the valve support structure in the setting of suboptimal valve positioning and/or 'small aortic root' anatomy • Embolization from calcium, thrombus, air, or endocarditis displacement of native aortic valve leaflets towards the coronary ostia during TAVR • Suture-related kinking or obstruction or cannulation related obstruction of the coronary ostia associated with surgical AVR The diagnosis of TAVR-associated coronary obstruction can be determined by imaging studies (coronary angiography, intravascular ultrasound, multi-slice CT angiography, or echocardiography), surgical exploration, or autopsy findings. Cardiac biomarker elevations and ECG changes indicating new ischemia provide corroborative evidence.
DATA CATEGORIES	Data categories as defined by GDPR are listed below. <u>Personal Data:</u> GDPR defines "Personal Data" to be any information relating to an identified or identifiable natural person ('data subject'); an identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person. <u>Sensitive Personal Data:</u> GDPR defines "Sensitive Personal Data" as a subset of Personal Data, which, due to their nature have been classified as deserving additional privacy and security protections because their processing may create a risk for an individual's fundamental right and freedom. This subset includes but is not limited to the following: racial, ethnic origin or ethnicity; political opinions; religious or philosophical beliefs; trade union membership; genetic data; biometric data for the purpose of uniquely identifying a natural person; health data (including gender, family medical history, etc.); sex life or sexual orientation; criminal records or allegations of crimes (requires an even higher standard of protection). <u>Identifiers:</u> "Identifiers" are Personal Data that can be used alone or in combination with other identifiers to identify an individual. Identifiers include but are not limited to the following: • All government-issued identification numbers (including but not limited to names, social security number, certificate/license numbers, passport, national ID) • All financial account numbers (including but not limited to bank account numbers, payment numbers, bank or credit card numbers) • All geographic subdivisions smaller than a state, including street address, city, county, precinct, ZIP code, and their equivalent geocodes, except for the

Table 25.2-1: Definitions

Term	Definition
	initial three digits of the ZIP code if, according to the current publicly available data from the Bureau of the Census, the geographic unit formed by combining all ZIP codes with the same three initial digits contains more than 20,000 people and/or the initial three digits of a ZIP code for all such geographic units containing 20,000 or fewer people is changed to 000 • All elements of dates (except year) for dates that are directly related to an individual, including birth date, admission date, discharge date, death date, and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older • Telephone numbers • Fax numbers • Device identifiers and serial numbers • E-mail addresses • Web Universal Resource Locators (URLs) • Internet Protocol (IP) addresses • Medical record numbers • Biometric identifiers, including finger and voice prints • Health plan beneficiary numbers • Full-face photographs and any comparable images Any other unique identifying number, characteristic, or code (including subject ID number)
DEATH	<u>All-cause Death</u> Death from any cause after a valve intervention. <u>Cardiovascular Death</u> Any one of the following criteria is met. • Any death due to proximate cardiac cause (e.g., myocardial infarction, cardiac tamponade, worsening heart failure) • Sudden or unwitnessed death • Death of unknown cause • Death caused by noncoronary 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 <u>Non-cardiovascular Death</u> • Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide)
DEVICE DEFICIENCY *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Any inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. ***Note:*** Device deficiencies may include malfunctions, use errors, or inadequacy in the information supplied by the manufacturer.
DEVICE FAILURE	A device failure is identified whenever the criteria for device success are not met.

Table 25.2-1: Definitions

Term	Definition
DEVICE MIGRATION	Device migration is defined as an upward or downward displacement of the implanted valve from its original implant location, after initial correct positioning within the aortic annulus from its initial position, with or without consequences. This can be confirmed by X-ray, echocardiography, CT scan or MRI or valve migration demonstrated by direct assessment during open heart surgery or at autopsy.
DEVICE RELATED COMPLICATIONS	Complications associated with the device as it relates to delivery, placement, efficacy or durability; these may involve the implanted device or the delivery system.
DEVICE SUCCESS (VARC 2 definition)[67]	Absence of procedural mortality, correct positioning of a single valve into the proper anatomical location and intended performance of the study device (indexed effective orifice area [iEOA] >0.85 cm^2/m^2 for BMI <30 kg/m^2 and iEOA >0.70 cm^2/m^2 for BMI ≥30 kg/m^2 plus either a mean aortic valve gradient <20 mmHg or a peak velocity <3m/sec, and no moderate or severe prosthetic valve aortic regurgitation).
ECTOPIC VALVE DEPLOYMENT	Permanent deployment of the valve prosthesis in a location other than the aortic root.
EMBOLISM	Examples include a free flowing blood clot or lesion material that is located in the systemic or pulmonary circulation. Embolism may be manifested by a neurological event or a noncerebral embolic event.
ENCEPHALOPATHY	Altered mental state (e.g., seizures, delirium, confusion, hallucinations, dementia, coma, psychiatric episode, etc.)
ENDOCARDITIS	**Infective endocarditis** is diagnosed based on Duke criteria[95] and necessitates the following. • Two major criteria -OR- • One major and three minor criteria -OR- • Five minor criteria <u>Major Criteria</u> • Positive blood culture for infective endocarditis o Typical microorganism consistent with infective endocarditis from 2 separate blood cultures, as noted below. ▪ Viridans streptococci, *Streptococcus bovis*, or HACEK group (*Haemophilus* [*Haemophilus parainfluenzae, Haemophilus aphrophilus, and Haemophilus paraphrophilus*], *Actinobacillus actinomycetemcomitans* [*Aggregatibacter actinomycetemcomitans*], *Cardiobacterium hominis, Eikenella corrodens, Kingella kingae* -OR- ▪ Community-acquired *Staphylococcus aureus* or enterococci, in the absence of a primary focus -OR- o Microorganisms consistent with infective endocarditis from persistently positive blood cultures defined as noted below. ▪ Two (2) positive cultures of blood samples drawn >12 hours apart -OR- ▪ All of 3 or a majority of 4 separate cultures of blood (with first and last sample drawn 1 hour apart) • Evidence of endocardial involvement o Positive echocardiogram for infective endocarditis defined as noted below.

Table 25.2-1: Definitions

Term	Definition
	▪ Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation -OR- ▪ Abscess -OR- ▪ New partial dehiscence of prosthetic valve -OR- o New valvular regurgitation (worsening or changing of preexisting murmur not sufficient) <u>Minor Criteria</u> • Predisposition: predisposing heart condition or intravenous drug use • Fever: temperature >38.0° C (100.4° F) • Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions • Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spots, and rheumatoid factor • Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with infective endocarditis • Echocardiographic findings: consistent with infective endocarditis but do not meet a major criterion as noted above **Implanted valve endocarditis** includes any infection involving an implanted valve. The diagnosis of operated valvular endocarditis is based on one of the following criteria. • Fulfillment of the Duke endocarditis criteria as defined above • Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriologic studies during a re-operation • Findings of abscess, pus, or vegetation involving a repaired or replaced valve during an autopsy.
EXPLANT	Removal of the investigational valve implant for any reason.
FRAILTY	Slowness, weakness, exhaustion, wasting and malnutrition, poor endurance and inactivity, loss of independence.
GENERAL DATA PROTECTION REGULATION	The General Data Protection Regulation (GDPR) is a legal framework that sets guidelines for the collection and processing of personal information of individuals within the European Union.
HEMOLYSIS	Two plasma free hemoglobin values >40 mg/dL with the two readings taken within a single 48-hour period. If the second plasma free hemoglobin assessment is not performed within 48 hours following an initial determination of >40 mg/dL, this would qualify as an AE.
HOSTILE CHEST	Any of the following or other reasons that make redo operation through sternotomy or right anterior thoracotomy prohibitively hazardous: • Abnormal chest wall anatomy due to severe kyphoscoliosis or other skeletal abnormalities (including thoracoplasty, Potts' disease) • Complications from prior surgery • Evidence of severe radiation damage (e.g. skin burns, bone destruction, muscle loss, lung fibrosis or esophageal stricture)

Table 25.2-1: Definitions

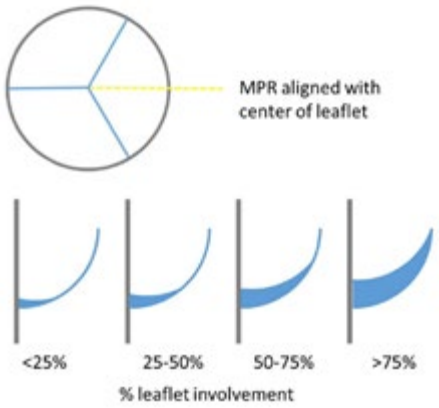
Term	Definition
	• History of multiple recurrent pleural effusions causing internal adhesions
HYPO-ATTENUATED LEAFLET THICKENING (HALT)[73]	Hypo-attenuated leaflet thickening (HALT) is defined as visually identifiable increased leaflet thickness on contrast-enhanced multi-planar reformats, carefully aligned with the long and short axis of the valve prosthesis. The extent of HALT is classified as follows:  The dashed yellow line indicates the orientation of the long axis views in the lower row, aligned with the center of the cusps. The extent of leaflet thickening can be graded on a subjective 4-tier grading scale along the curvilinear orientation of the leaflet. Typically, hypo-attenuated leaflet thickening appears meniscal-shaped on long axis reformats, with greater thickness at the base than towards the center of the leaflet.
IMPLANTED ANALYSIS SET	This population includes all subjects who sign an Informed Consent Form, are enrolled in the trial, and are implanted with the assigned, randomized study device. ***Note:*** If a subject receives 2 valves, the subject is assigned to the group corresponding to the first valve received.
INTENT TO TREAT (ITT) ANALYSIS SET	This population includes all subjects who sign an Informed Consent Form, are enrolled in the trial, and are randomized, whether or not an assigned study device is implanted. Subjects in the ITT population will be followed with their ITT cohort. ***Note:*** If a subject receives 2 valves, the subject is assigned to the group corresponding to the first valve received.
INTERNAL MAMMARY ARTERY OR OTHER CRITICAL CONDUIT(S) CROSSING MIDLINE AND/OR ADHERENT TO POSTERIOR TABLE OF STERNUM	A patent IMA graft that is adherent to the sternum such that injuring it during reoperation is likely. A patient may be considered extreme risk if any of the following are present: • The conduit(s) are radiographically indistinguishable from the posterior table of the sternum. • The conduit(s) are radiographically distinguishable from the posterior table of the sternum but lie within 2-3mm of the posterior table.
INTRACRANIAL HEMORRHAGE	Collection of blood between the brain and skull; subcategorized as epidural, subdural, and subarachnoid bleeds.

Table 25.2-1: Definitions

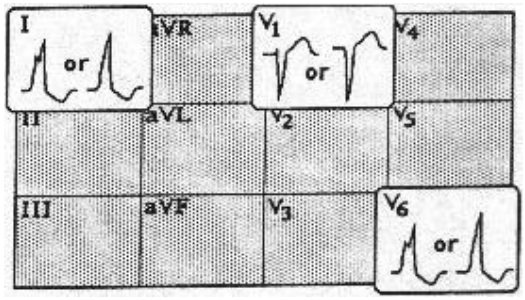
Term	Definition
LEFT BUNDLE BRANCH BLOCK (LBBB)	The appearance of typical complete LBBB in the three KEY leads (I, V1, and V6) with the following diagnostic criteria [see Figure below]. • The heart rhythm must be supraventricular in origin • QRS widening to at least 0.12 sec • An upright (monophasic) QRS complex in leads I and V6; the QRS may be notched, but there should not be any q wave in either lead I or lead V6. • A predominantly negative QRS complex in lead V1; there may or may not be an initial small r wave in lead V1, that is, lead V1 may show either a QS or RS complex. 
LIVER DISEASE (SEVERE) /CIRRHOSIS	Any of the following: • Child-Pugh class C • MELD score ≥10 • Portal-caval, spleno-renal, or transjugular intrahepatic portal shunt • Biopsy proven cirrhosis with portal hypertension or hepatocellular dysfunction
MITRAL VALVE APPARATUS DAMAGE	Angiographic or echocardiographic evidence of a new damage to the mitral valve apparatus (chordae papillary muscle, or leaflet) during or after the TAVR procedure.
MYOCARDIAL INFARCTION (MI)	**Periprocedural MI (≤72 hours after the index procedure)** • New ischemic symptoms (e.g., chest pain or shortness of breath) or new ischemic signs (e.g., ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q waves in at least two contiguous leads, or imaging evidence of new loss of viable myocardium or new wall motion abnormality) -AND- • Elevated cardiac biomarkers (preferably CK-MB) within 72 h after the index procedure, consisting of at least one sample post-procedure with a peak value exceeding 15× upper reference limit (troponin) or 5× for CK-MB. If cardiac biomarkers are increased at baseline (>99th percentile), a further increase of at least 50% post-procedure is required AND the peak value must exceed the previously stated limit. **Spontaneous MI (>72 hours after the index procedure)** Any one of the following criteria applies. • Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with evidence of myocardial ischemia with at least one of the following o Symptoms of ischemia

Table 25.2-1: Definitions

<table>
<tr><th>Term</th><th>Definition</th></tr>
<tr><td></td><td>

o ECG changes indicative of new ischemia [new ST-T changes or new LBBB]
o New pathological Q waves in at least two contiguous leads
o Imaging evidence of new loss of viable myocardium or new wall motion abnormality

Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST-segment elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/ or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
Pathological findings of an acute myocardial infarction[96].

</td></tr>
<tr><td>NEUROLOGICAL EVENT</td><td>Any central, new neurological deficit, whether temporary or permanent and whether focal or global, that occurs after the subject emerges from anesthesia</td></tr>
<tr><td>NEW YORK HEART ASSOCIATION CLASSIFICATION (NYHA)</td><td>Classification system for defining cardiac disease and related functional limitations into four broad categorizations:
<table>
<tr><td>Class I</td><td>Subject with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.</td></tr>
<tr><td>Class II</td><td>Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.</td></tr>
<tr><td>Class III</td><td>Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.</td></tr>
<tr><td>Class IV</td><td>Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.</td></tr>
</table>
</td></tr>
<tr><td>NONSTRUCTURAL DYSFUNCTION</td><td>Any abnormality not intrinsic to the valve itself that results in stenosis or regurgitation of the operated valve or hemolysis. The term nonstructural dysfunction refers to problems (exclusive of thrombosis and infection) that do not directly involve valve components yet result in dysfunction of an operated valve, as diagnosed by re-operation, autopsy, or clinical investigation. Nonstructural dysfunction includes the following.

Entrapment by pannus, tissue, or suture
Paravalvular leak
Inappropriate sizing or positioning
Residual leak or obstruction after valve implantation or repair
Clinically important intravascular hemolytic anemia
Development of aortic or pulmonic regurgitation as a result of technical errors
Dilatation of the sinotubular junction
Dilatation of the valve annulus after either valve replacement with stentless prostheses, new onset of coronary ischemia from coronary ostial obstruction, or paravalvular aortic regurgitation

</td></tr>
</table>

Table 25.2-1: Definitions

Term	Definition
OPERATIVE RISK[67]	Operative risk is determined by a center cardiac surgeon and must be confirmed by the Case Review Committee (including a cardiac surgeon). **Low**: Estimated 30-day risk of mortality is < 3% **Intermediate**: Estimated 30-day risk of mortality is 3–10% **High**: Estimated 30-day risk of mortality is >10–15% **Very High**: Estimated 30-day risk of mortality is >15% **Extreme**: Estimated 30-day risk of irreversible morbidity or mortality is ≥50%
PARAVALVULAR REGURGITATION	Leakage due to a separation of the prosthetic valve from the annulus. Any evidence of leakage of blood around the device. Diagnosis of paravalvular regurgitation may be obtained from TEE/TTE, however, definitive diagnosis is obtained at re-operation, explant, or autopsy.
PERMANENT PACEMAKER (PPM) IMPLANTATION[97]	Implantation of new PPM after the index procedure resulting from new or worsened conduction disturbances • Procedure-related: PPM is implanted in subjects with new onset or worsened conduction disturbances occurring post index procedure • Not related to procedure: PPM is implanted in subjects with known conduction disturbances that did not advance after the index procedure. ***Note:*** See also definitions for arrhythmia and conductance disturbance.
PORCELAIN AORTA	Heavy circumferential calcification of the entire ascending aorta extending to the arch such that aortic cross-clamping is not feasible
PROCEDURE RELATED COMPLICATIONS	Complications associated with any part of the vascular access procedure, associated treatments or necessary secondary interventions that do not necessarily involve the device. This includes morbidity associated with either pre-medication, or anesthesia, or other adjunct to the surgical procedure. Other technical errors including inappropriate subject selection, inappropriate operator techniques, measurements, or judgment that do not involve the device itself are also included.
PROCEDURE-RELATED EVENTS	Events occurring during or as a direct result of the index procedure.
REDUCED LEAFLET MOBILITY/MOTION (RLM)[98]	Systolic leaflet excursion/motion is classified as: • Grade 0: normal/unrestricted; • Grade 1: partially restricted – limited to base; • Grade 2: mildly restricted – involving more than the base, but less than 50% of the leaflet along curvilinear dimensions; • Grade 3: moderately restricted – involving more than 50% but less than 75% of the leaflet along curvilinear dimensions; • Grade 4: largely immobile. Quantitative assessment of leaflet motion is performed with a blood pool inversion volume rendered cine reconstruction throughout the cardiac cycle evaluating the bioprosthetic leaflets.
REPEAT PROCEDURE FOR VALVE-RELATED DYSFUNCTION	Any surgical or percutaneous interventional catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve. In addition to surgical re-operations, balloon dilatation, interventional manipulation, repositioning, or retrieval, and other catheter-based interventions for valve-related complications are also considered re-interventions. Cardiac re-interventions will be categorized as repeat TAVR, valvuloplasty, or surgical AVR.

Table 25.2-1: Definitions

Term	Definition
RESPIRATORY INSUFFICIENCY	Inadequate ventilation or oxygenation
RESPIRATORY FAILURE	The need for ventilatory support for >72 hours associated with an inability to wean from the respirator for any reason.
RIGHT VENTRICULAR INSUFFICIENCY	• Defined as sequelae of right ventricular failure including the following. o Significantly decreased right ventricular systolic and/or diastolic function o Tricuspid valvular regurgitation secondary to elevated pressure • Clinical symptoms to include the following. o Hepatic congestion o Ascites o Anasarca o Presence of "hepato-jugular reflux" o Edema Severe right ventricular dysfunction or severe pulmonary hypertension is primary or secondary pulmonary hypertension with PA systolic pressures greater than 2/3 of systemic pressure.
SAFETY ANALYSIS SET	This population includes all subjects in the ITT analysis set who have a study device implanted, regardless of the assigned treatment group.
SERIOUS ADVERSE EVENT (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event that: • Led to a death • Led to serious deterioration in the health of the subject, that either resulted in: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient hospitalization or prolongation of existing hospitalization, or o medical or surgical intervention to prevent life- threatening illness • Led to fetal distress, fetal death or a congenital abnormality or birth defect ***Note:*** Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.
SERIOUS ADVERSE DEVICE EFFECT (SADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event
SOURCE DATA (per ISO 14155)	All information in original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation
SOURCE DOCUMENT (per ISO 14155)	Printed, optical or electronic document containing source data. Examples: hospital records, laboratory notes, device accountability records, photograhic negatives, radiographs, records kept at the investigation center, at the laboratories and at the medico-technical departments involvced in the clinical investigation. ***Note:*** If thermal paper from a device programmer is to be used for source documentation, signed and dated photocopies or printed portable document format files should be used instead or the strips should be electronically saved.

Table 25.2-1: Definitions

Term	Definition
STROKE[66,67]	Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. **Stroke Classification** • Ischemic Stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue. • Hemorrhagic Stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by an intraparenchymal, intraventricular, or subarachnoid hemorrhage ***Note:*** The CEC will adjudicate ischemic versus hemorrhagic stroke. ***Note:*** A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic **Stroke Diagnostic Criteria** • Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke • Duration of a focal or global neurological deficit ≥24 h; OR <24 h, if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death • No other readily identifiable nonstroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with designated neurologist • Confirmation of the diagnosis by at least one of the following. o Neurology or neurosurgical specialist o Neuroimaging procedure (MRI or CT scan), but stroke may be diagnosed on clinical grounds alone ***Note:*** Subjects with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies (CT scan or brain MRI). **Stroke Definitions** Diagnosis as above, preferably with positive neuroimaging study • Non-disabling: Modified Rankin Scale (mRS) score <2 at 90 days OR one that does not result in an increase of at least one mRS category from an individual's pre-stroke baseline • Disabling: Modified Rankin Scale score ≥2 at 90 days AND an increase of at least one mRS category from an individual's pre-stroke baseline ***Note:*** Modified Rankin Scale assessments should be made by a neurology professional or by qualified individuals according to a certification process. ***Note:*** Assessment of the mRS score should occur at all scheduled visits in a study; mRS also should be performed after a stroke and at 90 days after the onset of any stroke.
TAV-IN-TAV DEPLOYMENT	An additional valve prosthesis is implanted within a previously implanted prosthesis because of suboptimal device position and/or function during or after the index procedure.

Table 25.2-1: Definitions

Term	Definition
TRANSIENT ISCHEMIC ATTACK (TIA)	• Transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction • Duration of a focal or global neurological deficit is <24 h • Neuroimaging does not demonstrate a new hemorrhage or infarct (if performed) ***Note:*** The difference between TIA and ischemic stroke is the presence of tissue damage or new sensory-motor deficit persisting >24 hours. By definition, TIA does not produce lasting disability.
UNANTICIPATED ADVERSE DEVICE EFFECT *Ref: 21CFR Part 812* (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
UNPLANNED USE OF CARDIOPUL-MONARY BYPASS	Unplanned use of cardiopulmonary bypass for hemodynamic support at any time during the TAVR procedure
VALVE EMBOLIZATION	The valve prosthesis moves during or after deployment such that it loses contact with the aortic annulus.
VALVE MALPOSITIONING	Includes valve migration, valve embolization, or ectopic valve deployment
VALVE MIGRATION	After initial correct positioning the valve prosthesis moves upward or downward within the aortic annulus from its initial position, with or without consequences (e.g., regurgitation).
VALVE-RELATED DYSFUNCTION	Mean aortic valve gradient ≥20 mmHg, EOA ≤0.9-1.1 cm^2, and/or DVI <0.35 AND/OR moderate or severe prosthetic valve aortic regurgitation (per VARC definition)
VALVE-RELATED SYMPTOMS/CHF REQUIRING HOSPITALIZATION	The need for hospitalization associated with valve-related symptoms or worsening CHF (NYHA Class III or IV) is intended to serve as a basis for calculation of a "days alive outside the hospital" endpoint. Included are heart failure, angina, or syncope due to aortic valve disease requiring intervention or intensified medical management; clinical symptoms of CHF with objective signs including pulmonary edema, hypoperfusion, or documented volume overload AND administration of intravenous diuresis or inotropic therapy, performance of aortic valvuloplasty, institution of mechanical support (intra-aortic balloon pump or ventilation for pulmonary edema), or hemodialysis for volume overload; clear documentation of anginal symptoms AND no clinical evidence that angina was related to coronary artery disease or acute coronary syndrome; documented loss of consciousness not related to seizure or tachyarrhythmia.
VALVE THROMBOSIS	Any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. Note that valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve-related or at operation for an unrelated indication should not be reported as valve thrombosis.
VASCULAR ACCESS SITE AND ACCESS	**Major Vascular Complications** • Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudoaneurysm

Table 25.2-1: Definitions

Term	Definition
RELATED COMPLICATIONS	• Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure*) ***leading to*** death, life-threatening or major bleeding**, visceral ischaemia, or neurological impairment • Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage • The use of unplanned endovascular or surgical intervention ***associated*** with death, major bleeding, visceral ischaemia or neurological impairment • Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram • Surgery for access site-related nerve injury • Permanent access site-related nerve injury **Minor Vascular Complications** • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysms, hematomas, percutaneous closure device failure*) not leading to death, life-threatening or major bleeding**, visceral ischaemia or neurological impairment • Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage • Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication • Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft) ***Percutaneous Closure Device Failure** Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning) ***Note:*** Pre-planned surgical access or a planned endovascular approach to vascular closure (e.g., "pre-closure")[99,100] should be considered as part of the TAVR procedure and not as a complication, unless untoward clinical consequences are documented (e.g., bleeding complications, limb ischemia, distal embolization, or neurological impairment). ***Note:*** If unplanned percutaneous or surgical intervention does not lead to adverse outcomes this is not considered a major vascular complication. ** Refers to VARC bleeding definitions[66,67]
VENTRICULAR SEPTAL PERFORATION	Angiographic or echocardiographic evidence of a new septal perforation during or after the TAVR procedure
VESSEL PERFORATION	Unexpected puncture of the vessel with evidence of extravasation into extraluminal surrounding tissue or space requiring treatment using interventional or surgical techniques
VULNERABLE SUBJECTS (per ISO 14155)	Individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response

Table 25.2-1: Definitions

Term	Definition

Abbreviations: ADE=adverse device effect; AE=adverse event; AR=aortic regurgitation; AVA=aortic valve area; AVR= aortic valve replacement; CEC= Clinical Events Committee; CK= creatine kinase; CT=computed tomography; DVI=Doppler velocity index; ECG=electrocardiogram; EOA=effective orifice area; FEV= forced expiratory volume; GDPR= General Data Protection Regulation; LBBB=left bundle branch block; LV= left ventricle; MI=myocardial infarction; MRI=magnetic resonance imaging; NYHA=New York Heart Association; PPM=permanent pacemaker; RBC=red blood cell; SADE=serious adverse device effect; SAE=serious adverse event; TAV=transcatheter aortic valve; TAVR=transcatheter aortic valve replacement; TEE=transesophageal Doppler echocardiography; TIA=transient ischemic attack; URL=upper reference limit (defined as 99th percentile of normal reference range); VARC=Valve Academic Research Consortium

26. Revision History

26.1. *Summary of Protocol Revision History*

Protocol revision history is provided in **Table 26.1-1**.

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
A	12-Oct-2018	90702637 Rev/Ver AJ	–	Not applicable.	–
B	10-Jan-2019	90702637 Rev/Ver AJ	Section 2, Synopsis, Study Design	• **Roll-In Cohort:** A non-randomized Roll-In phase… Centers with prior experience with ACURATE are not required to do Roll-In cases. Data…	Clarify that centers with ACURATE experience are not required to do Roll-In cases.
			Section 2, Synopsis, Method of Assigning…	**Roll-In Cohort:** For centers… cohort. Centers with prior experience with ACURATE are not required to do Roll-In cases.	
			Section 2, Synopsis, Inclusion Criteria IC1. Section 8.2, Table 8.2-1, Inclusion Criteria IC1.	Removed the following text: • Asymptomatic Subjects - Initial AVA ≤1.0 cm^2 (or AVA index ≤0.6 cm^2/m^2) and maximal aortic velocity ≥5.0 m/s as measured by echocardiography and/or invasive hemodynamics Updated remaining text to read as follows: IC1. Subject has documented severe symptomatic native aortic stenosis defined as follows: aortic…	Not applicable to approved devices.
			Section 5.1.3, Introducer Set	It is recommended that… or the commercially available 14F iSLEEVE™ Introducer Set (iSLEEVE; Boston Scientific Corporation, Marlborough, MA, USA) be used as… The sheath component of the iSLEEVE is expandable, which allows for transient sheath expansion during delivery system introduction. The LIS S is suitable for use in subjects with femoral vascular access ≥6.0 mm. The 14F iSLEEVE is suitable for use in subjects with femoral vascular access ≥5.5mm.	Added the iSLEEVE introducer. The iSLEEVE allows for entry into smaller femoral arteries and is expected to limit any tissue damage due to the transient nature of the expansion.

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 7.1, Scale and Duration	**Roll-In Cohort:** A non-randomized Roll-In phase… (in total). Centers with prior experience with ACURATE are not required to do Roll-In cases. Data…	Clarify that centers with ACURATE experience are not required to do Roll-In cases.
			Section 7.2, Treatment Assignment	***Note:*** Centers that do not have implantation experience with the ACURATE neo™ bioprosthesis (transfemoral delivery) will perform at least 2 non-randomized Roll-In cases before commencing enrollment in the randomized cohort. Centers with prior ACURATE experience may do Roll-In cases but are not required to do so. All…	
			Section 7.3, Justification…	…in the Roll-In phase of this study (centers without implantation experience with the ACURATE neo™ bioprosthesis [transfemoral delivery] are required to do 2 Roll-In cases each) and…	
			Section 9.1.1, Roll-In Subjects	There… bioprosthesis (transfemoral delivery) will perform at least 2 Roll-In cases before commencing enrollment in the randomized cohort; centers with prior experience with ACURATE neo are not required to do Roll-In cases. For…	
			Section 10.2.1, Strategies for Recruitment and Retention	All efforts will be made… Investigators are encouraged to enroll subjects who are willing to comply with the follow-up requirements of the study. If a visit is missed, the center should attempt to contact the subject to reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule.	Clarify information around subject retention efforts.
			Section 10.7.2, ACURATE Transfemoral…	…The commercially available LIS-S introducer or the commercially available 14F iSLEEVE introducer are recommended.	Added the iSLEEVE introducer.
			Section 11.1.1.4, Statistical Methods…	…in the SAP. Please also see Section 9.4, Section 10.1, and Section 10.2.1 regarding data collection and missing data.	Clarify information around missing data.

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 11.3.3, Subgroup Analyses for Randomized Subjects	Added 2 more subgroups: • Age (<75 years and ≥75 years) • Any race and ethnicity category with >100 enrolled subjects as described in the SAP Treatment groups will also be compared in the age, race, and gender subgroup analyses. No adjustments…	Additional subgroups requested by regulatory authority.
			Section 16.4.2, Training…	***Note:*** For centers… required proctored cases. Centers with prior experience with the ACURATE bioprosthesis who are proctor-free are not required to do Roll-In cases but may do Roll-In subjects without the presence of a proctor.	Clarify that centers with ACURATE experience are not required to do Roll-In cases.
			Section 25.2, Definitions REPEAT PROCEDURE FOR VALVE-RELATED DYSFUNCTION	Any surgical…re-operations, ~~enzymatic,~~ balloon… or surgical AVR. Also removed the following text: • Conversion to open surgery • Conversion to… complications • Unplanned use of CPB • Unplanned use… procedure	Text removed for clarity.
C	21-May-2019	90702637 Rev/Ver AL	First page	Added the following: National Clinical Trial Identification Number: NCT03735667	Required per protocol template version AL
			Page 2	Added date of current version: 21-May-2019	Updated protocol
			Section 2. Protocol Synopsis	Additional Measurements: Added reference to VARC 3 Inclusion Criteria: Updated as follows:	Expected publication of updated VARC 3 guidelines

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				IC4. Heart team (which must include an experienced cardiac interventionalist and an experienced cardiac surgeon) agrees that the subject ~~has an on-label United States Food and Drug Administration (FDA) approved indication for TAVR~~ is at intermediate risk or above for surgical valve replacement and TAVR is appropriate. The heart team should consider the Society of Thoracic Surgeons (STS) score as well as other factors including frailty, prior surgical history, malignancy or radiation therapy, pulmonary disease, renal disease, liver disease, neuromuscular disease, orthopedic disease, chest deformity, and aortic calcification. Subjects considered to be at intermediate surgical risk or above have a predicted risk of surgical mortality ≥ 3% based on the STS risk score and other clinical comorbidities unmeasured by the STS risk calculator.	Updated per FDA suggestion
			Table 4.1-4 Randomized Trials with ACURATE *neo* TF	The ACURATE neo Aortic Bioprosthesis together with the ACURATE neo TF Delivery System are also undergoing clinical assessment in two prospective, multicenter RCTs (SCOPE I and SCOPE II) as shown in Table 4.1 4~~; enrollment is currently ongoing in both studies~~. SCOPE I: N=730 planned subjects randomized 1:1 ~~Enrolling~~ SCOPE II: N=764 planned subjects randomized 1:1 ~~Enrolling~~	Updated for clarity
			Section 6.5 Additional Measurements	Added a reference to VARC 3 Additional measurements based on the VARC endpoints and definitions[66-68]	Expected publication of updated VARC 3 guidelines
			Section 7.1 Scale and Duration	The ACURATE IDE study is ~~will be~~ registered at ClinicalTrials.gov (NCT03735667)~~ prior to enrollment of the first subject~~.	Registered the trial
			Section 8.2 Inclusion Criteria	Table 8.2-1 Inclusion Criteria updated as follows:	Updated per FDA suggestion

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				IC4. Heart team (which must include an experienced cardiac interventionalist and an experienced cardiac surgeon) agrees that the subject ~~has an on-label United States Food and Drug Administration (FDA) approved indication for TAVR~~ is at intermediate risk or above for surgical valve replacement and TAVR is appropriate. The heart team should consider the Society of Thoracic Surgeons (STS) score as well as other factors including frailty, prior surgical history, malignancy or radiation therapy, pulmonary disease, renal disease, liver disease, neuromuscular disease, orthopedic disease, chest deformity, and aortic calcification. Subjects considered to be at intermediate surgical risk or above have a predicted risk of surgical mortality ≥ 3% based on the STS risk score and other clinical comorbidities unmeasured by the STS risk calculator.	
			Section 10.1 Data Collection	Additional text as follows: This section indicates the data needed to fulfill the objectives of this clinical study. Boston Scientific Corporation considers data collected from clinical trial subjects to be personal data (see definitions of different data categories in Table 25.2 1) and compliance with privacy and data protection laws and regulations (for example, the General Data Protection Regulation [GDPR]) to be critically important. Data collection for this clinical study has been carefully considered to comply with data privacy laws.	Include information on privacy considerations for clinical study data collection.

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 18.1.1 Reduced Leaflet Motion	New section added: Reduced leaflet motion (RLM) suggestive of subclinical leaflet thrombosis, as detected by high-resolution CT, has been reported with bioprosthetic TAVR and SAVR valves[85-88]. It is less common among subjects receiving anticoagulant therapy and has been shown to resolve with such treatment[85-91]. Clinical signs of RLM include elevation of transvalvular gradients (as determined by echocardiography), central or peripheral thromboembolic events, and unexpected recurrence of heart failure. Computed tomography imaging is recommended to appropriately assess subjects with echocardiographic and/or clinical suspicion of leaflet thrombosis. Additional anticoagulant therapy may be indicated based on symptoms/signs and subject bleeding risk[85-91].	Updated per FDA suggestion
			Section 24 Bibliography	Added new references on reduced leaflet motion	Support FDA suggestion
				Added new reference for VARC 3	Expected publication of updated VARC 3 guidelines
			Section 25.1 Abbreviations	Added abbreviations for “General Data Protection Regulation” (GDPR) and “reduced leaflet motion” (RLM).	Clarification
			Section 25.2 Definitions	Added definitions for the following terms in Table 25.2-1: • Data Categories • General Data Protection Regulation	Include information on privacy considerations for clinical study data collection
				Added a note to the definition of structural valve deterioration:	Expected publication of

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				Note: Additional outcomes may be measured per definitions set in the most current VARC guidelines (as released at the time of analysis).	updated VARC 3 guidelines
D	31-Jul-2019	90702637 Rev/Ver AL	Page 2 Contact Information Clinical Contact	Lisa Currier Senior Clinical Trial manager… Sarah Zanon… Chemin de la Venoge 11 ~~Dornacherplatz 7~~ ~~4500 Solothurn,~~ 1024 Ecublens, Switzerland	Updated title; Updated address
			10.4 Screening Assessments	Updated timing of screening imaging assessment for transthoracic echocardiography • Imaging assessments ○ Within ~~60~~ 90 days prior…	More closely align with what sites are doing for TTE assessments in clinical Standard of Care practice.
			16.4.2 Training with the Investigational Device	Device Demonstration: A live or hands-on training to simulate/practice the implantation procedure with demonstration devices or in a bench model or a robotic simulation.	Updated to clarify that demonstration devices can be used live to simulate the implantation
			18.1.1 Reduced Leaflet Motion…	Reduced leaflet… therapy and in some cases has been shown…	FDA request
E	08-Jan-2020	90702637 Rev/Ver AL	Contact Information	Beth Louh Clinical Trial Manager, Interventional Cardiology Boston Scientific Corporation 100 Boston Scientific Way, Marlborough, MA 01752 USA	Additional project manager
			Section 2, Synopsis, Study Design	• **Roll-In Cohort:** A non-randomized Roll-In phase… will perform at least 2 Roll-In cases before commencing ~~enrollment~~ treatment in the randomized cohort.	Clarify centers must have performed 2 Roll-In cases before

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 2, Synopsis, Method of Assigning Patients	• **Roll-In Cohort:** For centers… at least 2 Roll-In subjects will be treated before commencing ~~enrollment~~ treatment in the randomized cohort.	**treating** subjects in the randomized cohort.
			Section 2, Synopsis, Planned Number …	Subjects will be enrolled at up to ~~50~~ 65 centers… There will be up to ~~600~~630 subjects in ACURATE IDE… **Cohort** | **Number of Subjects** Roll-In | Up to ~~100~~ 130	Support faster enrollment
			Section 2, Synopsis, Adjunctive Pharmacologic Therapy	Aspirin A loading dose of aspirin… is ~~required~~ recommended for subjects... The loading dose ~~must~~ should be administered prior to the implant procedure…. $P2Y_{12}$ Inhibitor A loading dose of a $P2Y_{12}$ inhibitor… is ~~required~~ recommended for subjects... The loading dose ~~must~~ should be administered prior to the implant procedure…. **Note 5:** If a subject requires chronic anticoagulation, either a $P2Y_{12}$ inhibitor or aspirin is ~~required~~ recommended prior to and required after the implant procedure in addition to the anticoagulant therapy (but treatment with both aspirin and a $P2Y_{12}$ inhibitor after the implant procedure is ~~are~~ not required).	Current standard of care; updated text for clarification
			Section 2, Synopsis, Inclusion Criteria	IC4. Heart team… **Note 8:** At the time this protocol… and Canada. Subjects at low surgical risk were subsequently approved for TAVR with commercially available devices in the United States.	Reflects the updated FDA approval of TAVR in low-risk patients.
			4.1.3 Clinical Studies with the ACURATE Aortic Bioprosthesis	The ACURATE *neo* Aortic Bioprosthesis… multicenter RCTs (SCOPE I and SCOPE II) as shown in **Table 4.1-4**. To **Table 4.1-4**, added the following: SCOPE I: N=730 planned subjects; 739 subjects were randomized 1:1	SCOPE I results (30 days) have been published.

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				Primary endpoint outcomes (30 days) have been reported for 731 subjects[72]. SCOPE II: Primary endpoint outcomes (1 year) to be reported likely in the second half of 2020. Outcomes at 30 days in the SCOPE I trial are summarized in **Table 4.1-5** below. The primary safety and efficacy composite endpoint at 30 days included… The primary endpoint occurred in 87 subjects (24%) in the ACURATE *neo* cohort and in 60 subjects (16%) in the SAPIEN 3 group; thus, non-inferiority of ACURATE *neo* was not met (absolute risk difference of 7.1% [upper 95% confidence limit: 12.0%], *P*=0.42). The difference was largely driven by a higher rate of PVR with ACURATE *neo* compared to SAPIEN 3. Notably, most of the individual clinical components of the primary endpoint were similar between the 2 groups as were secondary clinical endpoints (**Table 4.1-5**). < **Table 4.1.5: SCOPE I – 30-Day Outcomes**> added.	
				The ACURATE *neo*2™ Transfemoral Aortic Valve System… N=120). Outcomes to 1 year[73] are shown in **Table 4.1-6**. Clinical results showed sustained safety and performance comparable to other TAVR valves in similar patient populations. The observed hemodynamic improvement post index procedure was maintained at 1 year. Notably, PVR was mild or less in 97.5% of subjects at 1 year. <**Table 4.1-6: Outcomes to 1 Year in ACURATE neo AS TF Study (N=120)**> added.	Data to 1 year have been presented.
			7.1 Scale and Duration	Subjects will be enrolled at up to ~~50~~65 centers… There will be up to ~~600~~630 subjects in… **Roll-In Cohort:** A non-randomized Roll-In phase… will perform at least 2 Roll-In cases before commencing ~~enrollment~~ treatment	Increased number of centers to support faster enrollment

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				in the randomized cohort (up to ~~100~~ 130 Roll-In subjects in total)...	Clarify centers must have performed 2 Roll-In cases before **treating** subjects in the randomized cohort.
			7.2 Treatment Assignment	***Note:*** Centers that do not have… will perform at least 2 Roll-In cases before commencing ~~enrollment~~ treatment in the randomized cohort.	
			7.3 Justification for the Study Design	There will be up to ~~600~~ 630 subjects in ACURATE IDE … limiting the potential exposure of study subjects to risk, up to ~~100~~130 subjects will be enrolled in the Roll-In phase… Up to ~~50~~65 centers…	Support faster enrollment
			Table 8.2-1	IC4. Heart team… ***Note 2:*** At the time this protocol… and Canada. Subjects at low surgical risk were subsequently approved for TAVR with commercially available devices in the United States.	Reflects the updated FDA approval of TAVR in low-risk patients.
			9.1.1 Roll-In Subjects	There will be… will perform at least 2 Roll-In cases before commencing ~~enrollment~~ treatment in the randomized cohort; centers...	Clarify centers must have performed 2 Roll-In cases before **treating** subjects in the randomized cohort.
			9.2 Discontinuation of Study Intervention	If a study valve is surgically explanted… followed for safety (no protocol-required echocardiography, electrocardiography or QOL assessment) through end of study.	Clarify subjects without a study valve do not need protocol required ECG or QOL assessments
			10.1 Data Collection	… Subjects who are enrolled but do not receive a study valve (test or control) will be followed for 1 year to assess for safety but do not need to have protocol required echocardiography, electrocardiography, or QOL assessments. If a study valve is surgically explanted, the subject will be followed for safety (no protocol required echocardiography, electrocardiography, or QOL assessments) through end of study.	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Table 10.1-1	Footnote b: All follow-up… do not need to have protocol-required TTE, ECG or QOL assessments.	
			Table 10.1-1	Footnote d: NIHSS and mRS… independent (not involved with the care of study subjects). In addition to the assessments noted in the table, there are additional requirements for administering NIHSS/mRS/neurological physical exams in subjects where stroke is suspected. A neurological physical exam…	Clarify that there are additional assessment requirements for subjects who may have experienced a stroke.
			Table 10.1-1	Assessment: Coronary angiogram/CT coronary angiogram Footnote j: A coronary angiogram/CT coronary angiogram must be performed… Footnote o: Procedural… for analysis. ~~Rotational angiography of the valve frame is required with results sent to the core laboratory.~~	Clarify that CT angiogram can be used for coronary assessment, which reflects current standard of care Clarify this is not required.
			Figure 10.1-1	In the "Clinical & Anatomic Eligibility Criteria Assessment" column added "/CT Coronary Angiogram" to the "Coronary Angiogram" box	Reflects current standard of care
			10.2 Study Candidate Screening	Subjects will be evaluated… In the United States, the Centers for Medicare and Medicaid Services (CMS) currently require independent evaluations by ~~2~~1 cardiac surgeon~~s~~ for reimbursement.	Updated CMS regulations
			10.4 Screening Assessments	• Clinical Assessments ○ Risk assessments: Society… In the United States, CMS currently requires independent evaluations by ~~2~~1 cardiac surgeon~~s~~ for reimbursement.	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			10.4 Screening Assessments	• Imaging Assessments ○ A coronary angiogram/CT angiogram must be performed....	Reflects current standard of care
			10.6 Pre-procedure Medication	• Antiplatelet therapy… ~~must be given~~ is recommended prior to valve implantation. ○ Aspirin: A loading dose… is ~~required~~ recommended for subjects… The loading dose ~~must~~ should be administered prior to the implant procedure…. ○ $P2Y_{12}$ Inhibitor: A loading dose… is ~~required~~ recommended for subjects… The loading dose ~~must~~ should be administered prior to the implant procedure…. ***Note:*** If a subject… or aspirin is ~~required~~ recommended prior to the implant procedure, but not both ~~aspirin and a $P2Y_{12}$ inhibitor are not required~~.	Current standard of care; updated text for clarification
			10.7 Index Procedure	The TAVR… In the United States, CMS coverage criteria currently require that ~~both~~ cardiac surgeon and interventional cardiologist members of the heart team…	Updated CMS regulations
			10.7.1 Control Cohort	The DFU… A final post-deployment aortogram of the ascending aorta ~~(including rotational angiography of the valve frame)~~ must be performed…	Clarify rotational angiography of the valve frame is not required
			10.7.2 ACURATE Transfemoral…	10.7.2.2 Preparing and Using the ACURATE Transfemoral Aortic Valve System 7) A final post-deployment aortogram of the ascending aorta ~~(including rotational angiography of the valve frame)~~ must be performed…	
			10.8 Post Index Procedure	○ If a subject is treated with anticoagulation, either a $P2Y_{12}$ inhibitor or aspirin is required after the implant procedure in addition to the anticoagulant therapy (but treatment with both aspirin and a $P2Y_{12}$ inhibitor after the implant procedure is ~~are~~ not required).	Current standard of care; updated text for clarification

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			10.9 Prior to… 10.10.1 30-Day… 10.10.2 6-Month… 10.10.4 Annual…	Added the following: • Weight	Updated for clarity
			10.10.3 1-Year…	Removed the following: • Height	
			11.1 Endpoints	Data will be summarized… Roll-In cohort (up to ~~100~~130 subjects).	Increased number of centers to increase enrollment rate
			11.3.3 Subgroup Analyses…	• Valve type (ACURATE *neo*, ACURATE *neo2*, SAPIEN~~-3~~, CoreValve)	Clarify subgroup analysis
			16.4.2 Training…	***Note:*** For centers that do not have implantation experience… at least 2 Roll-In cases will be performed before ~~enrollment~~ treatment can commence in the randomized cohort.	Centers must have performed 2 Roll-In cases before **treating** subjects in the randomized cohort.
			19.1 Reportable…	It is the responsibility of the investigator to assess and report to BSC any event that occurs in any of the following categories; reporting requirements are described below in **Table 19.4-1**. • All serious adverse events • All ~~device related~~ adverse events and adverse device effects (through 12 months) • ~~All study procedure related adverse events~~	To clarify that all AEs and ADEs are required to be reported through 12 months.
			24 Bibliography	Added new references 72 (Lanz) and 73 (Möllmann)	New publications with ACURATE
F	11-Feb-2020	90702637 Rev/Ver AL	4.1.3 Clinical Studies with the	Section removed in its entirety.	Removed per FDA request.

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			ACURATE Aortic Bioprosthesis		
			24 Bibliography	Removed references 59 (Schäfer), 60 (Kempfert 2013), 61 (Kempfert 2015), 62 (Börgermann), 63 (Möllmann 2017), 64 (Möllmann 2018), 65 (Möllmann 2017), 66 (Schaefer), 67 (Hamm), 68 (Mauri), 69 (Toggweiler), 70 (Husser), 71 (Kim), 72 (Lanz), 73 (Möllmann 2019)	
G	25-Feb-2020	90702637 Rev/Ver AL	2. Synopsis, Study Design	Updated ACURATE IDE Study Design Overview figure to show follow-up to 10 years post index procedure.	FDA request to extend study to 10 years

			2. Synopsis, Additional Measurements	Additional measurements… will be collected… and annually through 10 years post index procedure…
				• Safety endpoints…
				  ○ Bleeding: Life-threatening… (through 5 years)
				  ○ Major vascular complication (through 5 years)
				• Additional indications of prosthetic aortic valve performance as measured by transthoracic echocardiography (TTE; see **Note 2** and **Note 3** below)
				• Functional… (see **Note 3** below)
				• Neurological… (see **Note 4** below)
				- Modified Rankin… follow-up visits (see **Note 4** below)
				Note 3: Echocardiography and NYHA assessment are not required in years 6, 8, and 9 (telephone follow-up only).
				Note 4: The mRS is required at all follow-up visits up to 5 years. For subjects…	

			2. Synopsis, Follow-up Schedule	All subjects implanted… annually for up to 10 years post-procedure... The visits at 30 days, 6 months, 1–5 years, 7 years, and 10 years are to be an office/clinical or in-person visit but may be done in-hospital should the subject be admitted at the time. Telephone follow-up is allowed at 6, 8, and 9 years. Procedures…	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			2. Synopsis, Study Duration	Subjects implanted with a test or control device will be followed for 10 years after the index procedure. Enrollment is expected… approximately 24 months; therefore, the total study duration is estimated to be approximately 12 years.	
			2. Synopsis, Participant Duration	… study duration for each subject is estimated to be approximately 10 years.	
			4.1.2 Transcatheter Aortic Valve…	Newer-generation devices have aimed to address these limitations[59]. The ACURATE TA™ Aortic Bioprosthesis (Symetis SA, Ecublens, Switzerland) is a self-expandable nitinol TAVR stent housing a porcine bioprosthesis and placed in a supra-annular position via transapical delivery[60]. The device was designed to allow easy and intuitive implantation (single operator). The ACURATE *neo*™ Aortic Bioprosthesis was subsequently developed for transfemoral (TF) use with the ACURATE *neo*™ TF Delivery System. ACURATE *neo* has a pericardial skirt on the interior and exterior of the stent body which serves to limit PVR[60]. ~~Described below are clinical outcomes with the self-expanding Symetis ACURATE Aortic Bioprosthesis.~~	Added for clarity

			6.5 Additional Measurements	Additional measurements… collected… annually up to 10 years post index procedure…
				• Safety endpoints…
				  ○ Bleeding: Life-threatening… (through 5 years)
				  ○ Major vascular complication (through 5 years)
				• Functional status… (see ***Note 3*** below)
				• Neurological status…
				  ○ Modified Rankin… visits up to 5 years
				
				Note 3: Echocardiography and NYHA assessment are not required in years 6, 8, and 9 (telephone follow-up only).
					FDA request to extend study to 10 years

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			6.6 Overview of Objectives…	Table 6.6-1 Safety measures at discharge, 30 days, 6 months, and annually up to 10 years post index procedure	
			7.1 Scale and Duration	Updated ACURATE IDE Study Design figure to show follow-up to 10 years post index procedure.	
			9.5 End of Study Definition	… All subjects who receive a test or control device will be evaluated at discharge or 7 days (whichever comes first), 30 days, 6 months and annually up to 10 years post index procedure. ~~All~~ Visits at 30 days, 6-months, 1–5 years, 7 years and 10 years are office/in-person visits. Telephone follow-up is allowed at 6, 8, and 9 years. A subject's participation in the study will be considered complete after the 10-year visit…	
			10.1 Data Collection	All subjects… will be evaluated at discharge or 7 days (whichever comes first), 30 days, 6 months, 1 year, and then annually through 10 years post index procedure. Physical clinic visits or in-person follow-up visits are scheduled for appointed times after the date of the index procedure through 5 years and at 7 and 10 years. Telephone follow-up is allowed at 6, 8, and 9 years. It is important… Visits/telephone follow-up not completed will be considered… Visits/telephone follow-up completed outside… Each follow-up ~~visit~~ must… Table 10.1-1 Data Collection for ACURATE IDE updated to show extension of study to 10 years post index procedure Figure 10.1-1 Data Collection for ACURATE IDE updated to show extension of study to 10 years post index procedure	
			10.2 Study Candidate Screening	Subjects will be… ~~In the United States, the Centers for Medicare and Medicaid Services (CMS) require independent evaluations by 2 cardiac surgeons for reimbursement.~~ The heart team…	Change to CMS requirements

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			10.10 Follow-up	All subjects implanted with a study valve (test or control) will be evaluated ~~via physical clinical visits~~ per the schedule… ***Note 2:*** Where indicated in **Table 10.1 1**, the follow-up…	Updated for clarity
			10.10.4 Annual Follow-up (±45 Days)…	Added "to 5 Years" to the section title All implanted subjects must be evaluated in person at 2, 3, 4, and 5 years…	
			10.10.5 Follow-up (±60 Days) at 7 and 10 Years	Added new section 10.10.5 All implanted subjects must be evaluated in person at 7 and 10 years after the index procedure, with a window of ±60 days. The following assessments must be completed. The ACURATE IDE eCRFs identify the specific data points to be collected. • NYHA classification • Current antiplatelet/anticoagulant (if applicable) • TTE, including assessment of effective orifice area, peak and mean aortic valve gradient pressure, aortic regurgitation assessment, peak aortic velocity, and LVEF per the Echocardiography Core Laboratory procedure guidelines. All TTEs must be forwarded to the core laboratory for independent analyses. ***Note:*** TTE must be done for all subjects who have a transcatheter valve implanted in the aortic position during the index procedure. • Serious adverse event (SAE, SADE, UADE, and relevant VARC events to be adjudicated by the CEC) assessment for test device(s) and device deficiencies assessment for test device(s) with associated treatment. ***Note:*** Relevant VARC events to be adjudicated by the CEC include the following: mortality, stroke, spontaneous myocardial infarction, acute kidney injury, repeat procedure for valve-related	FDA Request to extend study to 10 years

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				dysfunction, hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA III or IV), new pacemaker, new onset atrial fibrillation or atrial flutter, prosthetic aortic valve malpositioning (valve migration, valve embolization, or ectopic valve deployment), TAV-in-TAV, prosthetic aortic valve thrombosis and endocarditis.	
			10.10.6 Follow-up (±60 Days) at 6, 8 and 9 Years	Added new section 10.10.6 All implanted subjects must be evaluated at 6, 7, and 9 years after the index procedure, with a window of ±60 days. This evaluation may be conducted by telephone. The following assessments must be completed. The ACURATE IDE eCRFs identify the specific data points to be collected. • Current antiplatelet/anticoagulant (if applicable) • Serious adverse event (SAE, SADE, UADE, and relevant VARC events to be adjudicated by the CEC) assessment for test device(s) and device deficiencies assessment for test device(s) with associated treatment. Please see Section **10.10.5** for a list of relevant VARC events.	
			10.11 Study Completion	All subjects who receive a test device will be evaluated at… 6 months, and then annually up to 10 years post index procedure. ~~All~~ Visits in the first 5 years and at 7 and 10 years are office or in-person visits. Evaluations may be conducted by telephone at 6, 8 and 9 years. A subject's participation in the study will be considered complete after the 10-year visit.	
			11.1 Endpoints	The randomized data from the ACURATE IDE trial and data from the randomized populations of the SCOPE I (NCT03011346) and SCOPE II (NCT03192813) trials ~~(see Table 4.1 4)~~ will…	Added for clarity

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			11.2.4 Reporting Events	For time based clinical events, the cut-off … for endpoints at 2-10 year it will be 365 days times the number of years…	FDA Request to extend study to 10 years
			19.1 Reportable Events	Based on the VARC… • Bleeding events: Life-threatening… (through 5 years) Vascular complications: major (including annular rupture; through 5 years)	Updated for clarity
H	06-Mar-20	90702637 Rev/Ver AL	10.10.6 Follow-up (±60 Days)…	All implanted subjects must be evaluated at 6, ~~7~~8, and 9 years…	Updated for clarity
			16.4.2 Training with…	Proctoring: The investigator and co-investigators as well as the scrub team will be proctored by an individual experienced with the ACURATE valve and TAVR ~~physician~~ on a minimum…	Allow for non-physician proctors
I	22-Apr-20	90702637 Rev/Ver AL	Page 3, Revision History	Moved Revision History Table from page 3 to new **Table 26.1-1 Revision History**.	Updated for clarity
			Synopsis, Study Design	• **4D CT Imaging Substudy:** Selected centers with the ability to perform high quality 4D computed tomography (CT) scans will include subjects in a 4D CT Imaging Substudy to assess the prevalence of reduced leaflet mobility and hypoattenuated leaflet thickening (HALT) and the relationship, if any, to clinical events. Subjects will be randomized to test (ACURATE) and control device Updated Study Design figure to include 4D CT Imaging Substudy	4D CT Substudy added per FDA request
			Synopsis, Planned Number of Subjects…	* A subset of subjects in the randomized cohort will also be enrolled in the 4D CT Imaging Substudy.	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Synopsis, Additional Measurements	• For subjects in the CT Imaging Substudy, assessments using 4D CT at 30 days and 1 year will be done as listed below. Data will be evaluated by an independent CT core laboratory. - Assessment of leaflet mobility - Assessment of hypoattenuated leaflet thickening (HALT) - Assessment of leaflet thrombosis	
			Synopsis, Method of Assigning…	**Randomized Cohort:** A computer… to Control. A subset of subjects in the randomized cohort will also be enrolled in the 4D CT Imaging Substudy.	
			Synopsis, Follow-up Schedule	**Note 5:** For subjects in the CT Imaging Substudy, the visits at 30 days and 1 year must be done in the clinic (or in-hospital).	
			Synopsis, Adjunctive Pharmacologic Therapy	**Note 8:** Subjects who are expected to undergo chronic anticoagulation therapy after the TAVR procedure are not eligible to be included in the 4D CT Imaging Substudy (see Additional Exclusion Criteria below).	
			Synopsis, Additional Exclusion Criteria	Added another row: Additional exclusion criteria apply to subjects considered for enrollment in the CT Imaging Substudy as listed below. AEC1. Subject has eGFR <30 mL/min (chronic kidney disease stage IV or stage V). AEC2. Subject has atrial fibrillation that cannot be rate controlled to ventricular response rate < 60 bpm. AEC3. Subject is expected to undergo chronic anticoagulation therapy after the index procedure. **Note 12:** Subjects treated with short-term anticoagulation post procedure can be included in the CT Imaging Substudy; in these subjects the 30-day imaging will be performed 30 days after discontinuation of anticoagulation.	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 6.4 Additional Measurements	• For subjects in the 4D CT Imaging Substudy, assessments using 4D CT at 30 days and 1 year will be done as listed below. Data will be evaluated by an independent CT core laboratory and should be blinded to local investigators for cardiac valve findings (local reading should be only for non-cardiac valve findings such as unexpected lung pathology; see Section **10.10.1** for additional information). - Assessment of leaflet mobility - Assessment of hypoattenuated leaflet thickening (HALT) - Assessment of leaflet thrombosis	
			Section 7.1 Scale and Duration	Added bullet: • **4D CT Imaging Substudy:** Select centers with the ability to perform high quality 4D computed tomography (CT) scans will include subjects from the randomized cohort in a 4D CT Imaging Substudy to assess the prevalence of reduced leaflet mobility and hypoattenuated leaflet thickening (HALT)[64] and the relationship, if any, to clinical events. Centers should ask all eligible subjects to consider participation in the substudy. … 10 years post procedure. Implanted subjects participating in the 4D CT Imaging Substudy will undergo additional 4D CT assessment at 30 days and 1 year. Enrolled… Updated Figure 7.1-1	
			Section 7.3 Justification…	…reporting). Selected centers with the ability to perform high quality 4D CT scans will include subjects from the randomized cohort in a 4D CT Imaging Substudy to assess the prevalence of reduced leaflet mobility and HALT[64] and their relationship, if any, to clinical events. In addition…	
			Section 8.2 Inclusion…	Subjects… is met. Centers participating in the 4D CT Imaging Substudy must have the ability to perform high quality 4D CT	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				scans; subjects in this substudy must meet none of the additional exclusion criteria listed in **Table 8.3 2**.	
			Section 8.3 Exclusion…	Additional exclusion criteria apply to subjects considered for enrollment in the 4D CT Imaging Substudy as listed below in **Table 8.3 2**. New Table 8.3-2 …Additional Exclusion Criteria…	
			Section 10.1 Data Collection	Updated **Table 10.1-1** and **Figure 10.1-1** Add row and footnote for 4D CT imaging of prosthetic valve s: This applies to subjects in the 4D CT Imaging Substudy. Please refer to the CT Core Laboratory procedure guidelines (see study Manual of Operations). Results must be sent to the CT Core Laboratory (see Section 13.3.2). ***Note***: For subjects in the CT Imaging Substudy, the visits at 30 days and 1 year must be done in the clinic (or in-hospital).	
			Section 10.10.1 30-Day Follow-up…	Added bullet: • For subjects enrolled in the 4D CT Imaging Substudy, assessment of prosthetic valve leaflet mobility using 4D CT must be performed per the CT Core Laboratory (Section **13.3.2**) procedure guidelines (see study Manual of Operations). All 4D CT scans for subjects enrolled in the 4D CT Imaging Substudy must be sent to the CT Core Laboratory for independent analyses. ***Note:*** The CT scans will be read by the CT Core Laboratory and will not be provided to local investigators except as per below. Local reading should be done only for non-cardiac valve findings such as unexpected lung pathology. A study CT scan can be unblinded upon investigator request based on any of the following if the event occurs within 2 weeks of the study CT scan. o Any neurological event	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				○ Any potential embolic event ○ Any MI (ST segment elevation MI or non-ST segment elevation MI) ○ Increase in aortic regurgitation to moderate or severe ○ A change in echocardiographic parameters including an increase in mean gradient of >10 mmHg or a change in Doppler velocity index (DVI) of >0.05. If any of the above events occurs outside of the 2-week window around the study CT scan, the investigator must not be unblinded to the core laboratory assessment of the study CT scan and instead should perform a separate CT scan if clinically indicated. If an additional CT scan is performed for clinical indications, it should be sent to the CT Core Laboratory for analysis.	
			Section 10.10.3 1-Year Follow-up…	Added bullet: • For subjects enrolled in the 4D CT Imaging Substudy, assessment of prosthetic valve leaflet mobility using 4D CT must be performed per the CT Core Laboratory procedure guidelines (see study Manual of Operations). The 4D CT scans done for the 4D CT Imaging Substudy must be sent to the CT Core Laboratory for independent analyses. ***Note:*** The CT scans will be read by the CT Core Laboratory and findings will not be provided to local investigators except as noted above. Local reading should be done only for non-cardiac valve findings such as unexpected lung pathology. A study CT scan can be unblinded upon investigator request based on the conditions described in Section **10.10.1** if the event occurs within 2 weeks of the study CT scan	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 13.3.2 CT and Angiography Core Laboratory	…of Operations. Data from subjects in the 4D CT Imaging Substudy will also be evaluated by the independent CT core laboratory; procedure guidelines for 4D CT scanning are provided by the core laboratory in the Manual of Operations.	
			Section 18.1.1 Reduced Leaflet Motion/Leaflet Thrombosis	Added paragraph: The subset of subjects undergoing 4D CT scans at 30 days and 1 year, will be exposed to an additional radiation dose of about 20 milliSieverts (mSv) which is equivalent to about 10 years' worth of natural background radiation. The contrast dye used during the image acquisition can cause medical problems such as allergic reactions and increase the risk of worsening kidney function or failure.	Added risk associated with 4D CT Imaging Substudy participation
			Section 25.2 Definitions	Remove definitions for structural valve deterioration and resheathing/repositioning Add definition for hypo-attenuated leaflet thickening (HALT) and reduced leaflet mobility/motion (RLM)	Updated definitions
			Section 26.1 Revision History	Added new Section 26.1 Revision History Moved Revision History Table from page 3 to **Table 26.1-1 Revision History**.	Updated for clarity
J	18-Nov-2020	90702637 Rev/Ver AO	Page 1	European Authorized Representative Boston Scientific International S.A. Le Val Saint-Quentin 2 rue René Caudron, 78960 Voisins le Bretonneux, France Australian Representative Boston Scientific Pty. Ltd. Building 1, Level 6 191 O'Riordan Street Mascot, NSW 2020, Australia	Added to allow for additional centers in Australia and Europe

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 2 Study Design	…regulations. The study… from the Institutional Review Board/Research Ethics Board/Human Research Ethics Committee/ Independent Ethics Committee (IRB/REB/HREC/IEC) and/or…	
			Section 2 Synopsis Planned Number of Subjects…	Subjects will be enrolled at up to ~~65~~85 centers in the United States, Canada, Australia, and Europe. There will be up to ~~630~~ 1220 subjects in… Randomized Cohort: ~~500~~ 1050 Roll: In Cohort: Up to ~~130~~170	Revised statistical approach per discussion with FDA
			Section 2 Synopsis Primary Endpoint	Removed Primary Safety Endpoint: ~~Composite of all… 30 days.~~ Renamed "Primary Effectiveness Endpoint" to "Primary Endpoint" and updated the definition as follows: Composite of all-cause mortality, ~~and disabling~~ all stroke, and rehospitalization† at 1 year. † Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV); per VARC-2 definition	
			Section 2 Synopsis Adjunctive Pharmacologic Therapy	**Anti-Platelet Therapy** Per US society guidelines[b], antiplatelet therapy ~~with aspirin and a $P2Y_{12}$ inhibitor~~ is recommended…medications. ACURATE IDE study subjects must receive some antiplatelet therapy (aspirin and/or a $P2Y_{12}$ inhibitor) for at least 1 month following valve implant (see below for recommended doses). It should be noted, however, that recent clinical evidence points to increased bleeding risk post TAVR among subjects receiving dual antiplatelet therapy or antiplatelet therapy plus anti-coagulation (among subjects indicated for anti-coagulation) [c]. Aspirin A loading… After the valve implant procedure, ~~aspirin (~~the recommended aspirin dose ~~of~~ is ≥75 mg daily. Post TAVR, aspirin and/or a $P2Y_{12}$ inhibitor~~)~~ must be given…	Updated for clarity; new reports on antiplatelet therapy and TAVR.

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				$P2Y_{12}$ inhibitor A loading dose… After the valve implant procedure, a $P2Y_{12}$ inhibitor and/or aspirin is… **Note 7:** If a subject… recommended prior to and ~~required~~ after the implant procedure in addition to the anticoagulant therapy (but ~~treatment with~~ both aspirin and a $P2Y_{12}$ inhibitor ~~after the implant procedure is~~ are not ~~required~~ recommended). After the implant procedure, the subject ~~must~~ should be treated… c: Nijenhuis VJ, et al. N Engl J Med 2020;382:1696–1707 Brouwer J, et al. N Engl J Med 2020;383:1447–1457	
			Section 2, Inclusion Criteria	Protocol Version J: As of this update to the protocol (Version J), subjects in all surgical risk classes were approved for TAVR in the United States, Canada, Australia, and European countries.	Updated for clarity
			Section 2, Synopsis ~~Primary Safety Endpoint~~	Removed Primary Safety Endpoint and the associated statistical measures (Statistical Hypothesis, Statistical Test, Sample Size Calculations, Success Criteria)	Revised statistical approach per discussion with FDA
			Section 2, Synopsis Primary ~~Effectiveness~~ Endpoint Statistical Hypothesis	In the randomized cohort, the primary ~~effectiveness~~ endpoint (composite of all-cause mortality, ~~and disabling~~ all stroke, and rehospitalization at 1 year) rate for the ACURATE group is non-inferior to that for the Control group.	
			Section 2, Synopsis Statistical Test for the Primary ~~Effectiveness~~ Endpoint	A Farrington-Manning… primary ~~effectiveness~~ endpoint rate… …where PE… primary ~~effectiveness~~ endpoint rates… The primary analysis set for the primary ~~effectiveness~~ endpoint...	
			Section 2, Synopsis Sample Size Parameters for the Primary	The sample size calculation for the primary ~~effectiveness~~ endpoint is based on the following assumptions. • Expected rate for both arms = ~~15~~25.9% (based on weighted average of TAVR data; see Note 14 below)	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			~~Effectiveness~~ Endpoint	• Non-inferiority margin (Δ) = ~~6~~ 9.1% (~~40~~35% relative to the expected rate) • Test significance level (α) = 0.025 (1-sided) • Test (ACURATE): Control ratio = 1:1 • Power (1 minus ß) ~~≥ 85%~~ = 90% • Expected rate of attrition = 5% • Total sample size = 1050 (525 per group) • Number of evaluable subjects per group = 499~~700†~~ • Analyses: Two interim plus one final (see Note 15 below) Note 14: The estimated proportions of subjects by operative risk level is 10% extreme risk, 30% high risk, and 60% intermediate risk. Note 15: The Haybittle-Peto method is used to specify and calculate the alphas for the first interim, second interim, and final analyses as 0.0001, 0.0001, and 0.025, respectively. The first interim analysis is an administrative analysis for regulatory agency review after 350 randomized subjects have completed 1-year follow-up. The second interim analysis is planned to occur after 850 randomized subjects have completed 1-year follow-up. The final analysis for the primary endpoint will be performed with 1-year data from all subjects. ~~† The planned 730 subjects from the SCOPE I study and 764 subjects from the SCOPE II study will form the analysis population for a total of 1,494 subjects for the primary effectiveness endpoint analysis.~~	
			Section 2, Synopsis Success Criteria for the Primary ~~Effectiveness~~ Endpoint	If the *P* value from the Farrington-Manning standardized test for non-inferiority is <0.025 for the final analysis, the rate of the primary ~~effectiveness~~ endpoint… primary ~~effectiveness~~ endpoint being less than delta (Δ).	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 4.1.2 Transcatheter…	…application to lower risk patients[25,26] and ~~Two recent~~ randomized… intermediate-risk and low-risk surgical… Currently, …inoperable or at ~~intermediate~~ low to high… Updated **Table 4.1-1**: Add 2 rows for PORTICO IDE (2020) study; add text "The PORTICO™ Transcatheter Aortic Heart Valve Implantation System is manufactured by Abbott Structural Heart, St. Paul, MN, USA."	Updated literature information
			Section 5.2 Control Device	…catheterization techniques~~, is commercially available in both the United States and Canada,~~ and is approved…	For clarity
			Section 6.2 Study Endpoints	…study device. ~~For the ITT randomized cohort analysis set, if a subject receives 2 valves, the subject is assigned to the group corresponding to the first valve received.~~ For the implanted…	
			~~Section 6.3 Primary Safety Endpoint~~	Removed Primary Safety Endpoint	Revised statistical approach per discussion with FDA
			Section 6.3 ~~6.4~~ Primary ~~Effectiveness~~ Endpoint	The primary ~~effectiveness~~ endpoint is a composite of all-cause mortality, ~~and disabling~~ all stroke, and rehospitalization at 1 year. The primary analysis set for the primary ~~effectiveness~~ endpoint is the ITT analysis set. *Note:* For the primary endpoint, rehospitalization includes hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV); per VARC-2 definition	
			Section 6.5 Overview of Objectives…	Table 6.6-1: Removed Primary Safety row. Updated Primary Safety and Effectiveness row as follows: Objective: Determine safety and effectiveness… Endpoint: 1-Year Composite: mortality, ~~and disabling~~ all stroke, and rehospitalization	
			Section 7.1 Scale and Duration	Subjects will be enrolled at up to ~~65~~85 centers in the United States, Canada, Australia, and Europe. There will be up to ~~630~~	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				1220 subjects in ACURATE IDE… There will be up to ~~500~~ 1050 subjects in the RCT.	
			Section 7.1 Scale and Duration	Roll-In Cohort: A non-randomized… randomized cohort (up to ~~130~~ 170 Roll-In subjects in total). The study… from the Institutional Review Board/Research Ethics Board/Human Research Ethics Committee/ Independent Ethics Committee (IRB/REB/HREC/IEC) and/or… *NOTE: The modification IRB/REB/HREC/IEC has been made wherever IRB/REB occurs in the document.*	To allow for centers in Australia and Europe
			Section 7.2.1 Treatment and Control	Update Table 7.2-1 Column headings: ~~Objective~~ Treatment; ~~Endpoint~~ Device; ~~Rationale for Endpoint,~~ Device Description	Correct headings and to allow for centers in Australia and Europe
				Control Device SAPIEN 3*; CoreValve* * Or future iteration	Balloon-expandable SAPIEN 3… commercially available in ~~both~~ the ~~United States, and Canada~~ applicable region.
			Section 7.3 Justification…	There will be up to ~~630~~ 1220 subjects in… study subjects to risk, up to ~~130~~ 170 subjects will be enrolled in the Roll-In phase of this study (centers without… 2 Roll-In cases each) and ~~500~~ 1050 subjects will be randomized… Up to ~~65~~ 85 centers in the United States, ~~and~~ Canada, Australia, and Europe will participate…	Revised statistical approach per discussion with FDA
			Section 8.2 Inclusion Criteria	Added to Table 8.2-1: Protocol Version J: As of this update to the protocol (Version J), subjects in all surgical risk classes were approved for TAVR in the United States, Canada, Australia, and European countries.	For clarity

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 10.10 Follow-up	Note 1: A subject who has received… reached the ACURATE IDE ~~effectiveness~~ primary endpoint (1 year).	
			Section 10.1 Data Collection	Updated <Figure 10.1-1> to include up to 1220 subjects, 1050 randomized, up to 170 Roll-In Table 10.1-1 footnote m: …Baseline QOLs ~~should~~ must be performed within 30 days prior to the index procedure	
			Section 10.8 Post Index Procedure	The following are to be performed post-procedure. • Per society guidelines antiplatelet therapy ~~with aspirin and a P2Y12 inhibitor~~ is … Subjects must be treated with antiplatelet therapy (aspirin and/or a $P2Y_{12}$ inhibitor) for… physician choice. It should be noted, however, that recent clinical evidence points to increased bleeding risk post TAVR among subjects receiving dual antiplatelet therapy or antiplatelet therapy plus anti-coagulation (among subjects indicated for anti-coagulation)[77,78]. o After the valve implant procedure, aspirin (recommended dose of ≥75 mg daily) and/or a $P2Y_{12}$ inhibitor must be given for… availability. The $P2Y_{12}$ inhibitor choice and dosing should be per local standard of care. o ~~After the valve implant procedure, a $P2Y_{12}$ inhibitor is required for at least 1 month.~~ o If a subject is treated with anticoagulation, either a $P2Y_{12}$ inhibitor or aspirin is ~~required~~ recommended after… (but treatment… is not ~~required~~ recommended). The subject ~~must~~ should be treated…	Updated for clarity; new reports on antiplatelet therapy and TAVR.
			Section 10.10.1 30-Day Follow-up	• For subjects… analyses. ***Note:*** Images will be read in a standard fashion for cardiac and non-cardiac findings by the clinical center CT imaging specialist. Clinical guidelines support anticoagulation with warfarin or another vitamin K inhibitor as a Class I recommendation for patients with established valve thrombosis[4,5]. However, there is no established guidance	Allow centers to request access to core lab findings if they think it is needed to address subject health.

Table 26.1-1: Revision History

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				for pharmaceutical management of subclinical leaflet thrombosis. If deterioration of subject health due to suspected thrombosis occurs, the clinical center may request an unblinding of the Core Laboratory findings. ~~***Note:*** The CT scans will be read… sent to the CT Core Laboratory for analysis.~~	
			Section 10.10.3 1-Year Follow-up	• For subjects… analyses. ***Note:*** Images will be read in a standard fashion for cardiac and non-cardiac findings by the clinical center CT imaging specialist. Clinical guidelines support anticoagulation with warfarin or another vitamin K inhibitor as a Class I recommendation for patients with established valve thrombosis[4,5]. However, there is no established guidance for pharmaceutical management of subclinical leaflet thrombosis. If deterioration of subject health due to suspected thrombosis occurs, the clinical center may request an unblinding of the Core Laboratory findings. ~~***Note:*** The CT scans will be read… within 2 weeks of the study CT scan.~~	
			Section 11.1 Endpoints	The randomized data from the ACURATE IDE trial ~~and data from the randomized populations of the SCOPE I (NCT03011346) and SCOPE II (NCT03192813) trials~~ will be used ~~in~~ for primary endpoint analyses. ~~The study must meet both the primary safety endpoint (Section 11.1.1) and the primary effectiveness endpoint (Section 11.1.2) to claim study success; therefore, no adjustment is needed for multiplicity.~~ Data will be summarized separately for subjects in the ACURATE IDE Roll-In cohort (up to ~~130~~ 170 subjects).	Revised statistical approach per discussion with FDA
			~~Section 11.1.1 Primary Safety Endpoint~~	Removed Primary Safety Endpoint and the associated statistical measures sections: Statistical Hypothesis, Statistical Test, Sample Size Calculations, Success Criteria	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 11.1.1 Primary ~~Effectiveness~~ Endpoint	Renamed "Primary Effectiveness Endpoint" to "Primary Endpoint" and updated the text as follows: The primary ~~effectiveness~~ endpoint is the composite of all-cause mortality, ~~and disabling~~ all stroke, and rehospitalization† at 1 year. The events… *Note 1*: For the primary endpoint, rehospitalization is hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV); per VARC-2 definition	
			Section 11.1.1.1 Statistical Hypothesis for the Primary ~~Effective-ness~~ Endpoint	The statistical hypothesis is that the primary ~~effectiveness~~ endpoint (composite of all-cause mortality, all ~~and disabling~~ stroke, and rehospitalization at 1 year) rate… The null… primary ~~effectiveness~~ endpoint… …correspond to primary ~~effectiveness~~ endpoint rates… The primary analysis set for the primary ~~effectiveness~~ endpoint...	
			Section 11.1.1.2 Sample Size Parameters for the Primary ~~Effectiveness~~ Endpoint	The sample size calculation for the primary ~~effectiveness~~ endpoint is based on the following assumptions. • Expected rate for both arms = ~~15~~25.9% (based on... see *Note 2* below) • Non-inferiority margin (Δ) = ~~6~~ 9.1% (~~40~~35% relative to expected rate) … • Power (1 minus ß) ~~≥ 85%~~ = 90% • Expected rate of attrition = 5% • Total sample size = 1050 (525 per group) • Number of evaluable subjects per group = 499 ~~700†~~ • ~~Overall~~ Analyses: Two interim plus one final ~~population=1494~~ (see *Note 3* below) *Note 2*: The estimated proportions of subjects by operative risk level is 10% extreme risk, 30% high risk, and 60% intermediate risk.	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				Note 3: The Haybittle-Peto method is used to specify and calculate the alphas for the first interim, second interim, and final analyses as 0.0001, 0.0001, and 0.025, respectively. The first interim analysis is an administrative analysis for regulatory agency review after 350 randomized subjects have completed 1-year follow-up visits. The second interim analysis is planned to occur after 850 randomized subjects have completed 1-year follow-up visits. The final analysis for the primary endpoint will be performed with 1-year data from all subjects. ~~The randomized cohorts of the ongoing SCOPE I (N=730 subjects planned, 365 per treatment group) and SCOPE II (N=764 subjects planned, 382 per treatment group) trials will be pooled to form the analysis population for the primary effectiveness endpoint (N=1494).~~	
			Section 11.1.1.3 Success Criteria for the Primary ~~Effectiveness~~ Endpoint	A Farrington… as described in the statistical analysis plan (SAP). If… test for non-inferiority is <0.025 in the final analysis, the rate of the primary ~~effectiveness~~ endpoint… rate of the primary ~~effectiveness~~ endpoint being less than delta (Δ).	
			Section 11.1.1.4 Statistical Methods-Primary ~~Effectiveness~~ Endpoint	All subjects who are enrolled and randomized will be eligible for evaluation. Any events or hospitalizations occurring after enrollment but prior to the index procedure should be entered in the electronic data capture system. Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measure. Sensitivity analyses (e.g., tipping-point analysis) will be performed to assess the impact of subjects with inadequate follow-up (i.e., missing data) on the primary endpoint and to assess the robustness of the conclusion of the primary analysis. A sensitivity analysis of the primary endpoint, including events occurring after enrollment but prior to the index procedure, will be performed. Statistical	

Table 26.1-1: Revision History

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				models that account for censored data will be employed in appropriate circumstances (e.g., for time-to-event outcomes). Suspected invalid data will be queried and corrected in the database prior to statistical analysis. Additional information may be found in the SAP. Please also see Section 9.4, Section 10.1, and Section 10.2.1 regarding data collection and missing data. ~~Procedures similar to that described in Section 11.1.1.4 and discussed in the SAP will be applied to analysis of the primary effectiveness endpoint.~~	
			Section 11.2.1 Analysis Sets	…in the analysis. ~~For the ITT randomized cohort analysis set, if a subject receives 2 valves, the subject is assigned to the group corresponding to the first valve received.~~ For the implanted…	Updated for clarity
			Section 11.2.3 Number of Subjects	The number of subjects enrolled per investigational center should not exceed 180 without prior authorization by the sponsor.	Updated per new protocol template
			Section 11.3 Data Analyses	Baseline… analysis of the primary ~~safety~~ endpoint~~, primary effectiveness endpoint,~~ and additional measurements.	Revised statistical approach per discussion with FDA
			Section 11.3.2 Interim/ Administrative Analyses	There will be 2 interim analyses as described in the SAP. The Haybittle-Peto method is used to adjust the alpha-levels for the first interim, second interim, and final analyses to 0.0001, 0.0001, and 0.025, respectively. The first interim analysis is an administrative analysis for regulatory agency review after 350 randomized subjects have completed 1-year follow-up visits. The second interim analysis is planned to occur after 850 randomized subjects have completed 1-year follow-up visits. ~~An administrative analysis for regulatory agency review after all 500 ACURATE IDE randomized subjects have completed their 1-year follow-up visits may be performed as described in the SAP.~~ Additional… review. ~~No formal interim analyses are planned for the purpose of stopping this trial early for effectiveness or futility.~~ A Data … charter.	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 11.3.3 Subgroup Analyses	• Valve type (~~ACURATE neo,~~ ACURATE *neo2*, SAPIEN, CoreValve)	
			Section 11.3.4 Justification of Pooling	Analyses for the primary ~~safety and primary effectiveness~~ endpoint~~s~~ will be presented using data pooled across ~~studies (see Section 11.1.1 and Section 11.1.2)~~ study centers. Poolability analyses across study centers ~~and studies~~ will be performed for the primary endpoint~~s~~. The differences of treatment effects on the primary endpoint~~s~~ across study centers ~~and between studies~~ will be…	
			Section 13.1 Data Collection…	All access to the clinical database will be changed to "Read Only" after all data are either "Hard Locked" or "Entry Locked." Once acceptance of the final study report or finalization of publications (as applicable) is received, final database storage and archiving activities can begin. When all closeout activities are completed, a request to the BSC Information Technology department is submitted to have the database locked or decommissioned and all database access revoked.	Updated per new protocol template
			Section 13.3.1 Echocardiography Core Laboratory	An independent… Operations. ~~This same independent core lab will also analyze echocardiography data from SCOPE I and SCOPE II (see Section 11.1.1.2 for additional information on the SCOPE I and SCOPE II trials).~~	Revised statistical approach per discussion with FDA
			14.0 Deviations	…by the Sponsor. The sponsor will not approve protocol waivers.	Updated per new protocol template
			16.1 Statement of Compliance	This clinical investigation is financed by the study sponsor. Before the investigational site can be "Authorized to Enroll," the investigational site must enter into a Clinical Study Agreement with the sponsor that details the financing of the study as well as the rights and obligations of the investigational site and the investigator.	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			16.2 Investigator Responsibilities	All investigators will provide their qualifications and experience to assume responsibility for their delegated tasks through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.	
			16.3 Institutional Review Board/ Research Ethics Board/Human Research Ethics Committee/ Independent Ethics Committee	The investigational center will obtain the written and dated approval/favorable opinion of the Institutional Review Board/Research Ethics Board/Human Research Ethics Committee/ Independent Ethics Committee (IRB/REB/HREC/IEC) for the clinical… *NOTE: The modification IRB/REB/HREC/IEC has been made wherever IRB/REB occurs in the document.*	
			17 Monitoring	…and appropriate regulatory authorities. The sponsor will put a plan in place to document the specific monitoring requirements. The study…	
			19.1 Reportable Events…	Any ~~AE~~ reportable event required…	
			Section 19.2 Definitions and Classification	Updated **Table 19.2-1**: **Serious Health Threat:** Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health of subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. ***Note 1:*** This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				The following definitions will be used for defining hospitalization or prolongation of hospitalization for SAE classification purposes: **Hospitalization:** Hospitalization does not include: • Emergency room visit that does not result in in-patient admission ***Note 1:*** Although an emergency room visit does not itself meet the definition for hospitalization, it may meet other serious criteria (e.g., medical or surgical intervention to prevent permanent impairment or damage) • Elective and pre-planned treatment/surgery for a pre-existing condition that is documented in the subject's record at the time of consent/enrollment • Admission for social reasons and/or respite care in the absence of any deterioration in the subject's general condition (e.g., subject is homeless, caregiver relief) • Pre-planned, protocol-specified admission related to the clinical study (e.g., procedure required by protocol) **Prolongation of Hospitalization:** In-patient admission to the hospital that is prolonged beyond the expected standard duration for the condition under treatment. ***Note 1:*** New adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criterion.	
			19.5.1 Boston Scientific Device Deficiencies	~~Device deficiencies that did not lead to an AE but could have led to a SAE if a) suitable action had not been taken, or b) intervention had not been made, or c) circumstances had been less fortunate must be reported as described in Table 19.4-1.~~	
			21.1 Safety Monitoring Process	~~To promote early detection of safety issues, the Clinical Events Committee (CEC) and Data Monitoring Committee (DMC; see below) will provide evaluations of safety events. Success of this~~	

Table 26.1-1: Revision History

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				~~program requires dynamic collection of unmonitored data as soon as the event is reported. This is expedited through the Sponsor or designee, which is responsible for coordinating the collection of information for the subject dossier from the centers and core laboratories.~~ The BSC personnel from the Medical Safety and Safety Trial Operations teams review safety data as they are reported by the centers throughout the duration of the study. During ~~regularly~~ scheduled monitoring activities, clinical research monitors ~~will~~ further support ~~the dynamic reporting process~~ this review through their review of source documents and other data information. The BSC Medical Safety and Safety Trial Operations teams ~~group~~ includes ~~physicians~~ health care providers with expertise…	
			Section 21.1.1 Clinical Events…	…the CEC Charter. ~~This same CEC will also adjudicate clinical event data from SCOPE I and SCOPE II (see Section 11.1.1.2 for additional information on the SCOPE I and SCOPE II trials).~~	Revised statistical approach per discussion with FDA
			22.1.1 Criteria for Premature Termination…	Possible reasons for premature study termination include, but are not limited to, the following. • Suspicion of an unacceptable risk. In this case, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed. ~~The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study~~ • Instructions by the IRB/REB/HREC/IEC or regulatory authorities to suspend or terminate the clinical investigation. • An enrollment…	Updated per new protocol template
			Section 23 Study Registration and Results	Updated Section 23 as follows: **23.1 Study Registration** To comply with applicable laws and regulations, the study has	

Table 26.1-1: Revision History

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				been registered on the publicly accessible database ClinicalTrials.gov (NCT03735667). **23.2 Clinical Investigation Report** Study results will be made available in accordance with the legal requirements and the recognized ethical principles, in accordance with the Boston Scientific Policy. A Clinical Investigation Report will be made available to all investigators, IRB/REB/ HREC/IEC and regulatory authorities, as applicable in accordance with the Boston Scientific Policy and local requirements. As applicable an abbreviated Clinical Investigation Report will be made available on a publicly accessible database. **23.3 Publication Policy** Boston Scientific Corporation requires…	
			Section 24 Bibliography	Added new references: 29. Mack MJ… Transcatheter aortic… balloon-expandable valve in low-risk patients… 30. Popma JJ… Transcatheter aortic… self-expanding valve in low-risk patients… 33. Bonow RO… Appropriate use… 38. Makkar RR… Self-expanding intra-annular… (PORTICO IDE): a randomised… 77. Brouwer J… Aspirin with or without clopidogrel… 78. Nijenhuis VJ… Anticoagulation with or without clopidogrel…	Updated literature information
K	23-Mar-2021	90702637 Rev/Ver AO	Section 2, Synopsis Study Design	**Roll-In Cohort:** A non-randomized… (transfemoral delivery; ~~Symetis SA, Ecublens, Switzerland~~ Boston Scientific Corporation, Marlborough, MA, USA) will perform…	Change in legal manufacturer

Table 26.1-1: Revision History

<table>
<tr><th>Revision Version</th><th>Protocol Date</th><th>Template Number and Version</th><th>Protocol Sections Modified</th><th>Summary of Changes</th><th>Justification for Changes</th></tr>
<tr><td rowspan="4"></td><td rowspan="4"></td><td rowspan="4"></td><td>Section 2, Synopsis Planned Number of Subjects…</td><td>There will be up to ~~1220~~ 1670 subjects…
<table><tr><th>Cohort</th><th>Number of Subjects</th></tr><tr><td>Randomized</td><td>~~1050~~ 1500*</td></tr><tr><td>Roll-In</td><td>Up to 170</td></tr></table>* A subset of subjects (minimum of 200) in the randomized cohort will also be enrolled in the 4D CT Imaging Substudy.
To achieve sufficient distribution of lower risk subjects, there will be ≥ 30% intermediate risk and ≥ 35% low risk randomized subjects enrolled.</td><td rowspan="4">Per discussion with FDA, added cohort with low surgical risk. Updates regarding subject number and statistical approach are provided.

Other changes have been made for clarity or to update guideline references.</td></tr>
<tr><td>Section 2, Synopsis Study Duration</td><td>Enrollment is expected to be completed in approximately ~~24~~ 36 months; therefore, the total study duration is estimated to be approximately ~~12~~ 13 years.</td></tr>
<tr><td>Section 2, Synopsis Adjunctive Pharmacologic…</td><td>…daily. ~~Post-TAVR, aspirin and/or a P2Y12 inhibitor must be given for at least 1 month.~~ It is recommended that daily aspirin be given indefinitely ~~thereafter~~ as per local standard of care.
b: Otto CM, et al. J Am Coll Cardiol. 2021;77:e25-e197
~~Holmes… e1159-e96~~</td></tr>
<tr><td>Section 2, Synopsis Inclusion Criteria</td><td>IC4. Heart team (which must include an experienced cardiac interventionalist and an experienced cardiac surgeon) agrees that the subject is indicated for TAVR, is likely to benefit from ~~at intermediate risk or above for surgical~~ valve replacement, and TAVR is appropriate. ~~The heart team should consider the Society of Thoracic Surgeons (STS) score as well as other factors including frailty, prior surgical history, malignancy or radiation therapy, pulmonary disease, renal disease, liver disease, neuromuscular disease, orthopedic disease, chest deformity, and aortic calcification. Subjects considered to be at intermediate surgical risk or above have a predicted risk of surgical mortality ≥ 3% based on the STS risk score and other clinical comorbidities unmeasured by the STS risk calculator.~~</td></tr>
</table>

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				~~**Note 10:** Risk of operative mortality must be assessed via an in-person evaluation by a center cardiac surgeon and must be confirmed by the CRC (which must include an experienced cardiac surgeon).~~ ~~**Note 11:** At the time this protocol was written, subjects at extreme and high surgical risk were approved for TAVR with commercially available devices in the United States and Canada. Subjects at intermediate surgical risk were approved for TAVR with select commercially available devices in the United States and Canada. Subjects at low surgical risk were subsequently approved for TAVR with commercially available devices in the United States.~~ ~~IC5. Heart team (which must include an experienced cardiac interventionalist and an experienced cardiac surgeon) agrees that the subject is likely to benefit from valve replacement.~~ IC~~6~~5. Subject… IC~~7~~6. Subject, family… IC~~8~~7. Subject is expected… ~~d~~b: Otto CM, et al. J Am Coll Cardiol. 2021;77:e25-e197 ~~Nishimura RA, et al. J Am Coll Cardiol. 2014;63:e57–185~~ ~~Protocol Version J: As of this update to the protocol (Version J), subjects in all surgical risk classes were approved for TAVR in the United States, Canada, Australia, and European countries.~~	
			Section 2, Synopsis Statistical Test Method	~~A Farrington-Manning standardized test will be used to test the one-sided~~ The statistical hypothesis is that the primary endpoint rate for… A Bayesian analysis[d] will be performed to estimate the treatment difference between ACURATE and Control through posterior probability. Details are shown below. d: Popma JJ, et al. N Engl J Med 2019;380:1706-15 Reardon MJ, et al. N Engl J Med 2017;376:1321-31	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 2, Synopsis Sample Size Parameters…	Although the primary endpoint analysis is performed using the Bayesian method, the sample size calculation (see **Note 12** below) is based on a standard non-inferiority two-sample test approach. The sample size calculation for the primary endpoint is based on the following assumptions. • Expected rate for both arms = ~~25.9~~22.3% (based on weighted average of TAVR data[e]; see **Note 13** below) • Non-inferiority margin (Δ) = ~~9.1~~8.0% (~~35~~36% relative to the expected rate) • Test significance level (α) = 0.025 (1-sided) (see **Note 14** below) • Test (ACURATE): Control ratio = 1:1 • Power (1 minus ß) = ~~=~~ ≥ > 90% • Expected rate of attrition = 5% • Total sample size = ~~1050~~1500 (~~525~~750 per group) • Number of evaluable subjects per group = ~~499~~712 • Analyses: ~~Two~~ One administrative, one formal interim, ~~plus~~ one final (see **Note 15** below) **Note 12~~5~~:** The ~~Haybittle-Peto~~Pocock-type method[f] is used during sample size calculations. The statistical software EAST® 6.5 is used for the sample size calculations. **Note 13~~4~~:** The estimated proportions of subjects by operative risk level is 10% extreme risk, ~~30~~25% high risk, ~~and 6~~30% intermediate risk, and 35% low risk. **Note 14:** A statistically equivalent posterior probability threshold for the Bayesian analysis is empirically chosen through extensive simulations and is pre-specified in the Statistical Analysis Plan (SAP).	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				Note 15: ~~The Haybittle-Peto method is used to specify and calculate the alphas for the first interim, second interim, and final analyses as 0.0001, 0.0001, and 0.025, respectively.~~ The ~~first~~ administrative interim analysis will be conducted when the first ~~is an administrative analysis for regulatory agency review after~~ 350 randomized subjects have completed 1-year follow-up. The ~~second~~ formal interim analysis will be carried out after enrollment in the randomized cohort is completed. This formal interim analysis will be conducted on the full N=1500 randomized subject cohort when a subset of the ~~is planned to occur after 850~~ randomized subjects have completed 1-year follow-up (pending regulatory approval). The piecewise exponential model[g] based on outcomes among these subjects will be used to predict the 1-year results by treatment group for the remaining enrolled subjects. The Bayesian method will be used to perform the hypothesis testing on the combined data sets. ~~The~~ A final analysis for the primary endpoint will be performed on all subjects with completed 1-year data if non-inferiority cannot be claimed at the formal interim analysis (see Success Criteria below) ~~from all subjects~~. e: Adams DH, et al. N Engl J Med 2014;370:1790-8 ~~Leon MB, et al. N Engl J Med 2010;363:1597-607~~ ~~Leon MB, et al. N Engl J Med 2016;374:1609-20~~ Mack MJ, et al. N Engl J Med 2019;380:1695-705 Popma JJ, et al. J Am Coll Cardiol 2014;63:1972-81 Popma JJ, et al. N Engl J Med 2019;380:1706-15 Reardon MJ, et al. N Engl J Med 2017;376:1321-31 Smith CR, et al. N Engl J Med 2011;364:2187-98 Thourani VH, et al. Lancet 2016;387:2218-25 Waksman R, et al. J Am Coll Cardiol Intv 2019;12:901–7 Webb JG, et al. J Am Coll Cardiol Intv 2015;8:1797-806 Medtronic CoreValve System PMA P130021/S002: FDA Summary of Safety and Effectiveness Data	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				f: Lan KKG and DeMets DL. Biometrika 1983;70:659–63 g: Popma JJ, et al. N Engl J Med 2019;380:1706-15	
			Section 2, Synopsis Success Criteria for the Primary Endpoint	The Bayesian method is used to test the non-inferiority hypothesis of the primary endpoint. To establish that the ACURATE device is non-inferior to the Control, the results will need to meet the following equation: Pr(H1 | Data) > ξ where • Pr(H1 | Data) is the posterior probability of H1 given the observed data at either the interim or the final analysis; • H1 is the alternative hypothesis for non-inferiority: PE_ACURATE minus PE_Control < Δ; • ξ is a prespecified threshold, which is empirically chosen through extensive simulations using the Bayesian approach for the non-inferiority tests. If non-inferiority has been declared at the formal interim analysis, the non-inferiority test will not be performed at the final analysis. If non-inferiority cannot be declared at this interim analysis, the non-inferiority test will be performed at the final analysis for all subjects using the Bayesian method with the same pre-specified threshold. The study will not stop for futility at the interim analysis. The detailed study operating characteristics and simulation results will be provided in the SAP. ~~If the P-value from the Farrington-Manning standardized test for non-inferiority is <0.025 for the final analysis, the rate of the primary endpoint for ACURATE will be concluded to be non-inferior to the Control rate. This corresponds to the one-sided upper 97.5% confidence bound on the difference between treatment groups (ACURATE minus Control) for the observed rate of the primary endpoint being less than delta (Δ).~~	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 4 Introduction	This protocol… manufactured by ~~Symetis SA, an indirect subsidiary of~~ Boston Scientific Corporation, Marlborough, MA, USA ~~Ecublens, Switzerland~~.	
			Section 4.1.2 Transcatheter…	**<<Table 4.1-1 TAVR Outcomes…>>** Updated table with references on outcomes in low risk subjects.	
			Section 5.1 ACURATE…	The investigational… is designed by ~~Symetis SA, an indirect subsidiary of~~ Boston Scientific Corporation, Marlborough, MA, USA ~~Ecublens, Switzerland~~. It is…	
			Section 5.1.1 ACURATE…	The ACURATE… Bioprosthesis (~~Symetis SA, Ecublens, Switzerland~~ Boston Scientific Corporation, Marlborough, MA, USA). There…	
			Section 5.1.2 ACURATE…	…Delivery System (~~Symetis SA, Ecublens, Switzerland~~ Boston Scientific Corporation, Marlborough, MA, USA).	
			Section 5.1.3 Introducer Set	Note: In countries where the iSLEEVE and LIS-S are approved, the commercial device will be used. They will be considered investigational devices in countries where they are not approved.	
			Section 6.4 Additional Measurements	• For subjects… ~~Data will be evaluated by an independent CT core laboratory and should be blinded to local investigators for cardiac valve findings (local reading should be only for non-cardiac valve findings such as unexpected lung pathology; see Section 10.10.1 for additional information).~~(See ***Note 5*** below). ***Note 5:*** Images will be read in a standard fashion for cardiac and non-cardiac findings by the clinical center CT imaging specialist. Clinical guidelines support anticoagulation with warfarin or another vitamin K inhibitor as a Class I recommendation for patients with established valve thrombosis[4,5]. However, there is no established guidance for pharmaceutical management of subclinical leaflet thrombosis. If deterioration of subject health	

Table 26.1-1: Revision History

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				due to suspected thrombosis occurs, the clinical center may request an unblinding of the Core Laboratory findings.	
			Section 7.1 Scale and Duration	Subjects will be enrolled at up to 85 centers in the United States, Canada, Australia, and Europe. There will be up to ~~1220~~ 1670 subjects in ACURATE IDE. It is expected that >80% of enrolled subjects will be from the United States. To achieve sufficient distribution of lower risk subjects, there will be ≥ 30% intermediate risk and ≥ 35% low risk randomized subjects enrolled (please see definition of operative risk in Section 25.2). • Randomized Cohort: A prospective… up to ~~1050~~1500 subjects… • 4D CT Imaging Substudy: Select… include subjects (minimum of 200) from… All subjects … Enrollment is expected to be completed in approximately 36 months; therefore, the total study duration is estimated to be approximately 13 years. The study duration for each subject is expected to be approximately 10 years…	
			Section 7.3 Justification…	There will be up to ~~1220~~ 1670 subjects… In order… and ~~1050~~ 1500 subjects will be randomized… post index procedure. To achieve sufficient distribution of lower risk subjects, there will be ≥ 30% intermediate risk and ≥ 35% low risk randomized subjects enrolled. Per… aspirin and/or a…	
			Section 8.2 Inclusion Criteria	IC4. Heart team… the subject is indicated for TAVR, is likely to benefit from valve replacement~~, at intermediate risk or above for surgical valve replacement~~ and TAVR is appropriate. ~~The heart team should consider the STS score as well as other factors including frailty, prior surgical history, malignancy or radiation therapy, pulmonary disease, renal disease, liver disease, neuromuscular disease, orthopedic disease, chest deformity, and aortic calcification. Subjects considered to be at intermediate surgical risk or above have a predicted risk of surgical mortality~~	

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				~~≥ 3% based on the STS risk score and other clinical comorbidities unmeasured by the STS risk calculator.~~ ~~Note 1: Risk of operative mortality must be assessed via an in-person evaluation by a center cardiac surgeon and must be confirmed by the CRC (which must include an experienced cardiac surgeon).~~ ~~Note 2: At the time this protocol was written, subjects at extreme and high surgical risk were approved for TAVR with commercially available devices in the United States and Canada. Subjects at intermediate surgical risk were approved for TAVR with select commercially available devices in the United States and Canada. Subjects at low surgical risk were subsequently approved for TAVR with commercially available devices in the United States.~~ ~~IC5. Heart team (which must include an experienced cardiac interventionalist and an experienced cardiac surgeon) agrees that the subject is likely to benefit from valve replacement.~~ ~~Protocol Version J: As of this update to the protocol (Version J), subjects in all surgical risk classes were approved for TAVR in the United States, Canada, Australia, and European countries.~~	
			Section 10.1 Data Collection	**<<Figure 10.1-1 Data Collection…>>** Updated figure.	
			Section 11.1.1.1 Statistical Hypothesis…	The statistical hypothesis… analysis sets). A Bayesian analysis will be performed to estimate the treatment difference between ACURATE and Control through posterior probability. Additional information is provided below.	
			Section 11.1.1.2 Sample Size Parameters…	Although the primary endpoint analysis is performed using the Bayesian method, the sample size calculation (see **Note 2** below) is based on a standard non-inferiority two-sample test approach. The…assumptions.	

Table 26.1-1: Revision History

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				• Expected rate for both arms = ~~25.9~~22.3% (based on a weighted average of TAVR data; see **Note ~~23~~** below) • Non-inferiority margin (Δ) = ~~9.1~~8.0% (36~~5~~% relative to expected rate) • Test significance level (α) = 0.025 (1-sided) (see **Note 4** below) • Test (ACURATE): Control ratio = 1:1 • Power (1 minus ß) = >90% • Expected rate of attrition = 5% • Total sample size = ~~1050~~ 1500 (~~525~~ 750 per group) • Number of evaluable subjects per group = ~~499~~ 712 • Analyses: ~~Two~~ One administrative, one formal interim, ~~plus~~ one final (see **Note ~~3~~ 5** below) **Note ~~23~~:** The ~~Haybittle-Peto~~ Pocock-type method is used for sample size calculations.~~to specify and calculate the alphas for the first interim, second interim, and final analyses as 0.0001, 0.0001, and 0.025, respectively. The first interim analysis is an administrative analysis for regulatory agency review after 350 randomized subjects have completed 1-year follow-up visits. The second interim analysis is planned to occur after 850 randomized subjects have completed 1-year follow-up visits. The final analysis for the primary endpoint will be performed with 1-year data from all subjects.~~ The statistical software EAST® 6.5 is used for the sample size calculations. **Note ~~23~~:** The estimated proportions of subjects by operative risk level is 10% extreme risk, ~~30~~25% high risk, ~~and 60~~30% intermediate risk, and 35% low risk. **Note 4:** A statistically equivalent posterior probability threshold for the Bayesian analysis is empirically chosen through extensive	

Table 26.1-1: Revision History

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				simulations and is pre-specified in the Statistical Analysis Plan (SAP). **Note 5:** The administrative interim analysis will be conducted when the first 350 randomized subjects have completed 1-year follow-up. The formal interim analysis will be carried out after enrollment in the randomized cohort is completed. This formal interim analysis will be conducted on the full N=1500 randomized subject cohort when a subset of the randomized subjects has completed 1-year follow-up (pending regulatory approval). The piecewise exponential model[30] based on outcomes among these subjects will be used to predict the 1-year results by treatment group for the remaining enrolled subjects. The Bayesian method will be used to perform the hypothesis testing on the combined data sets. A final analysis will be performed on all subjects with completed 1-year data if non-inferiority cannot be claimed at the formal interim analysis (see Section **11.1.1.3**).	
			Section 11.1.1.3 Success Criteria…	~~A Farrington-Manning standardized test will be used to test the hypothesis of non-inferiority in the difference between the rates of the two treatment groups, as described in the statistical analysis plan (SAP). If the P-value from the Farrington-Manning standardized test for non-inferiority is <0.025 in the final analysis, the rate of the primary endpoint for the ACURATE group will be concluded to be non-inferior to the Control rate. This corresponds to the one-sided upper 97.5% confidence bound on the difference between treatment groups (ACURATE minus Control) for the observed rate of the primary endpoint being less than delta (Δ).~~ The Bayesian method is used to test the non-inferiority hypothesis of the primary endpoint. To establish that the ACURATE device is non-inferior to the Control, the results will need to meet the following equation: $Pr(H1 \mid Data) > \xi$	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				where • Pr(H1 | Data) is the posterior probability of H1 given the observed data at either the interim or the final analysis; • H1 is the alternative hypothesis for non-inferiority: PE_ACURATE minus PE_Control < Δ; • ξ is a prespecified threshold, which is empirically chosen through extensive simulations using the Bayesian approach for the non-inferiority tests. If non-inferiority has been declared at the formal interim analysis, the non-inferiority test will not be performed at the final analysis. If non-inferiority cannot be declared at this interim analysis, the non-inferiority test will be performed at the final analysis for all subjects using the Bayesian method with the same pre-specified threshold. The study will not stop for futility at the interim analysis. The detailed study operating characteristics and simulation results will be provided in the SAP.	
			11.3.2 Interim/ Administrative Analyses	There will be 2 interim analyses as described in the SAP. ~~The Haybittle-Peto method is used to adjust the alpha levels for the first interim, second interim, and final analyses to 0.0001, 0.0001, and 0.025, respectively.~~ The ~~first interim analysis is an~~ administrative interim analysis will be conducted when the first ~~for regulatory agency review after~~ 350 randomized subjects have completed 1-year follow-up visits. The ~~second~~ formal interim analysis will be carried out after enrollment in the randomized cohort is completed. This formal interim analysis will be conducted on the full N=1500 randomized subject cohort when a subset of the ~~is planned to occur after 850~~ randomized subjects has completed 1-year follow-up (pending regulatory approval)~~visits~~. The piecewise exponential model[30] based on outcomes among these subjects will be used to predict the 1-year	

Table 26.1-1: Revision History

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				results by treatment group for the remaining enrolled subjects. The Bayesian method will be used to perform the hypothesis testing on the combined data sets. A final analysis will be performed on all subjects with completed 1-year data if non-inferiority cannot be claimed at the formal interim analysis (see Section 11.1.1.3). Additional information may be found in the SAP. ~~Additional analyses not defined in the protocol may also be conducted for regulatory agency review.~~	
			11.3.3 Subgroup Analyses…	Primary and pre-specified… as appropriate. In the 4D CT Imaging Substudy, computed tomography data will be analyzed after 200 subjects have reached 1-year follow-up.	
			Section 25.2 Definitions	OPERA-TIVE RISK: Operative risk is determined… **Low**: Estimated 30-day risk of mortality is <3% **Intermediate**: Estimated 30-day risk…	
L	08-Sep-2022	90702637 Rev/Ver AQ	Contact Information	Beth Louh Senior Clinical Trial Manager… Sarah Zanon… ~~Chemin de la Venoge~~ 11 Ritterquai 8 ~~1024 Ecublens~~ 4500 Solothurn, Switzerland	Updated title Updated address
			Section 2, Synopsis Test Device and Sizes	Addition of the ACURATE *Prime* Aortic Valve XL, ACURATE *Prime* Transfemoral Delivery System XL and ACURATE Prime Loading Kit XL. **Device Name/Size** / **Description** ACURATE neo2™ Transfemoral Delivery System The delivery system is compatible with the S, M, and L ~~all 3~~ valve sizes. / Allows… access.	Addition of the ACURATE *Prime* XL Nested Registry; updated for clarity

Table 26.1-1: Revision History

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				ACURATE *Prime*™ Aortic Valve XL Valve size: - XL (extra-large) with 29mm nominal diameter at waist level	Includes 3 main components: - A three-leaflet porcine pericardial bioprosthetic aortic valve. - A self-expandable Nitinol stent. - A double porcine pericardium skirt sutured on the inner and outer surface of the stent to prevent paravalvular leaks. Introduced via the iliofemoral artery.	
				ACURATE *Prime*™ Transfemoral Delivery System XL	Allows positioning and delivery of the transcatheter XL valve via iliofemoral access.	
				ACURATE *Prime*™ Loading Kit XL	Allows loading of the XL valve onto the delivery system.	
			Section 2, Synopsis Study Design	Study cohorts include the following: • **ACURATE *Prime*™ XL Nested Registry:** A non-randomized, nested registry cohort of subjects who will receive the ACURATE *Prime*™ Transfemoral Aortic Valve System XL (ACURATE *Prime* XL Nested Registry). Participating centers will be a subset of United States centers that have enrolled subjects in ACURATE IDE. Data from subjects in this nested registry will be summarized separately from the randomized and Roll-In cohorts. **ACURATE IDE Study Design Overview** Updated figure to include the ACURATE *Prime* Nested Registry.		
			Section 2, Synopsis Planned Number of Subjects…	Subjects will be enrolled… up to ~~1670~~ 1720 subjects total in the ACURATE IDE Roll-In and randomized cohorts and the ACURATE *Prime* XL Nested Registry as shown below.		
				Cohort	**Number of Subjects**	
				ACURATE *Prime* XL Nested Registry	50‡	

Table 26.1-1: Revision History

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				* A subset... ‡ Subjects will be enrolled at up to 20 centers in the United States.	
			Section 2, Synopsis Method of Assigning …	For the randomized cohort and Roll-In cohort, subjects will have a documented aortic annulus size of ≥21mm and ≤27mm based on pre-procedure diagnostic imaging. **ACURATE *Prime* XL Nested Registry:** Subjects will have a documented aortic annulus size of ≥26.5 mm and ≤29 mm based on pre-procedure diagnostic imaging.	
			Section 2, Synopsis Follow-up Schedule	The visits at 30 days, 6 months, 1−5 years, 7 years, and 10 years are to be an office/clinical/in-person or telehealth visit…	Add telehealth option
			Section 2, Synopsis Study Duration	Enrollment is expected to be completed in approximately ~~36~~ 45 months; therefore, the total study duration is estimated to be approximately ~~13~~14 years.	Updated estimate
			Section 2, Synopsis Inclusion Criteria	IC2. Subject has… and ≤ 29~~7~~ mm based…	Allow for XL size valve
			Section 2, Synopsis Exclusion Criteria	Vulnerable subjects (ISO 14155) will not be enrolled in ACURATE IDE.	Per ISO 14155.
			Section 2, Synopsis Analysis Sets	Among the Roll-In and ACURATE *Prime* XL cohorts, for the ITT analysis, all subjects… implanted. The Implanted analysis set will include all subjects who sign an Informed Consent Form and are implanted with an ACURATE valve. For these single-arm cohorts…	Allow for XL size valve
			Section 2, Synopsis Sample Size Parameters for the Primary Endpoint	Although the primary endpoint analysis is performed using the Bayesian method, the sample size calculation for the randomized cohort (see… **Note 15:** The… This formal interim analysis will be conducted on the full N=1500 randomized subject cohort after the first 1050~~a~~	Updated for clarity

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				~~subset of the~~ randomized subjects have completed 1-year follow-up ~~(pending regulatory approval)~~.	
			Section 2, Synopsis ACURATE *Prime* XL Nested Registry Statistical Hypothesis	Mean aortic valve pressure gradient at 30 days post implant procedure is less than a performance goal (PG): H_0: $Gradient_{30D} \geq PG$ H_1: $Gradient_{30D} < PG$ where $Gradient_{30D}$ is the 30-day mean aortic valve pressure gradient for the ACURATE *Prime* XL valve and PG is 15 mmHg.	Addition of the ACURATE *Prime* XL Nested Registry
			Section 2, Synopsis Statistical Test Method for the ACURATE *Prime* XL Nested Registry	A one-sample *t*-test will be used to test the one-sided hypothesis at a significance level of 2.5%.	
			Section 2, Synopsis Sample Size Parameters for the ACURATE *Prime* XL Nested Registry	• Expected 30-day mean pressure gradient from ACURATE Prime XL = 10 mmHg[h] • Expected standard deviation = 7 mmHg • PG = 15 mmHg • Test significance level (α) = 0.025 (1-sided) • Power > 90% • Evaluable number of subjects = Minimum of 40 subjects • Expected rate of attrition = 20% (8 subjects) • Planned enrollment of 50 subjects • The analysis population for the hypothesis testing will be the subject population implanted with the ACURATE *Prime* XL valve. h: Based on Boston Scientific data on file and published data for large-annulus CoreValve devices:	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				Tang GHL, et al. Am J Cardiol 2019;124:1091-8 Kalogeras K, et al. Catheter Cardiovasc Interv 2019;93:685-91 Ussia GP, et al. EuroIntervention 2015;10:e1-e8	
			Section 2, Synopsis Success Criteria for the ACURATE *Prime* XL Nested Registry	If the *P* value from the one-sample *t*-test is < 0.025, the ACURATE *Prime* XL valve will be concluded to have a 30-day mean aortic valve pressure gradient < 15 mmHg. This corresponds to the one-sided upper 2.5% confidence bound of the observed 30-day mean aortic valve pressure gradient being < 15 mmHg.	
			Section 2, Synopsis Descriptive Statistics	Descriptive statistics will be used to summarize data from subjects in the single-arm Roll-In and ACURATE *Prime* XL cohorts.	
			Section 4.1.2 Transcatheter Aortic Valve…	Updated Table 4.1-1 with additional references regarding TAVR in large annuli: CoreValve – Large Annuli (2015)[43]; UK & Ireland Implanters' Registry (2019)[47]; EVOLUT R – Large Annuli (2019)[48]; TVT Registry – Large Annulus (2019)[49]	
			Section 4.2 Study Rationale	The ACURATE device… limit PVR. The subsequent ACURATE *neo2* and ACURATE *Prime* Transfemoral Valve Systems ~~was~~were designed…	
			Section 5.1 ACURATE Transfemoral Aortic Valve System (Test)	• A single use aortic valve, the ACURATE *neo2*™ Aortic Valve (valve sizes S, M, and L) or the ACURATE *Prime*™ Aortic Valve (valve size XL) • A single use transfemoral delivery system, the ACURATE *neo2*™ Transfemoral Delivery System (for use with valve sizes S, M, and L) or the ACURATE *Prime* Transfemoral Delivery System (for use with valve size XL) • A single use loading kit, ACURATE *Prime*™ Loading Kit XL (to allow loading of the XL valve onto the delivery system)	

Table 26.1-1: Revision History

<table>
<tr><th>Revision Version</th><th>Protocol Date</th><th>Template Number and Version</th><th>Protocol Sections Modified</th><th>Summary of Changes</th><th>Justification for Changes</th></tr>
<tr><td rowspan="2"></td><td rowspan="2"></td><td rowspan="2"></td><td></td><td>Note: The single use ACURATE neo2™ Loading Kit is packaged with the ACURATE neo2™ Transfemoral Delivery System.

Valves ~~and the delivery system~~ are manufactured in Belo Horizonte, Brazil. Delivery systems and loading kits are manufactured in Ecublens, Switzerland and/or Galway, Ireland. All components are investigational and are labeled as such. The device components are described briefly below. Additional information is provided in the ACURATE neo and ACURATE Prime Clinical Directions/Instructions for Use (DFU/IFU) and the IB.
Note: Throughout this document DFU and IFU are used interchangeably.</td><td rowspan="2"></td></tr>
<tr><td>Section 5.1.1. ACURATE neo2™ Aortic Valve and ACURATE Prime™ Aortic Valve XL</td><td>The ACURATE neo2 Aortic Valve is an iteration of the CE Mark-approved ACURATE neo™ Aortic Bioprosthesis (Boston Scientific Corporation, Marlborough, MA, USA). The ACURATE Prime Aortic Valve XL is an iteration of the CE Mark-approved ACURATE neo2 Aortic Valve. There are 3 valve sizes of ACURATE neo2 (Small, Medium, and Large) intended for a native annulus diameter range between 21 mm and 27 mm and 1 valve size of ACURATE Prime (Extra Large) intended for a native annulus diameter range between 26.5 mm and 29 mm as shown in Table 5.1-1.
Added rows to Table 5.1-1 ACURATE neo2 and ACURATE Prime Aortic Valve Size Chart
<table>
<tr><td>Extra Large (XL)</td><td>29mm</td><td>26.5 mm < native annulus diameter ≤ 29 mm</td></tr>
<tr><td colspan="3">a: ACURATE neo2™ available in sizes S, M, L and ACURATE Prime™ available in size XL</td></tr>
</table></td></tr>
</table>

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				The valves are shown in Figure 5.1-1 (ACURATE *neo2* Aortic Valve in Panel A and ACURATE *Prime* Aortic Valve XL in Panel B). Each valve consists of… …intended to limit further the extent of PVR. The ACURATE *Prime* Aortic Valve XL iteration allows easier removal of a fully loaded valve and has optimized radial force with the addition of connected links. The valve… UPDATED **Figure 5.1-1** with addition of a picture of the ACURATE *Prime* Aortic Valve XL (Panel B).	
			Section 5.1.2. ACURATE neo2™ Transfemoral Delivery System and ACURATE Prime Transfemoral Delivery System XL	The ACURATE *neo2* Transfemoral Delivery System and ACURATE *Prime* Transfemoral Delivery System XL are ~~is~~ transfemoral delivery systems for the guidance and placement of the valve implant. ACURATE *neo2* is a slightly… The ACURATE *Prime* Transfemoral Delivery System XL is a slightly modified version of the ACURATE *neo2* Transfemoral Delivery System. The system is compatible with the 14F iSLEEVE introducer (see Section 5.1.3 below) and has a new distal release mechanism to allow quicker final valve release and improved Figure 5.1 5 shows an overview of the system and Figure 5.1 6 shows a close-up of the distal end. Prior to use, the ACURATE Prime Aortic Valve XL is loaded onto the delivery system with the investigational ACURATE Prime Loading Kit XL. ADDED **Figure 5.1-5** and **Figure 5.1-6** The delivery systems are single-use catheters. Please see Section 10.7.2.2 for additional information on preparing and using the investigational devices… Only BSC authorized and trained personnel may load the ACURATE Valve.	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 5.1.3 Introducer Set	Only the iSLEEVE shall be used with the ACURATE *Prime* Transfemoral Delivery System XL.	
			Section 5.3.1 Test Device	The study Manual of Operations includes the DFU/IFU for the ACURATE *neo2* Valve, ~~and the~~ ACURATE *neo2* Transfemoral Delivery System, ACURATE *Prime* Aortic Valve, ACURATE *Prime* Transfemoral Delivery System, and ACURATE *Prime* Loading Kit.	Addition of the ACURATE *Prime* XL Nested Registry; updated for clarity
			Section 6.2 Study Endpoints	Among the Roll-In and ACURATE Prime XL cohorts of ACURATE IDE, all subjects…	
			Section 7.1 Scale…	Subjects… There will be up to ~~1670~~ 1720 subjects total in… The ACURATE IDE study cohorts… • **ACURATE *Prime*™ XL Nested Registry:** A non-randomized, nested registry cohort of subjects who will receive the ACURATE *Prime*™ Transfemoral Aortic Valve System XL (ACURATE *Prime* XL Nested Registry). Participating centers will be a subset of United States centers that have enrolled subjects in ACURATE IDE. Data from subjects in this nested registry will be summarized separately from the randomized and Roll-In cohorts. There will be 50 subjects at centers in the United States enrolled in this registry. All subjects implanted… Enrollment is expected to be completed in approximately ~~36~~ 45 months; therefore, the total study duration is estimated to be approximately ~~13~~ 14 years. UPDATED **Figure 7.1-1** to include the ACURATE *Prime* Nested Registry.	
			Section 7.2 Treatment Assignment	Subjects in the non-randomized, nested registry cohort will all receive ACURATE Prime™ Transfemoral Aortic Valve System XL valves.	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				UPDATED **Table 7.2-1** to reflect addition of ACURATE *Prime* XL valve, delivery system, and loading kit. ***Note 2:*** Subjects in the Roll-In (Section 9.1.1) and randomized (Section 9.1.2) cohorts will have a documented aortic annulus size of ≥21mm and ≤27mm based on pre-procedure diagnostic imaging. Subjects in the ACURATE Prime XL Nested Registry (Section 9.1.3) will have a documented aortic annulus size of ≥26.5mm and ≤29mm based on pre-procedure diagnostic imaging.	
			Section 7.3 Justification for the Study Design	There will be up to ~~1670~~ 1720 subjects total in ACURATE IDE. In order …do 2 Roll-In cases each), ~~and~~1500 subjects will be randomized and enrolled, and 50 subjects will be enrolled in the ACURATE Prime XL Nested Registry.	
			Section 8.2 Inclusion Criteria	Table 8.2-1: Updated IC2: …annulus size of ≥21 mm and ≤29~~7~~ mm	
			Section 8.3 Exclusion Criteria	…clinical study. No vulnerable populations will be enrolled in this study. See Section **25.2** for the definition of a vulnerable subject.	Updated per ISO 14155
			Section 9.1.3 ACURATE *Prime* XL Nested Registry	For the ACURATE Prime XL Nested Registry, subjects confirmed eligible for the study by the CRC (see Section 21.2) and who provided written informed consent (see Section 20) are considered enrolled in the study as soon as an attempt is made to insert the test device into the subject's femoral artery.	Addition of the ACURATE *Prime* XL Nested Registry
			Section 9.5 End-of-Study Definition	Visits at 30 days, 6 months, 1–5 years, 7 years and 10 years are office/clinical/in-person or telehealth visits.	Allow for telehealth
			Section 10.1 Data Collection	All subjects... ~~Physical~~ Office/clinical/ ~~visits/or~~ in-person or telehealth follow-up visits… **Note:** All required ECG measurements and transthoracic echocardiography measurements must be done for all subjects who have a transcatheter valve implanted in the aortic position during the index procedure, even if the associated follow-up assessment is carried out via telehealth.	Allow for telehealth; add ACURATE *Prime* XL Registry

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				Table 10.1-1: Added "Telehealth" to column header and "Visits at 30 days, 6 months, 1–5 years, 7 years and 10 years are office/clinical/in-person or telehealth visits; all required ECG measurements and TTE measurements must be done for all subjects who have a transcatheter valve implanted in the aortic position during the index procedure, even if the associated follow-up assessment is carried out via telehealth." UPDATED Figure 10.1-1 to show addition of ACURATE *Prime* XL Registry	
			Section 10.7.2 ACURATE Transfemoral…	Only the iSLEEVE introducer shall be used with the ACURATE *Prime* Transfemoral Delivery System XL (see Section **5.1.3**).	Addition of ACURATE *Prime* XL Registry
			Section 10.7.2.2 Preparing…	The appropriate DFU… A similar procedure is used for preparation of the ACURATE *Prime* Aortic Valve XL; please see the corresponding DFU/IFU and other training material provided by BSC. • Device size (Small, Medium, ~~or~~ Large, or Extra Large) Figure 10.7-1: ***Note:*** This example shows the ACURATE *neo2* valve.	
			Section 10.10 Follow-up	***Note 2:*** Where indicated in Table 10.1-1, the follow-up visits must be conducted in-person or as telehealth visits. If an in-person/telehealth assessment cannot be performed, follow-up by telephone call should be attempted. The subject or the subject's physician should provide rationale for why the subject cannot ~~come in for~~ comply with the follow-up in-person/telehealth assessment ~~visit~~.	Allow for telehealth
			Section 10.10.1 30-day Follow-up	All enrolled subjects must be evaluated 30 (±7) days after the index procedure in person or via telehealth. During…	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				Note 1: A 12-lead ECG must be obtained for all subjects, even if the associated follow-up assessment is carried out via telehealth. ***Note 2:*** TTE must be done for all subjects who have a transcatheter valve implanted in the aortic position during the index procedure, even if the associated follow-up assessment is carried out via telehealth.	
			Section 10.10.2 6-month Follow-up	All enrolled subjects must be evaluated 180 (±30) days after the index procedure in person or via telehealth. During… ***Note 1:*** A 12-lead ECG must be obtained for all subjects, even if the associated follow-up assessment is carried out via telehealth. ***Note 2:*** TTE must be done for all subjects who have a transcatheter valve implanted in the aortic position during the index procedure, even if the associated follow-up assessment is carried out via telehealth.	
			Section 10.10.3 1-year Follow-up	All enrolled subjects must be evaluated 30 (±7) days after the index procedure in person or via telehealth. During… ***Note 1:*** A 12-lead ECG must be obtained for all subjects, even if the associated follow-up assessment is carried out via telehealth. ***Note 2:*** TTE must be done for all subjects who have a transcatheter valve implanted in the aortic position during the index procedure, even if the associated follow-up assessment is carried out via telehealth.	
			Section 10.10.4 Annual Follow-up…	All implanted subjects must be evaluated in person or by telehealth visit at 2… ***Note:*** TTE must be done for all subjects who have a transcatheter valve implanted in the aortic position during the index procedure, even if the associated follow-up assessment is carried out via telehealth.	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 10.10.5 Follow-up (±60 Days) at 7 and 10…	All implanted subjects must be evaluated in person or via telehealth at 7 and… ***Note:*** TTE must be done for all subjects who have a transcatheter valve implanted in the aortic position during the index procedure, even if the associated follow-up assessment is carried out via telehealth.	
			Section 10.10.11 Study Completion	Visits in the first 5 years and at 7 and 10 years are office ~~or~~ /in-person/telehealth visits. Visits in the first 5 years and at 7 and 10 years are office/in-person/telehealth visits.	
			Section 11.1 Endpoints	Data will be summarized separately for the specific statistical hypothesis associated with the ACURATE Prime™ XL Nested Registry. Descriptive statistics also will be used to summarize data from subjects in the single-arm ACURATE Prime XL cohort.	Statistical hypothesis for the ACURATE Prime XL Nested Registry.
			Section 11.1.1.2 Sample Size…	***Note 5:*** The administrative... after the first 1050 ~~a subset of the~~ randomized subjects have completed 1-year follow-up ~~(pending regulatory approval)~~. The…	Updated for clarity
			Section 11.1.2 ACURATE *Prime* XL Nested Registry Statistical Assessment	The statistical assessment for the ACURATE *Prime* XL Nested Registry is summarized in the sections below. Additional information may be found in the SAP. **11.1.2.1 Statistical Hypothesis – ACURATE *Prime* XL Nested Registry** The statistical hypothesis is that the mean aortic valve pressure gradient at 30 days post implant procedure is less than a performance goal (PG): H_0: $Gradient_{30D} \geq PG$ H_1: $Gradient_{30D} < PG$	Statistical hypothesis for the ACURATE Prime XL Nested Registry.

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				where $Gradient_{30D}$ is the 30-day mean aortic valve pressure gradient for the ACURATE *Prime* XL valve and PG is 15 mmHg. A one-sample *t*-test will be used to test the one-sided hypothesis at a significance level of 2.5%. **11.1.2.2 Sample Size Parameters for the ACURATE *Prime* XL Nested Registry** The sample size calculation is based on the following assumptions. • Expected 30-day mean pressure gradient from ACURATE *Prime* XL = 10 mmHg • Expected standard deviation = 7 mmHg • PG = 15 mmHg • Test significance level (α) = 0.025 (1-sided) • Power > 90% • Evaluable number of subjects = Minimum of 40 subjects • Expected rate of attrition = 20% (8 subjects) • Planned enrollment of 50 subjects • The analysis population for the hypothesis testing will be the subject population implanted with the ACURATE *Prime* XL valve. ***Note:*** The expected mean gradient is based on Boston Scientific data on file and published data for large-annulus CoreValve devices[43.48.49]. **11.1.2.3 Success Criteria for the ACURATE Prime XL Nested Registry** If the *P* value from the one-sample *t*-test is < 0.025, the ACURATE *Prime* XL valve will be concluded to have a 30-day	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				mean aortic valve pressure gradient < 15 mmHg. This corresponds to the one-sided upper 2.5% confidence bound of the observed 30-day mean aortic valve pressure gradient being < 15 mmHg.	
			11.1.3 Baseline Comparability	Baseline data will be summarized by treatment group for the randomized subjects and separately for the Roll-In and ACURATE *Prime* XL Nested Registry subjects. Please see Section **11.1.2** regarding statistical testing for the ACURATE *Prime* XL Nested Registry.	Statistics for ACURATE *Prime* XL Nested Registry
			11.1.4 Post-procedure…	Please see Section **11.1.2** regarding statistical testing for the ACURATE *Prime* XL Nested Registry.	
			11.2.1 Analysis Sets	Subjects in the randomized cohort are considered enrolled in the study upon randomization. Among the randomized… …With the Roll-In and ACURATE *Prime*™ XL Nested Registry cohorts, the subject is considered enrolled in the trial when there is an attempt made to insert the ACURATE Transfemoral Aortic Valve System into the subject's femoral artery. … The implanted population includes all subjects who sign an ICF and are implanted with ~~the~~ an ACURATE valve.	Updated for clarity Statistics for ACURATE *Prime* XL Nested Registry Updated for clarity
			11.2.5 Reporting Events	For all subjects in the ACURATE IDE Roll-In and ACURATE *Prime*™ XL Nested Registry cohort, all events that occur from the time of enrollment will be reported.	Statistics for ACURATE *Prime* XL Nested Registry
			11.3.2 Interim/ Administrative Analyses	This formal interim analysis will be conducted on the full N=1500 randomized subject cohort after the first 1050~~a subset of the~~ randomized subjects have completed 1-year follow-up ~~(pending regulatory approval)~~.	Updated for clarity
			11.3.3 Subgroup Analyses for	Added 2 subgroups: • Valve size (Small, Medium, Large)	Gain additional information on

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes		Justification for Changes
			Randomized Subjects	• Operative risk (low, intermediate, high/extreme)		outcomes in other subgroups
			16.2 Investigator Responsibilities	• Ensure that, if appropriate… participation in the clinical investigation (e.g., implant card) …		Added for clarity
			16.4.2 Training with the Investigational Device	The ACURATE ~~neo2 Transfemoral Aortic Valve System~~ Healthcare Personnel (HCP) Training Plan developed for this study meets the requirements of ISO 5840-3 and includes the following elements. ***Note 3:*** Centers selected to participate in the ACURATE *Prime* XL Nested Registry will receive additional training on the ACURATE *Prime* investigational device. An experienced BSC representative will provide technical support as needed during valve preparation and implantation.		Updated name of the training plan Addition of ACURATE *Prime* XL Nested Registry
			Section 25.2 Definitions	VULNERABLE SUBJECTS (per ISO 14155)	Individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response	Updated to comply with ISO 14155
M	20-Jan-2023	90702637 Rev/Ver AQ	Section 2, Synopsis, Test Device and Sizes	Added * to ACURATE *Prime*™ in the size table. * ACURATE *Prime* XL is only available in the United States.		Added for clarity
			Section 2, Synopsis, Control Device and Sizes	In the Main Randomized Cohort and in the Extended Durability Study (see study cohorts described below), subjects… **Note 1:** Every subject in the Main Randomized Cohort and the Extended Durability Study must be deemed…		

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 2, Synopsis, Study Design	• **Main Randomized Cohort**… • **Roll-In Cohort:** …at least 2 Roll-In cases with ACURATE *neo2* before… • **4D CT Imaging Substudy:** …will include subjects from the Main Randomized Cohort in a… • **ACURATE *Prime* XL Nested Registry:** A nonrandomized… separately from the ~~randomized and Roll-In~~ other cohorts. • **ACURATE Extended Durability Study:** An additional 1:1 randomized study (ACURATE versus Control [commercially available SAPIEN 3 or CoreValve] TAVR device) including only subjects considered to be at low surgical risk. Subjects will receive ACURATE *neo2* (S, M, or L valve sizes) or ACURATE *Prime* XL. Randomization will be stratified by center and by intended control device. Low-risk subjects receiving ACURATE *neo2* will be enrolled in the Extended Durability Study only after enrollment of the Main Randomized Cohort is completed. Enrollment of low-risk subjects with ACURATE *Prime* XL will start after enrollment in both the ACURATE *Prime* XL Nested Registry and the Main Randomized Cohort is completed. Data from subjects in the Extended Durability Study will be summarized separately from other cohorts. **Note:** Centers must complete the roll-in phase of the study, if applicable, before participating in the ACURATE Extended Durability Study. • **ACURATE Continued Access Study (CAS):** An additional cohort of subjects receiving ACURATE *neo2* (S, M, and L valve sizes) or ACURATE *Prime* XL. Enrollment of subjects with ACURATE neo2 will start after enrollment of the ACURATE IDE Main Randomized Cohort is completed. Enrollment of subjects with ACURATE *Prime* XL will start after enrollment in both the ACURATE *Prime* XL Nested Registry and Main Randomized	Added for clarity and to include the Extended Durability Study and the Continued Access Study

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				Cohort is completed. Subjects at all surgical risks may be enrolled in ACURATE CAS, but low-risk subjects will be considered for enrollment only after enrollment in the Extended Durability Study is completed. Data from subjects in the ACURATE CAS will be summarized separately from other cohorts and will be used to further assess performance and safety. **Note**: Centers must complete the roll-in phase of the study, if applicable, before participating in ACURATE CAS. The devices and risk levels for the ACURATE IDE cohorts are summarized in the table below. Added a table showing "Devices And Risk Levels for the ACURATE IDE Cohorts." Updated ACURATE IDE Study Design Overview figure	

Table 26.1-1: Revision History

<table>
<tr><th>Revision Version</th><th>Protocol Date</th><th>Template Number and Version</th><th>Protocol Sections Modified</th><th>Summary of Changes</th><th>Justification for Changes</th></tr>
<tr><td></td><td></td><td></td><td>Section 2, Synopsis, Planned Number of Subjects…</td><td>Subjects… Europe. In total, there will be up to ~~1720~~ 2820 subjects ~~total~~ enrolled in ~~the~~ ACURATE IDE ~~roll-in and randomized~~ across the various cohorts ~~and the ACURATE Prime XL Nested Registry as shown below~~. It is expected that >80% of enrolled subjects will be from the United States. The number of subjects intended for each cohort is shown in the table below.

<table>
<tr><th>Cohort</th><th>Number of Subjects</th></tr>
<tr><td>Main Randomized Cohort</td><td>1500*</td></tr>
<tr><td>Roll-In Cohort</td><td>Up to 170</td></tr>
<tr><td>ACURATE Prime XL Nested Registry</td><td>50‡</td></tr>
<tr><td>ACURATE Extended Durability Study</td><td>A minimum of 100†</td></tr>
<tr><td>ACURATE Continued Access Study (CAS)</td><td>Up to 1000§</td></tr>
<tr><td colspan="2">* A subset of subjects (minimum of 200) in the Main Randomized Cohort will also be enrolled in the 4D CT Imaging Substudy.
‡ Subjects will be enrolled at up to 20 centers in the United States.
† Only low-risk subjects will be included in the Extended Durability Study.
§ Low-risk subjects will be considered for enrollment in ACURATE CAS after enrollment is completed in the Extended Durability Study.</td></tr>
</table>
</td><td></td></tr>
<tr><td></td><td></td><td></td><td>Section 2, Synopsis, Method of Assigning…</td><td>Main Randomized Cohort: A computer…

ACURATE Extended Durability Study: A computer generated list of random treatment allocations (randomization schedule) will be used to assign subjects to treatment in a 1:1 ratio of ACURATE to Control. Only subjects considered to be at low surgical risk will</td><td>Added for the additional cohorts. Annulus size updated for the additional cohorts for better valve</td></tr>
</table>

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				be included in this cohort. Randomization will be stratified by center and by intended control device. Subjects will receive ACURATE *neo2* (S, M, or L valve sizes) or ACURATE *Prime* XL. Subjects with a documented aortic annulus size of ≥20.5mm and ≤27 mm may be enrolled in the Extended Durability Study after enrollment is concluded in the Main Randomized Cohort. Subjects with a documented aortic annulus size of ≥26.5mm and ≤29mm may be enrolled in the Extended Durability Study after enrollment is concluded in both the Main Randomized Cohort and the ACURATE *Prime* XL Nested Registry. **Note**: Centers must complete the roll-in phase of the study, if applicable, before participating in the ACURATE Extended Durability Study. **ACURATE Continued Access Study:** Subjects will receive ACURATE *neo2* (S, M, or L valve sizes) or ACURATE *Prime* XL. Subjects with a documented aortic annulus size of ≥20.5mm and ≤27mm may be enrolled in ACURATE CAS after enrollment is concluded in the Main Randomized Cohort. Subjects with a documented aortic annulus size of ≥26.5mm and ≤29mm may be enrolled in ACURATE CAS after enrollment is concluded in both the Main Randomized Cohort and the ACURATE *Prime* XL Nested Registry. Subjects at all surgical risk levels may be enrolled in ACURATE CAS but low-risk subjects will be considered for enrollment only after enrollment is completed in the Extended Durability Study. **Note:** Centers must complete the roll-in phase of the study, if applicable, before participating in ACURATE CAS.	sizing based on operator experience.
			Section 2, Synopsis, Follow-up Schedule	The visits… or telehealth (https/telehealth.HHS.gov) visit…	Added for clarity

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 2, Synopsis, Study Duration	…Enrollment is expected to be completed in approximately ~~45~~ 62 months; therefore, the total study duration is estimated to be approximately ~~14~~ 16 years.	Added for the additional cohorts.
			Section 2, Synopsis, Inclusion Criteria	IC2. Subject… size of ≥~~21~~ 20.5 mm… and, for the Main Randomized Cohort and Extended Durability Study, is deemed…	Annulus size updated for the additional cohorts for better valve sizing based on operator experience.
			Section 2, Synopsis, Statistical Methods, Analysis Sets	Analysis sets for the ACURATE IDE Main Randomized Cohort, and the Extended Durability Study are listed below. Subjects in the Main Randomized Cohort and the Extended Durability Study are considered… **Note 11:** For the ~~Implanted~~ Main Randomized Cohort and Extended Durability Study ~~analysis set~~, if a subject… Among the Roll-In, ~~and~~ ACURATE *Prime* XL, and Continued Access Study cohorts, for…	Added for clarity and to include the Extended Durability Study and the Continued Access Study
			Section 2, Synopsis, Statistical Methods, Primary Endpoint	In the Main Randomized Cohort, the primary endpoint…	
			Section 2, Synopsis, Statistical Methods, Statistical Test Method for the Primary Endpoint	For the Main Randomized Cohort, the statistical hypothesis…	
			Section 2, Synopsis, Sample Size Parameters for the Primary Endpoint	**Note 15:** The administrative… the first 350 ~~randomized~~ subjects in the Main Randomized Cohort have completed… The formal interim… enrollment in the Main Randomized Cohort is completed. This formal interim analysis will be conducted on the full N=1500 ~~randomized~~ subject cohort of the Main Randomized	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				Cohort after the first 1050 ~~randomized~~ subjects in the Main Randomized Cohort have completed…	
			Section 2, Synopsis, Success Criteria for the Primary Endpoint	The Bayesian method is used to test the non-inferiority hypothesis of the primary endpoint on the Main Randomized Cohort. To establish…	
			Section 2, Synopsis, Statistical Methods, ~~Descriptive~~ Statistics Summary	Data will be summarized separately for each cohort. In addition to the hypothesis tests listed above, descriptive statistics will be used ~~to summarize data from subjects in the single-arm Roll-In and ACURATE Prime XL cohorts~~. Full methods will be described in the statistical analysis plan.	Updated for clarity
			Section 5.1.1 ACURATE *neo2* Aortic Valve and ACURATE *Prime* Aortic Valve XL	There are 3 valve sizes of ACURATE neo2 (Small, Medium, and Large~~) intended for a native annulus diameter range between 21 mm and 27 mm~~ and 1 valve size of ACURATE Prime (Extra Large). ~~intended for a native annulus diameter range between 26.5 mm and 29 mm as shown in~~ Table 5.1-1 shows the sizing chart used for the ACURATE IDE Roll-In Cohort, Main Randomized Cohort, and ACURATE Prime XL Nested Registry. Table 5.1-2 shows the sizing chart used for the Extended Durability Study and the Continued Access Study. Please see Section 7.1 below for study cohort descriptions. **Note:** ACURATE *Prime*™ XL is only available in the United States. **Table 5.1-1:** ACURATE neo2 and ACURATE Prime Aortic Valve Size Chart – Main Randomized Cohort, Roll-In Cohort and ACURATE Prime XL Nested Registry Added superscript b to Extra Large (XL) in the size table. b: ACURATE *Prime* XL is only available in the United States.	Added for the additional cohorts. Annulus size updated for the additional cohorts for better valve sizing based on operator experience.

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				Table 5.1-2: ACURATE *neo2* and ACURATE *Prime* Aortic Valve Size Chart – Extended Durability Study and Continued Access Study [Added table]	
			Section 5.1.3 Introducer Set	~~It is recommended that the commercially available Lotus Introducer Set (size Small [LIS-S]; manufactured by Creganna-Tactx Medical and distributed by Boston Scientific Corporation, Marlborough, MA, USA) or~~ The commercially available 14F iSLEEVE™ Introducer Set (iSLEEVE; Boston Scientific Corporation, Marlborough, MA, USA) shall be used as an accessory to the ACURATE *neo2* Transfemoral Aortic Valve System and the ACURATE *Prime* Transfemoral Aortic Valve System during the procedure. ~~Only~~ The iSLEEVE ~~shall be used with the ACURATE Prime Transfemoral Delivery System XL. Both introducers are~~is composed of a dilator and an introducer sheath manufactured with materials commonly used in medical devices having contact with circulating blood. ~~Both introducers~~ It has ~~ve~~ a … introduction. ~~The LIS-S is suitable for use in subjects with femoral vascular access ≥6.0 mm.~~ The 14F iSLEEVE... **Note:** In countries where the iSLEEVE ~~and LIS-S are~~is approved, the commercial device will be used. ~~They~~ It will be considered an investigational device~~s~~ in countries where ~~they are~~ it is not approved.	Lotus Introducer Set is no longer on the market
			Section 5.2 Control Device	The control device… native annulus range between ~~21~~20.5mm and ~~27~~29mm ***Note:*** Every subject in the Main Randomized Cohort and the Extended Durability Study must…	Updated for the Extended Durability study
			Section 6.2 Study Endpoints	Outcomes in the randomized cohorts of the ACURATE IDE trial (Main Randomized Cohort and Extended Durability Study) will… Among the Roll-In, ~~and~~ ACURATE *Prime* XL, and CAS cohorts…	Added due to inclusion of the Extended Durability Study and the

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 6.3 Primary Endpoint	The primary endpoint… The primary analysis set for the primary endpoint for the Main Randomized Cohort is the ITT…	Continued Access Study and updated for clarity
			Section 7.1 Scale and Duration	Subjects will be enrolled… up to ~~1720~~2380 subjects total… To achieve sufficient distribution of lower risk subjects in the Main Randomized Cohort, there… • **ACURATE Extended Durability Study**: An additional 1:1 randomized study (ACURATE versus Control [commercially available SAPIEN 3 or CoreValve] TAVR device) including only subjects considered to be at low surgical risk. Randomization will be stratified by center and by intended control device. Low-risk subjects receiving ACURATE *neo2* will be enrolled in the Extended Durability Study only after enrollment of the Main Randomized Cohort is completed. Enrollment of low-risk subjects with ACURATE *Prime* XL will start after enrollment in both the Main Randomized Cohort and the ACURATE Prime XL Nested Registry is completed. Data from subjects in the Extended Durability Study will be summarized separately from other cohorts. **Note:** Centers must complete the roll-in phase of the study, if applicable, before participating in ACURATE Extended Durability Study. • **ACURATE Continued Access Study (CAS):** An additional cohort of subjects receiving ACURATE *neo2* (S, M, and L valve sizes) or ACURATE *Prime* XL. Enrollment of subjects with ACURATE *neo2* will start after enrollment of the ACURATE IDE Main Randomized Cohort is completed. Enrollment of subjects with ACURATE *Prime* XL will start after enrollment in both the Main Randomized Cohort and the ACURATE *Prime* XL Nested Registry is completed. Subjects at all surgical risks may be	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
				enrolled in ACURATE CAS, but low-risk subjects will be considered for enrollment only after enrollment in the Extended Durability Study is completed. Data from subjects in ACURATE CAS will be summarized separately from other cohorts and will be used to further assess performance and safety. **Note:** Centers must complete the roll-in phase of the study, if applicable, before participating in ACURATE CAS. The devices to be used and the subject risk levels for the ACURATE IDE cohorts are summarized below in Table7.1-1. Added new **Table 7.1-1: Risk Levels and Devices for ACURATE IDE Cohorts** All subjects implanted… be completed in approximately ~~45~~ 62 months; therefore, the total study duration is estimated to be approximately ~~14~~ 16 years… The study design is summarized below in **Figure 7.1-1**. As noted above, enrollment in the Extended Durability Study will commence for low-risk subjects receiving ACURATE *neo2* after enrollment of the Main Randomized Cohort is completed. Enrollment of low-risk subjects receiving ACURATE *neo2* in ACURATE CAS will begin after enrollment in the Extended Durability Study is completed. Enrollment of low-risk subjects with ACURATE *Prime* XL will start after enrollment in both the Main Randomized Cohort and the ACURATE *Prime* XL Nested Registry is completed. Updated **Figure 7.1-1 ACURATE IDE Study Design.**	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 7.2 Treatment Assignment	For the randomized cohorts (Main Randomized Cohort and Extended Durability Cohort), eligible subjects… Subjects in the non-randomized ACURATE *Prime* XL Nested Registry cohort will all receive ACURATE Prime™ Transfemoral Aortic Valve System XL valves. Subjects in the non-randomized ACURATE CAS will receive ACURATE *neo2* or ACURATE *Prime* XL valves. **Note 2:** Subjects in the Roll-In cohort (Section **9.1.1**) and Main Randomized Cohort (Section **9.1.2**) will have a documented aortic annulus size of ≥21mm and ≤27mm based on pre-procedure diagnostic imaging (see **Table 5.1-1**). Subjects in the ACURATE Prime XL Nested Registry (Section **9.1.3**) will have a documented aortic annulus size of ≥26.5mm and ≤29mm based on pre-procedure diagnostic imaging (see **Table 5.1-1**). Subjects in the Extended Durability Study (Section **9.1.4**) and the Continued Access Study (Section **9.1.5**) will have a documented aortic annulus size of ≥20.5mm and ≤29mm based on pre-procedure diagnostic imaging (see **Table 5.1-2**).	
			Section 7.3 Justification for the Study Design	There will be up to ~~1720~~ 2820 subjects total in ACURATE IDE… In order to support… and enrolled in the Main Randomized Cohort, ~~and~~ 50 subjects will be enrolled in the ACURATE Prime XL Nested Registry at a subset of U.S. centers, a minimum of 100 subjects will be randomized in the Extended Durability Study, and up to 1000 subjects will be enrolled in the ACURATE Continued Access Study… and ≥ 35% low risk subjects enrolled in the Main Randomized Cohort.	
			Section 8.2 Inclusion Criteria	**Table 8.2-1 ACURATE IDE Inclusion Criteria** IC2. Subject… size of ≥~~21~~ 20.5 mm… and, for the Main Randomized Cohort and Extended Durability Study, is deemed…	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 9.1.2 Main Randomized Cohort Subjects	For the Main Randomized Cohort, subjects…	
			Section 9.1.4 ACURATE Extended Durability Study Subjects	Subjects confirmed eligible for the ACURATE Extended Durability Study by the CRC (see Section **21.2**) and who provided written informed consent (see Section **20**) are considered enrolled in the study upon randomization.	
			Section 9.1.5 ACURATE Continued Access Study Subjects	For the ACURATE Continued Access Study, subjects confirmed eligible for the study by the CRC (see Section **21.2**) and who provided written informed consent (see Section **20**) are considered enrolled in the study as soon as an attempt is made to insert the test device into the subject's femoral artery.	
			Section 10.1 Data Collection	All subjects… Office/clinical/in-person or telehealth (https/telehealth.hhs.gov) follow-up… **Table 10.1-1:** Updated note *r* to clarify that after 5 years adverse events should be collected for both the test and control devices. Updated **Figure 10.1 1: Data Collection Schedule for ACURATE IDE**	
			Section 10.3 Informed Consent	**Note**: Centers may use remote consent as allowed by institutional policy and the center's IRB/REB/HREC/IEC.	Updated for clarity
			Section 10.7.2 ACURATE Transfemoral…	The DFUs/IFUs for the ACURATE Transfemoral Aortic Valve System should be followed. The commercially available 14F iSLEEVE~~A compatible~~ introducer sheath (see Section **5.1.3**) ~~should~~shall be prepared and placed in the subject's femoral artery as per the introducer DFU/IFU. ~~The commercially available LIS-S introducer or the commercially available 14F iSLEEVE introducer are is recommended for the ACURATE neo2 Transfemoral Aortic Valve System. Only the iSLEEVE introducer shall be used with the ACURATE Prime Transfemoral Delivery System XL (see Section 5.1.3).~~	Lotus Introducer Set is no longer on the market. The iSLEEVE has been fully tested with ACURATE *neo2* and ACURATE *Prime*.

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 11 **Statistical Considerations**	Full methods are described in the statistical analysis plan.	Updated for clarity
			Section 11.1 Statistical Considerations, Endpoints	The randomized data from the Main Randomized Cohort of the ACURATE IDE trial… Data will be summarized separately for subjects in the ACURATE Extended Durability Study. Descriptive statistics will be used to summarize these data and no statistical inference will be made. Data will be summarized separately for subjects in the single-arm ACURATE Continued Access Study. Descriptive statistics will be used to summarize these data and no statistical inference will be made.	Updated for clarity and added due to inclusion of the Extended Durability Study and the Continued Access Study
			Section 11.1.1.2 Sample Size Parameters for the Primary Endpoint – Main Randomized Cohort	• Analyses: One administrative, one formal interim, one final (see ***Note 5*** and ***Note 6*** below) ***Note 3:*** The estimated proportions of subjects in the Main Randomized Cohort by operative risk level ~~is~~are 10%... ***Note 5:*** The administrative… first 350 Main Randomized Cohort subjects… after enrollment in the Main Randomized Cohort is completed. This formal interim analysis will be conducted on the full N=1500 ~~randomized~~ subject cohort of the Main Randomized Cohort after the first 1050 ~~randomized~~ subjects in the Main Randomized Cohort have completed… ***Note 6:*** Analyses of the Extended Durability Study and the ACURATE CAS are not expected to occur when the formal interim analysis is performed on the Main Randomized Cohort. See Section **11.1.2** below for information on analyses associated with the ACURATE *Prime* XL cohort.	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 11.1.1.3 Statistical… Endpoint – Main Randomized Cohort	For the Main Randomized Cohort…	
			Section 11.1.3 Baseline Comparability	Baseline data will be summarized by treatment group for the randomized subjects (Main Randomized Cohort and Extended Durability Study) and separately for the Roll-In, ACURATE Prime XL Nested Registry, and CAS subjects… No formal statistical testing will be done for the Roll-In, Extended Durability Study, or ACURATE CAS subjects.	
			Section 11.1.4 Post-procedure Measurements	Post-procedure information… for randomized subjects (Main Randomized Cohort and Extended Durability Study), differences between… No formal statistical testing will be done for the Roll-In, Extended Durability Study, or ACURATE CAS subjects. Please see Section **11.1.1.1** and Section **11.1.2**, respectively, regarding statistical testing for the Main Randomized Cohort and the ACURATE Prime XL Nested Registry.	
			Section 11.2.1 Analysis Sets	Subjects in the randomized cohorts (Main Randomized Cohort and Extended Durability Study) are considered enrolled… With the Roll-In, ACURATE Prime™ XL Nested Registry, and ACURATE CAS cohorts, the subject is considered enrolled… For the Main Randomized Cohort…	
			Section 11.2.4 Randomization Scheme	For the Main Randomized Cohort and Extended Durability Study, a computer-generated list… treatment in a 1:1 ratio of ACURATE ~~*neo2*~~ to Control.	
			Section 11.2.5 Reporting Events	For all subjects in the ACURATE IDE Roll-In, ACURATE Prime™ XL Nested Registry, and ACURATE CAS cohorts, all events that occur from the time of enrollment will be reported. For all subjects in the ACURATE IDE randomized cohorts (Main Randomized Cohort and Extended Durability Study), events…	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 11.3.2 Interim/ Administrative Analyses	… when the first 350 subjects in the Main Randomized Cohort have completed 1-year… The formal interim analysis will be carried out after enrollment in the Main Randomized Cohort is completed (see ***Note 1*** below). This formal interim analysis will be conducted on ~~the full~~ all (N=1500) Main Randomized Cohort subjects after the first 1050 Main Randomized Cohort subjects have completed… A final analysis will be performed on all subjects in the Main Randomized Cohort with… ***Note 1:*** Analyses of the Extended Durability Study and the ACURATE CAS are not expected to occur when the formal interim analysis is performed on the Main Randomized Cohort. See Section **11.1.2** for information on analyses associated with the ACURATE *Prime* XL cohort.	
			Section 11.3.3 Subgroup Analyses for Main Randomized Cohort Subjects	Primary and pre-specified additional endpoints will be summarized for the following subgroups of the Main Randomized Cohort ~~subjects~~ as described…	Updated for clarity
			Section 11.3.4 Justification of Pooling	Analyses for the primary endpoint in the Main Randomized Cohort will be presented…	
			Section 11.3.5 Multivariable Analyses	… assess the effect of potential predictors on the primary endpoint in the Main Randomized Cohort as described…	
			Section 16.4.2 Training with the Investigational…	***Note 3:*** Centers ~~selected to participate in the ACURATE Prime XL Nested Registry~~ will receive…	

Table 26.1-1: Revision History

Revision Version	Protocol Date	Template Number and Version	Protocol Sections Modified	Summary of Changes	Justification for Changes
			Section 18.1 Anticipated Risks…	**Table 18.1 1**: Risks Associated with Transcatheter Aortic Valve Replacement – Added Radiation injury	
			Section 20. Informed Consent	**Note:** Centers may use remote consent as allowed by institutional policy and the center's IRB/REB/HREC/IEC.	
			Section 26.1 Summary of Protocol Revision History	Updated **Table 26.1-1** with revision history associated with protocol version M.	