Safety and Effectiveness of Edwards Lifesciences SAPIEN XT™ Transcatheter Heart Valve (THV) in the Chinese Population

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1. Study Synopsis

Title	Safety and Effectiveness of Edwards Lifesciences SAPIEN XT™ Transcatheter Heart Valve (THV) in the Chinese Population
Study Purpose	To evaluate the safety and effectiveness of the SAPIEN XT (Edwards Lifesciences, Irvine, California) transcatheter heart valve implantation (TAVI) in Chinese patients with symptomatic severe calcific aortic stenosis who are considered at high risk for surgical valve replacement.
Study Design	Prospective, single-arm, multi-center study. The study is expected to take 5.5 years to complete.
Study Device	Edwards SAPIEN XT™ Transcatheter Heart Valve and NovaFlex+ delivery system
Study Population	A maximum of 60 patients with symptomatic severe calcific aortic stenosis requiring transcatheter aortic valve implantation (TAVI), who are considered high risk for surgical valve replacement who receive a SAPIEN XT THV.
Inclusion Criteria	1. Subjects who are considered to be operable and high risk for surgical valve replacement: 8 ≤ STS Score ≤ 15 or 15 ≤ Logistic EuroSCORE ≤ 40. If STS score is below 8 and/or Logistic EuroSCORE is below 15, patients should have other clinical or anatomical risk factors that would be considered high risk for surgery and documented by the heart team 2. Severe symptomatic aortic stenosis requiring aortic valve replacement characterized by one or more of the following within 60 days prior to the index procedure: AVA < 0.8 cm^2, Indexed AVA <0.5 cm^2/m^2, mean gradient > 40mmHg, or peak aortic jet velocity > 4.0m/sec. [41] 3. NYHA Functional Class II or greater. 4. The study patient or the study patient's legal representative has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the EC of the respective clinical site. 5. The study patient agrees to comply with all required post-procedure follow-up visits. 6. Native aortic valve annulus area between 314 mm^2 - 660 mm^2 as measured by CT.

	7. Native aortic annulus diameter between 20 mm – 29 mm as measured by CT.
Exclusion Criteria	1. Evidence of an acute myocardial infarction ≤ 1 month (30 days) before the intended treatment [(defined as: Q wave MI, or non-Q wave MI with total CK elevation of CK-MB ≥ twice normal in the presence of MB elevation and/or troponin level elevation (WHO definition)]. 2. Aortic valve is a congenital unicuspid or is non-calcified. 3. Aortic valve is bicuspid and the patient is less than 60 years old, or the aortic valve is bicuspid with no raphe (Sievers classification type 0) [42] 4. Anomalous coronary artery that would interfere with proper placement of the valve. 5. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+). 6. Pre-existing mechanical or bioprosthetic valve in any position. 7. Any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days of the index procedure. Implantation of a permanent pacemaker or ICD is not considered exclusion criteria. 8. Any patient with a balloon valvuloplasty (BAV) within 30 days of the procedure (unless BAV is a bridge to procedure after a qualifying echocardiogram). 9. Leukopenia (WBC < 3000 cell/mL), acute anemia (Hgb < 9 g/dL), Thrombocytopenia (Plt < 50,000 cell/mL). 10. Renal insufficiency (creatinine > 3.0 mg/dL) and/or renal replacement therapy at the time of screening. 11. Untreated clinically significant coronary artery disease requiring revascularization. 12. Emergency interventional/surgical procedures within one month (30 days) prior to the TAVI procedure. 13. Hypertrophic cardiomyopathy with or without obstruction (HOCM). 14. Severe ventricular dysfunction with LVEF < 20%. 15. Echocardiographic evidence of intracardiac mass, thrombus or vegetation. 16. Active upper GI bleeding within 3 months (90 days) prior to procedure. 17. A known contraindication or hypersensitivity to all anticoagulation regimens, or inability to be anticoagulated for the study procedure.

	18. Stroke or transient ischemic attack (TIA) within 3 months (90 days) of the procedure. 19. Estimated life expectancy < 12 months (365 days) due to carcinomas, chronic liver disease, chronic renal disease or chronic end stage pulmonary disease. 20. Significant aortic disease, including marked tortuosity (hyperacute bend), aortic arch atheroma [especially if thick (> 5 mm), protruding or ulcerated] or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe "unfolding" and tortuosity of the thoracic aorta. 21. Iliofemoral vessel characteristics that would preclude safe placement of the introducer sheath. 22. Currently participating in an investigational drug or another device study. Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials. 23. Active bacterial endocarditis within 6 months (180 days) of procedure, with our without treatment.
Primary Endpoint	All-cause mortality at 30 days
Secondary Endpoints	Safety • Cardiovascular mortality at 30 days • Stroke at 30 days • TIA at 30 days • All-cause mortality & stroke at 30 days • Vascular complications (major) at 30 days • Bleeding complications (life threatening or disabling, and major) at 30 days • Myocardial infarction at 30 days • Acute kidney injury at 30 days (stages II and III) • Coronary obstruction requiring intervention at 30 days • Permanent pacemaker implantation at 30 days Device Success • Absence of procedural mortality AND • Correct positioning of a single prosthetic heart valve into the proper anatomic location AND • Intended performance of the prosthetic heart valve (no prosthesis-patient mismatch and mean aortic valve

	gradient <20mmHg or peak velocity <3m/s, AND no moderate or severe prosthetic valve regurgitation) at 30 Days Efficacy • New York Heart Association (NYHA) Classification at 30 days • Hemodynamic valve performance evaluation by echocardiography for aortic valve stenosis and aortic valve regurgitation (paravalvular & central) at 30 Days as determined by Echo core lab
Patient Follow-up Schedule	Patients consented to trial and implanted with a SAPIEN XT THV will be assessed at Baseline, Peri- and Post-Procedure, Index Hospitalisation Discharge, and 30 Days, 6 Months, 1 Year, 2 Years, 3 Years, 4 Years and 5 Years post-procedure.
Study Duration	Subjects implanted with SAPIEN XT THV will be followed for 5 years after the procedure
Statistical Considerations	The sample size of 50-60 patients is determined per Chinese regulatory requirements and agreement for a regional study of a medical device already approved in other regions based on a well-designed prospective study.
Sponsor	Edwards Lifesciences LLC One Edwards Way Irvine, CA 92614 USA
Local Sponsor	Edwards (Shanghai) Medical Products Co. Ltd [redacted]
Sponsor Representative / Study Manager	[redacted] THV Clinical Project Manager Edwards Lifesciences Pty Ltd [redacted]
Principal Investigator	Prof Runlin GAO Fuwai Hospital [redacted]

	Beijing, China
Study Centers	Fuwai Hospital, CAMS&PUMC Beijing, China Prof Mai CHEN WestChina Hospital, Sichuan University Chengdu, China Prof Jianan WANG The Second Affiliated Hospital of Zhejiang University School of Medicine Hangzhou, China
Contract Research Organization (CRO)	[redacted]

2. Introduction

2.1 Study Purpose

The purpose of this trial is to evaluate the safety and effectiveness of the SAPIEN XT transcatheter heart valve implantation (TAVI) in Chinese patients with symptomatic severe calcific aortic stenosis who are considered at high risk for surgical valve replacement. Clinical data will be submitted for the purposes of obtaining Chinese regulatory approval.

2.2 Clinical Background

Prolonged average life expectancy has resulted in an aging population and consequently, an increase in the number of patients with acquired, calcific, severe, symptomatic aortic stenosis (AS). The standard of care therapy for patients suffering from severe AS is aortic valve replacement surgery (AVR). In the aged population, many patients are too sick to be operated or have co-morbidities that preclude the option for surgery [1].

AS is a progressive, debilitating and life-threatening disease if left untreated. Affected individuals are typically > 65 years of age. The pathology involves progressive calcification of the leaflet bodies which limits normal cusp opening during systole. Cellular aging and degeneration have been implicated in this form of the disease and diabetes mellitus and hypercholesterolemia are risk factors.

2.2.1 Disease Process

The pathophysiology of AS includes an increase in afterload, progressive hypertrophy of the left ventricle, and a decrease in systemic and coronary blood flow as consequences of valve obstruction. Typically, patients with AS are free from cardiovascular symptoms (e.g. angina, syncope and/or heart failure) until late in the course of the disease. However, once symptoms manifest, the prognosis is poor, especially when associated with congestive heart failure. Death in general, including sudden death, occurs primarily in symptomatic patients. Survival analyses have demonstrated that the interval from onset of symptoms to time of death is approximately two years in patients with heart failure, three years in those with syncope, and five years in those with angina [2]. Among symptomatic patients with moderate-to-severe AS treated medically, mortality rates after the onset of symptoms were approximately 25% at 1 year and 50% at 2 years and more than 50% of deaths were sudden [3].

Grading the severity of AS is based on a variety of hemodynamic and natural history data. According to the ACC/AHA guideline authors, AS is best described as a continuum. In patients with moderate-to-severe AS, valve area may decline up to 0.3 cm^2 per year and the systolic pressure gradient across the valve can increase by as much as 15-19 mmHg per year, with a higher rate of progression observed in elderly patients with coronary artery disease (CAD) and chronic renal insufficiency [4]. Relief of aortic valve obstruction typically results in an improvement of symptoms, hemodynamic parameters, and global left ventricle systolic function, as well as reversal of left ventricular hypertrophy [4,5].

2.2.2 Alternative Therapies/Techniques

Treatment options for patients suffering from symptomatic AS include palliation of symptoms without valve replacement (non-surgical standard therapy), surgical aortic valve replacement (AVR) or TAVI with another valve. Treatment options are determined by patient risk for morbidity or mortality after surgery and patient choice. Non-surgical treatment options including balloon aortic valvuloplasty have been demonstrated to lead to shortened life expectancies and poor quality of life [6-8]. Patients considered poor candidates for AVR typically present with significant morbidities or anatomic limitations, such as severely calcified aorta, chest wall radiation, etc. [9]. Also a state of frailty may lead to a patient or physician decision to forego surgery. AVR has been demonstrated to have excellent long term outcomes for patients with aortic valve stenosis, including patients who were operable but had predicted high risk for surgery (by STS PROM > 10) [10-15].

Transcatheter aortic valve implantation (TAVI) was first performed in man in 2002 and was followed by European commercialization in 2007 [16-18]. Today more than 160,000 patients worldwide have undergone TAVI and there is a proliferation of published literature supporting

the safety and performance of the SAPIEN balloon expandable heart valve (SAPIEN, SAPIEN XT, and SAPIEN 3). The Edwards THV clinical research program includes more than 15,000 patients enrolled in approximately 23 clinical studies which include first-in-man, feasibility, pivotal randomized controlled trials and post-market registries. Results from these trials have been publicly reported in the scientific congresses and journals [19-34].

The PARTNER (I) trial was the first of its kind to randomize patients to THV versus the current standard of care, and has produced the most conclusive evidence of the safety and effectiveness of the Edwards SAPIEN THV in both high risk surgical (Cohort A) and inoperable patients with symptomatic aortic stenosis (Cohort B). Cohort B randomized patients between medical therapy and transfemoral (TF) TAVI. The one-year results for survival and functional improvements in both New York Heart Association (NYHA) class and Quality of Life indices indicated that TAVI should be the new standard of treatment for patients with severe AS considered to be at too high a risk to undergo surgical AVR [24, 35]. Recent results support the sustained benefit up to five years post TAVI [19, 21, 36].

The Cohort A randomized TAVI to AVR in patients who were considered at high operative risk for surgery based on the STS score [37]. While peri-procedural stroke rates were higher in the TAVI arm (3.8% vs. 2.1% [p=0.20]), the overall composite endpoint of all-cause mortality or stroke at 1 year was not different between the two arms (24.2% for TAVI vs. 26.8% for AVR (difference -2.6%, 95% upper confidence limit 3.0%, pre-defined margin 7.5%; p = 0.001 for non-inferiority). Moreover, despite the initial higher 30-day stroke rate in the TAVI arm, the mortality at 30 days was numerically lower in the TAVI arm (3.4% vs. 6.5% for TAVI and AVR, respectively). This difference did not reach statistical significance, however (p=0.07). Major vascular complications were more frequent after TAVI (11.0% vs. 3.2%, P<0.001), whereas major bleeding (9.3% vs. 19.5%, P<0.001) and new-onset atrial fibrillation (8.6% vs. 16.0%, P<0.001) were more frequent after AVR. Both NYHA Class and Quality of Life index improvements favoured TAVI at 30 days, but were similar after 1 year. Paravalvular aortic regurgitation (PAR) was more frequent after TAVI than AVR (P<0.001), and a late association between residual PAR and mortality has been subsequently revealed [21].

Three year data demonstrate sustained benefits for aortic valve replacement in both the TAVI and AVR arms with the SAPIEN valve demonstrating a sustained durability similar to surgical bioprostheses with no differences in long term mortality (44.2 vs. 44.8%, for TAVI vs. AVR, respectively)[38].

Conclusions from the first randomized Edwards SAPIEN THV studies indicate that balloon expandable TAVI should be recognized as the standard of care for inoperable patients and is an

acceptable alternative to AVR in high risk patients. Also reported were significant outcomes related to the study device versus standard therapy control, such as stroke, major vascular complications and major bleeding events which had significant impact on overall mortality. These findings were consistent with earlier published reports. Despite the high-risk nature of the population studied, it is a widely held belief that design improvements in the profile and ease of use of the delivery system may reduce procedure-related adverse events and thus support expansion of the study population to include patients previously excluded due to anatomical limitations. Two year data from the SOURCE XT post-approval study of the SAPIEN XT demonstrate similar long-term performance to the SAPIEN valve [39], with more favourable long-term survival for patients presenting with few comorbidities at baseline. The SAPIEN 3 is the most recent SAPIEN THV to obtain the CE Mark (January 2014). The SAPIEN 3 has been designed to be placed via a fully percutaneous TF approach using the Edwards Expandable Sheath ("eSheath"), and its TF delivery has demonstrated the lowest rates of death, stroke, and major vascular complications (2.1, 1.0 and 4.2%, respectively) for any SAPIEN THV [40].
The robust body of consistently improving clinical evidence presented by Edwards SAPIEN transcatheter valve platforms attests to the Edwards history of leadership in heart valve bioprosthesis technology.

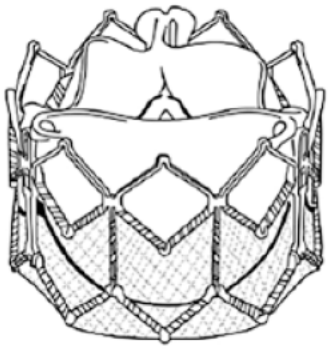
3. Study Device

3.1 SAPIEN XT Transcatheter Heart Valve

The Edwards SAPIEN XT Transcatheter Heart Valve (Figure 1) is indicated for use in patients with severe, symptomatic, calcified aortic stenosis.

The Edwards SAPIEN XT transcatheter heart valve (THV) is comprised of a balloon-expandable, radiopaque, nickel cobalt chromium frame, trileaflet bovine pericardial tissue valve, and polyethylene terephthalate (PET) fabric skirt. It is treated according to the Edwards ThermaFix process, and is packaged and terminally sterilized in glutaraldehyde.

Figure 1 SAPIEN XT Transcatheter Heart Valve (THV)



23mm and 26mm SAPIEN XT THV

29mm SAPIEN XT THV

The THV is intended to be implanted in a native annulus size range comparable to the following measurements:

Table 1 SAPIEN XT Annulus and Valve Sizing

Native Valve Annulus Size (TEE)	Native Valve Annulus size (CT)		THV size
	Area	Area Derived Diameter	
18-22mm	314-415 mm^2	20-23 mm	23 mm
21-25mm	415-530 mm^2	23-26 mm	26 mm
24-27mm	530-660 mm^2	26-29 mm	29 mm

3.1.1 NovaFlex+ Delivery System

The NovaFlex+ delivery system includes a handle that provides a Flex Wheel for articulation of the Flex Catheter, a tapered tip at the distal end of the delivery system to facilitate crossing the native valve, and a Balloon Catheter for deployment of the THV. The handle contains a Flex Indicator that shows whether or not the Flex Catheter is articulated, a Valve Alignment Wheel for fine adjustment of the THV during Valve Alignment, a Press/Release Button that enables movement between handle positions, and a flush port to flush the Flex Catheter. A stylet is included within the guidewire lumen of the delivery system. The Balloon Catheter has radiopaque Valve Alignment Markers defining the Valve Alignment Position and the working length of the balloon. A radiopaque Double Marker proximal to the balloon indicates the Flex Catheter position during deployment.

Table 2 SAPIEN XT THV NovaFlex+ Kit

Product Name	23mm System (9355NF23)	26mm System (9355NF26)	29mm System (9355NF29)
	Model/REF		
NovaFlex+ Kit, compromised of the following:			

Edwards SAPIEN XT Transcatheter Heart Valve	9300TFX (23mm)	9300TFX (26mm)	9300TFX (29mm)
NovaFlex+ Delivery System[1]	9355FS23	9355FS26	9355FS29
Edwards Expandable Introducer Sheath Set ("eSheath")	916ES23	918ES26	920ES29
RetroFlex Dilator Kit	9100DKS		
Edwards Transfemoral Balloon Catheter	9350BC20	9350BC23	9350BC25
Crimper	9350CR		
Inflation Devices (x2)			
[1]Includes the Qualcrimp Crimping Accessory, and 2-piece Crimp Stopper			

3.1.2 Expandable Introducer Sheath Set

The Edwards eSheath Introducer Set is intended for introduction of interventional devices in the vascular system. The product is intended for use by physicians trained and experienced in interventional techniques. Standard techniques for placement of vascular access sheaths should be employed.

3.1.3 Edwards Transfemoral Balloon Catheter

The balloon catheter is indicated for dilation of stenotic native aortic valve leaflets.

3.1.4 RetroFlex Dilator Kit

The RetroFlex dilator kit contains a set of four hydrophilically coated tapered dilators used for arterial dilatation.

3.1.5 Crimper

The crimper reduces the diameter of the THV to mount it to the delivery system. The crimper is comprised of a compression mechanism that is closed with a handle located on the housing. The crimper includes a 2-piece Crimp Stopper (packaged with the delivery system) used to correctly crimp the THV.

3.1.6 Qualcrimp

The Qualcrimp crimping accessory (packaged with the NovaFlex+ delivery system) is used during crimping of the THV.

3.1.7 Inflation Devices

Inflation devices with a locking mechanism are used during native valve predilation and THV deployment.

3.2 Instructions for Use (IFU)

These devices must always be used according to the current IFU provided with each product

4. Study Objective

The objective of the study is to evaluate the safety and effectiveness of the SAPIEN XT transcatheter heart valve implantation in Chinese patients with symptomatic severe calcific aortic stenosis who are considered at high risk for surgical valve replacement.

4.1 Primary Endpoint

The primary endpoint is all-cause mortality at 30 days post-index procedure.

4.2 Secondary Endpoints

Safety

- Cardiovascular mortality at 30 days
- Stroke at 30 days
- TIA at 30 days
- All-cause mortality & stroke at 30 days
- Vascular complications (major) at 30 days
- Bleeding complications (life threatening or disabling, and major) at 30 days
- Myocardial infarction at 30 days
- Acute kidney injury at 30 days (stages II and III)
- Coronary obstruction requiring intervention at 30 days
- Permanent pacemaker implantation at 30 days

Device Success

- Absence of procedural mortality AND
- Correct positioning of a single prosthetic heart valve into the proper anatomic location AND
- Intended performance of the prosthetic heart valve (no prosthesis-patient mismatch and mean aortic valve gradient <20mmHg or peak velocity <3m/s, AND no moderate or severe prosthetic valve regurgitation) at 30 Days

Efficacy

- New York Heart Association (NYHA) Classification at 30 days
- Hemodynamic valve performance evaluation by echocardiography for aortic valve stenosis and aortic valve regurgitation (paravalvular & central) at 30 Days as determined by Echo core lab

5. Patient Population

To ensure that a minimum of 50 patients are implanted with the SAPIEN XT THV and complete the 30 Day follow-up for Primary Endpoint, up to 60 patients will be enrolled and implanted with SAPIEN XT THV. Each site may not contribute more than 30 implanted patients to the study population. All patients will be followed for 5 years.

Enrolment will be closely monitored to ensure not more than 60 patients are implanted with SAPIEN XT THV.

5.1 Inclusion Criteria

Patients must meet all of the Inclusion Criteria in order to participate in the study

1. Subjects who are considered to be operable and high risk for surgical valve replacement: 8 ≤ STS Score ≤ 15 or 15 ≤ Logistic EuroSCORE ≤ 40. If STS score is below 8 and/or Logistic EuroSCORE is below 15, patients should have other clinical or anatomical risk factors that would be considered high risk for surgery and documented by the heart team
2. Severe symptomatic aortic stenosis requiring aortic valve replacement characterized by one or more of the following within 60 days prior to the index procedure: AVA < 0.8 cm^2, Indexed AVA <0.5 cm^2/m^2, mean gradient > 40mmHg, or peak aortic jet velocity > 4.0m/sec. [41]
3. NYHA Functional Class II or greater.
4. The study patient or the study patient's legal representative has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the EC of the respective clinical site.
5. The study patient agrees to comply with all required post-procedure follow-up visits.
6. Native aortic valve annulus area between 314 mm^2 - 660 mm^2 as measured by CT.
7. Native aortic annulus diameter between 20 mm – 29 mm as measured by CT.

5.2 Exclusion Criteria

Patients must not meet any of the Exclusion Criteria in order participate in the study

1. Evidence of an acute myocardial infarction ≤ 1 month (30 days) before the intended treatment [(defined as: Q wave MI, or non-Q wave MI with total CK elevation of CK-MB ≥ twice normal in the presence of MB elevation and/or troponin level elevation (WHO definition)].
2. Aortic valve is a congenital unicuspid or is non-calcified.
3. Aortic valve is bicuspid and the patient is less than 60 years old, or the aortic valve is bicuspid with no raphe (Sievers classification type 0) [42]
4. Anomalous coronary artery that would interfere with proper placement of the valve.
5. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).

6. Pre-existing mechanical or bioprosthetic valve in any position.
7. Any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days of the index procedure. Implantation of a permanent pacemaker or ICD is not considered exclusion criteria.
8. Any patient with a balloon valvuloplasty (BAV) within 30 days of the procedure (unless BAV is a bridge to procedure after a qualifying echocardiogram).
9. Leukopenia (WBC < 3000 cell/mL), acute anemia (Hgb < 9 g/dL), Thrombocytopenia (Plt < 50,000 cell/mL).
10. Renal insufficiency (creatinine > 3.0 mg/dL) and/or renal replacement therapy at the time of screening.
11. Untreated clinically significant coronary artery disease requiring revascularization.
12. Emergency interventional/surgical procedures within one month (30 days) prior to the TAVI procedure.
13. Hypertrophic cardiomyopathy with or without obstruction (HOCM).
14. Severe ventricular dysfunction with LVEF < 20%.
15. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
16. Active upper GI bleeding within 3 months (90 days) prior to procedure.
17. A known contraindication or hypersensitivity to all anticoagulation regimens, or inability to be anticoagulated for the study procedure.
18. Stroke or transient ischemic attack (TIA) within 3 months (90 days) of the procedure.
19. Estimated life expectancy < 12 months (365 days) due to carcinomas, chronic liver disease, chronic renal disease or chronic end stage pulmonary disease.
20. Significant aortic disease, including marked tortuosity (hyperacute bend), aortic arch atheroma [especially if thick (> 5 mm), protruding or ulcerated] or narrowing (especially with calcification and surface irregularities) of the abdominal or thoracic aorta, severe “unfolding” and tortuosity of the thoracic aorta.
21. Iliofemoral vessel characteristics that would preclude safe placement of the introducer sheath.
22. Currently participating in an investigational drug or another device study. Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.
23. Active bacterial endocarditis within 6 months (180 days) of procedure, with our without treatment.

6. Investigation Plan

6.1 Study Design

This is a prospective, single-arm, multi-center study to assess the safety and effectiveness of the SAPIEN XT THV. Up to 60 patients will be enrolled and implanted with the device at three sites in China over an estimated six month enrolment period with a follow-up period to 5 years.

An Echocardiography Core Lab will be established for standardizing echocardiographic secondary endpoints. A Medical Reviewer will review all endpoint-related adverse events.

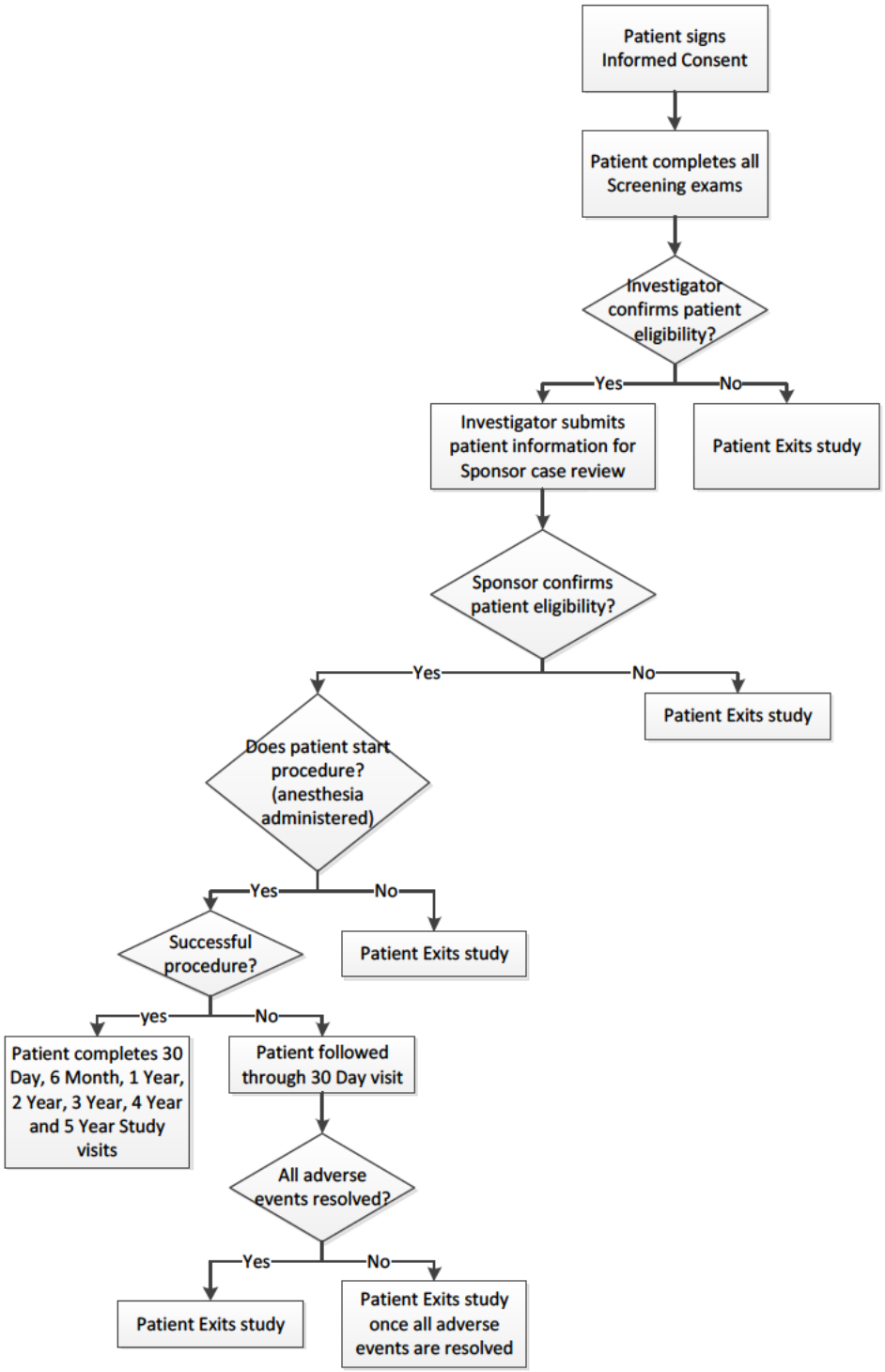
6.2 Study Compliance and Regulations

The SAPIEN XT THV System is not commercially available in China. The clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (as updated in Fortaleza Brazil in 2013) and in compliance with China's Good Clinical Practice (GCP) for Medical Devices and any national regulations. The clinical investigation plan and Patient Informed Consent form used to study the SAPIEN XT THV System must be reviewed and approved by the appropriate national authority and local or regional Ethics Committee (EC) where the clinical investigation is to be conducted before enrolment of patients may begin. Any additional requirements imposed by the EC or regulatory authority shall be followed.

Changes to the investigational plan that may increase the risk or present new risks to the patient must be approved in writing by Edwards Lifesciences and the EC before the change is implemented.

6.3 Study Procedures

Figure 2 Trial Process Diagram



6.3.1 Informed Consent

The Patient Informed Consent Form must be approved by Edwards Lifesciences and the site's EC.

The study investigator(s) and support staff will approach patients with symptomatic aortic stenosis to assess their interest in participating in the study. They will provide an overview of the study and device, including the background, benefits, risks, and study procedures. If patients are interested in participating in the study, then they will be provided with the full Patient Informed Consent Form document. Patients will be allowed to read the document in its entirety, and then delegated study personnel will answer all of their questions. If the patient is comfortable with proceeding, then they will be asked to sign and date the Patient Informed Consent Form. Informed consent must be obtained prior to the screening procedures or baseline tests that are specific to this study.

During the course of the study, if new information becomes available that can affect a patient's future health and medical care, then the information will be provided to the patient and the process documented. If relevant, all affected patients will be asked to confirm their continuing informed consent in writing.

All patients who sign a Patient Informed Consent Form should be entered in the database. Data should not be entered until a Patient Informed Consent Form is signed. Patients that are screened and do sign a Patient Informed Consent Form should be documented on the Screening Log.

6.3.2 Patient Screening and Enrolment

The study site shall have a committed Heart Team involved in the screening process. The Heart Team will include at least two cardiac surgeon, one interventional cardiologist, one radiologist, and one anesthesiologist but could also include (without being limited to) the following specialties:

- Echocardiography
- Gerontology

The screening of patients in cardiovascular and cardiac surgery departments will be conducted by one or more delegated study team members. The study team will be responsible for ensuring and reporting study patient screening for study eligibility. Cumulative screening and enrollment logs will be maintained by study sites. Reasons for screen failures will be documented in study logs.

To accommodate the implant procedure learning curve, a roll-in strategy will be available. Each study site will be allowed up to two roll-in patients. Edwards Lifesciences will document if the

patient is a roll-in patient before the implant procedure begins. Roll-in patients will complete all study visits and procedures, and not be counted toward the 60 implanted patients.

In addition, the Heart Team will be required to assess all patients for study inclusion to ensure compliance to surgical risk criteria, screening procedures to assess valve size and delivery method, and other inclusion/exclusion criteria. After heart team identifies a patient, the Sponsor will review and confirm eligibility during the case review process.

All patients who sign a study informed consent will be entered into the database. Subjects will be included in analysis of the trial if an Edwards' investigational device is inserted into the patient. Only patients that leave the procedure room with a SAPIEN XT THV in place will be counted toward the 60 implanted patients.

6.3.3 Study Procedures

The Study Visit Schedule is outlined in Table 4 for enrolled subjects for the duration of the study from Screening and Baseline through the 30 Day visit (Primary Endpoint) and 5 year follow-up visits.

Table 3 Study Visit Schedule

	Screening	Baseline (≤30 days of procedure)	Procedure	Post-Procedure (Within 48 hours)	Discharge	30 Day Follow-Up (+14 days)	6 Month (+/-30 days)	1 Year (+/-60 days)	2-5 Years (+/-60 days)
Informed Consent	X								
Medical History	X								
Physical Exam	X				X	X		X	X
CSS Angina	X				X	X		X	X
NYHA Classification	X				X	X		X	X
STS Risk Score, Logistic EuroSCORE, and EuroSCORE II	X								
Operability Risk Assessment	X								
Cardiac Medications		X	X	X	X	X	X	X	X
Adverse Event Assessment[1]			X	X	X	X	X	X	X

Frailty Assessment		X							
NIH Stroke Scale		X[2]		X[2]	X[2]	X[2]			
Modified Rankin Scale		X[2]		X[2]	X[2]	X[2]			
Six Minute Walk Test (6MWT)		X				X			
Labs									
Hemoglobin, Hematocrit, Platelet Count and White Blood Cells		X		X	X	X			
PTT or PT/INR		X		X	X				
CK/CK-MB and/or Troponins		X[3]		X[4]		X			
Creatinine		X		X	X	X			
Liver Panel (ALT, AST)		X							
Albumin		X				X			
Non-Invasive Tests									
ECG		X		X	X	X		X	
Chest X-ray		X							
Transthoracic Echocardiogram (TTE)[6]	X				X	X		X	X
Fluoroscopic imaging implanted valve			X			X[5]		X[5]	X[5]
Invasive Tests									
CT Thoracic/Abdomen with visualization of iliac and femoral arteries	X								
Cardiac Catheterization or CT angiogram	X								
Supra-aortic Angiogram or (TEE)	X		X						
Invasive hemodynamics			X						

[1] Collection of adverse events begins when the patient starts the procedure. This is defined as when anesthesia is first administered

[2]A neurologist or a neurology fellow will assess patients at Baseline, Post Procedure and Discharge. If the neurologist or neurology fellow is not available at the time of patient's baseline or discharge visit, a certified team member may perform the tests. A neurologist or neurology fellow must perform the Post Procedure assessment.

[3] Baseline CK/CKMB and/or Troponins are required ≤ 72 hours before the procedure.

[4]Post Procedure CK/CKMB and/or Troponins are required at 3 different time intervals: 1) the first lab draw post procedure (within 8 hours of exiting the cath lab or operating room) 2) the second lab draw 6 – 8 hours after the first lab draw 3) the third lab draw 6 – 8 hours after the second lab draw.

[5]For patients with abnormal findings related to valve integrity and position and patients with Adverse Events related to worsening valve function.

[6]Transesophogeal Echocardiogram (TEE) may be used if TTE is not available

6.3.3.1 Screening

The following screening data will be collected for all study patients to assess eligibility as per standard of care:

- Operability Risk Assessment
- Medical history, pertinent physical examination [include blood pressure, height, weight and all major systems findings]
- NYHA functional classification
- CSS Angina classification
- Risk assessment (STS Risk Score, Logistic EuroSCORE, and EuroSCORE II)

Non-Invasive Studies (must be completed within 60 days before procedure date)

- Comprehensive transthoracic echocardiogram (TTE) (transesophageal echocardiogram (TEE) may be used as an alternative)

Invasive Studies (must be completed before the procedure date)

- Cardiac and abdominal CT angiogram with visualization of the aortic arch, both iliac and femoral arteries to the aorta. In the situation where patients have compromised renal function that precludes the use of contrast agents, MR imaging may be used as an alternative to CT (≤180 days before procedure)
- Left heart catheterization to assess the severity of aortic stenosis and severity of coronary artery disease (≤180 days before procedure)

If any assessments need to be completed or repeated outside of standard of care, a patient will need to sign a Patient Informed Consent prior to completing assessments.

6.3.3.2 Baseline

Assessments and laboratory tests are required to be completed within 30 days prior to the procedure date. Assessments and laboratory tests completed outside of the 30 days will need to be repeated. If completed outside of standard of care, then a Patient Informed Consent Form will need to be signed first.

The following Baseline data will be collected for all study patients prior to procedure:

- Current cardiac medications and all medications given for cardiovascular effect;
- Neurological assessment (Appendix A)
    - NIHSS
    - MRS
- Frailty Assessment (Appendix B)

- Six Minute Walk Test (Appendix C)
- Clinical Laboratory Tests
    - Blood count (hemoglobin, hematocrit, platelet count, white blood cells)
    - PTT or PT/INR
    - CK/CK-MB and/or Troponins
    - Creatinine
    - Liver Panel (ALT, AST)
    - Albumin
- Non-invasive studies
    - 12-Lead ECG
    - Chest x-ray
- Adverse Event Assessment

6.3.3.3 Procedure

Transfemoral access technique will be used by the investigator in his/her normal practice of interventional cardiology and patient selection process.

6.3.3.3.1 Recommended Antiplatelet/Anticoagulation Regimen

Table 5 outlines the recommended antiplatelet regimen. The categories were developed by The PARTNER II Trial Patient and Procedure Management Steering Committee. There are no current validated guidelines in this specific study population, however, the literature was surveyed and used as guidance for the following proposed guidelines. It is expected that specific agents and dosing regimens may vary from site to site. Patients will be assessed by the heart team for Category of Stroke Risk prior to prescribing treatment regimen. The Category and specific treatment regimen will be documented in the discharge case report form. Committee Categories are based on CHADS 2 score for stroke risk [40].

NOTE: The CHADS 2 score only applies to patients in atrial fibrillation (AF) and has not been validated in non-AF patient populations; therefore the CHADS 2 score reference was used as one among many guidelines to establish the risk stratification for intensity of anticoagulation regimen.

Table 4 Summary of Recommended Antiplatelet/Anticoagulation Therapy

Pre procedure	Aspirin 75-100 mg once daily • Patients with bare metal stent (BMS) within one month or drug eluting stent (DES) within 12 months should be continued on Clopidogrel/Prasugrel prior to their procedure • Patients in atrial fibrillation on warfarin should be bridged with

	LMW or UF heparin prior to the procedure • Patients with persistent or paroxysmal atrial fibrillation, not on anticoagulation, will not be required to have a TEE to rule out LA thrombus prior to procedure. If intra-procedural TEE during TAVI reveals thrombus, procedure will be aborted and delayed until patient has been on warfarin or dabigatran for 30 days. • In patients under concomitant TAVI/PCI, Clopidogrel loading with either 300mg or 600mg prior to the procedure is recommended in addition to ASA:
Intra procedure	Heparin will be given to achieve/ maintain ACT≥250 sec.
Post procedure	
Category I for Stroke Risk No atrial fibrillation, No recent stents	• ASA 75mg once daily • Clopidogrel 300mg load within 6 hours of procedure (either pre or post) • Clopidogrel 75mg once daily for at least one month post procedure
Category II for Stroke Risk No atrial fibrillation, recent stents	• ASA 75mg once daily • Clopidogrel 75mg once daily should be continued prior to the procedure and after the procedure without interruption for at least one month after BMS and 12 months after DES
Category III for Stroke Risk Atrial fibrillation, no recent stents	• ASA 75mg once daily • Patients should be started on warfarin or dabigatran 24 hours post TAVI if clinically safe and this should be continued for at least one month or indefinitely if possible. If clinically safe, patients started on warfarin should be bridged with unfractionated or low molecular weight heparin until INR therapeutic. • If patients are not a candidate for warfarin or dabigatran, Clopidogrel 75mg once daily can be considered as an alternative
Category IV for Stroke Risk Atrial fibrillation, recent stents	• ASA 75mg once daily • Clopidogrel 75mg once daily for at least one month post BMS or 12 months post DES • Patients should be started on warfarin or dabigatran 24 hours post TAVI if clinically safe and continued indefinitely. If

	clinically safe, patient's being started on warfarin should be bridged with UF or LMW heparin until INR therapeutic.

Note: Any changes to anticoagulation regimen from study visit to study visit will be noted on the CRF including reason for change.

6.3.3.3.2 Antibiotic Prophylaxis

Study subjects should be treated prophylactically with antibiotics for endocarditis per the recommendations of the American Heart Association [43].

6.3.3.3.3 Procedure Assessments

Procedural information, findings, results, and SAPIEN XT delivery system and device identification will be recorded on the Case Report Form and are listed below:

- Duration of the procedure, defined as the time from skin incision to access closure;
- All cardiac medications and all medications given for cardiovascular effect;
- A supra-aortic angiogram or TEE to assess valve performance and coronary patency
- Fluoroscopic imaging of implanted valve to assess acute deployment (e.g. proper annular placement, fully vs. under deployed, circularity/ovality)
- Contrast media quantity
- Total fluoroscopy time and dose
- Adverse events

Subjects will be continuously monitored clinically, hemodynamically, and electrocardiographically during the index procedure for all local and systemic side-effects.

It is recommended subjects are monitored in the operating room for at least 15 minutes after completion of the procedure, with special attention to hemodynamic condition and cardiac rhythm. The sheaths may be removed when ACTs reach <150 sec after implantation of the study valve (for non-surgical closures).

6.3.3.4 Post-Procedure

Post-procedure clinical evaluations should be performed within 48 hours of the index procedure. Specific assessments include the following:

- Current cardiac medications and all medications given for cardiovascular effect
- Adverse events
- Neurological assessment
    - NIHSS
    - MRS

- Clinical Laboratory Test
  - Blood count (hemoglobin, hematocrit, platelet count, white blood cells)
  - PTT or PT/INR
  - CK/CK-MB and/or Troponins
  - Creatinine
- 12-Lead ECG

6.3.3.5 Discharge Visit

The following data will be collected for all study patients before discharge from the index hospitalization. If patient is discharged over a weekend, the discharge tests may be completed on the last weekday prior to discharge. For patients that are discharged within the 48 hours of exiting the cath lab / operating room, it is not required to repeat tests collected during the Post Procedure period that are also required for the Discharge visit.

- Pertinent physical examination [include blood pressure, weight and all major systems findings]
- Current cardiac medications and all medications given for cardiovascular effect
- NYHA functional classification
- CSS Angina Classification
- Adverse events
- Neurological assessments
  - NIHSS
  - MRS
- Clinical Laboratory Test
  - Blood count (hemoglobin, hematocrit, platelet count, white blood cells)
  - PTT or PT/INR
  - Creatinine
- 12-Lead ECG
- Comprehensive TTE. If not adequate, a TEE will be performed

6.3.3.6 Follow-Up Visits

The determination of the study endpoints will require rigorous clinical follow-up and quality data collection. The Investigator or delegated study personnel will ensure the patient is scheduled for follow-up visits according to Table 6.

Table 5 Follow-up Visit Windows.

Follow-Up Visit	Visit Window (days following Procedure)
30 Day	30 days, +14 days
6 Month	180 days +/-30 days

1 Year	365 days +/-60 days
2 Year	730 days +/-60 days
3 Year	1095 days +/-60 days
4 Year	1460 days +/-60 days
5 Year	1825 days +/-60 days

The importance of attending the 30 Day follow-up visit should be discussed with the patient. Planned absences should be recorded to facilitate continued ability to contact a study patient during the course of the study. If a patient cannot be reached for a follow-up visit, the investigator will document on the follow-up data form, the efforts undertaken to contact the patient, referring physicians, including internists as well as cardiologists, family members, or other alternate contacts noted in the study patient's records. These efforts should include 3 attempts of telephone contacts at separate dates and times, and a registered letter. If a patient can no longer be located, the investigator must contact an intermediary (e.g. patient's private physician) without delay.

Patients for whom the study procedure was begun but do not receive and retain the study valve will be followed up until the 30-day assessment or resolution of any AE for safety purposes. Patients with an ongoing AE at the 30 Day visit should have AEs reassessed at 30 day window closure (day 44). These patients should then be exited from the study. In the event that the patient's implanted valve is explanted, the patient needs to be followed up until resolution of any AE for safety purposes. These patients should then be exited from the study.

6.3.3.6.1 30-Day Visit

All patients will undergo the following assessments within the 30-Day follow-up period +14 days):

- Pertinent physical examination [include blood pressure, weight and all major systems findings]
- Adverse events
- Current cardiac medications and all medications given for cardiovascular effect
- NYHA functional classification
- CSS Angina Classification
- Neurological assessments
    - NIHSS
    - MRS
- 6 Minute Walk Test (6MWT)
- Clinical Laboratory Test
    - Blood count (hemoglobin, hematocrit, platelet count, white blood cells)
    - Creatinine

  - CK/CK-MB and/or troponins
  - Albumin
- 12-Lead ECG
- Comprehensive TTE. If not adequate, a TEE will be performed

For patients with abnormal findings related to valve integrity and position and patients with adverse events related to worsening valve function, fluoroscopic imaging of the implanted valve will be completed.

6.3.3.6.2 6 Month Visit

All patients will undergo the following assessments within the 6 Month follow-up period:

- Adverse events
- Current cardiac medications and all medications given for cardiovascular effect

The 6 month visit may be completed via a telephone conversation with a delegated study team member. The telephone call must be documented in the patient's study records.

6.3.3.6.3 1 Year Visit

All patients will undergo the following assessments within the 12 Month follow-up period:

- Pertinent physical examination [include blood pressure, weight and all major systems findings]
- Adverse events
- Current cardiac medications and all medications given for cardiovascular effect
- NYHA functional classification
- CSS Angina Classification
- 12-Lead ECG
- Comprehensive TTE. If not adequate, a TEE will be performed

For patients with abnormal findings related to valve integrity and position and patients with adverse events related to worsening valve function, fluoroscopic imaging of the implanted valve will be completed.

6.3.3.6.4 2-5 Year Annual Follow-up Visit

All patients will undergo the following assessments within the 2-5 Year annual follow-up period:

- Pertinent physical examination [include blood pressure, weight and all major systems findings]
- Adverse events
- Current cardiac medications and all medications given for cardiovascular effect

- NYHA functional classification
- CSS Angina Classification
- Comprehensive TTE. If not adequate, a TEE will be performed

For patients with abnormal findings related to valve integrity and position and patients with adverse events related to worsening valve function, fluoroscopic imaging of the implanted valve will be completed.

6.3.4 Missed Visits

Every patient should be encouraged to remain in the study until they have completed the protocol-required follow-up period. If the patient discontinues prematurely from the study, the reason for discontinuation must be documented on the appropriate case report form (CRF). Possible reasons for premature discontinuation may include, but are not limited to the following:

- Withdrawal of consent: Patient decides to withdraw from the study. If a subject withdraws from the clinical investigation, the reason(s) should be recorded. If such withdrawal is due to problems related to the investigational device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside the investigation.
- Lost to follow-up: All patients should be encouraged to return to the clinic for evaluation during follow-up (excluding 6 Month telephone visit). If a patient is unable to return to the clinic, 3 separate telephone calls should be made to attempt to bring the patient back into the clinic or obtain safety information. All attempts should be documented in the source documents. If the patient does not respond to the 3 telephone calls then the Investigator should send a certified letter to the subject.

6.3.5 Study Termination

The Sponsor has the right to discontinue a site or terminate the trial for the following reasons:

- The Sponsor may terminate the study for safety reasons
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product for any reason
- The Sponsor may decide to close a study site when the Investigator fails to enroll patients
- Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities
- Insufficient adherence to protocol requirements

- Submission of knowingly false information from the research facility to the Sponsor, the Sponsor's representatives or appropriate regulatory authorities

If the study is terminated early, all specified follow-up data on subjects enrolled prior to termination will be collected and reported

6.3.6 Standard of Care

All enrolled patients will receive the standard of care during the clinical trial as well as following the conclusion of their participation. Any patients with symptoms of valve failure at any time throughout the study duration should undergo standard diagnostic imaging (e.g. (TTE)) to assess valve function. Each patient will be provided with an implant card. This implant card can be carried by the patient to be shown to any clinician to inform a treating physician of the implanted SAPIEN XT THV. Subjects that are enrolled, but not treated with the SAPIEN XT THV will likely be screened for alternative treatments (when available) or continue with the care they have been receiving to date.

7. Study Material & Methods

7.1 Study Device

The SAPIEN XT and its delivery components will have a unique product identifier. This information will be recorded in the study subject's medical file. The Instructions for Use for the SAPIEN XT THV System are provided with the device.

7.2 Storage & Labeling

The SAPIEN XT THV System is to be stored as specified on the unit labels. All investigational stock will be stored in a secure and controlled area.

7.3 Device Accountability

The Investigator shall maintain accurate records of the receipt and disposition of the investigational devices. A device disposition log supplied by Edwards will be used to record device receipt, uses, discards, or returns. Device disposition will be verified by the Sponsor periodically throughout the study. All unused devices shall return to Edwards, along with the completed device disposition log at completion of the enrolment period. The Investigator's copy of the device disposition log must document the devices used in study subjects as well as unused devices that are returned to Edwards. Use of the SAPIEN XT THV System is prohibited outside of this protocol.

8. Evaluation of Safety

8.1 Adverse Event Assessments

Adverse events may be volunteered by patients, elicited from questioning by Investigator or delegated study personnel, or collected via observation by the Investigator. In addition, patients will be instructed to contact the investigator, and/or study coordinator if any significant adverse events (e.g., expanded safety composite events) occur between study evaluation visits.

Adverse event collection begins when the patient starts the procedure. This is defined as when anesthesia is first administered.

8.1.1 Investigator Assessment Responsibilities

The Investigator will determine if an adverse event is serious and not related, possibly related, or related to the device or procedure.

Pre-existing medical conditions or symptoms reported prior enrolment will be recorded in medical history form and will not be recorded as an adverse event. In the event there is a worsening in the pre-existing medical condition or symptoms after enrolment, then an adverse event will be recorded.

8.1.2 Sponsor Assessment Responsibilities

All adverse events will be reviewed by the Study Safety Officer who will determine if the adverse event is serious; anticipated or unanticipated; and not related, possibly related, or related to the device or procedure.

8.1.3 Medical Reviewer Responsibilities

All endpoint related adverse events will be reviewed by a Medical Reviewer who will determine if the adverse event is serious; and not related, possibly related, or related to the device or procedure.

8.2 Device Deficiency

Device deficiency is an inadequacy of a medical device with respect to its integrity, quality, durability, reliability, safety or performance. It includes malfunctions, user errors and inadequate labeling.

Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence:

a) If either suitable action had not been taken,
b) If intervention had not been made, or
c) If circumstances had been less fortunate.

Reporting conventions for device deficiencies that could result in a Serious Adverse Event (SAE) are the same as those for an actual SAE.

8.3 Adverse Event Reporting

All adverse events are reported from the start of the procedure, which is defined as when anesthesia is firsts administered, and are reported until subject participation has ended (i.e. completion of the study or withdrawal of consent). Adverse events must be reviewed at every follow-up visit until resolution, AE has stabilized (according to Investigator), or the study has been completed. Should the adverse event be ongoing at time of study completion, the database should be updated to reflect status.

Reporting guidelines for adverse events:

- Record the number of units of blood needed for any transfusion associated with any overt bleeding event
- Failure of a percutaneous closure device shall be reported as an access site vascular closure device complication
- Vascular complications shall be designated as access or non-access related;

8.4 SAE and USADE Reporting

All Serious Adverse Events (SAE) and Unanticipated Serious Adverse Device Effect (USADE) must be reported to Edwards Lifesciences within 24 hours of the Investigator or delegated study personnel becoming aware of the event or according to local regulations (whatever is most stringent). SAEs and USADEs will be reported to the EC and regulatory authorities as required by national regulations or by the EC itself.

Information may be entered into the Case Report Form or reported directly to the Edwards Lifesciences, with documentation of such notification being recorded and filed. Notifications and source documents will be provided to Safety Officer.

At the time of initial notification, the following minimal information should be provided:

- Identifiable patient: subject number
- Identifiable reporter: study site
- Adverse event summary
- Causal relationship to device and procedure
- Awareness date

The USADE Case Report Forms should be completed within five working days. All USADEs must be followed until resolution or until a stable clinical endpoint is reached. All required treatments and outcomes of the USADE must be recorded.

Edwards will notify all participating clinical Investigators, ECs, and regulatory bodies as necessary of all USADEs that occur during the study within the specified reporting time frame following event notification. Investigators are responsible for reviewing information received about USADEs.

8.5 Device Deficiency and Vigilance Reporting

Device deficiencies which could have led to a serious adverse device effect should undergo the same reporting as serious adverse events. They should be reported to Edwards Lifesciences within 24 hours of awareness and to the EC and regulatory authorities as required by regulations or the EC.

Adverse device effects, device malfunctions and device failures must be reported to Edwards Lifesciences in accordance with the regulations and Edwards Lifesciences policies.

The Edwards Lifesciences 'Complaint Reporting Process' form is available in the site study document file.

8.6 Source Documents

The site will provide to Edwards Lifesciences a copy of anonymized supporting documentation (such as hospital record, laboratory results, autopsy results) of all SAES and safety related composite events.

9. Risk Evaluation

9.1 Potential Risk to Study Subjects

For the purposes of this study, adverse events that may be anticipated are associated with the use of the SAPIEN XT THV System as well as the anesthesia and interventional procedures used to deliver and deploy the SAPIEN XT THV.

Anticipated risks have been minimized to the furthest extent possible, but the nature of the procedure and the severity of the patient's disease state has inherent risks. Exposure to ionizing radiation associated with fluoroscopy, x-rays and CT is no more than is associated with routine clinical practice for transcatheter aortic heart valve replacement.

Risks are outlined in the SAPIEN XT THV System Instructions for Use (IFU)

9.2 Methods to Minimize Risk

Product handling and procedure guidance are provided in the Training Materials and IFU and will be used for device training to minimize risks associated with device use.

Additionally, efforts will be made to minimize these possible risks though site/investigator selection and management. First, site and investigator selection criteria are established to ensure that the study personnel and their institutions are qualified to screen, perform and manage the study procedures as well as support the associated requirements for research. Second, the trial management structure is designed to provide disciplined oversight of the trial activities including close monitoring of site and personnel performance and also support opportunities for investigators and study personnel to share best practices through investigator meetings, ongoing education and case reviews.

9.3 Study Site Criteria

Site and investigator criteria include the following:

- Interventional cardiologists must be experienced and skilled in percutaneous balloon valvuloplasty.
- Strong interdepartmental collaboration between cardiac surgery and interventional cardiology operators will be assessed by an experienced trial study team. The study site team must be trained in the use of the investigational devices prior to enrollment of study patients.
- The procedure setting must include a fixed C-arm angiography imaging capability in the catheterization lab or operative suite and/or a hybrid catheterization/operating room suite.
- The study site must have an operating room.
- The study site must have an adequately staffed research department with a minimum of one dedicated study coordinator.

9.4 Benefits

Participation in the study does not guarantee any benefits. The potential benefits resulting from this study fall into the following categories:

- Direct benefit patient(s) may receive from participation in the study and being treated with the investigational device,
- Possible benefit patient(s) may receive from participation in the study and being treated with the investigational device,
- Possible benefit for future patient(s) receiving the SAPIEN XT THV based upon results of the study.

Aortic valve replacement with the Edwards SAPIEN XT THV System may result in one or more of the following benefits: improved valvular function, acute alleviation of symptoms related to

aortic stenosis, improved quality of life in patients that may prefer or be more suitable for alternative treatments for aortic valve stenosis, and/or improved morbidity and mortality.

Information gained from the conduct of this study may be of benefit to other people with the same medical condition in the future. Alternative treatments include palliative medical therapy, aortic balloon valvuloplasty and high-risk surgical replacement of the aortic valve.

9.5 Risk-Benefit Analysis

The body of clinical evidence supporting treatment with the SAPIEN XT THV is robust, and is described in Section 2.2. The device design and implantation procedure for the SAPIEN XT valve is similar to other Edwards SAPIEN THVs.

The relative safety of the TAVI procedure in comparison to surgical AVR in high risk patients is being studied in the PARTNER Cohort A, as previously described in Section 2.2. The 2-year outcome data from the PARTNER study demonstrate that TAVI is non-inferior to surgical AVR (SAVR) in terms of all-cause mortality [32]. Strokes and major vascular events were statistically more prevalent with TAVI, whereas major bleeding and new onset atrial fibrillation events were more prevalent in the AVR subjects. Both stroke and major bleeding had a significant impact on mortality. Major vascular complications had impact on mortality only in the TAVI arm. Although strokes were more frequent in the TAVI arm, those that occurred in the SAVR arm were twice as likely to be associated with mortality than those that occurred in the TAVI arm (hazard ratio = 2.76 for TAVI and 4.99 for SAVR) [49]. Major bleeding complications were not only 2 to 3 times more frequent in the AVR arm than TAVI arm, but were also associated with a significantly increased 1-year mortality in the AVR arm, whereas major bleeding complications after TF-TAVR were not [50].

Benefits of TAVI over AVR include shorter hospital stay and faster resolution of symptoms of congestive heart failure demonstrated by greater reductions in NYHA class observed at 30 days [32]. Concomitant to the improvement in NYHA class, quality of life also improved significantly more over the first 30 days post-procedure for TAVI patients. Patients undergoing TAVI via the transfemoral approach demonstrated significant health status benefits with TAVI versus SAVR at 1 month (difference, 9.9 points; 95% confidence interval: 4.9 to 14.9; $p<0.001$) on the Kansas City Cardiomyopathy Questionnaire [30].

10. Definitions

The definitions used in this protocol are consistent with those initiated with the initial set of standardized end-points proposed by the Valve Academic Research Consortium (VARC) [45] and updated in VARC-2 publication [46] as well as those used in the PARTNER clinical trials.

Term	Definition	Reference/ Justification
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational device.	ISO 14155: 2011
Serious Adverse Event (SAE)	Adverse Event that: a) led to a death, b) led to a serious deterioration in the health of a study patient that • resulted in a life-threatening illness or injury, • resulted in permanent impairment of a body structure or body function, • required inpatient hospitalization or prolongation of existing hospitalization, • resulted in a medical or surgical intervention to prevent permanent impairment to body structure or a body function. c) leads to fetal distress, fetal death or a congenital abnormality or birth defect Important medical events not resulting in the above should be assessed as an SAE. Any major or clinically significant adverse event occurring during and after the study valve implantation or BAV procedure: The following is not considered an SAE: Hospitalization for diagnostic or elective surgical procedures, planned at or before the enrollment for a pre-existing condition.	ISO 14155: 2011 FDA (21 CFR 312.32 (a)
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device. This definition also includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational device. And events resulting from use error or from intentional misuse.	ISO 14155: 2011
Serious Adverse Device Effect (SADE)	Adverse Device Effect that resulted in any of the consequences characteristics of a Serious Adverse Event.	ISO 14155: 2011
Unanticipated Serious Adverse Device Effect (USADE)	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 problems associated with a device that relates to the rights, safety, or welfare of patients.	ISO 14155: 2011
Acute Kidney Injury	Increase in serum creatinine (up to 7 days) compared with baseline Stage 1: Increase in serum creatinine to 150% to 199% (1.5 to 1.99 increase compared with baseline) OR increase of 0.3 mg/dl (26.4 mmol/l), OR Urine output < 0.5ml/kg/hr for > 6 hours but < 12 hours Stage 2: Increase in serum creatinine to 200% to 299% (2.0 to 2.99 increase compared with baseline), OR Urine output < 0.5ml/kg/hr for > 12 hours but < 24 hours 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 Urine output < 0.3ml/kg/hr for ≥ 24 hours OR anuria ≥ 12 hours The Increase in creatinine must occur within 48 hours *Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.	VARC-2
Aortic Prosthetic Valve Dysfunction	Prosthetic Valve Stenosis	VARC-2

Term	Definition	Reference/ Justification
	Prosthetic valve regurgitation: Mean aortic valve gradient ≥20 mmHg, EOA ≤0.9-1.1 cm2‡ and/or DVI<0.35, AND/OR moderate or severe prosthetic valve regurgitation* ‡Depending on body surface area * Refers to VARC-2 definitions listed in this table	
Bleeding Event	Life-threatening or Disabling Bleeding • Fatal bleeding (BARC Type 5), OR • Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC Type 3b or 3c), OR • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery, OR • Overt source of bleeding with drop in hemoglobin of ≥5 g/dL or whole blood of packed red blood cells (RBC) transfusion ≥4 units* (BARC type 3b) Major Bleeding (BARC type 3a) Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring transfusion of 2-3 units of whole blood/RBC AND Does not meet criteria of life-threatening or disabling bleeding. Minor Bleeding (BARC type 2 or 3a, depending on severity) 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. BARC = Bleeding Academic Research Consortium	VARC-2
Cardiac Tamponade (TAVI-related)	Evidence of a new pericardial effusion associated with hemodynamic instability and clearly related to the TAVI procedure	VARC-2
Cardiomyopathy	A chronic disease of the myocardium in which the muscle is abnormally enlarged, thickened, and/or stiffened. Indicate "Yes" on the Baseline CRF if the patient has a documented history of cardiomyopathy.	
Cardiopulmonary Bypass, Unplanned Use (TAVI-related)	Unplanned use of CPB for hemodynamic support at any time during the TAVI procedure	VARC-2
Conduction Disturbances and Arrhythmias	Up to 72 h, continuous rhythm monitoring is recommended in order to maximize detection of arrhythmias Data elements to be collected should include: • Baseline conduction abnormalities, paroxysmal or permanent atrial fibrillation (or flutter), and presence of permanent pacemaker* • Implant-related new or worsened cardiac conduction disturbance (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, right bundle branch block, intraventricular conduction delay, left bundle branch block, left anterior fascicular block, or left posterior fascicular block, including block requiring permanent pacemaker implant • Persistent or transient high degree AV block. High grade AV block is persistent if it is present every time the underlying rhythm is checked • New permanent pacemaker implantation, with precision of the indication and number of days post-implant of placement of new permanent pacemaker • New-onset atrial fibrillation (or flutter)† • Any new arrhythmia resulting in hemodynamic instability or requiring therapy‡	VARC-2

Term	Definition	Reference/ Justification
	* Type of permanent pacemaker should be recorded (e.g. defibrillator, single versus dual chamber, biventricular) † New-onset atrial fibrillation (or flutter)* is diagnosed as any arrhythmia within hospitalization that has the ECG characteristics of atrial fibrillation (or flutter) and lasts sufficiently long to be recorded on a 12-lead ECG, or at least 30 seconds on a rhythm strip ‡ Therapy includes electrical/medical cardioversion or initiation of a new medication (oral anticoagulation, rhythm or rate controlling therapy).	
Conversion to Open Surgery (TAVI-related)	Conversion to open sternotomy during the TAVI procedure secondary to any procedure-related complications	VARC-2
Coronary obstruction (TAVI-related)	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 TAVI procedure	VARC-2
Device Malfunction	The failure of a device to meet any of its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling of the device.	ISO14155:2011
Device Success	Absence of procedural mortality AND Correct positioning of a single prosthetic heart valve into the proper anatomical location AND Intended performance of the prosthetic heart valve (no prosthesis-patient mismatch and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, AND no moderate or severe prosthetic valve regurgitation*) *Refers to VARC definitions detailed elsewhere in this Table If success or failure cannot be determined due to missing or unevaluable echos, device success will be considered missing.	VARC-2
Endocarditis (Operated Valvular Endocarditis)	Any one of the following: • The diagnosis of operated valvular endocarditis based on customary clinical criteria including an appropriate combination of positive blood cultures, clinical signs and histologic confirmation of endocarditis at reoperation or autopsy (using revised Duke criteria). • Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during a re-operation • Findings of abscess, pus, or vegetation involving a repaired or replaced valve during an autopsy	VARC-2
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) • History of multiple recurrent pleural effusions causing internal adhesions	VARC-2
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	VARC-2
Mitral Valve Apparatus Damage (TAVI-related)	Angiographic or echocardiographic evidence of new damage to the mitral valve apparatus (chordae papillary muscle, or leaflet) during or after the TAVI procedure	VARC-2

Term	Definition	Reference/ Justification
Mortality	Cardiovascular Death Any one of the following criteria: • Any death due to proximate cardiac disease cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure); • Death caused by non-coronary vascular conditions such as cerebrovascular disease, pulmonary embolism, ruptured aortic 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 including structural or nonstructural valve dysfunction or other valve-related adverse events • Sudden or unwitnessed death • Death of unknown cause Non-Cardiovascular Death Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide)	VARC-2
Myocardial Infarction	Peri-Procedural MI (≤72 hours of the index procedure): 1. New ischemic symptoms (e.g. chest pain or shortness of breath),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 2 contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality) AND 2. Elevated cardiac biomarkers (preferably CK-MB) within 72 hours after the index procedure, consisting of at least one sample post-procedure with a peak value exceeding 15x upper reference limit (troponin) or 5x for CK-MB. If cardiac biomarkers are increased at baseline (>99th percentile), a further increase of at least 50% post-procedure is required AND the peak value must exceed the previously stated limit. Spontaneous MI (>72 h after the index procedure): Any one of the following criteria: • Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with evidence of myocardial ischemia with at least one of the following: ○ Symptoms of ischemia ○ ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block [LBBB]); ○ New pathological Q waves in at least 2 contiguous leads; ○ Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST 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.	VARC-2
New York Heart Association Classification (NYHA)	Class I: Patients with cardiac disease but without resulting limitations of physical activity. Class II: Patients with cardiac disease resulting in slight limitation of physical activity. Patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	New York Heart Association

Term	Definition	Reference/ Justification
	Class III: Patients 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. Class IV:Patients 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.	
Paravalvular Leak (See Also "Nonstructural Dysfunction")	See " Aortic Valve (Prosthesis) Regurgitation"	VARC-2
Porcelain Aorta	Heavy circumferential calcification of the entire ascending aorta extending to the arch such that cross-clamping is not feasible.	VARC-2
Pulmonary Hypertension, Severe **Right Ventricular Dysfunction, Severe**	Primary or secondary pulmonary hypertension with PA systolic pressures greater than 2/3 of systemic pressure	VARC-2
Stroke and Transient Ischemic Attack (TIA)	Diagnostic Criteria: Acute episode 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 • Other new neurological sign(s)/symptom(s) consistent with stroke Stroke: Duration of a focal or global neurological deficit ≥ 24 hours OR < 24 hours if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death. Transient Ischemic Attack (TIA): Duration of a focal or global neurological deficit < 24 hours; any variable neuroimaging does no demonstrate a new hemorrhage or infarct. No other readily identifiable non-stroke 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: • Neurology or neurosurgical specialist • Neuroimaging procedure (CT or brain MRI), but stroke may be diagnosed on clinical grounds alone. *Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence of cerebral infarction based upon neuroimaging studies (CT scan or brain MRI).	VARC-2
Stroke Classifications	Ischemic – An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue Hemorrhagic – An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic	VARC-2
Structural Valvular Deterioration (SVD)	See: "Time-Related Valve Safety"	VARC-2

Term	Definition	Reference/ Justification
Transcatheter Aortic Valve in Transcatheter Aortic Valve (TAV-TAV)	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.	VARC-2
Valve Malpositioning	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 Valve embolization The valve prosthesis moves during or after deployment such that it loses contact with the aortic annulus Ectopic valve deployment Permanent deployment of the valve prosthesis in a location other than the aortic root	VARC-2
Valve-Related Mortality	See: "Mortality"	VARC-2
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	VARC-2
Vascular Access Site and Access- Related Complications	Major Vascular Complications: • Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm OR • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) leading to death, life-threatening or major bleeding*, visceral ischemia or neurological impairment OR • Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR • The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia or neurological impairment OR • Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR • Surgery for access site-related nerve injury OR • Permanent access site-related nerve injury OR Minor Vascular Complications: • Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneuysms, hematomas, percutaneous closure device failure) not leading to death, life-threatening or major bleeding*, visceral ischemia or neurological impairment OR • Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR • Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR • Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft) OR Percutaneous closure device failure	VARC-2

Term	Definition	Reference/ Justification
	• Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning) *Refers to VARC bleeding definitions	
Ventricular Septal Perforation (TAVI-related)	Angiographic or echocardiographic evidence of a new septal perforation during or after the TAVI procedure	VARC-2
Note: The Valve Academic Research Consortium (VARC) consists of representatives from several independent Academic Research Organizations (Cardialysis, Rotterdam, the Netherlands, Cardiovascular Research Foundation, New York City, NY, Duke Clinical Research Institute, Durham, NC, and Harvard Clinical Research Institute, Boston, MA), several Surgery and Cardiology Societies (American Association of Thoracic Surgeons, American College of Cardiology, American Heart Association, European Association of CardioThoracic Surgeons, European Society of Cardiology, Society of Cardiac Angiography and Intervention, and Society of Thoracic Surgeons) and several independent expert scientists and consultants.		

11. Statistical Considerations

The clinical study is a single-arm prospective study intended to demonstrate the safety and performance of the SAPIEN XT THV in the Chinese population. The sample size was determined based on the regulatory requirement and includes the following considerations:

11.1 Sample Size

The sample size of 50-60 patients is determined per Chinese regulatory requirements and agreement for a regional study of a medical device already approved in other regions based on a well-designed prospective study.

11.2 Timing

Study subjects will undergo screening and pre-procedure visits, and then follow-up visits at Discharge, and 30 Days (+14 days) for Endpoint analysis. Long-term follow-up data is collected at 6 Months (+/- 30 days), 1 Year (+/- 60 days), 2 Years (+/- 60 days), 3 Years (+/- 60 days), 4 Years (+/- 60 days), and 5 Years (+/- 60 days).

11.3 Analysis Sets

- *As Treated (AT) Population:* all patients that were enrolled in the trial for whom the SAPIEN XT valve implant procedure was begun, defined as the time in which the first Edwards' investigational device is inserted into the patient.
- *Valve Implant (VI) Population:* all AT patient who received and retained the SAPIEN XT valve upon leaving the procedure room

All patients documented as part of the roll-in patient strategy will not be included in analysis population and evaluated separately.

The primary and secondary endpoints will be reported based on the AT Population. AT patients that did not receive the SAPIEN XT valve will be censored at 30 days or at resolution of any AE.

Descriptive and summary statistical analysis will be performed on all endpoints. Patient listings for adverse events, deaths, and reinterventions will include all enrolled patients.

11.4 Missing Data

All possible steps will be taken to minimize missing data in the study, including monitoring of data forms for completeness and efforts to track and maintain contact with study subjects during the follow-up period.

11.5 Endpoint Analysis

Patient data listings and tabular and graphical presentations of results will be provided. All clinically relevant baseline and follow-up variables will be tabulated. Descriptive statistics will be used for continuous variables (e.g., mean, standard deviation, sample size, minimum, and maximum) and frequency tables or proportions for discrete variables.

Kaplan Meier estimates will be performed at the pre-specified follow-up times to project the estimates for time-related safety endpoints. The Kaplan-Meier analysis will be used to compute the 30-day mortality rate, the primary endpoint; the standard error and confidence limits will be computed using Greenwood's algorithm.

Echocardiographic data will be analyzed by an Echo core laboratory with respect to the degree of total aortic valve regurgitation (TVR) and paravalvular aortic valve regurgitation (PAR) according to the VARC-2 definitions [46].

These data and other categorical data (e.g., NYHA class) will also be presented as shift from baseline for each of the pre-specified follow-up periods.

More specific information regarding the statistical analysis will be presented in the Statistical Analysis Plan (SAP).

12. Study Administration

12.1 General Study Organization

Edwards Lifesciences is the Study Sponsor, and has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the appropriate regulatory bodies. Edwards Lifesciences will have certain direct responsibilities and will coordinate other responsibilities to the specified committees, Echo core lab and other support services as necessary

Edwards Lifesciences will be responsible for submitting the Clinical Investigation Plan and all changes to it to the regulatory body and local EC to obtain ongoing approvals as needed.

Edwards Lifesciences will submit all reports required by the appropriate regulatory authorities as identified in this section of the regulation. This may include unanticipated and serious adverse device effects, withdrawal of EC approval, current investigators list, annual progress reports, recall information, final reports and protocol violations.

Edwards Lifesciences and Core Laboratories will maintain copies of correspondence, data, shipment of devices, adverse device effects and other records related to the study as appropriate.

12.2 Medical Reviewers

Medical Reviewers will review and classify adverse events in accordance with the study protocol.

12.3 Echocardiography Core Laboratory

A Core laboratory will be established for Echocardiography endpoint analysis. Standardized protocols for acquiring and transmitting electronic records will be developed and documented prior to study initiation.

Clinical Sites will upload a qualifying echocardiography prior to the enrolment of the first subject in accordance with the standardized protocol.

Edwards Lifesciences will review echocardiography data for the duration of the study.

12.4 Clinical Sites

Edwards Lifesciences will select qualified investigators, ship devices only to participating investigators, obtain a signed Clinical Study Agreement and provide the investigators with the information and training necessary to conduct the study. Edwards Lifesciences will retain copies of all study-related correspondence with study sites.

12.5 Site Training

Clinical sites will be chosen that have proper facilities in place to complete THV procedures. Additional training of appropriate clinical site personnel will be the responsibility of the Sponsor. To ensure proper device usage, uniform data collection, and protocol compliance, the Sponsor will present a formal training session to study site personnel which will review the instructions for use of the device, the Investigational Plan, techniques for the identification of eligible patients, instructions on in-hospital data collection, CT recommendations, echocardiography data collection for core laboratory analysis, methods for soliciting data from

alternative sources, schedules for follow-up with the study site coordinators, and regulatory requirements. Detailed feedback regarding completion of forms will be provided by the Sponsor, and through regular site monitoring. Edwards Lifesciences reserves the right to enforce retraining for sites who have demonstrated study or procedure compliance issues.

12.6 Study Monitoring

Edwards Lifesciences will contract with a Clinical Research Organization (CRO) to provide a CRA(s) to monitor the study sites to ensure that all investigators are in compliance with the protocol and the Investigator's Agreement, and that all study subjects have been properly consented with the current version of the informed consent document. Edwards Lifesciences will evaluate circumstances where an investigator deviates from the clinical protocol and will retain the right to remove either the investigator or the investigational site from the study.

Routine on-site monitoring visits shall include verification of the following:

- Compliance with the protocol, any subsequent amendment(s), GCP and maintenance of regulatory and EC requirements. Deviations shall be discussed with the Investigator(s) or delegated personnel, documented and reported
- Only authorized and delegated individuals are participating in the study
- The SAPIEN XT THV System is being used according to the protocol and IFU
- Study Site resources, equipment and study personnel, remain adequate throughout the duration of the study
- Patient Informed Consent is completed in accordance to the protocol and regulations
- Only Patient Informed Consents Forms approved by the EC are used appropriately
- Source documents and other clinical records are accurate, complete up to date, stored and maintained properly
- CRFs and queries are complete, recorded in a timely manner, and consistent with source documents
- All adverse events and device deficiencies are reported to Edwards without unjustified delay
- All serious adverse events and deviations are reported to the EC, if required
- All other required reports, notifications, applications, submissions and correspondence are maintained in the investigator's files and are accurate, complete, timely, legible, dated and identify the clinical investigation
- Current laboratory normal values, laboratory certifications, accreditations, or other validations are present in the investigator's file
- Subject withdrawal has been documented; the monitor shall discuss this with the principal investigator or his/her authorized designee

- Subject non-compliance with the requirements stated in the informed consent has been documented; the monitor shall discuss this with the principal investigator or his/her authorized designee
- Suitability of the attempts to contact lost to follow-up patients and any intermediaries
- The principal investigator and investigation site team are informed and knowledgeable of all relevant document updates concerning the clinical investigation
- Any corrective and preventive actions, as needed, have been implemented and are effective.

Monitors shall be appropriately qualified per the following requirements:

- Qualified in the field of the applicable regulations and GCP through training and experience as well as scientific or clinical knowledge;
- Knowledgeable on the use of the investigational device(s) and relevant requirements, protocol and informed consent process;
- Trained on the Edwards' clinical quality assurance and quality control system

All monitoring activities shall be documented in a written report. The frequency of monitoring visits will depend on enrollment and center compliance, but each center will at least be visited once per year. Further details are laid out in the monitoring plan.

Edwards Lifesciences will review significant new information, including unanticipated adverse events and ensure that such information is provided to the study investigators and to all reviewing ECs and regulatory agencies as necessary. Efforts will be made to ensure that data collection compliance is monitored and communicated to the Investigators in a timely manner throughout the trial.

12.7 Data Collection and Quality Assurance

Data will be captured and managed through an electronic data capture (EDC) system. Passwords will be issued to appropriate data management personnel to ensure confidentiality and protection of the data by allowing variable levels of access to the computer system. Electronic CRFs (eCRFs) will be used to collect all patient data during the trial. eCRFs must be fully completed for each patient, and signed electronically by the investigator and/or designee. The investigator, or an individual designated by him/her, is responsible for recording all data from the trial onto the eCRFs on a dedicated website. The investigator is required to provide an electronic signature on the appropriate eCRF pages to verify that he/she has reviewed the recorded data.

Completed eCRFs will be reviewed at the investigational site and remotely by authorized Edwards Lifesciences personnel at regular intervals throughout the trial. All eCRFs will be

tracked at Edwards Lifesciences and missing or unclear data will be requested as necessary throughout the trial.

12.8 Publication Policy

Clinical sites have the right, consistent with academic standards, to publish their individual registry results provided such publication does not constitute a violation of the Study Agreement. The site agrees to submit any proposed submission for publication to Edwards Lifesciences for review and approval before any submission. Consent cannot be denied without a sensible reason.

The results of the clinical investigation will be submitted, whether positive or negative for publication. The publication policy will be part of Study Agreement.

13. Ethical Review and Consideration

13.1 Confidentiality

All information and data sent to the data management center concerning patients or their participation in this trial will be considered confidential. Only authorized data management center personnel will have access to these confidential files. Authorized personnel from Edwards Lifesciences and its contractors and regulatory authorities have the right to inspect and copy all records pertinent to this trial. All data used in the analysis and reporting of this evaluation will be without identifiable reference to the patient.

13.2 Records and Reports

13.2.1 Records

All records related to the study and qualifications of site personnel must be kept on file and available for review. These documents may include but are not limited to:

- Clinical trial investigational plan and all amendments, all approved versions
- Signed clinical trial agreement
- EC approval letter, including final informed consent
- EC membership list
- Correspondence relating to the trial
- CVs for all investigators and research coordinator
- Site personnel signature list
- Clinical monitor sign-in log
- Patient screening/enrollment log
- Lab certification and lab test normal ranges
- Reports (includes annual reports, final reports from investigator and sponsor)

All records related to the patients' consent and study data must be maintained for each patient enrolled in the trial. These records include and are not limited to:

- Signed Patient Informed Consent Form (latest approved site version)
- All completed eCRFs
- Supporting documentation of any complications and/or safety events.

Edwards Lifesciences requests that the investigator retain copies of procedure reports, procedure nursing notes and the results of any interventional procedures that occurs post trial procedure. Edwards Lifesciences reserves the right to secure data clarification and additional medical documentation on patients enrolled in this trial.

13.2.2 Deviations from Protocol

The investigator will not deviate from the protocol without the prior written approval of Edwards Lifesciences except in medical emergencies or in unforeseen, isolated instances where minor changes are made that will not increase the patient's risk or affect the validity of the trial. In medical emergencies, prior approval for protocol deviations will not be required, but the Edwards Lifesciences clinical research personnel must be notified within 24 hours of the incident.

All protocol deviations need to be recorded in the respective section of the eCRF and reported according national and ethics committee requirements. Periodic monitoring of protocol compliance will be performed for each site. The sponsor maintains the right to place a moratorium on enrollment in sites deemed to have excessive protocol compliance issues. A major protocol violation is the instance where a deviation significantly affects the integrity of the study and guidelines for Good Clinical Practice, such as when there is failure to obtain informed consent or violation of inclusion/exclusion criteria. In cases of major protocol violation, the principal investigator is required to make a written statement attesting to retraining or other action(s) to be taken at his/her site to avoid such violations in the future.

13.2.3 Record Retention Policy

All clinical sites will maintain study records for a minimum of 15 years after marketing approval is obtained. After 15 years, clinical sites should following hospital and regulatory guidelines for record retention. Record retention dates will be provided to all parties concerned by Edwards Lifesciences.

14. Financial and Insurance Considerations

14.1 Clinical Trial Funding

As the Sponsor, Edwards Lifesciences will fund the duration of the trial.

14.2 Clinical Trial Insurance

As required by local/country regulation, Edwards Lifesciences will obtain clinical trial insurance for the duration of the clinical trial and provide evidence of coverage.

15. References

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