SAPIEN 3 Ultra EU Post-Market Observational Study

NCT 04860752
June 2021

Edwards

SAPIEN 3 Ultra EU Post-Market Observational Study

Clinical Investigation Plan

Study Number: 2020-02
Version 3.0
18 June 2021

Study Sponsor:
Edwards Lifesciences LLC
One Edwards Way
Irvine, CA 92614
USA

TABLE OF CONTENTS

LIST OF TABLES

STUDY SYNOPSIS

Title	SAPIEN 3 Ultra EU Post-Market Observational Study
Objective	To evaluate real-world outcomes for the SAPIEN 3 Ultra Transcatheter Heart Valve (THV) System in transcatheter aortic valve implantation (TAVI) centres that are implementing minimalist periprocedural practices and facilitating early discharge home
Device	Edwards SAPIEN 3 Ultra THV System
Study Design	Prospective, observational, single-arm, multicentre, post-market study
Subject Population	Subjects who will undergo TAVI with the Edwards SAPIEN 3 Ultra System as part of standard-of-care treatment.
Sample Size	Up to 500 subjects will be enrolled
Study Sites	Up to 50 centres predominantly in the European Union
Data Collection Schedule	Clinical data and imaging available from routine clinical assessments performed pre-procedure and through 1-year post-procedure will be collected.

Outcome Measures	The following outcomes will be reported:
	• Death
	• Stroke
	• New requirement for permanent pacemaker
	• Aortic valve reintervention
	• Valve haemodynamics
	  o Aortic regurgitation
	  o Mean aortic valve gradient
	  o Effective orifice area
	• Length of index hospitalization
	• Discharge location

Inclusion Criteria	1. Will undergo TAVI with the Edwards SAPIEN 3 Ultra System as part of standard-of-care treatment 2. Less than 80 years of age at time of the procedure 3. Low surgical risk as determined by the Heart Team 4. Meets clinical and procedural requirements for early discharge as determined by the Heart Team

	5. The subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent
Exclusion Criteria	1. Medical, social, or psychological conditions that preclude appropriate consent and follow-up, including subjects under guardianship 2. Considered to be part of a vulnerable population 3. Active SARS-CoV-2 infection (Coronavirus-19 [COVID-19]) or previously diagnosed with COVID-19 with sequelae that could confound endpoint assessments 4. Cannot tolerate an anticoagulation/antiplatelet regimen 5. Active bacterial endocarditis 6. Participating in a drug or device study that has not reached its primary endpoint. Note: Participation in required national registries is not an exclusion.
Statistical Analysis	No statistical hypothesis testing will be performed. Only descriptive and summary statistical analysis will be provided for baseline/pre-procedure, procedure and outcome variables.
Sponsor	Edwards Lifesciences LLC One Edwards Way Irvine, CA 92614 USA
Legal Representative	Edwards Lifesciences Services GmbH Edisonstrasse 6 85716 Unterschleissheim Germany

INVESTIGATOR SIGNATURE PAGE

Title: SAPIEN 3 Ultra EU Post-Market Observational Study

I have read this plan and agree to adhere to its requirements. I will ensure that the study is conducted in compliance with the plan, Good Clinical Practice, Declaration of Helsinki and all applicable regulatory requirements.

_____
Study Site Name

_____
Site Principal Investigator Name (print)

_____ _____
Site Principal Investigator Signature Date

1 INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is an established treatment for patients with severe aortic stenosis and has been performed for over a decade, however, there are currently no recommendations for the duration of post-procedure monitoring for patients undergoing TAVI and practices vary widely by institution and country.

Several studies have evaluated minimalist periprocedural approaches based on individual patient risk and criteria-driven discharge in order to standardize post-procedure care and reduce length of stay; these approaches also ultimately maximize the efficiency of hospital resources. In the European FAST-TAVI trial, a set of pre-specified discharge criteria established to allow safe and timely discharge were applied to a group of patients undergoing TAVI with the SAPIEN 3 transcatheter heart valve (THV) and 30-day outcomes were evaluated. A total of 328 patients had a low risk of complications and were discharged between 1- and 3-days post procedure.[1] Similarly, the 3M TAVR study evaluated the safety, effectiveness and feasibility of next-day discharge in patients undergoing balloon-expandable transfemoral TAVI when implementing objective pre-procedural screening criteria and standardized peri- and post-procedural management guidelines. A total of 411 patients with a mean age of 84 years and STS score of 4.9% had a median length of stay of 1.0 days, with next-day discharge achieved in 80.1% of patients and 89.5% discharged within 48 hours of the procedure.[2] The discharge criteria used in these studies are shown in **Table 1**; thirty-day outcomes are shown in **Table 2.** Both studies concluded that the event rates compare favourably with other recent trials and, thus, have demonstrated that early discharge home is safe and feasible for selected patients.

Table 1. FAST-TAVI and 3M TAVR Study Discharge Criteria

FAST-TAVI [1]	3M TAVR Study [2]
• NYHA Class ≤II • no chest pain attributable to cardiac ischaemia • no untreated major arrhythmias • patients having complications on day 0 to 1, but free of signs or symptoms on day 3 • no fever during the last 24 hours and no signs of an infectious cause • independent mobilisation and self-caring • preserved diuresis (>40 ml/hour during the preceding 24 hours) • no unresolved AKI type 3 (according to VARC-2 criteria) • no RBC transfusion during the preceding 72 hours • stable haemoglobin in two consecutive samples (defined as a decrease of no more than 2 mg/dl) • no paravalvular leak (PVL) with aortic regurgitation less than moderate • no stroke/transient ischaemic attack (TIA) • no haemodynamic instability	**Monitoring** • Completion and review of post-procedure transthoracic echocardiogram to confirm acceptable bioprosthetic haemodynamic with the absence of delayed complications • Absence of persistent intraventricular conduction delay • Absence of vascular access site complications • Absence of laboratory contraindications. If Hgb <100 g/L and eGFR <30 mL/min, obtain and review outpatient bloodwork 2 and 4 d after discharge • Facilitated reconditioning • Return to baseline mobilization • Absence of elimination issues (e.g., urinary retention) **Communication** • Multidisciplinary agreement of safety of discharge • Confirmation of discharge plan with patient/family • Confirmation of availability of social support during the initial 48 h after discharge • Completion of verbal discharge teaching and confirmation of patients/family's understanding of the discharge guidelines and provision of written discharge education resources and prescription of medications

Table 2. FAST-TAVI and 3M TAVR Study 30-Day Outcomes (%)

Outcome	FAST-TAVI [1]	3M TAVR Study [2]
Mortality	0.6	1.5
Stroke	0	1.5
Permanent pacemaker	4.3	5.7
Cardiac rehospitalization	3.4	5.7

2 STUDY OBJECTIVE

The SAPIEN 3 Ultra THV design builds upon the technical knowledge and experience gained from the SAPIEN 3 THV. CE Mark approval was received in November 2018 for patients with severe aortic stenosis and at least intermediate surgical risk, and in March 2020 for patients at low surgical risk.

This post-market study will further evaluate real-world outcomes for the SAPIEN 3 Ultra THV System in TAVI centres that are implementing minimalist periprocedural practices and facilitating early discharge home.

3 STUDY DESIGN

This is a prospective, observational, single-arm, multicentre post-market study. Up to 500 subjects who will undergo TAVI with the SAPIEN 3 Ultra THV will be enrolled at up to 50 centres predominantly in the European Union.

Clinical data and imaging available from routine clinical assessments performed pre-procedure and through 1-year post-procedure will be collected.

4 STUDY DEVICES

The study will use the following commercially available devices:

- Edwards SAPIEN 3 Ultra THV
- Edwards Commander Delivery System
- Edwards eSheath Introducer Set
- Edwards Loader
- Edwards Crimper and Crimp Stopper
- Edwards Qualcrimp Crimping Accessory

Descriptions of all study devices are provided in the respective Instructions for Use (IFU).

5 OUTCOME MEASURES

The outcome measures for the study are as follows:

- Death
- Stroke
- New requirement for permanent pacemaker
- Aortic valve reintervention
- Valve haemodynamics
  - Aortic regurgitation
  - Mean aortic valve gradient
  - Effective orifice area
- Length of index hospitalization
- Discharge location

6 STUDY POPULATION

6.1 Inclusion Criteria

Subjects must meet **all** of the following criteria to be included in the study:

1. Will undergo TAVI with the Edwards SAPIEN 3 Ultra System as part of standard-of-care treatment
2. Less than 80 years of age at time of the procedure
3. Low surgical risk as determined by the Heart Team
4. Meets clinical and procedural requirements for early discharge as determined by the Heart Team
5. The subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent

6.2 Exclusion Criteria

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

1. Medical, social, or psychological conditions that preclude appropriate consent and follow-up, including subjects under guardianship
2. Considered to be part of a vulnerable population
3. Active SARS-CoV-2 infection (Coronavirus-19 [COVID-19]) or previously diagnosed with COVID-19 with sequelae that could confound endpoint assessments
4. Cannot tolerate an anticoagulation/antiplatelet regimen
5. Active bacterial endocarditis

6. Participating in a drug or device study that has not reached its primary endpoint. Note: Participation in required national registries is not an exclusion.

7 STUDY PROCEDURES

7.1 Informed Consent

Eligible subjects who will undergo TAVI with the Edwards SAPIEN 3 Ultra THV System will be given an overview of the study. If subjects are interested in participating and are willing to authorize the use of their data, they must sign the Ethics Committee (EC)-approved informed consent form (ICF) before data collection can commence.

7.2 Data Collection

Clinical data and imaging available from routine clinical assessments performed pre-procedure and through 1-year post-procedure will be collected. Imaging obtained during this time frame should be uploaded and information entered in the CRF. It is expected that the sites' standard-of-care for the management of subjects undergoing TAVI will be aligned and consistent with established guidelines and recommendations (e.g., 2017 ESC/EACTS Guidelines for the Management of Valvular Heart Disease [3], Valve Academic Research Consortium-2 Consensus Document [4], echocardiographic recommendations [5-7]) and will include, but not be limited to, the following assessments:

7.2.1 Baseline/Pre-Procedure

Data from the following assessments will be collected:

- Medical history
- Physical assessment (height and weight only)
- Risk assessment
- New York Heart Association (NYHA) functional class
- Valve-related imaging (Cardiac computed tomography angiography (CTA), transthoracic echocardiogram (TTE), transoesophageal echocardiogram (TEE), etc)

7.2.2 Procedure

The study devices will be used in accordance with the most current IFU.

The valve implant procedure will be considered to have started when the first interventional access-related puncture/incision is established. Subjects will be considered enrolled once the ICF is signed and the procedure has begun.

Data from the following assessments will be collected:

- Fluoroscopic imaging of valve deployment

- Post-deployment valve haemodynamics
- Adverse events

7.2.3 Post-Procedure Follow-up

The day of the procedure is considered Day 0 and one year is defined as 365 days.

Data from the following assessments will be collected post-procedure through 1-year (+ 60 days):

- Adverse events
- Valve-related imaging (CTA, TTE, TEE, etc.)
- Valve haemodynamics

7.3 Imaging Assessments

Imaging performed during the study should follow current guidelines and recommendations, which are noted in the imaging reference guide supplied for this trial.

7.4 COVID-19 Assessments

Results of all available SARS-CoV-2 (Coronavirus-19 [COVID-19]) testing should be recorded in the CRFs.

7.5 Subject Disposition

The following categories of subject disposition have been defined for this study:

Screen Failure: Subjects who have provided informed consent will be considered a screen failure if they do not meet the eligibility criteria or do not have the procedure started.

Enrolled: Subjects will be considered enrolled once the ICF is signed and the procedure has begun.

Discontinued: Enrolled subjects will be considered discontinued for the following reasons:

- **Study Device Never Implanted**: Subjects considered enrolled but did not receive a study valve will be exited from the study.
- **Study Device Explanted**: Subjects who have a surgical reintervention where the study valve is explanted will be exited from the study.
- **Subject Withdrew Consent**
- **Death**

If a subject discontinues, an exit form indicating the reason for discontinuation will be completed. Subjects who discontinue will not be replaced.

Complete: Enrolled subjects will be considered complete when data through 1-year post-procedure has been entered.

Table 3 summarizes the data that will be collected.

Table 3. Data Collection Schedule

Assessment	Baseline/ Pre-procedure [1]	Procedure [1]	Post-procedure through 1 Year [1]
Informed Consent	X		
Medical History	X		
Physical Assessment	X		
Risk Assessment	X		
NYHA Functional Class	X		
Valve-related Imaging [2]	X	X [3]	X
Valve Haemodynamics		X	X
Adverse Events		X	X

1. Results of all available SARS-CoV-2 (Coronavirus-19) testing should be recorded in the CRFs.
2. All imaging (CTA, TTE, TEE, etc.) obtained from pre-procedure through 1 year (+ 60 days) should be uploaded and information entered in the CRF.
3. Includes fluoroscopic imaging of valve deployment.

8 ADVERSE EVENTS

8.1 Definitions

An **Adverse Event** (AE) is 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 study device or procedures involved and whether anticipated or unanticipated. For users or other persons, this definition is restricted to events related to the study device.

A **Serious Adverse Event** (SAE) is any adverse event that:

- Led to death;
- Led to serious deterioration in the health of the subject that either resulted in:
  - a life-threatening illness or injury;
  - a permanent impairment of a body structure or a body function including chronic diseases;
  - in-patient or prolonged hospitalization;
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function;
- Led to foetal distress, foetal death. a congenital abnormality or birth defect including physical or mental impairment;

NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.

NOTE 2: Permanent impairment of a body structure or a body function - An AE, which results in a substantial disruption of a person's ability to conduct normal life functions. This does not pertain to minor events, but to serious events which result in a significant, persistent or permanent change, impairment, damage or disruption in the subject's body function/structure, physical activities and/or quality of life.

NOTE 3: Life-threatening – an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Adverse Device Effects (ADE) and **Serious Adverse Device Effects** (SADE) are AEs related to the use of a medical device.

NOTE 1: This includes any AE resulting from insufficiencies or inadequacies in the IFU, the deployment, the implantation, the installation, the operation, or any malfunction of the medical device.

NOTE 2: This includes any event that is a result of a use error or intentional abnormal use of the medical device.

Anticipated AE means an effect, which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report. The potential AEs associated with the procedures involved and study devices are listed in the current IFU.

Unanticipated Serious Adverse Device Effect (USADE) is defined as any SADE, which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report or IFU.

Device Deficiency is defined as an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error or inadequacy in the information supplied by the manufacturer, including labelling.

A malfunction or deterioration is defined as the failure of a device to perform in accordance with its intended purpose when used in accordance with the manufacturer´s instructions. The intended performance of a device refers to the intended use for which the device is labelled or marketed.

Reporting conventions for device deficiencies that could result in an SAE are the same as those for an actual SAE.

8.2 Investigator Assessment of AEs

For each AE, the Investigator will determine whether the event is related to the device and/or the implant procedure, whether it was anticipated or not anticipated (based on the list of potential risks provided in the IFU) and whether the event meets the definition of an SAE or USADE.

The causal relationship of the event to the device and the implant procedure will be categorized as follows:

1. **Not related**: relationship to the device or procedures can be excluded when there is no temporal relationship, the event is not a known adverse effect of similar devices or procedures, it is not clinically plausible, or the event can be attributed to another cause.
2. **Possible:** the relationship with the use of the device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
3. **Probable:** the relationship with the use of the device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.
4. **Causal relationship:** the event is associated with the device or with procedures beyond reasonable doubt when there is a temporal relationship, the event is a known adverse effect of similar devices or procedures, it is clinically plausible, or the event cannot be attributed to another cause.

8.3 AE Reporting Requirements

All AEs will be captured from the time of enrolment until subject participation has ended (i.e. completion of study or discontinuation). See **Section 8.3.1** for events that are not required to be reported to Edwards.

Pre-existing medical conditions or symptoms reported prior to subject enrolment will not be recorded as an AE. In the event there is a worsening in the pre-existing medical condition or symptoms due to the device or study-related procedure, then an AE must be recorded.

Death should not be recorded as an AE but should be reflected as an outcome to another specific AE.

If known, the diagnosis for an AE should be recorded, rather than listing individual signs and symptoms.

All AEs will be reported in subject medical records and the appropriate electronic case report form (eCRF) throughout the duration of the study, and will be followed until resolution, stabilization or study completion.

All SAEs and Device Deficiencies that might have led to a SAE must be reported to Edwards **immediately, but not later than 3 calendar days after site study personnel's awareness of the event**. Other AEs must be reported to Edwards as soon as practical but no later than 10 working days of awareness.

AE information must be entered into the EDC. When EDC system is not available/accessible, AE information must be reported directly via email to EUTHVSafety@edwards.com, copying the Safety Officer of the study.

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

- Subject ID
- AE term/diagnosis
- AE onset date
- AE seriousness
- AE device and procedure relationships

Source documentation may be requested by the Edwards Safety Officer for AEs and SAEs on a case-by-case basis (i.e., device deficiencies, device- and procedure-related events, USADEs, etc.).

The AEs will be reviewed by the Edwards Safety Officer. Each AE will be assessed as to its relationship to the study device and/or implant procedure, whether it was anticipated or not anticipated, and whether it qualifies as an SAE or USADE.

Depending on the local requirements or following agreement between both parties, Edwards or the Principal Investigator will be responsible for performing safety reporting to the EC according to the relevant local regulatory requirements.

Edwards will be responsible for reporting to the National Competent Authority according to national requirements and in line with MEDDEV 2.7/3 (Serious Adverse Event Reporting) and/or MEDDEV 2.12-1 (Medical Devices Vigilance System), as applicable.

8.3.1 Events that do not require reporting to Edwards

For purposes of this study, the following events will not be required to be reported as AEs to Edwards, because they are normally expected to occur in conjunction with transcatheter valve implantation or are associated with customary, standard care of subjects undergoing THV implantation:

- Post-operative pain.
- Post-anaesthesia emesis, nausea or headache (within 24 hours of procedure).
- Electrolyte imbalance without clinical sequelae following procedure, even if requiring correction.
- Low grade temperature increase (≤ 101°F or 38.5°C).
- Elevated white blood count, outside the standard laboratory normal value, without signs and symptoms of infection.
- Minor, localized tenderness, swelling, induration, oozing, etc. at incision / delivery system insertion site.
- Systolic or diastolic blood pressure changes that do not require treatment or intervention.
- Thrombocytopenia: does not become an AE until treatment is administered; Suspected heparin-induced thrombocytopenia should be reported.
- Hyperglycaemia – The use of insulin in the post-operative period does not constitute hyperglycaemia if during the index hospitalization. An elevated blood sugar of less than 250 mg/dL during the first 48 hours post-operative does not constitute hyperglycaemia.
- Expected, non-clinically significant events such as non-significant lab variances.
- Dizziness: imprecise term commonly used to describe various symptoms such as faintness, giddiness, imbalance, light-headedness, unsteadiness or vertigo without signs of TIA or stroke.

In addition, pre-planned future surgical procedures not associated with the study procedure or device and not due to worsening of an existing condition, do not need to be reported.

9 RISK AND BENEFIT ANALYSIS

Subjects participating in this observational study will undergo TAVI with the SAPIEN 3 Ultra THV System as part of their standard-of-care treatment for severe AS. No study-specific procedures will be performed. There are no increased risks related to the participation in this study. There are potential risks related to the overall procedure (standard cardiac catheterization, valvuloplasty and use of anaesthesia) as well as potential risks associated with the TAVI procedure, the bioprosthesis, and the use of its associated devices and accessories; risks are summarized in the IFU.

10 STATISTICAL CONSIDERATIONS

10.1 Analysis Populations

As Treated (AT) Population: Will consist of all subjects that were enrolled in the trial.

Valve Implant (VI) Population: Will consist of all enrolled subjects who receive and retain the study valve upon leaving the procedure room.

10.2 Statistical Analyses

No statistical inference will be performed, and only descriptive statistics will be presented. Descriptive statistics include number of subjects and frequencies in percentage for categorical variables and mean and standard deviation/standard error for continuous variables. Kaplan-Meier estimates will be used for time-to-event measures and where appropriate for adverse event outcomes.

11 STUDY ADMINISTRATION

11.1 General Study Organization

Edwards is the Sponsor and has the overall responsibility for the conduct of the study, including assurance that the study meets applicable regulatory requirements.

Edwards will be responsible for obtaining appropriate approvals prior to study commencement, selecting investigators, and conducting clinical site monitoring to ensure that subjects are being properly consented and the study is being conducted according to the plan. Edwards will notify investigative sites of enrolment closure.

11.2 Steering Committee

A Steering Committee will be selected to provide oversight and medical expertise to the study. Steering Committee activities are defined in the Steering Committee Charter.

11.3 Echocardiographic Core Lab

An independent echocardiographic core lab will review and analyse echocardiographic images. A manual of procedures describing current guidelines and recommendations will be provided to

the study sites prior to study initiation.

11.4 Image Management

An image transfer vendor will receive, maintain and provide angiographic and echocardiographic images to the appropriate personnel for analysis.

Instructions for image upload will be provided to study site personnel prior to study initiation. Study site personnel should make every reasonable effort to upload all images to the image transfer vendor within 5 business days of image acquisition. Any unscheduled imaging performed related to the safety or performance of the device should also be uploaded.

11.5 Histopathology

Histopathology will be performed on all explanted valves. Explants will be prepared, preserved and shipped to the Histopathology Core Lab per instructions provided by Edwards.

11.6 Study Site Personnel Training

Training by Edwards or its designee is required for study site personnel in accordance with the roles outlined in the DoA log. Training may include review of the clinical investigation plan, identification of eligible subjects, and instructions on data collection and entry.

Ongoing training may be provided by Edwards or by already trained site staff. Retraining may be performed for sites who have demonstrated protocol or implant procedure compliance issues.

Documentation of study site personnel qualifications and training will be maintained in the site's study files with copies sent to Edwards.

11.7 Data Management

This study will use a secure, password protected electronic data capture (EDC) system accessible via the Internet. A unique Subject ID will be assigned for each subject enrolled in the study. All pertinent data will be entered by the study site and core lab personnel into the eCRFs.

Every reasonable effort should be made to complete data entry within 5 business days of data collection. Data review by Edwards personnel will occur remotely as well as during on-site monitoring. Data discrepancies will be queried and resolved through the EDC system.

The site Principal Investigator or designee must ensure the accuracy and completeness of the recorded data and provide his/her electronic signature on the appropriate eCRFs at regular intervals during the study, as requested by Edwards. If changes are made to data previously signed-off, a new electronic signature will be required to acknowledge/approve the changes.

11.8 Monitoring Procedures

All study sites will be monitored periodically by Edwards or designee to ensure compliance with

the plan and the Investigator's Agreement, and that all study subjects have been properly consented. The monitor will ensure that the completed eCRFs match the medical records and work with the site to resolve differences through queries or formal action items.

11.9 Site Discontinuation

Edwards has the right to discontinue an Investigator or study site for the following reasons:

- Failure of the Investigator to enrol subjects into the study at an acceptable rate
- Failure of the Investigator to comply with pertinent regulations of appropriate regulatory authorities
- Insufficient adherence to plan requirements
- Submission of knowingly false information from the research facility to Edwards, Study Monitor, EC or appropriate regulatory authority.

If a study site is discontinued, subjects enrolled prior to discontinuation will continue to be followed per the plan.

11.10 Auditing

The study site may be subject to a quality assurance audit by Edwards or a designee, as well as inspection by appropriate regulatory authorities. It is important that the Investigator and relevant study site personnel are available during any audits and that sufficient time is devoted to the process. In the event of an audit by regulatory authorities, the Investigator should contact Edwards as soon as possible.

11.11 Publication Policy

Publication or presentation of the overall clinical study results and/or site-specific results requires prior written approval of Edwards. If Edwards approves the publication or presentation of the overall clinical study results and/or site-specific results, then Institutions and Investigators will comply with the Publications and Public Disclosure Section of the Clinical Trial Agreement. Edwards will provide statistical support for the publication process.

Results from this study will be made publicly available.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Applicable Principles and Regulations

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki (as updated in Fortaleza Brazil in 2013).

The following regulations and guidelines will be followed, as applicable:

- ISO 14155: 2020 Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice
- Medical Device Regulation 2017/745 (MDR)
- MDCG 2020-10/1 guidance
- General Data Protection Regulation 2016/679
- Specific country regulations will be fulfilled, as applicable.

12.2 Ethics Committee

This plan, the proposed ICF, other written subject information and any proposed advertising material for subject recruitment must be submitted to the EC for written approval. A copy of the written EC approval of the plan and ICF must be received by Edwards before recruitment of subjects into the study.

The Investigator must submit and, where necessary, obtain approval from the EC for all subsequent plan amendments and changes to the ICF.

The Investigator is responsible for obtaining annual EC approval and renewal throughout the duration of the study. Copies of the Investigator's reports and the EC continuance of approval must be sent to Edwards.

12.3 Informed Consent

Edwards will provide a sample ICF to the Investigator to prepare for use at his/her site. The site-specific ICF, and any subsequent modifications, must agree with current regulations and guidelines and must be approved by Edwards prior to submission to the EC. The reviewing EC must approve the ICF before use at the site.

Before participating in the study, each subject must give written Informed Consent after the context of the study has been fully explained in a language that is easily understood by the subject. The subject must also be given sufficient time to read and understand the ICF per local regulations, as applicable, as well as the opportunity to ask questions and have those questions answered to his/her satisfaction.

A copy of each subject's signed and dated consent form must be maintained by each Investigator in a designated clinical study administrative file. A signed copy of the consent form must be given

to each subject. The consent process must be documented in the subject's medical record; the documentation should minimally include that consent was obtained prior to participation in the study, the date consent was obtained, and confirmation that a copy of the consent was given to the subject.

12.4 Confidentiality

The Investigator is responsible for maintaining confidentiality throughout the clinical study. All data used in the analysis and reporting of this evaluation will be without identifiable reference to the subject. Authorized personnel assigned by Edwards will have access to the confidential files and will have the right to inspect and copy all records pertinent to this study.

12.5 Investigator Records

Records to be maintained by the Investigator include, but are not limited to, the following:

- Study plan and all amendments
- Signed Clinical Trial Agreement and any amendments
- EC approval letters, including continuing reviews and all amendments/changes
- EC-approved informed consent documents
- Relevant correspondence with another study site, EC, Edwards, monitor, including required reports

The following records must be maintained for each subject enrolled in the study:

- Signed ICF
- All relevant source documentation
- Supporting documentation of any AEs

All clinical sites will maintain the study records according to their country-specific record retention requirements.

12.6 Plan Amendments

The plan can be altered only by written amendments made by Edwards. The amended plan will be submitted to the EC before being distributed to sites. Each site must obtain EC approval and complete required training (if any, and as required by Delegation of Authority role) before implementing the amended plan.

12.7 Plan Deviations

Each deviation from the plan must be documented with the date and reason for the deviation and reported to Edwards as soon as possible, and to the EC per local guidelines and government regulations.

APPENDIX A ABBREVIATIONS

Abbreviation	Full Term
ADE	Adverse Device Effect
AE	Adverse Event
AT	As Treated
CTA	Computed Tomography Angiography
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ICF	Informed Consent Form
IFU	Instructions for Use
NYHA	New York Heart Association
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
STS	Society of Thoracic Surgeons
TAVI	Transcatheter Aortic Valve Implantation
THV	Transcatheter Heart Valve
TEE	Transoesophageal Echocardiogram
TTE	Transthoracic Echocardiogram
USADE	Unanticipated Serious Adverse Device Effect
VI	Valve Implant

APPENDIX B DEFINITIONS

Term	Definition	Reference/ Justification
Arrhythmia / Conduction System Injury (Defect)	Arrhythmia: an irregular heart rate (increased > 100 beats/min or decreased < 60 beats/min) or abnormal rhythm resulting in symptoms or requiring medical intervention. Conduction system defect: an impairment of the electrical pathways and specialized muscular fibres that conduct impulses through the heart (ex. bundle branch block, heart block, internodal fibres, Bundle of His, Purkinje fibres, etc.).	Sponsor
Mortality, All-Cause	**Cardiovascular mortality** Any of the following criteria: • Death due to proximate cardiac cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure) • Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease • All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure • All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related adverse events • Sudden or unwitnessed death • Death of unknown cause **Non-cardiovascular mortality** Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide).	VARC-2
Paravalvular Leak	Paravalvular or paraprosthetic leak (PVL) is a complication associated with the implantation of a prosthetic heart valve whether traditional (surgical) or a transcatheter (TAVR) approach. PVL refers to blood flowing through a channel between the structure of the implanted valve and cardiac tissue as a result of a lack of appropriate sealing	ESC

<table>
<tr><th>Term</th><th>Definition</th><th>Reference/ Justification</th></tr>
<tr><td>Prosthetic Aortic Valve Regurgitation Criteria</td><td>
<table>
<tr><th></th><th>Normal</th><th>Mild</th><th>Moderate/ severe</th></tr>
<tr><td colspan="4">Semi-quantitative Parameters</td></tr>
<tr><td>Diastolic flow reversal in the descending aorta - PW</td><td>Absent or brief early diastolic</td><td>Intermediate</td><td>Prominent, holodiastolic</td></tr>
<tr><td>Circumferential extent of prosthetic valve paravalvular regurgitation (%) [a]</td><td><10%</td><td>10-29%</td><td>≥30%</td></tr>
<tr><td colspan="4">Quantitative parameters [b]</td></tr>
<tr><td>Regurgitant volume (mL/beat)</td><td><30 mL</td><td>30-59 mL</td><td>≥60 mL</td></tr>
<tr><td>Regurgitant fraction (%)</td><td><30%</td><td>30-49%</td><td>≥50%</td></tr>
<tr><td>EROA (cm^2)</td><td>0.10 cm^2</td><td>0.10-0.29 cm^2</td><td>≥0.30 cm^2</td></tr>
</table>
[a] Not well-validated and may overestimate the severity compared with the quantitative Doppler. Circumferential extent of PVR best not to be used alone, but in combination with vena contracta width and/or area.
[b] For LVOT >2.5 cm, significant stenosis criteria is <0.20.
</td><td>VARC-2</td></tr>
<tr><td>Prosthetic Aortic Valve Stenosis Criteria [a]</td><td>
<table>
<tr><th></th><th>Normal</th><th>Mild</th><th>Moderate/ severe</th></tr>
<tr><td colspan="4">Quantitative Parameters (flow-dependent) [b]</td></tr>
<tr><td>Peak velocity (m/s)</td><td><3 m/s</td><td>3-4 m/s</td><td>>4m/s</td></tr>
<tr><td>Mean gradient (mmHg)</td><td><20 mmHg</td><td>20-40 mmHg</td><td>>40 mmHg</td></tr>
<tr><td colspan="4">Quantitative parameters (flow-independent)</td></tr>
<tr><td>Doppler velocity index [c]</td><td>>0.35</td><td>0.35-0.25</td><td><0.25</td></tr>
<tr><td>Effective orifice area [d]</td><td>>1.1 cm^2</td><td>>1.1-0.8 cm^2</td><td><0.8 cm^2</td></tr>
<tr><td>Effective orifice area [e]</td><td>>0.9 cm^2</td><td>>0.9-0.6 cm^2</td><td><0.6 cm^2</td></tr>
</table>
[a] In conditions of normal or near normal stroke volume (50–70 mL).
[b] These parameters are more affected by flow, including concomitant aortic regurgitation.
[c] For LVOT >2.5 cm, significant stenosis criteria is <0.20.
[d] Use in setting of BSA ≥1.6 cm^2 (note: dependent on the size of the valve and the size of the native annulus).
[e] Use in setting of BSA <1.6 cm^2.
</td><td>VARC-2</td></tr>
<tr><td>Reintervention</td><td>Any intervention that repairs, alters or replaces a previously implanted or operated valve, which occurs after the completion of the valve implant procedure and the transfer to the procedure room. These interventions include:
Balloon aortic valvuloplasty
Surgical aortic valve replacement
Valve in valve
Paravalvular leak closure</td><td>STS/AATS</td></tr>
</table>

Term	Definition	Reference/ Justification
Stroke / 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 • or other neurological signs or symptoms consistent with stroke Duration of a focal or global neurological deficit >24 h; **OR** <24 h, if available neuroimaging documents a new haemorrhage or infarct; **OR** the neurological deficit results in death No other readily identifiable nonstroke cause for the clinical presentation (e.g., brain tumour, trauma, infection, hypoglycaemia, 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 (MR or CT scan) • Clinical presentation alone **Stroke definitions†:** • Non-disabling: a mRS score of less than 2 at 90 days or the last available clinical visit with evaluable data or one that does not result in an increase of at least one mRS category from an individual's pre-stroke baseline • Disabling: a mRS score of 2 or more at 90 days or the last available clinical visit with evaluable data and an increase of at least one mRS category from an individual's pre-stroke baseline **Stroke classification:** • Haemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid haemorrhage. • Ischemic: an acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of the central nervous system tissue • Undetermined: stroke with insufficient information to allow categorization as ischemic or haemorrhagic. **Transient Ischemic Attack (TIA)** Duration of focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new haemorrhage or infarct *Subjects with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies. #If a stroke is reported without evidence of confirmation of the diagnosis by one of these methods, the event may still be considered a stroke based on the clinical presentation alone. †Modified Rankin score assessments should be made by qualified individuals according to a certification process.	VARC-2

Term	Definition	Reference/ Justification
Vulnerable Population	Individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response	ISO 14155:2020

APPENDIX C REFERENCES

1. Barbanti M, Baan J, Spence MS, et al. Feasibility and safety of early discharge after transfemoral transcatheter aortic valve implantation–rationale and design of the FAST-TAVI registry. *BMC cardiovascular disorders.* 2017;17(1):259.
2. Wood DA, Lauck SB, Cairns JA, et al. The Vancouver 3M (Multidisciplinary, Multimodality, But Minimalist) Clinical Pathway Facilitates Safe Next-Day Discharge Home at Low-, Medium-, and High-Volume Transfemoral Transcatheter Aortic Valve Replacement Centers. *JACC: Cardiovascular Interventions.* 2019;12(5):459.
3. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *European Heart Journal.* 2017;38(36):2739-2791.
4. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). *Eur J Cardiothorac Surg.* 2012;42(5):S45-60.
5. Zamorano JL, Badano LP, Bruce C, et al. EAE/ASE recommendations for the use of echocardiography in new transcatheter interventions for valvular heart disease. *Eur J Echocardiogr.* 2011;12(8):557-584.
6. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for Noninvasive Evaluation of Native Valvular Regurgitation. *Journal of the American Society of Echocardiography.* 2017;30(4):303-371.
7. Baumgartner H, Hung J, Bermejo J, et al. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *European Heart Journal-Cardiovascular Imaging.* 2016;18(3):254-275.