International Multicenter Study of the Navitor/Navitor Vision Transcatheter Aortic Valve Platform

The INTENSIVE Study

Protocol Name	International Multicenter Study of the Navitor/Navitor Vision Transcatheter Aortic Valve Platform (The INTENSIVE Study)
Protocol Acronym	INTENSIVE
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Promoter	IRCCS Policlinico S. Donato, San Donato M.se, Milan, Italy
Number of Sites and Regions	Up to 25 sites in multiple countries (including Germany, Italy, Spain, UK, France)
Number of Patients	Up to 1000
Estimated Enrollment	12 Months
Clinical Follow-up Duration	Up to 5 years, per standard of care
Clinical Investigation Type	No-profit, Investigator Initiated Observational Study
Electronic Data Capture	Catchtrial EDC Platform (www.catchtrial.com)
CRO	• Regulatory Support, Ethic Committee Submissions: Meditrial Srl (www.meditrial.net) • Trial Management, Monitoring, Data Management and Safety Management: IRCCS Policlinico S. Donato, Clinical Research Unit, San Donato M.se, Milan, Italy

PROTOCOL AMENDMENT HISTORY

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COORDINATING INVESTIGATOR SIGNATURE PAGE

Protocol Title: The **INTENSIVE Study**

International Multicenter Study of the Navitor/Navitor Vision Transcatheter Aortic Valve platform

Declaration of the Coordinating Investigator:

The present Intensive Study protocol was subject to critical review. Its content is consistent with the current risk/benefit evaluation of the Medical Device as well as with the ethical and scientific principles of good clinical practice, the latest version of the Declaration of Helsinki, the local laws and the regulations and the applicable regulatory requirements of the Countries where this Study will be conducted.

Coordinating Investigator Signature:

18 Jul 2025

Name: Dr. Luca Testa

Date

Title: Head of Coronary Revascularisation Unit,

IRCCS Policlinico S. Donato, San Donato M.se, Milan, Italy

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I, the undersigned Investigator, am responsible for the conduct of the study at my site and have read and understood the specified protocol and all applicable regulatory requirements.

Study Principal Investigator

Printed name:
Signature:
Date:

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1 INTRODUCTION

INTENSIVE is a prospective, single-arm, multi-center, international, investigator-initiated study of the Navitor/Navitor Vision Transcatheter Aortic Valve (Navitor/Navitor Vision Valve) in patients with symptomatic, severe native aortic stenosis to monitor the outcomes of this valve in a real-world clinical setting. The investigators involved in the conduct of the clinical investigation will be qualified by education, training, or experience to perform their tasks.

1.1 TAVI Evolving Indications

Aortic stenosis (AS) remains the most common primary valve disease leading to surgery or catheter intervention in Europe and North America. Its prevalence increases with age, ranging from approximately 2% in adults 70-80 years of age to 9% in adults older than 80 years.[1] Although symptoms may remain latent for a period of time, the progression of AS can lead to the narrowing of aortic valve area by approximately 0.3 cm^2 per year and an increase in the systolic pressure gradient by as much as 15-19 mmHg per year. Functional deterioration of the aortic valve is usually coupled with coronary artery disease (CAD) and chronic renal insufficiency, leading to clinical symptoms and the need for treatment.[2]

Symptomatic, severe aortic stenosis is treated by aortic valve replacement.[3] The primary goals of aortic valve replacement are to reduce the risk for mortality, which can be as high as 25% per year if left untreated, and alleviate clinical symptoms, such as angina and dyspnea.[4] While aortic valve replacement has traditionally been done surgically, a less invasive transcatheter aortic valve implant technique that was first introduced in 2002, has evolved significantly.[5] The PARTNER trial was the first randomized trial evaluating the use of the balloon-expandable **Sapien (Edwards Lifesciences)** transcatheter valve in patients with severe, symptomatic AS at very high surgical risk. Cohort B of the trial enrolled subjects who were not considered suitable candidates for surgical aortic valve replacement (SAVR) and demonstrated a reduction in the rate of the composite of all cause death or repeat hospitalization with transcatheter aortic valve implantation (TAVI) over standard medical therapy (from 71.6% to 42.5%; P < 0.001).[6] Cohort A of the trial studied subjects at high surgical risk and demonstrated that TAVI was non-inferior to SAVR in 1-year all-cause mortality (3.4% vs. 6.5%; P = 0.001 for noninferiority).[7]

1.2 TAVI Indications

By 2012, the TAVI technique was recognized in the ESC/EACTS guidelines on the management of valvular heart disease with a Class I indication for patients that are not suitable for surgery and a Class IIA indication for patients at high surgical risk.[8] In 2014, similar Class I indications for TAVI were included in the ACC/AHA valvular heart disease guidelines.[9]

Also in 2014, two studies were published evaluating the use of self-expanding **CoreValve (Medtronic)** in extreme and high-risk patients. The CoreValve Extreme Risk Pivotal Trial was a single-arm trial that compared a composite of all-cause mortality or major stroke at 1 year to a performance goal. At 1 year, the trial met its primary endpoint with observed event rates of 24.3% for all-cause mortality and 4.3% for major stroke (composite rate of 26.0% vs. 43.0% performance goal; P < 0.0001).[10] The CoreValve US Pivotal Trial randomized high surgical risk subjects in a 1:1 ratio between TAVI and SAVR. The primary endpoint of all-cause mortality at 1 year was significantly lower in the TAVI arm compared to the SAVR arm (14.2% vs.19.1%; P = 0.04 for superiority).[11]

Further clinical research was conducted to evaluate the safety and effectiveness of TAVI in patients considered to be at intermediate surgical risk. The PARTNER 2 clinical trial included Cohort A (PARTNER 2 A), which was a randomized comparison of TAVI with the second-generation **Sapien XT valve** to SAVR in intermediate risk patients. The primary endpoint was a composite of all-cause mortality or disabling stroke at 2 years. The Sapien XT valve was shown to be non-inferior to SAVR for the endpoint at 2 years (19.3% vs 21.1%; P=0.001 for non-inferiority; TAVI outcomes: all-cause mortality 16.7%, disabling stroke 6.2%).[12] At 2 years, Sapien XT cohort subjects had a mean aortic valve area of 1.5 ± 0.4 cm^2 with a mean gradient of 10.8 mmHg, and moderate or severe paravalvular leak in 8% of subjects.[12] A separate observational arm

of the PARNTER 2 trial (PARTNER 2 - S3i), which evaluated the third generation **Sapien 3 valve**. The PARTNER 2 – S3i cohort enrolled 1077 intermediate risk subjects to be implanted with the Sapien 3 valve and compared a composite of all-cause mortality, stroke, and moderate or severe aortic valve regurgitation at 1 year with a propensity matched cohort of subjects from the SAVR arm of PARTNER 2 A. This analysis found the outcomes of subjects implanted with the Sapien 3 valve to be superior to SAVR in this composite (pooled weighted proportion difference -9.2%; P < 0.0001; Sapien 3 cohort outcomes: all-cause mortality 7.4%, stroke 4.6%, moderate or severe paravalvular regurgitation 1.5%).[13] At 1 year, subjects had a mean aortic valve area of 1.7 ± 0.4 cm^2 with a mean gradient of 11.4 mmHg.[13] Based on evidence from PARTNER 2, the AHA/ACC 2017 valvular heart disease guidelines were revised to include a class IIA indication for TAVI as a reasonable alternative for patients deemed intermediate surgical risk.[14, 15]

In parallel to PARTNER 2, the SURTAVI trial randomized 1746 intermediate risk subjects between TAVI with the CoreValve family (**CoreValve and Evolut R**) of valves and SAVR. The primary endpoint was a composite of all-cause mortality or disabling stroke at 2 years, and TAVI was found non-inferior to SAVR (Bayesian analysis, estimated incidence 12.6% vs. 14.0%; posterior probability of noninferiority >0.999; TAVI cohort outcomes at 2 years: all-cause mortality 12.6%, disabling stroke 2.6%).[15] In 2017, with the inclusion of the SURTAVI clinical trial results, ESC/EACTS upgraded their guidelines for transcatheter intervention in patients suffering from severe aortic stenosis who are determined to be at increased (i.e. intermediate and high) surgical risk to a Class I indication and that the decision between TAVI and SAVR be made by the local Heart Team based on individual patient characteristics.[3]

Since the 2017 AHA/ACC and ESC/EACTS guidelines revisions, results from the PARTNER 3 and Evolut Low Risk clinical trials reported the use of TAVI in low surgical risk patients. The PARTNER 3 trial randomized 1000 low risk subjects between TAVI with Sapien 3 and SAVR. The primary endpoint was a composite of all-cause mortality, stroke, or rehospitalization at 1 year. TAVI with Sapien 3 was shown to be superior to SAVR (composite 8.5% vs 15.1%; P = 0.001 for superiority; TAVI cohort outcomes at 1 year: all-cause mortality 1.0%, stroke 1.2%, rehospitalization 7.3%).[16] At 1 year Sapien 3 subjects had a mean aortic valve area of 1.7 ± 0.02 cm^2 with a mean gradient of 13.7 ± 0.26 mmHg.[16] The Evolut Low Risk trial randomized 1468 low risk subjects between TAVI with CoreValve family of valves (CoreValve, Evolut R, or Evolut PRO) and SAVR. The primary endpoint was a composite of all-cause mortality or disabling stroke at 2 years. TAVI was demonstrated to be noninferior to SAVR (Bayesian analysis, estimated incidence 5.3% vs. 6.7%; posterior probability of noninferiority >0.999; 1-year all-cause mortality 2.4%, stroke 4.1%, disabling stroke 0.8%).[17] The echocardiographic results at 1 year show TAVI subjects had a mean aortic valve area of 2.3 ± 0.7 cm^2 with a mean gradient of 11.2 ± 4.9 mmHg, and moderate or severe paravalvular leak in 3.6%.[18]

1.3 TAVI Market Approvals

In 2019, **Sapien 3** received CE Mark and FDA approval for the expanded indication to include all surgical risk classifications. The **Evolut R and Evolut Pro valve** indications have also been approved for all surgical risk classifications by FDA and have since received CE Mark for all surgical risk classifications.

In 2020, the **ACURATE neo2** aortic valve (Boston Scientific) received CE Mark for all surgical risk classifications. Currently, Sapien 3, Evolut R and Evolut Pro valves are the only valves approved for lower risk patients in both the US and Europe. These valves have performed well in particular aspects in low and intermediate risk patient populations; however, opportunity exists for a single valve to demonstrate strong performance across all measures. First, long-term durability of these transcatheter aortic valves remains unknown. Second, while Sapien 3 has demonstrated positive outcomes in terms of 1-year mortality and stroke, the hemodynamic performance (aortic valve area and gradients) has not been as good as the Evolut valves. In a similar vein, the self-expanding Evolut valves have not performed as well in as Sapien 3 in mortality, or stroke, and have had higher rates of permanent pacemaker implant following TAVI; however, Evolut valves have demonstrated excellent hemodynamic performance.

Abbott's self-expanding **Portico™ Transcatheter Aortic Valve** received CE Mark in 2012 and FDA approval in 2021 for use in patients with symptomatic, severe AS who are considered high or extreme surgical risk. The Portico Valve was studied in the prospective, randomized-controlled Portico IDE Study,

in which 750 subjects were randomized 1:1 between implantation with the Portico Valve and commercially available valves. The primary safety endpoint was a composite of all-cause mortality, disabling stroke, life-threatening bleeding requiring blood transfusion, acute kidney injury requiring dialysis, or major vascular complications at 30 days. The primary effectiveness endpoint was a composite of all-cause mortality or disabling stroke at 1 year. In the intention-to-treat analysis, the Portico Valve was shown to be non-inferior to commercially available valves for both the primary safety endpoint at 30 days (13.8% vs 9.6%; P=0.03 for non-inferiority) and the primary effectiveness endpoint at 1 year (14.9% vs 13.4%; P=0.006 for non-inferiority). The echocardiographic results at 1 year show Portico subjects had a mean aortic valve area of 1.8 ± 0.7 cm^2 (vs. 1.7 ± 0.5 cm^2) with a mean gradient of 8.6 ± 3.8 mmHg (vs. 10.6 ± 5.1 mmHg), and moderate or severe paravalvular leak present in 6.3% (vs. 2.1%) of subjects. In comparison, at 1 year Sapien 3 and Evolut R/Evolut PRO subjects had a mean aortic valve area of 1.6 ± 0.5 cm^2 and 1.8 ± 0.5 cm^2 with a mean gradient of 12.4 ± 5.3 mmHg and 7.8 ± 3.6 mmHg respectively.[19]

Following completion of enrollment of the randomized cohort, the **FlexNavTM Delivery System** was introduced into the Portico IDE study. The FlexNav Delivery System represents a design modification to the first-generation Portico Delivery System. Key design features include a hydrophilic stability layer to minimize system manipulations and support precise valve placement and an integrated sheath to reduce the delivery profile diameter to minimize vessel trauma at the access site. The FlexNav Delivery System was studied in 180 subjects via 2 concurrent, prospective, non-randomized single-arm studies (FlexNav DS arm within the Portico IDE Study and FlexNav EU CE Mark Study). Compared to the Portico group of the randomized cohort, introduction of the FlexNav Delivery System was associated with lower rate of major vascular complications (5.0% vs 9.6%). Safety outcomes in the FlexNav cohort were favorable with 0.6% mortality and 1.1% disabling stroke rates within 30 days.[20]

1.4 The Navitor/Navitor Vision TAVI

The Navitor/Navitor Vision Transcatheter Aortic Valve is a design iteration that builds on the Portico Valve system with the addition of a fabric outer cuff to the exterior portion of the stent to optimize valve sealing and improve paravalvular leak (PVL) performance.

The Navitor/Navitor Vision Valve has been studied in the Portico NG trial, which is a prospective, single-arm, multi-center clinical investigation designed to evaluate the safety and effectiveness of the Navitor/Navitor Vision Valve in subjects with symptomatic, severe AS at high or extreme surgical risk. The primary safety endpoint was all-cause mortality at 30 days, and the primary effectiveness endpoint was moderate or greater PVL at 30 days. Based on data from 120 subjects in Australia, Europe, and the U.S., the rate of all-cause mortality at 30 days was 0%, and there were no cases of moderate or severe PVL at 30 days as evaluated by an independent core laboratory, resulting in a 30- day rate of 0% of moderate or greater PVL. The echocardiographic results at 30 days show Navitor/Navitor Vision subjects had a mean aortic valve area of 2.0 ± 0.5 cm^2 with a mean gradient of 8.1 ± 3.7 mmHg. The combination of the Navitor/Navitor Vision Valve delivered via the FlexNav Delivery System offers a favorable safety profile with the potential for strong hemodynamic performance and with reduced PVL.

The Navitor/Navitor Vision Transcatheter Valve System (including the FlexNav Delivery System and Navitor/Navitor Vision Loading System) received CE Mark in May 2021 as well as approval in Japan, India, and Canada in 2022 for the treatment of patients with symptomatic, severe AS that are considered high or extreme surgical risk, and is currently under regulatory review in other geographies.

1.5 Rationale for the Intensive Study

The INTENSIVE Study will provide comprehensive real-world evidence on the safety, performance, and clinical outcomes of the Navitor/Navitor Vision Valve with the FlexNav Delivery System in routine clinical practice. By enrolling a broad, unrestricted TAVI population across multiple interventional centers, the study captures the diversity and complexity of patients typically encountered in daily clinical settings. This

comprehensive dataset will offer valuable insights into device performance, inform clinical decision-making, and support best practices in the evolving field of transcatheter valve therapy.

2 CLINICAL STUDY OVERVIEW

2.1 Clinical Investigation Objective

The INTENSIVE Study aims to gather and monitor real-world outcomes of the Navitor/Navitor Vision Valve with the FlexNav Delivery System in a diverse population undergoing TAVR. For a detailed description of primary and secondary endpoints see Section 4.1 and 4.2. This comprehensive data collection across 25 interventional centers, aligned with standard clinical care practices, seeks to provide an objective benchmark for current TAVR practice.

2.2 The Navitor System

The Navitor System include the Navitor Transcatheter Aortic Valve (23 mm, 25 mm, 27 mm, 29 mm, and the 35 mm), FlexNav Delivery System (small and large), and Navitor Loading System (small, large, and LG+). The FlexNav Delivery System (small and large) is commercially available in Europe. The 23 mm, 25 mm, 27 mm, 29 mm, and 35 mm valves and their loading systems are currently CE Marked.

Model numbers for the Navitor Valve, FlexNav Delivery System, and Navitor Loading System and their regulatory status are provided below in **Table 1**. The matching components of the Navitor Implantation System are listed in **Table 2**.

Table 1: Devices Included in the Intensive Study

Device name	Model/Type
Navitor 23 mm Valve	PRT-NG- 23/NVTR-23
Navitor 25 mm Valve	PRT-NG- 25/NVTR-25
Navitor 27 mm Valve	PRT-NG- 27/NVTR-27
Navitor 29 mm Valve	PRT-NG- 29/NVTR-29
Navitor Titan 35 mm Valve	PRT-NG-35
FlexNav Small Delivery System	FN-DS-SM-IDE/ FNAV-DS-SM
FlexNav Large Delivery System	FN-DS-LG-IDE/ FNAV-DS-LG
Navitor Small Loading System	PRT-NG-LS- SM/NVTR-LS-SM
Navitor Large Loading System	PRT-NG-LS- LG/NVTR-LS-LG
Navitor Titan Loading System LG+	PRT-NG-LS-35

Table 2: Matching Components in the Navitor Implantation System

Navitor Valve Catalog Numbers	FlexNav Delivery System Catalog Numbers	Navitor Loading System Catalog Numbers
PRT-NG-23/NVTR-23 (23 mm) or	FN-DS-SM-IDE/FNAV-DS-SM	PRT-NG-LS-SM/NVTR-LS-SM

Navitor Valve Catalog Numbers	FlexNav Delivery System Catalog Numbers	Navitor Loading System Catalog Numbers
PRT-NG-25/NVTR-25 (25 mm)		
PRT-NG-27/NVTR-27 (27 mm) or PRT-NG-29/NVTR-29 (29 mm)	FN-DS-LG-IDE/FNAV-DS-LG	PRT-NG-LS-LG/NVTR-LS-LG
PRT-NG-35 (35 mm)	FN-DS-LG-IDE/FNAV-DS-LG	PRT-NG-LS-35

The intended Indication for Use statements for the products used in this Study are as follows:

For the native valve application, the Navitor Valve is indicated for transcatheter delivery in patients with symptomatic severe native aortic stenosis who are considered intermediate or low surgical risk.

The FlexNav Delivery System is indicated for transfemoral or subclavian/axillary delivery of the Navitor Valve.

The Navitor Loading System is indicated for loading the Navitor Valve in the FlexNav Delivery System.

The Navitor Valve, FlexNav Delivery System, and the Navitor Loading System will be used in accordance with the Instructions for Use (IFU). Please refer to the Navitor Transcatheter Aortic Valve Implantation System IFU for further details.

2.2.1 Navitor System Description

The Navitor Valve was developed based on iterative modifications to the first-generation Portico Transcatheter Aortic Valve and is designed to be used in combination with the FlexNav Delivery System and Navitor Loading System.

Key design features of the Navitor Valve include:

- A new fabric outer cuff on the exterior portion of the stent to optimize valve sealing and reduce paravalvular leak.
- Minor modifications to the stent design intended to minimize vessel trauma and aid retainer release from the delivery system, normalize the aortic/annular to stent height ratio, and provide uniform chronic outward radial force across the range of valve sizes to improve valve expansion, stability, and sealing.

2.2.1.1 Navitor/NavitorVision Valve

The Navitor Valve maintains several design features of the first-generation Portico Valve including same valve sizes and use range (except for the addition of the 35 mm valve to expand the use range as listed in **Table 3**), open stent cell design to provide easy coronary access and blood flow, repositionable with the ability to re-sheath and retrieve, leaflets derived from pericardial bovine tissue, and intra-annular placement of leaflets/cuff within the stent frame for early valve function to maintain hemodynamic stability during implant.

Table 3: Patient Anatomical Specification per the Navitor/Navitor Vision Valve

Model Number	Annulus Diameter	Ascending Aorta Diameter	Area	Perimeter	Eccentricity Ratio*
PRT-NG -23/NVTR-23	19-21 mm	26-36 mm	277-346 mm^2	60-66 mm	≥ 0.73
PRT-NG -25/NVTR-25	21-23 mm	28-38 mm	338-415 mm^2	66-73 mm	≥ 0.73

PRT-NG -27/NVTR-27	23-25 mm	30-40 mm	405-491 mm^2	72-79 mm	≥ 0.73
PRT-NG -29/NVTR-29	25-27 mm	32-42 mm	479-573 mm^2	79-85 mm	≥ 0.73
PRT-NG-35	27-30 mm	27-44 mm	559-707 mm2	85-95 mm	≥ 0.73

*Eccentricity ratio: minor/major diameter ratio

The valve is comprised of three main components: stent, leaflets, and cuff (**Figure 1**). The stent is made from nitinol, a nickel-titanium alloy that has self-expanding properties and is radiopaque. The leaflets are made from bovine pericardium and are sutured together into a tri-leaflet configuration on the stent frame.

The leaflet pericardial tissue is preserved and crosslinked in glutaraldehyde and undergo an anti-calcification treatment using Linx™ anti calcification technology. A new feature of the Navitor Valve is the addition of the outer cuff and updating the inner cuff material from porcine pericardium to fabric (**Figure 1**). Both the inner and outer cuff is made from polyethylene fabric and provides the sealing area for implantation to provide paravalvular leak reduction by allowing blood to fill any potential voids between the native valve and the stent.

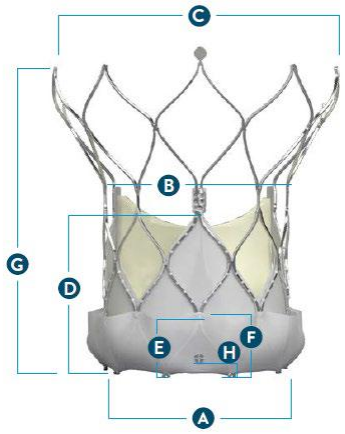
Figure 1a: Navitor Valve

In addition to the new outer cuff feature, the Navitor Valve incorporates the following key design enhancements:

- Addition of a slight inward curvature to the aortic end of the stent to minimize vessel trauma.
- Adjusted scaling of the stent across all valve sizes to normalize the aortic/annular to stent heightratio.
- Increased chronic outward radial (COR) force of the 23 mm and 25 mm valves to a common CORforce across the Navitor family to improve valve expansion, stability and sealing.

The valve is sterilized using a multi-component sterilant (i.e. glutaraldehyde, formaldehyde and ethanol) and provided sterile and non-pyrogenic.

Figure 1b. Navitor Vision Valve



VALVE	NVRO-23	NVRO -25	NVRO-27	NVRO-29	NVRO-35
A) Inflow Diameter (mm)	23	25	27	29	35
B) Outflow Diameter (mm)	23	25	27	29	35
C) Aortic Stent diameter (mm)	41	43	44	46	48
D) Commissure Height (mm)	21	23	24	25	27
E) Half Cell Height (mm)	7	7	8	8	9
F) NaviSeal™ cuff height (mm)	9	9	10	10	11
G) Stent Height (mm)	47	48	48	48	47
H) Marker's height (mm)	3	3	3	3	3

The Navitor Vision Valve differs from the Navitor Valve for the presence of the 3 markers.

Three tantalum radiopaque markers (Vision Technology) are positioned between the inner and outer skirt, aligned beneath each commissure of the bioprosthesis, 3 mm above the inflow leaflet edge. These markers assist with fluoroscopic positioning and ensure accurate depth implantation.

2.2.1.2 FlexNav Delivery System

The FlexNav Delivery System is an over-the-wire, 0.035"- compatible system that includes a hydrophilic-coated, integrated sheath to facilitate gradual, controlled deployment of the Portico or Navitor/Navitor Vision Valve in patients with a minimum vessel diameter of ≥ 5mm.

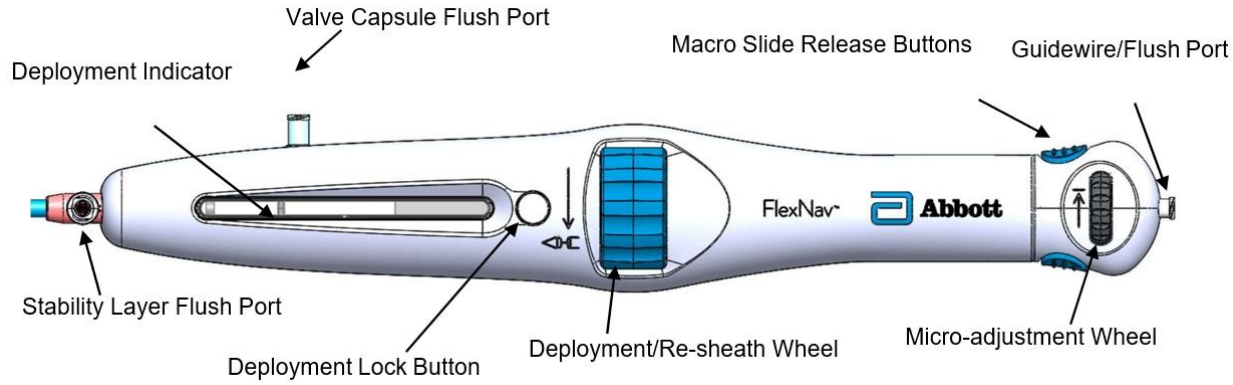
The FlexNav Delivery System allows for transfemoral or subclavian/axillary access methods with the current range of Navitor/Navitor Vision Valves size (23, 25, 27, 29, and 35 mm) (**Table 4**). The FlexNav Delivery System has a working length of 107 cm and is composed of a handle at the proximal end. The FlexNav Delivery System is available in two sizes with equivalent integrated sheath diameters of 14 F (small) or 15 F (large), and outer diameters of 6.0 mm (small) and 6.3 mm (large) at the distal end, respectively.

Table 4: FlexNav Delivery System Models and Compatibility with Navitor/Navitor Vision Valve Sizes

Description	Catalog Number	Equivalent Integrated Sheath Diameter	Distal End Outer Diameter	Integrated Sheath Working Length	Delivery System Length	Minimum Vessel Diameter	Compatible Valve Size
FlexNav Delivery System (small)	FNAV-DS-SM	14 F	6.0 mm	30 cm	107 cm	≥ 5.0 mm	23 mm and 25 mm
FlexNav Delivery System (large)	FNAV-DS-LG	15 F	6.3 mm	30 cm	107 cm	≥ 5.5 mm	27 mm, 29 mm, and 35 mm

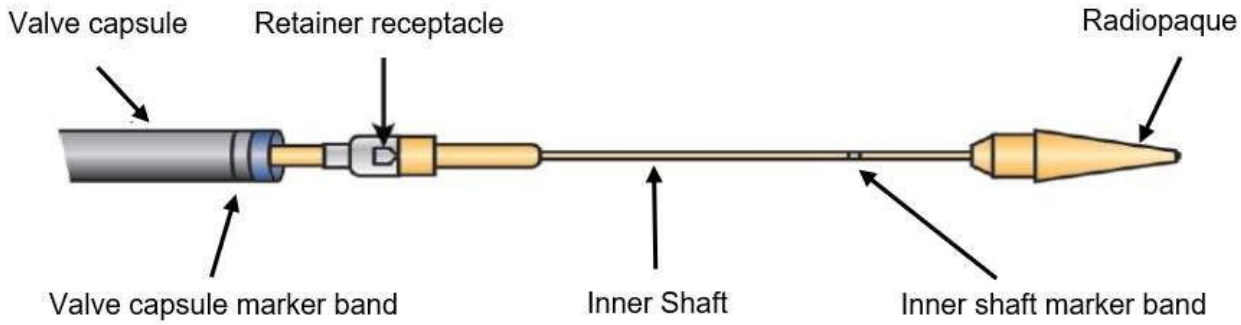
The FlexNav Delivery System shaft includes a stability layer over the outer member to improve control during positioning and deployment of the valve. The FlexNav Delivery System handle functions in a similar manner as the first-generation Portico Delivery System with modifications and added labeling. The macro slide that facilitates opening and closure of the delivery system is incorporated into the proximal end of the handle with two release buttons (**Figure 2**).

Figure 2: FlexNav Delivery System- Handle Detail



The distal end of the FlexNav Delivery System features an atraumatic, radiopaque tip with hydrophilic coating and a radiopaque inner member marker band to aid in visualizing. The FlexNav Delivery System includes the same retainer design as the first-generation Portico Delivery system (**Figure 3**)

Figure 3: FlexNav Delivery System - Distal End Detail



2.2.1.3 Navitor Loading System

The Navitor/Navitor Vision Loading System is an accessory used to compress and load the Navitor/Navitor Vision Valve onto the FlexNav Delivery System. The Navitor/Navitor Vision Loading System is similar in design and operation to the current FlexNav Loading System with changes to the loading funnel (angle increased) and base insert (flange height shortened). Additionally, a stent guide has been introduced to this system to assist in loading efficiency. All other Navitor/Navitor Vision Loading System components (loading base, loading tube, leaflet tester) are the same as the FlexNav Loading System. The method of loading the Navitor/Navitor Vision Valve onto the FlexNav Delivery System is also unchanged.

The Navitor/Navitor Vision Small Loading System is used for loading the 23 or 25 mm Navitor/Navitor Vision Valves on the FlexNav Small Delivery System, the Navitor/Navitor Vision Large Loading System is used for loading the 27 or 29 mm Navitor/Navitor Vision Valves on the FlexNav Large Delivery System, and the Navitor/Navitor Vision Titan Loading System - LG+ is used for loading the Navitor/Navitor Vision Titan 35 mm Valve on the FlexNav Large Delivery System.

Please refer to the IFU for additional information regarding the device used in this Study.

3 INTENSIVE STUDY OVERVIEW

The INTENSIVE Study is a prospective, single-arm, multi-center, international, investigator-initiated study in patients with symptomatic, severe native aortic stenosis to monitor the outcomes of Navitor/Navitor Vision Valve in a real-world clinical setting. The Study will collect clinical outcome data from a maximum of 1000 subjects from qualified interventional centers in multiple countries (including Germany, Italy, Spain, UK, France).

The Study will enroll subjects that, after comprehensive Heart Team evaluation, are scheduled for treatment with the Navitor/Navitor Vision Valve according to standard of care at up to 25 experienced TAVI implant centers across Europe and UK. All sites must either have prior Portico or Navitor/Navitor Vision TAVI system experience. Subjects who provide informed consent for the collection of their clinical data in this Study, will undergo Navitor/Navitor Vision Valve implantation via a transfemoral or alternative access (subclavian or axillary) approach using the site's anesthesia protocol for TAVI procedures.

In the Study, the **point of enrollment** is defined as informed consent signing, whereas the **point of registration** is defined as the insertion of the FlexNav Delivery System (loaded with a Navitor/Navitor Vision Valve) into the subject's vasculature (the subject is considered attempted with Navitor/Navitor Vision Valve implantation at this point) (Figure 4). Only registered subjects will be included in the analysis.

The endpoints of interest will be defined according to VARC-3 definitions.

Subjects participating in the Study will be followed for a total of 5 years with data collected at, baseline, procedure, prior to hospital discharge, and follow-up at 30 days, 12 months and annually thereafter up to 5 years.

Key clinical outcome assessments at each follow-up visit are described in **Section 6.0**.

The expected **duration of enrollment** is 12 months, and the **total duration of the Study** including final data cleaning, reporting, and site close-out is expected to be approximately 6.5 years.

For a discussion of the risks and benefit of participation in this Study, Refer to the Risks Analysis (Section 15.0) of this protocol for details.

4 ENDPOINTS

4.1 Primary Endpoint

The primary endpoint is all-cause mortality at 12 months post index Navitor/Navitor Vision implantation procedure

4.2 Secondary (Descriptive) Endpoints

The rate of the following key outcomes for the Study will be assessed as descriptive endpoints per the Valve Academic Research Consortium (VARC) 3 event definitions[21,22]:

1. Composite of all-cause mortality, fatal stroke/stroke with disability, type 3/type 4bleeding, stage 3/stage 4 acute kidney injury, major vascular complications, or major access- related non-vascular complications at 30 days
2. Composite of all-cause mortality or all stroke at 12 months
3. Procedural success defined as successful vascular access, delivery and deployment of the Navitor/Navitor Vision Valve; retrieval of the delivery system and correct positioning of a single Navitor/Navitor Vision Valve inthe proper anatomical location and the absence of procedural mortality
4. Mortality (all-cause, cardiovascular, and valve-related) at 30 days and 12 months
5. Stroke (All stroke, fatal stroke, stroke with disability, and stroke without disability) at 30 days and12 months
6. Transient ischemic attack (TIA) at 30 days and 12 months
7. Bleeding (type 4, type 3, and type 2) at 30 days
8. Major vascular complications at 30 days
9. Major access-related non-vascular complications at 30 days
10. Major cardiac structural complications at 30 days
11. Acute kidney injury (stage 4, stage 3, and stage 2) at 30 days
12. Permanent pacemaker insertion at 30 days and 12 months
13. Myocardial infarction at 30 days and 12 months
14. Coronary obstruction requiring intervention at 30 days and 12 months
15. Difference in Coronary arteries' cannulation time pre vs post Navitor/Navitor Vision implant
16. Differences in outcome of PVL, embolization / migration based on:
    a. no-predilation,
    b. pre-dilation with balloon not exceeding minimum diameter on CT scan
    c. pre-dilation with balloon exceeding the minor axis but not exceeding perimeter derived diameter on CT scan

Suggested to acquire a short cine during final release to visualize (or at least measure) any valve migration

17. Assessment of PM dependency at 3 months post implant
    a. *Suggested* methodology:
        i. PM will be set with
            1. baseline frequency equal to the one recorded by the ECG performed at rest at admission - 10 bpm
            2. all diagnostics ON
            3. rate-responsiveness OFF
            4. AV autosensing ON
            5. Spontaneous AV conduction favoring algorithm ON
        ii. at 3 months, based on the PM diagnostics, following data will be collected:
            1. % of total stimulation (stimulated beats vs total beats)
            2. weekly (if available) % stimulation evolution
        iii. True permanent PM is being defined by San Donato consensus and EP expertise – Prof. Pappone
        iv. Download diagnostic – if possible – at follow-up to be stored in the eCRF
18. Vascular access complication rate according to the "Hostile Score" (JACC Cardiovasc Interv 2023 Feb 27;16(4):396-411)
19. Changes in functional status from baseline to follow-up assessments at 30 days and 12 months (e.g., New York Heart Association (NYHA) functional classification, quality oflife measure: Kansas City Cardiomyopathy Questionnaire (KCCQ))
20. Rehospitalization (procedure-related or valve-related hospitalization, and other cardiovascular hospitalization) at 30 days and 12 months
21. Paravalvular leak (none/trace, mild, moderate or severe) at discharge, 30 days, 12 months and annually (when collected) through 5 years
22. Changes in echocardiographic parameters from baseline to follow-up at 30 days, 12 months and annually (when collected) through 5 years (e.g., mean effective orifice area, mean transvalvular gradient)
23. Aortic valve reintervention at 30 days, 12 months, and annually through 5 years
24. Prosthetic valve endocarditis at 12 months and annually through 5 years
25. Structural valve deterioration at 12 months and annually through 5 years
26. Non-structural valve dysfunction at 12 months and annually through 5 years
27. Successful coronary access as needed at 12 months and annually through 5 years
28. Clinically significant prosthetic valve thrombosis at 12 months and annually through 5 years

All endpoints will be assessed from the index procedure unless otherwise noted.

5 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This Study will enroll subjects of all genders who have symptomatic, severe AS, either in native or in a surgical bioprosthetic valve and are indicated for TAVI implantation. The latter can also be predominantly regurgitant to be suitable for enrolment. Complete clinical investigation eligibility criteria are described in **Section 5.3**. Subjects must meet all general eligibility criteria for the TAVI procedure and provide written informed consent prior to sites collecting any clinical data for this Study.

The operative risk determination of study candidates will be done by the local heart team. The assessment of surgical risk will include the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Risk Calculator score and/or EuroSCORE II, indices of frailty, and comorbidities not captured by risk calculators, as described below, and current TAVI practice guidelines.[23]

5.2 Subject Screening and Informed Consent

5.2.1 Subject Pre-Screening

A member of the site's clinical investigation team previously trained to the protocol must evaluate patients for the general eligibility criteria, and if applicable, will enter the patients into the site- specific Pre-Screening Log. A patient who does not satisfy all general eligibility criteria prior to informed consent is considered a screen failure and should not be enrolled in the Study.

Sites will ask patients meeting general inclusion criteria and no general exclusion criteria to sign an Informed Consent form following the established Informed Consent process (described in **Section 5.2.2**) if they wish to participate in the Study.

5.2.2 Informed Consent

The Investigator or his/her authorized designee (if applicable) will conduct the Informed Consent process, as required by applicable regulations and the center's Ethics Committee. This process will include a verbal discussion with the patient on all aspects of the Study. As this is a investigator initiated Study where the Navitor/Navitor Vision Valve is used according to the approved indications, the subject consent will be focused on the agreement to allow his/her clinical data collection and participation in the Study follow-up visits that will allow the evaluation of the relevant clinical outcomes.

None of the Study follow-up examinations expose the subject to potential risk or burden, therefore the risk of participation in the Study is limited to potential breach of confidentiality, which is mitigated through pseudonymization of all data collected in the Study. Sites must inform patients about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss of benefits to which the patient is otherwise entitled. Withdrawal from the study will not jeopardize their future medical care or relationship with the investigator.

During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the patient and will respect patient's legal rights. Financial incentives will not be given to patients.

The site shall provide the patient with the Informed Consent form written in a language that is understandable to the patient and that has been approved by the center's Ethics Commission. The patient shall have adequate time to review, ask questions, and consider participation. The Principal Investigator or his/her authorized designee will make efforts to ensure that the patient understands the information provided. If the patient agrees to participate, they must sign and date the Informed Consent form, along with the person obtaining the consent prior to any data collection. The site will file the signed original in the patient's hospital or research charts and provide a copy to the patient.

If, during the Study, new information becomes available that can significantly affect a subject's future health and medical care, the Principal Investigator or his/her authorized designee (if applicable) will provide this

information to the subject. If relevant, sites will ask the subject to confirm their continuing informed consent in writing.

5.2.2.1 Vulnerable Subjects Exclusion

Consistent with the Study exclusion criteria listed in **Section 5.3.3**, this Study excludes individuals unable to make the decision to participate in the study on their own or who are unable to fully understand all aspects of the study 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. Individuals under the age of 18 or age of legal consent are excluded from the study population. Individuals unable to read or write are excluded from the study population. Pregnant or breastfeeding women are also excluded from the study population.

All other aspects of the Informed Consent process will follow **Section 5.2.2**.

5.2.3 Subject Pre-Procedure Workup

Once a duly dated and signed Informed Consent form is obtained, sites will collect the following data that are routinely obtained in all patients scheduled for TAVI as part of the standard pre-procedural workup:

1. Demographics (age on consent date, gender)
2. Medical History (including major cardiovascular and arrhythmia history, vascular, and other coexisting medical conditions)
3. Physical Exam (including height, weight, resting heart rate, and blood pressure)
4. Surgical Risk Assessment tool (STS Risk Score and EuroSCORE II)
5. New York Heart Association (NYHA) Functional Classification
6. Frailty Index Assessment (Katz index of Activities of Daily Living plus Independence in Ambulation Index))
7. Echocardiography to include comprehensive 2D transthoracic echocardiogram (TTE), including assessment of aortic valve gradients (mean and peak), areas, indices, degree of regurgitation, cardiac output and cardiac index, left ventricle systolic function (global and segmental)
8. 12 Lead Electrocardiogram (ECG)
9. Computed Tomography (CT) Scan with Angiography of chest, abdomen and pelvis including aortic root and valve annulus for valve sizing, assessment of suitability of iliofemoral or alternate access (brachial approach or transcaval approach), and determination of appropriate coaxial angles for optimizing the valve implantation procedure. CT covering at least systole is required for valve sizing. CT scan performed up to 12 months prior to consent will be acceptable.

All cardiac medications and all medications given for cardiovascular effect may be continued at their prescribed dosages for the screening assessments.

Further details regarding Pre-Procedure Workup can be found in **Appendix III**.

5.3 Eligibility Criteria

5.3.1 General Eligibility Criteria

Assessment for general eligibility criteria is based on medical records of the site and interview with a candidate patient. Patients must meet ALL general inclusion criteria to participate in the clinical investigation. If ANY general exclusion criteria are met, the patient is excluded from the clinical investigation and cannot be enrolled.

5.3.2 Inclusion Criteria

5.3.2.1 General Inclusion Criteria

1. Subject is referred to receive a Navitor/Navitor Vision TAVI according to the local Heart Team. The Heart Team determines the indication to TAVI with Navitor/Navitor Vision before the possible enrolment and independently from the study.
2. Subject is of legal age for consent in the host country.
3. Subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent as approved by the Ethics Committee (EC) of the respective clinical site.

5.3.3 Exclusion Criteria

5.3.3.1 General Exclusion Criteria

1. Pregnant or nursing subjects
2. Need for emergency surgery for any reason
3. Contraindications to Navitor/Navitor Vision TAVI according to the IFU:
    a. Any sepsis, including active endocarditis
    b. Any evidence of left ventricular or atrial thrombus
    c. Vascular conditions (i.e., stenosis, tortuosity, or severe calcification) that make insertion and endovascular access to the aortic valve impossible
    d. Non-calcified aortic annulus
    e. Any leaflet configuration other than tricuspid
    f. Inability to tolerate antiplatelet/anticoagulant therapy
4. Incapacitated individuals, defined as persons who are mentally ill, mentally handicapped, individuals with severe dementia or individuals without legal authority
5. Individuals who are unable to read or write

5.4 Subject Enrollment Point

A patient is considered enrolled in the Intensive Study from the moment the patient provides written informed consent.

5.5 Subject Discontinuation

Each subject meeting all general eligibility criteria who is enrolled and receives the Navitor valveshall be followed up until completion of the recommended 5 year follow-up period; however, a subject's participation in any clinical study is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Subject death
- Subject undergoes the interventional procedure but exits the operating room without an implanted Navitor Valve; in this case, follow-up is limited to 30 days post-procedure for safety assessment
- After Navitor implantation, subject receives another aortic valve intervention during follow-up (eg, valve in valve intervention, surgical AVR, etc): in this case, follow-up is limited to 30 days after the additional procedure for safety assessment
- Subject voluntary withdrawal

- Subject lost-to follow-up as described below
- Subject's follow-up is terminated according to **Section 13.1**

Sites must collect and document the reason(s) for subject discontinuation. Investigators must also report this to their respective EC as defined by their institution's procedure(s).

No additional follow-up is required or data recorded from subjects once withdrawn from the Study, except for the status (deceased/alive).

In case of subject withdrawal of consent, the site should make attempts to schedule the subject for a final follow-up visit. At this final follow-up visit, the subject will undergo the following assessments (routine assessments during follow-up visit) and related data will be collected when available:

- Echocardiography to include comprehensive transthoracic echocardiogram, including assessment of aortic valve gradients (mean and peak), areas, indices, degree of regurgitation, cardiac output and cardiac index, left ventricle systolic function (global and segmental)
- Adverse Event assessment

Lost-to-Follow-up

If the subject misses two consecutive scheduled follow-up time points and the attempts at contacting the subject detailed below are unsuccessful, then the subject is considered lost-to-follow-up. Site personnel shall make all reasonable efforts to locate and communicate with the subject (and document these efforts in the source documents), including the following, at each contact time point:

- A minimum of two telephone calls on different days over the specified follow-up windows to contact the subject should be recorded in the source documentation, including date, time and initials of site personnel trying to make contact.
- If these attempts are unsuccessful, the site should send a letter (certified if applicable) to the subject.
- If a subject misses one or more non-consecutive follow-up contact time points, it will be considered a missed visit. The subject may then return for subsequent visits. If the subject misses two consecutive time points and the above-mentioned attempts at communicating with the subject are unsuccessful, the subject will be considered lost-to-follow-up.

Note: Telephone contact with General Practitioner, non-clinical investigation cardiologist or relative will be considered as subject contact for the purpose of collecting vital status information. The investigational site shall retain records of the contact.

5.6 Number of Subjects

Up to 1000 subjects will be included.

5.7 Total Expected Duration of the Clinical Investigation

The expected duration of enrollment is 12 months. The expected duration of each subject's participation is 5 years, including the scheduled visits and data collection for this Study. Subjects will be exited from the Study at the conclusion of their 5-year follow-up visit.

6 TREATMENT AND EVALUATION OF ENDPOINTS

Scheduled visits will be performed in the following order, which constitutes the routine clinical practice: Baseline, Index Procedure, Discharge, 30 days,12 months, and annual follow-up assessments to 5 years.

6.1 Baseline

6.1.1 Baseline Assessments

The following baseline assessments will be performed for all subjects prior to the index procedure.

- Cardiovascular medications documentation (including dosage)
- Modified Rankin Scale (mRS) Assessment
- Quality of Life Assessment: KCCQ
- Laboratory Measurements (international normalized ratio (INR) if subject is on warfarin or other anticoagulants/vitamin K antagonists in lieu of warfarin)
- Adverse events assessment

All baseline assessments are considered standard of care.

6.1.2 Pre-procedure Antiplatelet/Anticoagulation Medications

Antiplatelet/Anticoagulation and other medications should be administered pre-procedure per the standard of care at the investigational site.

6.1.3 Pre-procedure Blood Tests

The following blood tests will be performed, as per standard of care, at the investigational site within 72 hours prior to the index procedure:

1. Cardiac biomarkers (Troponin or CK-MB)
2. Creatinine

6.2 Index Procedure

6.2.1 Procedures Involved in the Use of the Device

Please refer to IFU for instructions on handling and preparation of the Navitor/Navitor Vision Valve, FlexNav Delivery System, Navitor/Navitor Vision Loading System. If the devices were not used according to the IFU, complete a Protocol Deviation form.

6.2.2 Procedural Anticoagulation

Anticoagulation use during the procedure is left to the physician's discretion or should be performed, as with any other transcatheter valve implantation, considering risks and benefits for the subject. The activated clotting time (ACT) should be monitored throughout the procedure (and recorded on source documentation). Medications should be adjusted to keep the subject's ACT > 250 seconds.

6.2.3 Implant Procedure

Navitor/Navitor Vision implants will be performed by experienced TAVI implanters that are board certified interventional cardiologist(s) and/or cardiac surgeon(s) and study investigators.

Operators are encouraged to utilize the Navitor/Navitor Vision Cusp Overlap technique (COT) to facilitate an accurate valve deployment. As per usual practice the COT will follow the following steps:

1. Perform pre-BAV sizing the balloon according to local practice

2. Initial positioning of the Navitor/Navitor Vision valve:
    a. Position the inflow edge of the constrained valve frame at the base of the NCC in the cus p overlap view
3. Valve deployment:
    a. Proceed with slow, steady deployment to allow the inflow edge of the valve to attain the t arget implant depth of 3mm.
4. At 80% deployment
    a. Confirm implant depth and proper valve position in both cusp overlap and an alternative v iew with frame parallax removed.
5. Final deployment
    a. Withdraw the guidewire to a mid-ventricular position and ensure neutral position of the Fl exNav Delivery system.
    b. Release the valve slowly and confirm all 3 retainer tabs have been released before withdr awing the FlexNav delivery system into the descending aorta.

If needed but not mandatory, an Echocardiographer or Echocardiographic Technician should be available and may perform a post t implantation on-table TTE to assess for both transvalvular gradient and PAR and complications, prior to leaving the procedure room. All patients will also undergo standardized invasive hemodynamics to determine invasive transvalvular gradients after TAVR.

Although not recommended, if a physician determines it is in the best interest of the subject to have a second transcatheter aortic valve placed, a subject may receive an additional transcatheter aortic valve.

Standardized imaging techniques will be used during the index procedure to implant the valve and to assess valve performance and coronary patency. Ultrasound guided arterial access is highly recommended.

The following data will be collected during the implant procedure:

1. Vascular access, deployment, final valve placement, performance, and closure data collection
2. Other product utilization (e.g., introducer sheaths, guide wires, balloon catheters)
3. Final hemodynamic assessment of mean aortic valve gradient can be performed by echocardiogram or invasive pressure measurement (post-implant only).
4. Final assessment of aortic regurgitation (including PVL) can be performed by echocardiogram or angiography (post-implant only).
5. Monitor the cardiac rhythm and any rhythm changes throughout the duration of the procedure
6. Procedural information and imaging (angiography, intra-procedure echocardiography to be stored and provided)

A 12-lead ECG is required daily following implant through discharge (refer to **Section 6.3**); the first one should be done as soon after the index procedure as possible.

Investigational sites should follow specific guidelines for the assessment of aortic regurgitation and implant depth. Refer to **Appendix IV** for a description of standardized methods for measuring aortic regurgitation according to VARC-2 criteria and instructions for assessing implant depth in the LVOT.

During the procedure, the implanting physician may determine implantation of the Navitor/Navitor Vision Valve is either not feasible or not in the best interest of the subject. Reasons may include, but are not limited to, anatomy that is not suitable for implantation, inability to gain access, ventricular arrhythmia, or any other contraindication.

All the required information must be recorded on the applicable Case Report Form (CRF). Following the procedure, the non-implantable devices (e.g., FlexNav Delivery and Navitor/Navitor Vision Loading Systems) should be securely disposed as per hospital requirements for hazardous materials.

If there are any concerns noted with the Navitor/Navitor Vision Valve, FlexNav Delivery System, or the Navitor/Navitor Vision Loading System during the procedure, these need to be notified to the Manufacturer and return these products for evaluation, if possible, as usually done via the regular channels for CE-marked products. See **Section 7.3.3** for Incident/Device Malfunction reporting requirements.

6.3 Discharge Assessments

The discharge visit will take place at the time of hospital discharge or at 7 days after the procedure, whichever occurs first. If the subject is expected to be discharged over the weekend, the discharge tests may be completed on the last weekday prior to discharge.

The discharge assessment will include:

1. Physical Examination (including weight, resting heart rate, and blood pressure)
2. Cardiovascular medications documentation
3. Modified Rankin Scale (mRS)
4. 12-lead ECG: to be done daily following implant through discharge, including observations from the daily ECG reviews since procedure (for subjects receiving a new permanent pacemaker, ECG should be completed showing the underlying rhythm as well as the current pacing programming)
5. Echocardiogram (TTE) (within 48 hours prior to the discharge visit)
6. Laboratory Measurements (Creatinine and Troponin or CK-MB) (within 48 hours prior to the discharge visit)
7. Adverse events assessment

6.4 Follow-up Assessments

6.4.1 Follow-up Medications

Cardiovascular medications administered to subjects during the follow-up period will be at the physician's discretion and recorded on the follow-up case report forms.

6.4.2 Follow-up

Required clinical follow-up will be performed at the following intervals for all subjects who were implanted with a Navitor/Navitor Vision Valve:

- 30 days (-7/+21 days) follow-up site visit (visit must be conducted even if subject is in hospital)
- 12 months (365 days + 45 days) follow up site visit
- Annual follow-up at 2 through 5 years (± 60 days)

Dates for follow-up visits will be calculated from the date of the implant procedure. Follow-up assessments can be performed at any point within the pre-specified follow-up visit window and should be conducted by the same individual who performed the baseline tests whenever possible.

Every effort should be made by the study site to have the subject return to the investigational site for all follow-up visits. In-person follow-up visits including an echocardiogram are highly recommended if the subject is experiencing signs or symptoms of aortic stenosis or heart failure. If, despite all efforts, the subject is unable to return to the study site during a follow-up window, subjects may undergo a remote follow-up assessment to collect applicable data.

Each site will be responsible for performing and interpreting the follow-up echocardiograms for potential adverse events. Echocardiograms will be submitted to the **Study Steering Committee** for further analysis. Examinations should be recorded in DICOM format and should be de- identified prior to submitting for analysis. If medically indicated, a subject may undergo additional imaging per standard of care (e.g.,

contrast CT scan or TEE) to evaluate device specific findings (e.g., valve thrombosis); if performed, this additional imaging will be submitted to the Study Steering Committee for analysis. For details, see 10.7.

6.4.2.1 30-day Follow-Up

The 30-day follow-up visit will occur 30 days (-7/+21 days) post-index procedure, and will include the following assessments:

1. Physical Examination (including weight, resting heart rate, and blood pressure)
2. Cardiovascular medications documentation
3. NYHA Functional Classification
4. 12 lead ECG (for subjects receiving a new permanent pacemaker, ECG should be completed showing the underlying rhythm as well as the current pacing programming)
5. Echocardiography (TTE)
6. Quality of Life Assessment (KCCQ)
7. Lab Measurements (INR if subject is on warfarin or other anticoagulants/vitamin K antagonists in lieu of warfarin)
8. Adverse events assessment

6.4.2.2 12-Month Follow-Up

The 12-month follow-up visit will take place at 12 months (365 days + 45 days) post-index procedure, and will include the following assessments:

1. Physical Examination (including weight, resting heart rate, and blood pressure)
2. Cardiovascular medications documentation
3. NYHA Functional Classification
4. Neurological assessment and Modified Rankin Scale (mRS)
5. 12 lead ECG (for subjects receiving a new permanent pacemaker, ECG should be completed showing the underlying rhythm as well as the current pacing programming)
6. Echocardiogram (TTE)
7. Quality of Life Assessment (KCCQ)
8. Lab measurements (INR if subject is on warfarin or other anticoagulants/vitamin K antagonists in lieu of warfarin)
9. Adverse events assessment

6.4.2.3 Annual Follow-Up

The following data should be collected at years 2 through 5 years (± 60 days) post index procedure:

1. Physical Examination (including weight, resting heart rate, and blood pressure)
2. Cardiovascular medications documentation
3. NYHA Functional Classification
4. Modified Rankin Scale (mRS) (optional for patients with neurological events)
5. Echocardiography (TTE)
6. Quality of Life Assessment (KCCQ)
7. Adverse event assessment

6.4.3 Unscheduled Follow-up

6.4.3.1 Evaluation of Suspected Neurological Event

If the subject experiences a neurological event (transient ischemic attack (TIA), stroke, or encephalopathy) throughout follow-up, the event should be documented on an adverse event form. The event (including all available imaging and NIH Stroke Severity (NIHSS) should be assessed and confirmed by a neurologist or neurology fellow. Further evaluation may be performed in accordance to routine clinical practice for neurological events at an unscheduled visit 90 days from the date of the neurological event. The unscheduled visit will include the following assessments:

- Neurological Assessment conducted by a neurologist or a neurology fellow
- Modified Rankin Score (mRS)

6.4.3.2 Survival Status Check

The Study Steering Committee may request a check on each subject's survival status for subjects.

6.4.4 Patient Reported Outcome (PRO) Measures

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is the only PRO measure that will be collected to assess whether the health of subjects has improved since enrollment in the Intensive Study.

The Principal Investigator, research coordinator or study designee will provide the subject the KCCQ before any other elements of visit. It is important the subject understands the meaning of all words and instructions in the measures. The subject should be instructed to ask any questions about the measures if further explanation is needed. Once the PRO measures are completed, the research coordinator or study designee will review for completeness to verify that all questions have been answered according to the directions provided.

6.4.4.1 Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ is a 12-item self-administered questionnaire developed to independently measure the patient's perception of their health status, which includes heart failure symptoms, impact on physical and social function, and how their heart failure impacts their quality of life (QOL) within a 2-week recall period. KCCQ responses are provided along a rating scale continuum with equal spacing from worst to best. On average, the 12-item version takes approximately 10 minutes to complete. The concepts quantified in the KCCQ are designed to be relevant and appreciable by all heart failure patients specified in the qualified context of use. The Flesch Reading Ease is 76 and the Flesch-Kincaid Grade level is 6.7. The tool can be used to evaluate the effectiveness of a heart failure medical device studied in a clinical study.

The tool quantifies six distinct domains (Symptom, Physical Function, Quality of Life, Social Limitation, Self-efficacy, Symptom Stability) and two summary scores (Clinical Summary and Overall Summary). Scores are transformed to a range of 0-100, in which higher scores reflect better health status.

6.4.5 Schedule of Assessments (SoA)

The study-required activities and standard of care data collection in the INTENSIVE Study are summarized in **Table 5**.

Table 5: Follow-up and Data Collection Requirements

Clinical Assessments	Screening/Baseline	Procedure	Discharge	30 days [-7/+21 days]	12 months [+45 days]	Annual visits [±60 days]
Subject Interview and Informed Consent	X					
Demographics	X					
Medical History	X					
Physical Examination	X		X	X	X	X
Surgical Risk Assessment (STS & EuroSCORE II)	X					
NYHA Classification	X			X	X	X
Frailty Index (Appendix III)	X					
Cardiovascular Medications documentation	X		X	X	X	X
CT Angiography (upload)	X					
Modified Rankin Scale (mRS)	X		X		X	(X)
Neurological Assessment					(X)[H]	(X)[H]
12 lead Electrocardiogram (ECG) [A,B]	X	X[B]	X[A,B]	X[A]	X[A]	
Cardiac Rhythm		X				
2D Transthoracic Echocardiogram (TTE-upload)	X	X[C]	X	X	X	X
Angiogram (upload)		X				
CT scan with Angiography of chest, abdomen and pelvis (upload)	X[D]					
KCCQ	X			X	X	X
CBC and Platelet Count	X					
Creatinine	X[E]	X[F]	X			
INR (if subject is on Warfarin)	X			X	X	
Troponin *or* CK-MB		X[F]	X			

Clinical Assessments	Screening/Baseline	Procedure	Discharge	30 days [-7/+21 days]	12 months [+45 days]	Annual visits [±60 days]
Adverse Event Assessment [G]	X	X	X	X	X	X
Deviation	(X)	(X)	(X)	(X)	(X)	(X)
Device Deficiency		(X)	(X)	(X)	(X)	(X)
Withdrawal		(X)	(X)	(X)	(X)	(X)
Survival Status			(X)	(X)	(X)	(X)
Death	(X)	(X)	(X)	(X)	(X)	(X)

[A] For subjects receiving a new permanent pacemaker, ECG should be completed showing the underlying rhythm as well as the current pacing programming.

[B] Record a 12-lead ECG following the implant of the valve and daily until day of discharge

[C] Copy of echocardiographic examination to be stored at the site and available to the Steering Committee upon request.

[D] To be done within 12 months prior to consent; CT covering at least systole is required for valve sizing.

[E] Includes eGFR

[F] To be collected within 72 hours before index procedure

[G] Transesophageal echocardiogram (TEE) is also recommended after adverse events of ischemic stroke and myocardial infarction

[H] In case of a suspected neurological event, a neurological assessment will be conducted as per standard clinical practice, usually at 90 days (±14 days) from the date of the suspected neurological event

(X) indicates if applicable

7 ADVERSE EVENTS AND INCIDENTS REPORTING

7.1 Requirements and definitions

To comply with worldwide standards and guidelines on adverse event /incident reporting for CE marked devices, the Promoter has adopted uniform and worldwide applicable standard definitions and reporting timelines to be used and adhered to by the investigators. As such, safety reporting will follow the applicable requirements for the Vigilance System as outlined in Medical Device Regulation No. 2017/745, Article 87, Reporting of serious incidents and field safety corrective actions.

The device manufacturer is responsible to reporting to the relevant competent authorities, in accordance with Articles 92(5) and (7), the following:

(a) any serious incident, except expected side-effects which are clearly documented in the product information and quantified in the technical documentation and are subject to trend reporting pursuant to Article 88;

(b) any field safety corrective action.

As such, Principal Investigators must inform the manufacturer of any incidents or serios incidents, as defined the table below.

Table 6: Safety Definitions

Term	Definition
Incident / Device Malfunction	Any malfunction or alteration in the characteristics or performance of a device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effects (adverse events).
Serious Incident or Serious Adverse Event	Any incident that directly or indirectly led, might have led or might lead to any of the following (serious adverse event): (a) the death of a patient, user or other person, (b) the temporary or permanent serious deterioration of a patient's, user's or other person's state of health, (c) a serious public health threat;
Serious Public Health Threat	An event which could result in imminent risk of death, serious deterioration in a person's state of health, or serious illness, that may require prompt remedial action, and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time

7.2 Reporting

As it is a post CE-mark Study, only endpoints related events and serious adverse events should be reported in the EDC (Electronic Data Capture) system, Catchtrial EDC (www.catchtrial.com). Endpoints related events and serious adverse events will be monitored. All events must be documented in the patient's medical file and on an "Adverse event" form of the EDC.

Adverse Event (AE) information will be collected throughout the study from the point of enrollment until the patient's study participation has ended (i.e. completion of study or withdrawal of consent).

It is the responsibility of the Investigator to report all product complaints and malfunctions immediately via the regular channels for CE-marked products. Safety Reports should be created and notified to Ethics Committee and Regulatory Authority according to local requirements.

8 STATISTICAL CONSIDERATIONS

The following section describes the statistical methods for the primary analysis.

8.1 Statistical Analyses

Sample Size Calculation and Assumptions

According to the FRANCE-2 registry (N Engl J Med 2012;366:1705-1715), the rate of overall mortality at 1 year is 24%. This national registry enrolled patients with minimal exclusion criteria and using current transcatheter bioprostheses according to the inherent IFU. We assume that at 1 year the results of our study, in terms of overall mortality (the primary endpoint) will be the same. Sample size was determined according to the method proposed by Nagashima et al. 2012 [Nagashima K, Noma H, Sato Y, Gosho M.

Sample size calculations for single-arm survival studies using transformations of the Kaplan–Meier estimator. Pharmaceutical Statistics 2021;20(3):499–511], implemented in an online calculator available at: https://nshi.jp/en/js/onesurvyr/.

Setting the null hypothesis to 76% survival at 1 year, the accrual time at 1 year and the follow up time at 5 years, there will be 80% power to detect an alternative hypothesis that the Survival at 1 year is lower, at a level of 72%, with a sample size equal to 943 patients. The type I error was fixed at 5% with a two-sided test. The arcsine transformation of the survival function was used. Considering a 5% dropout, the final sample size is rounded up to 1000 patients.

8.2 Timing of Analysis

The analysis for the primary endpoint will be done at the completion of 1 year FU of the last patient enrolled.

8.3 Subgroup Analysis

Subgroup analysis will be performed to evaluate specific conditions.

8.4 Planned Interim Analysis

No interim analyses are planned for this Study.

8.5 Statistical Criteria for Termination

There are no statistical criteria for termination of this clinical investigation.

9 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution will permit direct access to source data/documents for performing clinical investigation-related monitoring, audits, EC review and regulatory inspections.

Subjects providing informed consent are agreeing to allow clinical investigation monitors or regulatory authorities, including foreign countries, to review in confidence any records identifying the subjects in this Study. This information may be shared with regulatory agencies.

10 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Selection of Clinical Sites and Investigators

A list of the participating sites will be provided.

All investigators involved in the conduct of the clinical investigation will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

10.2 Site Principal Investigator Responsibilities

The role of the Site Principal Investigator is to implement and oversee the management of the day-to-day conduct of the study, as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the study. The principal investigator shall support monitoring and reporting to EC and local Competent Authorities as necessary, throughout the conduct of the study. The principal investigator is responsible for ensuring adequate training and qualification of the investigation site team and for maintaining oversight of their activities. The principal investigator may delegate tasks to members of the

investigation site team but retains responsibility for the study. This also applies when activities are outsourced to an external organization by the principal investigator, in which case he/she shall exercise oversight to ensure the integrity of all tasks performed and any data generated by this external organization.

10.3 Protocol Amendments

The Coordinating Investigator in agreement with the Study Steering Committee will provide approved protocol amendments to the Investigators prior to implementing the amendment. The site's Principal Investigator is responsible for notifying the EC or equivalent committee of the protocol amendment (administrative changes) or obtaining EC's approval of the protocol amendment (changes in subject care or safety).

Sites must document in writing acknowledgement/approval of the protocol amendment by the EC prior to implementation of the protocol amendment. Sites must also provide copies of this documentation to the Study Steering Committee.

10.4 Site Training

All Investigators and study personnel are required to attend training sessions, which may be conducted at an Investigator's meeting, site initiation visit, or other training sessions. Remote (e.g., telephone, on-line, etc.) or self-training may take place as necessary. Training of Investigators and study personnel will include, but is not limited to, the protocol requirements, electronic case report form completion, and clinical study personnel responsibilities. All Investigators and study personnel that are trained must sign a training log (or an equivalent) upon completion of the training.

10.5 Monitoring

The designated CRU, Clinical Research Unit, IRCCS Policlinico S. Donato, San Donato M.se, Milan, Italy, will monitor the clinical investigation over its duration according to the monitoring plan.

10.6 Protocol Deviations

The Investigator should not deviate from the protocol for any reason except in cases of medical emergencies when the deviation is necessary to protect the rights, safety, and well-being of the subject, or to eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify the Coordinating Investigator.

Sites must report all deviations in a timely manner using the Protocol Deviation form within the CRF. The occurrence of protocol deviations will be monitored in accordance with regulatory requirements and handle according to written procedures. Investigators will determine the cause of deviations, implement corrective actions and inform their EC or equivalent committee of protocol deviations in accordance with their specific EC or equivalent committee reporting policies and procedures.

Repeated non-compliance with the signed agreement, the protocol, or any other conditions of the clinical investigation may result in further escalation and consultation with the Study Steering Committee, including securing compliance or, at its sole discretion, the Coordinating Investigator may terminate the investigator's participation in the clinical investigation.

10.7 Study Steering Committee

The **Study Steering Committee** is responsible for overseeing the scientific and operational aspects of the clinical investigation.

This committee will meet regularly to monitor subject enrollment, general data collection and non-compliance with the Protocol at individual centers, to review operational issues that may arise and warrant a Protocol amendment or other corrective action, and to determine policy regarding the primary results publication arising from data generated from the performance of the Study.

11 DATA HANDLING AND RECORD KEEPING

The Study Steering Committee and/or its affiliates will maintain documentation of the systems and procedures used in data collection for the duration of the study.

CRF data collection will be performed through a secure web portal (www.catchtrial.com) and only authorized personnel will access the EDC system using a unique username and password to enter, review or correct data.

Passwords and electronic signatures will be strictly confidential.

The data will be subjected to consistency and validation checks within the EDC system and supplemental review by the Coordinating Investigator and the Study Steering Committee.

At the end of the study, completed CRF images with the date-and-time stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be provided to the investigational sites, if requested.

For the duration of the study, the Investigator will maintain complete and accurate documentation including, but not limited to, medical records, clinical investigation progress records, laboratory reports, CRFs, signed ICFs, correspondence with the EC,CRO and Coordinating Investigator/Steering Committee, adverse event reports, and information regarding subject discontinuation or completion of the study.

11.1 Protection of Personally Identifiable Information

Confidentiality of data shall be observed by all parties involved at all times throughout the study.

Technical and physical access controls will be implemented to ensure that Personal Information is accessible only to and processed only on a ‘need to know’ basis, including periodic review of access rights, and revocation of access when an individual’s employment is terminated or the individual transitions to a role that does not require access to Personal Information, and appropriate restrictions on physical access to premises, facilities, equipment, and records containing Personal Information.

Only pseudonymous Personal Information (key-coded) necessary to conduct the clinical investigation, such as the patient’s medical condition, treatment, dates of treatment, etc., will be entered into study data management systems. All subject data will be identified with the unique patient identifier number. As part of the study informed consent process, only authorized investigators or designated personnel will have access to confidential records for technical support of the participating physicians on the device implant or procedures, monitoring and quality control purposes. The EC and other regulatory authorities also have the right to inspect and copy records pertinent to the study. All parties will observe confidentiality of Personal Information always throughout the clinical investigation. All reports and data publications will preserve the privacy of each subject and confidentiality of his/her information.

The data management systems and processes designed, developed, and tested against unauthorized access and/or interference by third parties, intrusion, theft, destruction, loss or alteration will be used. Study data will be encrypted in transit and at rest.

All subject data will always be treated with strict adherence to professional standards of confidentiality and according to European General Data Protection Regulation (EU GDPR) guidelines and other applicable local regulations.

11.2 Case Report Form Completion

Site research personnel trained on the Protocol and CRF completion will perform the primary data collection clearly and accurately based on source-documented hospital and/or clinic chart reviews. The investigator will ensure accuracy, completeness, legibility, and timeliness of the data reported on the CRFs and in all required reports.

Sites will collect data on all subjects who sign an informed consent form.

Only authorized site personnel will be permitted to enter the CRF data through the EDC system an electronic audit trail to track any subsequent changes of the entered data will be used.

11.3 Record Retention

Investigator/Site will archive and retain all documents pertaining to the study as per the applicable regulatory record retention requirements. The Investigator must obtain permission from Coordinating Investigator in writing before destroying or transferring control of any study records.

12 ETHICAL CONSIDERATION

12.1 Ethics Committee Review and Approval

The Principal Investigator at each investigational site will obtain EC approval for the protocol and ICF/other written information provided to the patient prior to consenting and enrolling patients in this clinical investigation. The site must receive the approval letter prior to the start of this clinical investigation and provide a copy to the delegated CRO.

Sites will submit any amendments to the Protocol as well as associated ICF changes to the EC and written approval obtained prior to implementation, according to each institution's EC requirements.

No changes will be made to the Protocol or ICF or other written information provided to the patient without appropriate approvals, including EC, the Study Steering Committee, and the regulatory agencies (if applicable).

Until the Study is completed, the Investigator will advise his/her EC of the progress of this Study, per EC requirements. Written approval must be obtained from the EC to continue the study, or according to each institution's EC requirements.

13 CLINICAL INVESTIGATION CONCLUSION

The clinical investigation will be concluded when:

- All sites are closed AND
- The final report has been provided to investigators or it has been provided formal documentation of clinical investigation closure.

The Coordinating Investigator will submit the clinical investigation report within one year of the end of the investigation to the investigational sites, Competent Authorities (if applicable), and reviewing ECs.

13.1 Suspension or Early Termination of the Clinical Investigation

While no formal statistical rule for early termination of the Study, the Coordinating Investigator and Study Steering Committee reserves the right to discontinue the Study at any stage or reduce the follow-up period with suitable written notice to the investigator. Possible reason(s) may include, but are not limited to:

- An oversight committee (e.g., Steering Committee, Executive Committee, Data Monitoring Committee) makes a recommendation to stop or terminate the clinical investigation which is agreed with by the Coordinating Investigator
- Navitor/Navitor Vision is withdrawn from market for any reason
- Further data collection is cancelled

13.1.1 Subject Follow-up for Early Termination or Suspension of Study

If the Study Steering Committee suspends or prematurely terminates the clinical investigation at an individual site in the interest of safety, the Coordinating Investigator will inform all other Principal Investigators.

If suspension or premature termination occurs, the Principal Investigators will remain responsible for providing resources to fulfill the obligations from the Protocol and existing agreements for following the subjects enrolled in the Study. Details for such subjects follow up will be provided. The Principal Investigator or authorized site designee will promptly inform the enrolled subjects at his/her site, if appropriate.

All applicable clinical investigation document shall be subject to the same retention policy as detailed in **Section 11.0** of the protocol.

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

If a suspended investigation is to be resumed, a prior approval should be obtained from the EC and a notification should be sent to the regulatory bodies, and if subjects were informed of suspension, they shall be informed of the resumption of the clinical investigation.

14 PUBLICATION POLICY

The Coordinating Investigator will be responsible for registering this Study on ClinicalTrials.gov website, in accordance with the International Committee of Medical Journal Editors guidelines, or any other applicable guidelines. The Coordinating Investigator shall be responsible for any such registration and results posting as required by the ClinicalTrials.gov website. A full report of the outcomes, will be made public through the ClinicalTrials.gov website no later than 12 months after the study completion. If this Study is terminated early, the Coordinating Investigator will make every effort to hasten the release of the outcomes through the ClinicalTrials.gov website. The results of the study will be published in the major cardiological congresses and journals.

15 STUDY RISK BENEFIT ANALYSIS

15.1 Anticipated Clinical Benefits

The objective of the Study is to monitor outcomes in an all-comers population based on the routine clinical use of the Navitor/Navitor Vision Valve, according to the approved commercial indications.

The benefits of the Navitor/Navitor Vision valve are proven and the product has been CE marked in 2021. The Navitor/Navitor Vision Valve's performance was evaluated in the Portico NG trial, detailed in Section 1.4. Across 120 subjects in Australia, Europe, and the U.S., there were no instances of all-cause mortality or moderate to severe paravalvular leakage (PVL) at the 30-day mark, as confirmed by an independent core laboratory. Additionally, echocardiographic assessments at 30 days revealed Navitor/Navitor Vision subjects had a mean aortic valve area of 2.0 ± 0.5 cm^2 and a mean gradient of 8.1 ± 3.7 mmHg. The Navitor/Navitor Vision Valve, when delivered via the FlexNav Delivery System, demonstrates a promising safety profile, strong hemodynamic performance, and reduced risk of PVL.

While there are no guaranteed clinical benefits associated with participation in this study, subjects will be closely followed up and may receive more timely medical care and medication adjustments.

15.2 Potential procedure risks

Risks associated with the specified device and procedure, together with their likely incidence, are described in the consent form that will be provided to you as a part of the standard of care procedure for Navitor implantation. These risks are part of the routine use of the transcatheter valve replacement intervention, and not related to this Study, which focuses on collection of clinical outcomes.

Residual risks are likewise disclosed in the IFU in the form of clear instructions of what actions to take or to avoid, in order to avoid a hazardous situation of harm from occurring (contra-indications, warnings, and precautions). The anticipated AEs disclosed in the IFU provide further information to enable the user, and potentially the patient, to make an informed decision that weighs the residual risk against the benefit of using the device.

15.3 Risks Associated with Participation in Intensive Study

Protocol-required assessments are summarized in Table 5. All these tests are part of routine care, with the exception of the Quality of Life Questionnaire (KCCQ) which provides no additional burden to the patients. Possible risks and discomforts associated with participation in the Study are the same to those associated with any routine transcatheter aortic valve implantation procedure and related follow-up procedures.

Participation in the study requires patient data collection that may include protected heath information. This information will be kept confidential, and all data will be pseudonymized, but there is a marginal risk that some of the information could be unintentionally made non-confidential. The risk of this happening for this study is no greater than the risk of loss of confidentiality in any study.

16 APPENDICES

16.1 APPENDIX I: ABBREVIATIONS AND ACRONYMS

The following is a list of abbreviations and acronyms used in the Protocol.

Abbreviation	Term
ACT	Activated Clotting Time
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AHA	American Heart Association
AMI	Acute Myocardial Infarction
AS	Aortic Stenosis
AVA	Aortic Valve Area
AVR	Aortic Valve Replacement
BARC	Bleeding Academic Research Consortium
BNP	B-type Natriuretic Peptide
BUN	Blood urea nitrogen
BVF	Bioprosthetic Valve Failure
CAD	Coronary Artery Disease
CBC	Complete Blood Count
CE	Conformité Européene (European Conformity)
CPB	Cardiopulmonary Bypass
eCRF	Electronic Case Report Form
CT	Computed Tomography
CVA	Cerebral Vascular Accident
EC	Ethics Committee
ECG	Electrocardiogram
Echo	Echocardiography
EDC	Electronic Data Capture
EF	Ejection Fraction
EOA	Effective Orifice Area
EU	European Union
GI	Gastro Intestinal
GFR	Glomerular filtration rate
HALT	Hypo Attenuated Leaflet Thickening
HVD	Hemodynamic Valve Deterioration
IB	Investigator's Brochure
ICF	Informed Consent Form

Abbreviation	Term
IDC	Implantable Cardioverter Defibrillator
IDE	Investigational Device Exemption
IFU	Instructions For Use
INR	International Normalized Ratio
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAAO	Left Atrial Appendage Occlusion
LV	Left Ventricular
LVEF	Left Ventricular Ejection Fraction
LVOT	Left Ventricular Outflow Tract
MAC	Mitral Annular Calcification
MI	Myocardial Infarction
MR	Mitral Regurgitation
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NSTEMI	Non-ST-Segment Elevation Myocardial Infarction
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PI	Principal Investigator
PRO	Patient Reported Outcome
PVL	Paravalvular Leak
QoL	Quality of Life
RA	Right Atrium
RV	Right Ventricular
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAVR	Surgical Aortic Valve Replacement
STEMI	ST-Segment Elevation Myocardial Infarction
STS	Society of Thoracic Surgeons
SVD	Structural Valve Deterioration
TAVI	Transcatheter Aortic Valve Implantation
TEE	Transesophageal Echocardiogram (same as TOE)
TIA	Transient Ischemia Attack
TTE	Transthoracic Echocardiogram
UADE	Unanticipated Adverse Device Effect
USA	United States of America (same as US)
VARC	Valve Academic Research Consortium
ViV	Valve-in-Valve
WBC	White Blood Cell

16.2 APPENDIX II: DEFINITIONS

The following are definitions to be used in this clinical investigation. While some terms have not been used in the main body of the Protocol they may be used for coding of adverse events.

ACUTE KIDNEY INJURY[21]

1. **STAGE 1**
   - Increase in serum creatinine ≥150–200% (≥1.5–2.0x increase) within 7 days compared with baseline **OR**
   - Increase of ≥0.3 mg/dL (≥26.4 mmol/L) within 48 hours of the index procedure
2. **STAGE 2**
   - Increase in serum creatinine ≥200–300% (≥2.0–3.0x increase) within 7 days compared with baseline
3. **STAGE 3**
   - Increase in serum creatinine ≥300% (≥3.0x increase) within 7 days compared with baseline **OR**
   - Serum creatinine ≥4.0 mg/dL (≥354 µmol/L) with an acute increase of ≥0.5 mg/dL (≥44 µmol/L) procedure
4. **STAGE 4**
   - AKI requiring new temporary or permanent renal replacement therapy

BLEEDING AND TRANSFUSION[21, 30]

Overt bleeding that fulfills one of the following criteria:

1. **Type 1**
   - ☐ Overt bleeding that does not require surgical or percutaneous intervention, but does require medical intervention by a health care professional, leading to hospitalization, an increased level of care, or medical evaluation (BARC 2)
   - ☐ Overt bleeding that requires a transfusion of 1 unit of whole blood/red blood cells (BARC 3a)
2. **Type 2**
   - ☐ Overt bleeding that requires a transfusion of 2–4 units of whole blood/red blood cells (BARC 3a)
   - ☐ Overt bleeding associated with a hemoglobin drop of >3 g/dL (>1.86 mmol/L) but <5 g/d (<3.1 mmol/L) (BARC 3a)
3. **Type 3**
   - ☐ Overt bleeding in a critical organ, such as intracranial, intraspinal, intraocular, pericardial (associated with haemodynamic compromise/tamponade and necessitating intervention), or intramuscular with compartment syndrome (BARC 3b, BARC 3c)
   - ☐ Overt bleeding causing hypovolemic shock or severe hypotension (systolic blood pressure
   - ☐ <90 mmHg lasting >30 min and not responding to volume resuscitation) or requiring vasopressors or surgery (BARC 3b)

- ☐ Overt bleeding requiring reoperation, surgical exploration, or re-intervention for the purpose of controlling bleeding (BARC 3b, BARC 4)
- ☐ Post-thoracotomy chest tube output ≥2 L within a 24-h period (BARC 4)
- ☐ Overt bleeding requiring a transfusion of ≥5 units of whole blood/red blood cells (BARC 3a)
- ☐ Overt bleeding associated with a haemoglobin drop ≥5 g/dL (≥3.1 mmol/L) (BARC 3b)

4. **Type 4**
   - ☐ Overt bleeding leading to death. Should be classified as:
     - Probable: Clinical suspicion (BARC 5a)
     - Definite: Confirmed by autopsy or imaging (BARC 5b)

CARDIAC STRUCTURAL COMPLICATIONS[21]

1. **Major**

   One of the following:
   - Cardiac structure perforation, injury, or compromise resulting in death, VARC type ≥2 bleeding, haemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention
   - New pericardial effusion resulting in death, VARC type ≥2 bleeding, haemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention
   - Coronary obstruction resulting in death, haemodynamic compromise, myocardial infarction, or unplanned surgical or percutaneous intervention. Coronary obstruction may be acute (during the procedure) or delayed (after completion of the procedure).
   - Coronary artery access difficulties for needed coronary angiography or intervention, resulting in death, haemodynamic compromise, myocardial infarction, coronary or aortic root injury, compromise in aortic valve prosthesis integrity, unplanned surgical or percutaneous intervention, or the inability to perform the intended procedure
2. **Minor**

   One of the following:
   - Cardiac structure perforation, injury, or compromise not resulting in death, VARC type ≥2 bleeding, haemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention
   - New pericardial effusion not resulting in death, VARC type ≥2 bleeding, haemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention
   - Coronary obstruction not resulting in death, haemodynamic compromise, myocardial infarction, or unplanned surgical or percutaneous intervention
   - Coronary artery access difficulties for needed coronary angiography or intervention, not resulting in death, haemodynamic compromise, myocardial infarction, coronary or aortic root injury, compromise in aortic valve prosthesis integrity, unplanned surgical or percutaneous intervention, or the inability to perform the intended procedure

DEATH (MORTALITY)[21]

1. **ALL-CAUSE MORTALITY**
2. **CARDIOVASCULAR MORTALITY**

Death meeting one of the following criteria:

- Related to heart failure, cardiogenic shock, bioprosthetic valve dysfunction, myocardial infarction, stroke, thromboembolism, bleeding, tamponade, vascular complication, arrhythmia or conduction system disturbances, cardiovascular infection (e.g. mediastinitis, endocarditis) or other clear cardiovascular cause
- Intraprocedural death
- Sudden death
- Death of unknown cause

3. **VALVE-RELATED MORTALITY**
   Death presumed to be related to bioprosthetic valve dysfunction
4. **NON-CARDIOVASCULAR MORTALITY**
   Death clearly related to a non-cardiovascular cause: such as respiratory failure not related to heart failure, (e.g. pneumonia), renal failure, liver failure, infection (e.g. urosepsis), cancer trauma, and suicide)

HOSPITALIZATION (or REHOSPITALIZATION)[21]

Any admission after the index hospitalization or study enrollment to an inpatient unit or hospital ward for ≥ 24h, including an emergency department stay. Hospitalizations planned for pre-existing conditions are excluded unless there is worsening of the baseline condition. Visits to urgent care centers or emergency departments < 24 hours may also be included if substantive intensification of therapy changes (e.g. heart failure episodes) are enacted (e.g. intravenous diuretics, significant increases in drug therapy dosages or addition of new pharmacotherapy agents). Hospitalization is further categorized:

1. **CARDIOVASCULAR HOSPITALIZATION**
   - **Procedure-related or Valve-related Hospitalization**
     - **Hospitalization for new complications** such as stroke, bleeding (e.g. hemothorax, retroperitoneal hematoma), pericardial effusion, vascular or access-site complication (e.g. limb ischemia, wound infection), new conduction disturbance or arrhythmia (e.g. atrioventricular block, atrial fibrillation), acute kidney injury, or any other procedure-related new complication, including periprocedural valve-related heart failure (e.g. paravalvular leak, worsening LV function, worsening sub-valvular obstruction)
     - **Exacerbation or deterioration of previous in-hospital periprocedural complication** (e.g. ventilator-induced pneumonia, recurrent pericardial or pleural effusion, recurrent hemothorax, valve-related heart failure)
     - **Bioprosthetic valve dysfunction** such as valve thrombosis, endocarditis, structural valve deterioration, or non-structural valve dysfunction
     - **Bleeding complications related to oral anticoagulation or antiplatelet therapy** for valve-related thromboembolic prevention or atrial fibrillation
     - **Heart failure related hospitalizations** requiring that new or worsening heart failure be the predominant reason for a hospital stay ≥ 24h on the basis of symptoms and signs of heart failure with confirmation by diagnostic tests and necessitating treatment using intravenous or mechanical heart failure therapies. Includes primary (cardiac related) and secondary (non-cardiac related)

- **<u>Oher Cardiovascular Hospitalization</u>**
  - Cardiovascular hospitalization not directly related to the index procedure or the untreated native aortic valve
    Including: acute myocardial infarction or chronic coronary artery disease, hypertension, arrhythmia (not related to the procedure or aortic valve), heart failure from other specific and proven etiologies (e.g. cardiomyopathies, concomitant untreated non-aortic valvular disease, severe right ventricular dysfunction), peripheral vascular disease

2. **NON-CARDIOVASCULAR HOSPITALIZATION**
   - Hospitalization not due to cardiovascular causes as defined above
     Including: non-cardiovascular infection and sepsis (e.g. urosepsis), respiratory failure that is not related to heart failure (e.g. pneumonia), renal failure, liver failure, delirium or dementia, cancer, trauma, or psychiatric illness

<u>MYOCARDIAL INFARCTION[21]</u>

1. **Type 1 (Spontaneous MI) (>48 h after the index procedure)**
   - Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL with at least one of the following:
     - Symptoms of acute ischaemia
     - New ischaemic ECG changes (new ST-segment or T-wave changes or new LBBB)
     - New pathologic Q-waves in ≥2 contiguous leads
     - Imaging evidence of a new loss of viable myocardium or new wall motion abnormality in pattern consistent with an ischaemic aetiology
     - Identification of a coronary thrombus by angiography or autopsy
   - Post-mortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large circumscribed area of necrosis with or without intramyocardial haemorrhage, meets the type 1 MI criteria regardless of cTn values(troponin)
2. **Type 2 (Imbalance between myocardial oxygen supply and demand)**
   - Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following:
     - Symptoms of ischaemia
     - ECG changes indicative of new ischaemia (new ST-segment or T-wave changes or new LBBB)
     - New pathologic Q-waves in ≥2 contiguous leads
     - Imaging evidence of a new loss of viable myocardium or new wall motion abnormality
3. **Type 3 (MI associated with sudden cardiac death)**
   - Patients who suffer cardiac death, with symptoms suggestive of myocardial ischaemia accompanied by presumed new ischaemic ECG changes or ventricular fibrillation but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.
4. **Type 4A (Criteria for PCI-related MI ≤ 48 h after the index procedure)**

- In patients with normal baseline CK-MB: The peak CK-MB measured within 48 h of the procedure ≥10x the local laboratory ULN or CKMB ≥5x ULN with one or more of the following:
    - New pathologic Q-waves in ≥2 contiguous leads
    - New persistent LBBB
    - Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch
    - Substantial new loss of viable myocardium on imaging related to the procedure
- In the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the procedure rises to ≥70x the local laboratory ULN or ≥35x ULN with one or more of the following:
    - New pathologic Q-waves in ≥2 contiguous leads
    - New persistent LBBB
    - Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch
    - Substantial new loss of viable myocardium on imaging related to the procedure
- In patients with elevated baseline CK-MB (or cTn): The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level plus new ECG changes as described.

5. **Type 4B (Stent thrombosis)**
    - Stent thrombosis as documented by angiography or autopsy using the same criteria utilized for type 1 MI.
        - Acute: 0 to 24 h
        - Subacute: >24 h to 30 days
        - Late: >30 days to 1 year
        - Very late: >1 year after stent implantation
6. **Type 5 Periprocedural (post-SAVR, TAVR or CABG) MI (≤48 h after the index procedure)**
    - In patients with normal baseline CK-MB: The peak CK-MB measured within 48 h of the procedure ≥10x the local laboratory ULN or CKMB ≥5x ULN with one or more of the following:

New pathologic Q-waves in ≥2 contiguous leads

New persistent LBBB

Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch

Substantial new loss of viable myocardium on imaging related to the procedure

- In the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the procedure rises to ≥70x the local laboratory ULN or ≥35x ULN with one or more of the following:
    - New pathologic Q-waves in ≥2 contiguous leads
    - New persistent LBBB
    - Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch
    - Substantial new loss of viable myocardium on imaging related to the procedure
- In patients with elevated baseline CK-MB (or cTn): The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level plus new ECG changes as described.

NEW-ONSET ATRIAL FIBRILLATION (OR FLUTTER)[21]

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 s on a rhythm strip.

NON-STRUCTURAL VALVE DYSFUNCTION[21]

Any abnormality, not intrinsic to the prosthetic valve, resulting in valve dysfunction. Examples include residual intra- or paraprosthetic aortic regurgitation; leaflet entrapment by pannus, tissue, or suture; inappropriate positioning or sizing; dilatation of the aortic root after stentless prostheses or aortic valve sparing operations; prosthesis-patient mismatch; and embolization

Clinical Presentation

- Subclinical: Any bioprosthetic valve dysfunction associated with absent or mild haemodynamic changes, AND absent symptoms or sequelae
- Bioprosthetic valve failure (BVF):
    - Stage 1: Any bioprosthetic valve dysfunction associated with clinically expressive criteria (new-onset or worsening symptoms, LV dilation/hypertrophy/dysfunction, or pulmonary hypertension) or irreversible Stage 3 haemodynamic valve deterioration (HVD)
    - Stage 2: Aortic valve reoperation or re-intervention
    - Stage 3: Valve-related death

PROSTHETIC VALVE ENDOCARDITIS[21]

Any one of the following

- Fulfilment of the Duke endocarditis criteria31
- Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during a re-operation
- Evidence of abscess, pus, or vegetation confirmed on autopsy

Clinical Presentation

- Subclinical: Any bioprosthetic valve dysfunction associated with absent or mild haemodynamic changes, AND absent symptoms or sequelae
- Bioprosthetic valve failure (BVF):
    - Stage 1: Any bioprosthetic valve dysfunction associated with clinically expressive criteria (new-onset or worsening symptoms, LV dilation/hypertrophy/dysfunction, or pulmonary hypertension) or irreversible Stage 3 haemodynamic valve deterioration (HVD)
    - Stage 2: Aortic valve reoperation or re-intervention
    - Stage 3: Valve-related death

PROSTHETIC VALVE REGURGITATION CRITERIA[22]

	Mild	Moderate	Severe
Semi-quantitative Parameters			
Diastolic flow reversal in the descending aorta PW Doppler	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic

Circumferential extent of paraprosthetic AR	less than (<) 10%	10–29%	greater than or equal (>) 30%
Quantitative Parameters			
Regurgitant volume (ml/beat)	less than (<) 30 ml	30–59 ml	greater than or equal (>) 60 ml
Regurgitant fraction	less than (<) 30%	30–49%	greater than or equal (>) 50%
EROA (cm^2)	0.10 cm^2	0.10-0.29 cm^2	≥0.30 cm^2

STROKE/NEUROLOGICAL EVENTS[21]

Categories of Neurological Events

1. **Overt Central Nervous System (CNS) injury (NeuroARC Type 1)**
    - All Stroke
        - Ischemic Stroke: Acute onset of focal neurological signs or symptoms conforming to a focal or multifocal vascular territory within the brain, spinal cord, or retina (NeuroARC Type 1a or 1aH) and fulfilling one of the following criteria:
            - Signs or symptoms lasting ≥24 h or until death, with pathology or neuroimaging evidence of CNS infarction, or absence of other apparent causes
            - Symptoms lasting <24 h, with pathology or neuroimaging confirmation of CNS infarction in the corresponding vascular territory
        - Hemorrhagic Stroke: Acute onset of neurological signs or symptoms due to intracranial bleeding from intracerebral or subarachnoid hemorrhage not due to trauma (NeuroARC Types 1b or 1c)
        - Stroke, not otherwise specified: Acute onset of neurological signs or symptoms persisting ≥24 h or until death but without sufficient neuroimaging or pathology evidence to be classified (NeuroARC Type 1d)
    - **Symptomatic hypoxic-ischemic injury**: Non-focal (global) neurological signs or symptoms with diffuse brain, spinal cord, or retinal cell death confirmed by pathology or neuroimaging and attributable to hypotension or hypoxia (NeuroARC Type 1e)
2. **Covert CNS injury (NeuroARC Type 2)**
    - **Covert CNS infarction or hemorrhage**: Neuroimaging or pathological evidence of CNS focal or multifocal ischemia (NeuroARC Type 2a or 2aH) or hemorrhage (NeuroARC 2b) without acute neurological symptoms consistent with the lesion or bleeding location
3. **Neurologic dysfunction (acutely symptomatic) without CNS injury (NeuroARC Type 3)**
    - **TIA**: Transient focal neurological signs or symptoms lasting <24 h presumed to be due to focal brain, spinal cord, or retinal ischemia, but without evidence of acute infarction by neuroimaging or pathology, or with no imaging performed (NeuroARC Type 3a or Type 3aH)
    - **Delirium without CNS injury**: Transient non-focal neurological signs or symptoms, typically of variable duration, without evidence of infarction on neuroimaging or pathology, or with no imaging performed (NeuroARC Type 3b)

Stroke Grading

Acute Stroke Severity

- Mild neurological dysfunction: NIHSS 0-5
- Moderate neurological dysfunction: NIHSS 6-14
- Severe neurological dysfunction: NIHSS ≥1

Stroke Disability

- Fatal Stroke: death resulting from a stroke
- Stroke with disability: mRS score of ≥2 at 90 days and increase of ≥1 from pre-stroke baseline
- Stroke without disability: mRS score of 0 (no symptoms) or 1 (able to carry out all usual duties and activities) at 90 dayse or no increase in mRS category from pre-stroke baseline

STRUCTURAL VALVE DETERIORATION[21]

Intrinsic permanent changes to the prosthetic valve, including wear and tear, leaflet disruption, flail leaflet, leaflet fibrosis and/or calcification, or strut fracture or deformation.

Clinical Presentation

- Subclinical: Any bioprosthetic valve dysfunction associated with absent or mild haemodynamic changes, AND absent symptoms or sequelae
- Bioprosthetic valve failure (BVF):
  - Stage 1: Any bioprosthetic valve dysfunction associated with clinically expressive criteria (new-onset or worsening symptoms, LV dilation/hypertrophy/dysfunction, or pulmonary hypertension) or irreversible Stage 3 haemodynamic valve deterioration (HVD)
  - Stage 2: Aortic valve reoperation or re-intervention
  - Stage 3: Valve-related death

To be graded using the following stages:

Stage[A]	Description	Definition
1	Morphological valve deterioration	Evidence of structural valve deterioration, nonstructural valve dysfunction (other than paravalvular regurgitation or prosthesis- patient mismatch), thrombosis, or endocarditis without significant haemodynamic changes
2	Moderate hemodynamic valve deterioration	Increase in mean transvalvular gradient ≥10 mmHg resulting in mean gradient ≥20 mmHg[B] with concomitant decrease in EOA ≥0.3 cm^2 or ≥25% and/or decrease in Doppler velocity index ≥0.1 or ≥20% compared to echocardiographic assessment performed 1 to 3 months post-procedure, OR new occurrence or increase of ≥1 grade of intraprosthetic AR resulting in ≥ moderate AR.

Stage[A]	Description	Definition
3	Severe hemodynamic valvedeterioration	Increase in mean transvalvular gradient ≥20 mmHg resulting in mean gradient ≥30 mmHg[B] with concomitant decrease in EOA ≥0.6 cm^2 or ≥50% and/or decrease in Doppler velocity index ≥0.2 or ≥40% compared to echocardiographic assessment performed 1 to 3 months post-procedure, OR new occurrence, or increase of ≥2 grades, of intraprosthetic AR resulting in ≥ severe AR.

[A] When assessing the presence and severity of hemodynamic valve deterioration, it is important to differentiate true-hemodynamic changes versus inter-echo variability in the measurement of gradient, EOA, DVI, or AR. In particular, one should use the same window for continuous-wave Doppler interrogation when comparing gradients in early (1 to 3 months) post AVR echo versus follow-up echo. Each case with potential hemodynamic valve deterioration should be individually adjudicated to confirm presence, stage, and etiology. Hemodynamic valve deterioration may be caused by structural valve deterioration but also by non-structural dysfunction including valve thrombosis and endocarditis. The assessment of valve leaflet morphology and structure is key to make differential diagnosis between the different etiologies of hemodynamic valve deterioration.

[B] This criterion for hemodynamic dysfunction assumes normal flow.

CLINICALLY SIGNIFICANT VALVE THROMBOSIS[21]

Any thrombus attached to or near an implanted valve that occludes part of the blood flow path (as confirmed by imaging), interferes with valve function, or is sufficiently large to warrant treatment.

Clinical sequelae of a thromboembolic event (e.g. stroke, TIA, retinal occlusion, other evidence of systemic thromboembolism) or worsening valve stenosis/regurgitation (e.g. signs of heart failure, syncope) and

- Hemodynamic valve deterioration Stage 2 or 3 or
- Confirmatory imaging (CT evidence of HALT or TEE findings) In the absence of clinical sequelae, both:
- Hemodynamic valve deterioration Stage 3 and
- Confirmatory imaging (CT evidence of HALT or TEE findings)

Time

- Acute: Within 0–24 h of the index procedure
- Subacute: >24 h and ≤30 days after the index procedure
- Late: >30 days and ≤1 year after the index procedure
- Very late: >1 year after the index procedure

Response to Anticoagulant Therapy (≥3 months)

- Resolved: Partial or complete resolution of symptoms, imaging findings, and HVD
- Persistent: No improvement in symptoms, imaging findings, or HVD
- Recurrent: Recurrence of symptoms, imaging findings, or HVD

Certainty of Diagnosis

- Definite: Histopathological confirmation

- Probable: Haemodynamic changes and imaging findings compatible with valve thrombosis, with resolution of haemodynamic changes and imaging findings following anticoagulation therapy
- Possible: Imaging demonstrated findings compatible with leaflet thrombosis formation, but either haemodynamic changes or imaging findings persist following anticoagulation therapy or anticoagulation therapy is not (yet) administered

VASCULAR AND ACCESS-RELATED COMPLICATIONS[21]

VACULAR COMPLICATIONS

1. **MAJOR VASCULAR COMPLICATIONS**

   One of the following:

   - Aortic dissection or aortic rupture
   - Vascular (arterial or venous) injury (perforation, rupture, dissection, stenosis, ischaemia, arterial or venous thrombosis including pulmonary embolism, arteriovenous fistula, pseudoaneurysm, hematoma, retroperitoneal hematoma, infection) or compartment syndrome resulting in death VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment
   - Distal embolization (non-cerebral) from a vascular source resulting in death, amputation, limb or visceral ischemia, or irreversible end-organ damage
   - Unplanned endovascular or surgical intervention resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment
   - Closure device failure resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment

2. **MINOR VASCULAR COMPLICATIONS**

   One of the following:

   - Vascular (arterial or venous) injury (perforation, rupture, dissection, stenosis, ischaemia, arterial or venous thrombosis including pulmonary embolism, arteriovenous fistula, pseudoaneurysm, haematoma, retroperitoneal haematoma, infection) not resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment
   - Distal embolization treated with embolectomy and/or thrombectomy, not resulting in death, amputation, limb or visceral ischaemia, or irreversible end-organ damage
   - Any unplanned endovascular or surgical intervention, ultra-sound guided compression, or thrombin injection, not resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment
   - Closure device failure not resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment

ACCESS-RELATED NON-VASCULAR COMPLICATIONS

1. **MAJOR ACCESS-RELATED NON-VASCULAR COMPLICATIONS**

   One of the following:

- Non-vascular structure, non-cardiac structured perforation, injury, or infection resulting in death, VARC type ≥2 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention
- Non-vascular access site (e.g. trans-apical left ventricular) perforation, injury, or infection resulting in death, VARC type ≥2 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention

2. MINOR ACCESS-RELATED NON-VASCULAR COMPLICATIONS

One of the following:

- Non-vascular structure, non-cardiac structured perforation, injury, or infection not resulting in death, VARC type ≥2, irreversible nerve injury, or requiring unplanned surgery or percutaneous intervention
- Non-vascular access site (e.g. trans-apical left ventricular) perforation, injury, or infection not resulting in death, VARC type ≥2 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention

16.3 APPENDIX III: TAVI PRE-PROCEDURAL WORKUP

1. SURGICAL RISK ASSESSMENT

This Study requires the use of two surgical risk assessment tools:

1) The Society of Thoracic Surgeons' (STS) risk calculation tools, Version 4.2 (http://riskcalc.sts.org/stswebriskcalc/calculate)
2) Euro SCORE II (http://euroscore.org/calc.html)

2. FRAILTY ASSESSMENTS

The Frailty Index Data Collection Form will be used as an assessment tool to determine if frailty is a risk factor for subjects prior to enrollment. This assessment will be performed after the informed consent has been obtained and prior to procedure. The assessment can be administered by either an investigator or research coordinator.

Katz Index of Independence in Activities of Daily Living Activities plus Independence in Ambulation Index will be used within this Study.

I. Katz Index of Independence in Activities of Daily Living plus Independence in Ambulation Index

	Independence (1 point)	**Dependence (0 points)**
Bathing	Bathes himself/herself completely or needs partial help while cleaning her back or genital region	Needs help while getting in or out of the tub or shower, and while cleaning more than one part of the body
Dressing	Dress himself/herself completely. May sometimes need help when tying shoes	Completely needs help while dressing
Toileting	Goes to toilet, gets on and off, clean genital area and puts on his/her clothing without help	Needs help while going to the toilet, cleaning self, and dressing
Mobilization	Gets up from the bed and chair on his/ her own. May need help for carrying loads	Needs help while getting up from bed to the chair

Incontinence	May control himself/ herself while urinating and defecating	Partially or completely incontinent of bowel or bladder
Feeding	Gets foods from plate into mouth without help. May need help while preparing food	Needs complete or partial help with feeding or requires parenteral nutrition
Ambulation	No walking aid or assistance required, or completion of a 5-m walk in <6 s	Walking aid or assistance required, or completion of a 5-m walk in >6 s

3. NYHA FUNCTIONAL CLASSIFICATION

Class I	Patient has cardiac disease but without resulting limitations of ordinary physical activity. Ordinary physical activity (e.g., walking several blocks or climbing stairs) does not cause undue fatigue, palpitation, dyspnea, or anginal pain. Limiting symptoms may occur with marked exertion.
Class II	Patient has cardiac disease resulting in slight limitation of ordinary physical activity. Patient is comfortable at rest. Ordinary physical activity such as walking more than two blocks or climbing more than one flight of stairs results in limiting symptoms (e.g., fatigue, palpitation, dyspnea, or anginal pain).
Class III	Patient has cardiac disease resulting in marked limitation of physical activity. Patient is comfortable at rest. Less than ordinary physical activity (e.g., walking one to two level blocks or climbing one flight of stairs) causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Patient has dyspnea at rest that increases with any physical activity. Patient has cardiac disease resulting in inability to perform any physical activity without discomfort. Symptoms may be present even at rest. If any physical activity is undertaken, discomfort is increased.

16.4 APPENDIX IV: PERI-PROCEDURAL GUIDELINES

Assessment of aortic regurgitation

Angiography will be performed >5 minutes after valve deployment. Use projection where the valve frame is aligned / in-plane. Left ventricular (LV) apex must be included in the imaging field. The pigtail catheter should be located in the upper third part of the frame, give 20-30 mL non-diluted contrast for at least 5 heart cycles.

Echocardiography: Use color-Doppler in the short-axis, long-axis and 5 chamber views. The circumferential extent of the regurgitant jet determine the degree of paravalvular leak (PVL); <10% = mild (I), 10-29% = moderate (II), >30% = severe (III-IV).

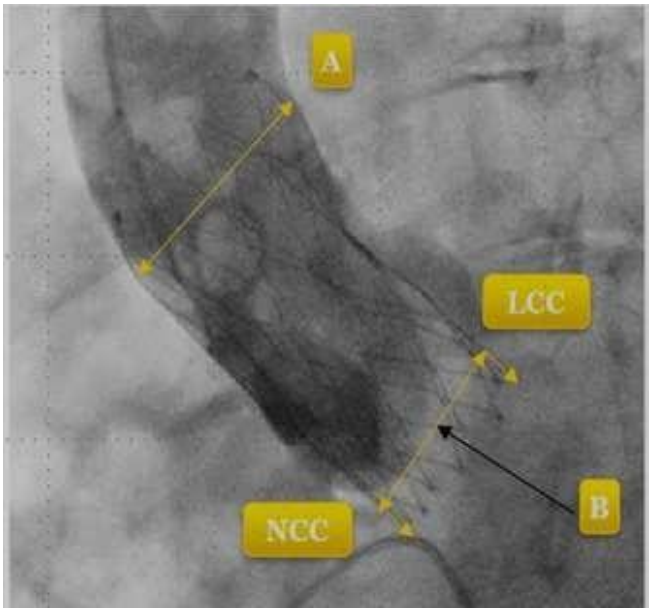
The pressure in the left ventricle and in the ascending aorta should be determined simultaneously after the procedure. The gradient between diastolic blood pressure (DBP) in the aorta and left ventricular end diastolic pressure (LVEDP) should be calculated over several cardiac cycles to evaluate the severity of paraprosthetic aortic regurgitation (PAR).

To adjust the gradient for the respective systolic blood pressure (SBP) of the patient, the dimensionless AR index may be calculated according to the following formula: [(DBP - LVEDP)/SBP] x100.

Assessment of implant depth

For implantation depth, use the angiography with the valve frame aligned with the imaging plane and measure both the distance from the non-coronary cusp (NCC) and left coronary cusp (LCC) to the ventricular end of the frame (two measurements in **Figure 4** blow).

Figure 4: Assessment of implant depth



Depth from NCC to valve inlet: _____
Depth from LCC to valve inlet: _____
Stent diameter at aortic side (A): _____
Stent diameter at annulus side (B): _____

16.5 APPENDIX V: REFERENCES

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