Clinical Investigation Plan

NCT Number: NCT04788888
VANTAGE
Evaluation of TAVI Using the NAVITOR Valve in a Global Investigation
Study Document No: ABT-CIP-10342
Version C
Date: 26-JUL-2024

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VANTAGE Clinical Trial
(Evaluation of TAVI Using the NAVITOR Valve in a Global Investigation)

CIP Name	VANTAGE
EU Unique Study ID Number	CIV-21-04-036306
Study Principal Investigators	[redacted]
Planned Number of Sites and Regions	Up to 40 sites in Australia, Europe, and Israel
Clinical Investigation Type	Prospective, single-arm, multi-center, international, pre-market clinical trial
Abbott Medical Expert	[redacted]
Sponsor	Abbott 5050 Nathan Lane N Plymouth, MN 55442 USA European Sponsor: St Jude Medical Coordination Center BV Da Vincilaan 11 Box F1 1935 Zaventem Belgium
Electronic Data Capture Software	Oracle Clinical
Core Laboratories	[redacted]

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Clinical Events Committee Administration	[redacted]
Data Monitoring Committee Administration	[redacted]
CIP Author of Current Version	[redacted]

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SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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

Site Principal Investigator

Printed name:

Signature:

Date:

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STUDY PRINCIPAL INVESTIGATOR
SIGNATURE PAGE

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Study Principal Investigator

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Signature:

Date:

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Abbreviations and definitions used throughout this investigational plan can be found in **Appendix I** and **II**. An investigational plan summary can be found in Appendix **III**. Further information regarding the literature review is in Appendix **IV**.

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COMPLIANCE STATEMENT:

This clinical investigation will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki, applicable Good Clinical Practices and regulations (e.g., OUS ISO14155:2020) and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the clinical investigation will be approved by the appropriate Institutional Review Board (IRB)/Ethics Committee (EC) of the respective investigational site and by the applicable regulatory authorities (e.g., BfArM, MHRA, TGA, etc.).

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1.0 INTRODUCTION

VANTAGE is a prospective, single-arm, multi-center, international, pre-market clinical trial of the Navitor™ Transcatheter Aortic Valve Implantation (TAVI) System at up to 40 sites in Australia, Europe, and Israel. This clinical trial is intended to demonstrate the safety and effectiveness of the Navitor TAVI system in intermediate and low surgical risk patients with symptomatic, severe native aortic stenosis. A valve-in-valve (ViV) cohort is nested within VANTAGE to evaluate the safety and effectiveness of the Navitor TAVI system in patients with failure of a surgical bioprosthetic aortic valve across all surgical risk categories. This clinical trial is sponsored by Abbott and will be conducted in accordance with this Clinical Investigational Plan (CIP). 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.

1.1 Background and Rationale

1.1.1 Background

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]

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%.[17]

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.[18]

Following completion of enrollment of the randomized cohort, the FlexNav™ 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.[19]

The Navitor 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 Valve (23 mm, 25 mm, 27 mm, 29 mm, and 35 mm)

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 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 260 subjects in Australia, Europe, and the U.S treated with 23, 25, 27 and 29 mm Navitor Valves, the rate of all-cause mortality at 30 days was 1.9%, 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 subjects had a mean aortic valve area of 2.0 ± 0.5 cm^2 with a mean gradient of 7.4 ± 3.5 mmHg. [20] The combination of the Navitor 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 Titan™ Valve (35 mm) was studied in a separate cohort of 73 subjects within the PORTICO NG trial. The rate of all-cause mortality at 30 days was low at 1.4%, 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 Titan subjects had a mean aortic valve area of 2.5 ± 0.5 cm^2 and a mean gradient of 6.0 ± 2.8 mmHg. The Navitor Titan Valve delivered via the FlexNav Delivery System offers a favorable safety profile with the potential for strong hemodynamic performance and reduced PVL.

The Navitor Transcatheter Aortic Valve Implantation System (including Navitor Valves (23mm-35mm), the FlexNav Delivery System and Navitor Loading System) has been approved in multiple geographies including Australia, Canada, Europe, Israel, and the United States for the treatment of patients with symptomatic, severe AS that are considered high or extreme surgical risk.

1.1.2 Rationale for Conducting this Clinical Investigation

The safety and effectiveness of the Navitor TAVI System for patients at high and extreme surgical risk have been investigated in the PORTICO NG trial. VANTAGE is intended to evaluate the safety and effectiveness of the Navitor TAVI System in an intermediate and low surgical risk patient population in order to support global regulatory approvals.

2.0 CLINICAL INVESTIGATION OVERVIEW

2.1 Clinical Investigation Objective

The objective of the proposed clinical trial is to evaluate the safety and effectiveness of the Navitor TAVI System in patients with severe, symptomatic native aortic stenosis who are at intermediate or low risk of surgical mortality. This trial will also evaluate the safety and effectiveness of the Navitor TAVI System in a valve-in-valve application in patients with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve across all surgical risk categories.

2.2 Devices To Be Used in the Clinical Investigation

2.2.1 Name of the Devices Under Investigation

Devices under investigation in this clinical trial include the Navitor Transcatheter Aortic Valve (23 mm, 25 mm, 27 mm, 29 mm, and 35 mm sizes), FlexNav Delivery System (small and large), and Navitor Loading System (small, large, and LG+), collectively named the Navitor TAVI System. Since the commercially available version of the Navitor TAVI System and the version labeled as investigational are physically identical (**Table 1**), the commercially available version may be used in VANTAGE in geographies where the Navitor TAVI System has been commercially approved for patients with symptomatic, severe aortic stenosis who are at high or extreme surgical risk and where the use of the commercially available version in this trial has also been approved by the applicable Competent Authority and/or Ethics Committee.

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

Table 1: Devices Included in the Clinical Trial

Device name	Model/Type	Serial/Lot Controlled	Manufacturer	Regions	Regulatory Status¶
Navitor 23 mm Valve	PRT-NG-23/NVTR-23*	Serial numbered	Abbott Medical	Australia, Europe, and Israel	Approved for high and extreme risk in Australia, Europe, and Israel *
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	Serial numbered	Abbott Medical	Australia, Europe, and Israel	
FlexNav Small Delivery System	FN-DS-SM-IDE/ FNAV-DS-SM*	Serial numbered/Lot numbered	Abbott Medical	Australia, Europe, and Israel	
FlexNav Large Delivery System	FN-DS-LG-IDE/ FNAV-DS-LG*				
Navitor Small Loading System	PRT-NG-LS-SM/NVTR-LS-SM*	Serial numbered/Lot numbered	Abbott Medical	Australia, Europe, and Israel	
Navitor Large Loading System	PRT-NG-LS-LG/NVTR-LS-LG*				
Navitor Titan Loading System LG+	PRT-NG-LS-35	Serial numbered	Abbott Medical	Australia, Europe, and Israel	

*Commercial model

¶The regulatory status listed is current as of the version date of this CIP.

Table 2: Compatible Components in the Navitor TAVI System

Navitor Valve Catalog Numbers	FlexNav Delivery System Catalog Numbers	Navitor Loading System Catalog Numbers
PRT-NG-23/NVTR-23* (23 mm) or PRT-NG-25/NVTR-25* (25 mm)	FN-DS-SM-IDE/FNAV-DS-SM*	PRT-NG-LS-SM/NVTR-LS-SM*
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

*Commercial model

2.2.2 Intended Indication for Use

The intended indication for use statements for the products used in this trial 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. For the valve-in-valve application, the Navitor Valve is indicated for use in patients, of any surgical risk category, with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve.

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.

2.2.3 Description of the Devices Under Investigation

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.

2.2.3.1 Navitor 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 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 mm^2	85-95 mm	≥ 0.73

*Commercial model
¶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™ anticalcification 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 1: 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 height ratio.
- Increased chronic outward radial (COR) force of the 23 mm and 25 mm valves to a common COR force 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.

2.2.3.2 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 Navitor 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 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.

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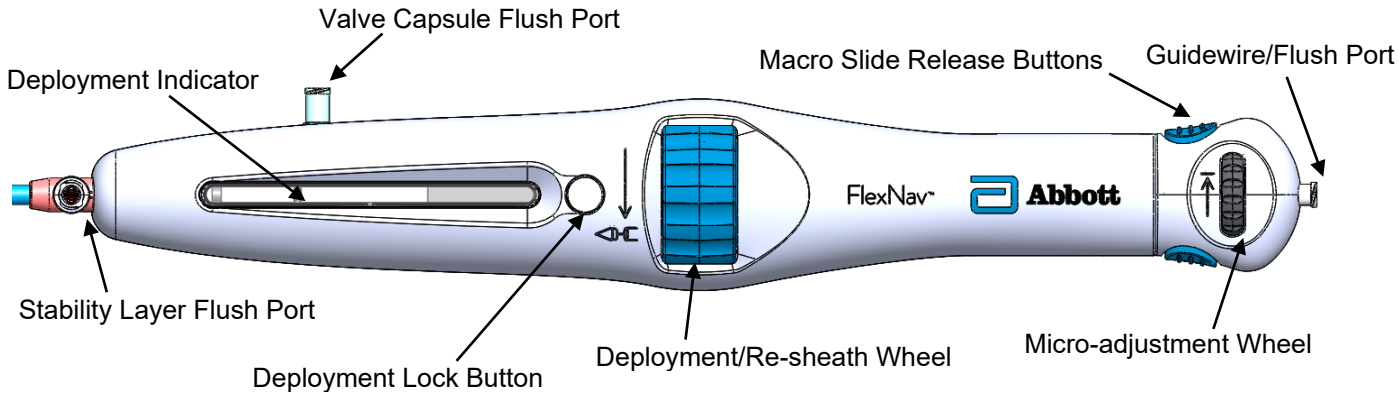
Table 4: FlexNav Delivery System Models and Compatibility with Navitor Valve Sizes

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

* Commercial model

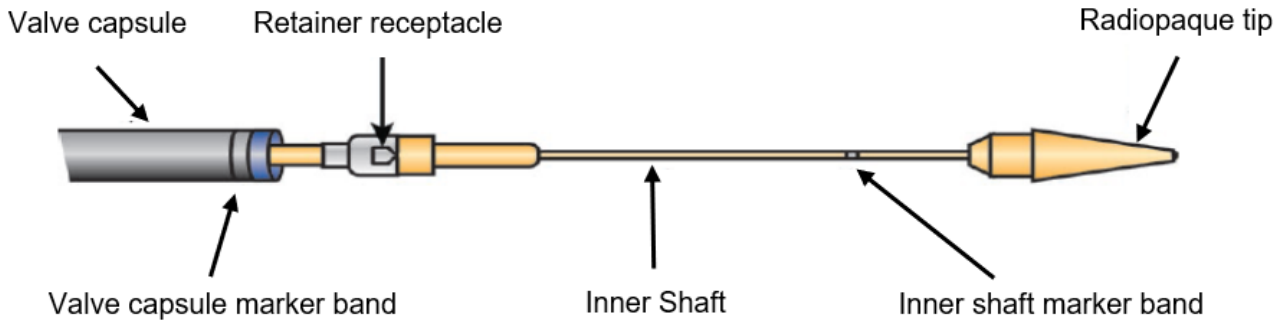
The FlexNav Delivery System shaft includes a stability layer over the outer member to improve control during positioning and deployment of the valve. The FlexNav Delivery System handle functions in a similar manner as the first-generation Portico Delivery System with modifications and added labeling. 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



2.2.3.3 Navitor Loading System

The Navitor Loading System is an accessory used to compress and load the Navitor Valve onto the FlexNav Delivery System. The Navitor 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 Loading System components (loading base, loading tube, leaflet tester) are the same as the FlexNav Loading System. The method of loading the Navitor Valve onto the FlexNav Delivery System is also unchanged.

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

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

2.2.4 Summary of Preclinical Studies

Refer to the Preclinical Studies section of the Investigator's Brochure (IB) for a summary of the results.

2.2.5 Device Handling

Sponsor requires clinical sites to store all investigational products according to the labeling and Instructions for Use in a secure area to prevent unauthorized access or use. Refer to **Appendix V** for the product labels and Instructions for Use.

3.0 CLINICAL INVESTIGATION DESIGN

The VANTAGE trial is a prospective, single-arm, multi-center, international, pre-market clinical investigation designed to evaluate the safety and effectiveness of the Navitor TAVI System in accordance with ISO standard 14155:2020. The trial will register subjects in three cohorts: (1) primary analysis cohort (up to 450 subjects), (2) roll-in cohort (up to 40 subjects), and (3) valve-in-valve (ViV) cohort (up to 100 subjects). To be eligible for participating in the primary analysis and roll-in cohorts, a

patient must have symptomatic, severe native aortic stenosis and have intermediate or low risk for surgical valve replacement. To be eligible for participating in the ViV cohort, a patient must have symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve, and the patient can be in any risk category.[A]

Subjects will be enrolled and treated with the Navitor Valve at up to 40 experienced TAVI implant centers across Australia, Europe, and Israel. All sites must either have prior Portico or Navitor TAVI system experience or must complete roll-in cases. Upon providing informed consent and approval by the Screening Committee (SC), subjects will undergo Navitor Valve implantation via a transfemoral or alternative access (subclavian or axillary) approach using the site's anesthesia protocol for TAVI procedures. In the trial, 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 Valve) into the subject's vasculature (the subject is considered attempted with Navitor Valve implantation at this point) (**Figure 4**). Only registered subjects will be included in the analysis.

There are two co-primary endpoints for the primary analysis cohort, each of which will be tested against a literature-derived performance goal. The primary safety endpoint is a composite of all-cause mortality or fatal stroke/stroke with disability at 12 months post index Navitor implantation procedure. The primary effectiveness endpoint is moderate or greater paravalvular leak (PVL) at 30 days post index Navitor implantation procedure. The number of subjects required to be registered in the primary analysis cohort is 434. In addition, per ISO 5840-3:2021, the standard for heart valve substitutes implanted by transcatheter techniques, 400 patient-years of follow-up are required to assess late adverse events.

Roll-in and ViV cohorts will be summarized separately and will not contribute to the required sample sizes for hypothesis testing or the 400 patient-year requirement.

Subjects participating in the clinical trial will be followed for a total of 10 years with data collected at screening, baseline, procedure, prior to hospital discharge, and follow-up at 30 days, 12 months and annually thereafter up to 10 years.[B] Key assessments required at each visit are described in **Section 6.0**. The expected duration of enrollment in the primary analysis cohort is [redacted] months, and the total duration of the clinical study including final data cleaning, reporting, and site close-out is expected to be approximately [redacted] years. Follow-up data through 10 years will be submitted as part of a final report to respective regulatory agencies.

The Sponsor has designed this clinical investigation to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects. Refer to the Risks Analysis (**Section 15.0**) of this clinical investigation plan for details.

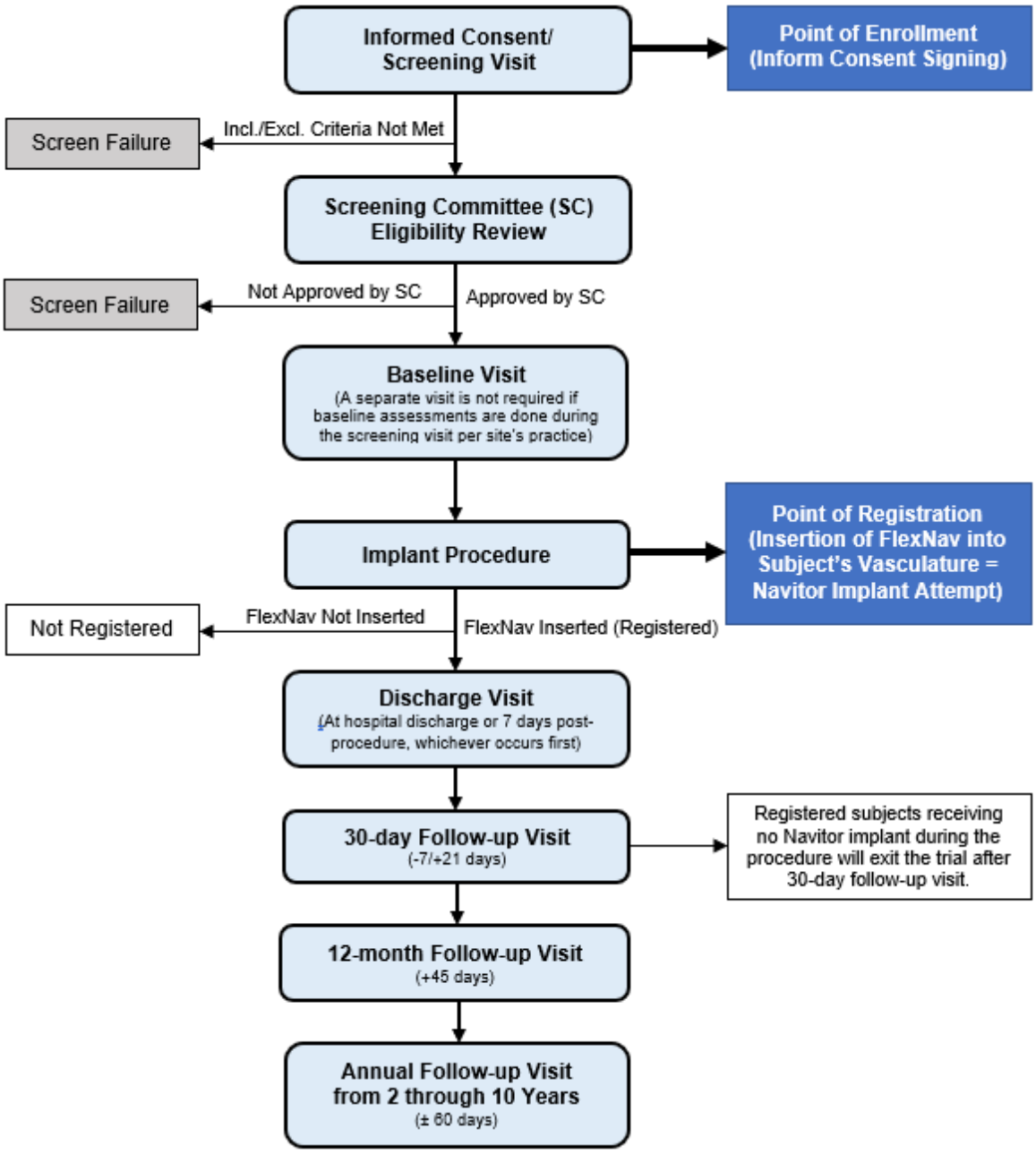
3.1 Clinical Investigation Procedures and Follow-up Schedule

The Flow Chart of this clinical investigation is shown in **Figure 4** below.

[A] In Germany, only subjects at high or extreme surgical risk can be included in the ViV cohort. Sites in Switzerland will not participate in the ViV enrollment.
[B] Subjects in the high or extreme risk category in the ViV cohort will be followed up to 5 years.

Clinical Investigation Plan

Figure 4: Clinical Trial Flow Chart



Note 1: Reasons for enrolled but not registered may include screen failure, death, and withdrawal.
Note 2: Subjects in the high or extreme risk category in the ViV cohort will be followed up to 5 years.
Note 3: Any subject who undergoes an explant of the Navitor Valve during the study follow-up period will be exited from the trial 30 days following the explant procedure.

4.0 ENDPOINTS

4.1 Primary Endpoints and Rationale

1. Primary Safety Endpoint:

   The primary safety endpoint is a composite of all-cause mortality or fatal stroke/stroke with disability at 12 months post index Navitor implantation procedure per the Valve Academic Research Consortium (VARC) 3 event definitions[21]. This endpoint is consistent with other trials evaluating the safety and effectiveness of TAVI in intermediate or low risk patients. Previous clinical trials testing the safety and effectiveness of TAVI valves in intermediate and low surgical risk subjects have used a single composite primary endpoint of all-cause mortality or disabling stroke per the VARC-2 event definitions[22] (disabling stroke per VARC-2 is equivalent to fatal stroke plus stroke with disability per VARC-3).[12,15,23] The 12-month timepoint for the VANTAGE primary safety endpoint is consistent with PARTNER 2 - S3I, PARTNER 3, and ACURATE IDE trials that investigated or are currently investigating TAVI in intermediate and/or low surgical risk subjects.

2. Primary Effectiveness Endpoint:

   The primary effectiveness endpoint is moderate or greater paravalvular leak at 30 days post index Navitor implantation procedure, assessed by the echocardiographic core laboratory. This endpoint will characterize the performance of the fabric outer cuff of the Navitor valve stent to optimize valve sealing and minimize paravalvular leak. Given more than mild paravalvular leak following valve deployment is shown to be associated with increased morbidity and mortality following aortic valve replacement, moderate or greater paravalvular leak at 30 days is an appropriate endpoint to assess the effectiveness of the valve. [24,25]

4.2 Secondary Endpoints

1. Mean change in mean transvalvular gradient between baseline and 12 months
2. Mean change in effective orifice area between baseline and 12 months
3. Mean change in Kansas City Cardiomyopathy Questionnaire (KCCQ) quality of life score between baseline and 12 months

4.3 Descriptive Endpoints[C]

1. Major adverse events (non-hierarchical composite of all-cause mortality, fatal stroke/stroke with disability, type 3/type 4 bleeding, stage 3/stage 4 acute kidney injury, major vascular complications, or major access-related non-vascular complications) at 30 days
2. Non-hierarchical composite of all-cause mortality or all stroke at 12 months

[C] Event definitions for descriptive endpoints #1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 13, 16, 20, 21, 22, and 24 are based on the VARC-3 definitions.

3. Procedural success defined as successful vascular access, delivery and deployment of the Navitor Valve; retrieval of the delivery system and correct positioning of a single Navitor Valve in the 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 and 12 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. 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, six-minute walk test, quality of life measure: Kansas City Cardiomyopathy Questionnaire (KCCQ))
16. Rehospitalization (procedure-related or valve-related hospitalization, and other cardiovascular hospitalization) at 30 days and 12 months
17. Paravalvular leak (none/trace, mild, moderate or severe) at discharge, 30 days, 12 months and annually (when collected) through 10 years
18. Changes in echocardiographic parameters from baseline to follow-up at 30 days, 12 months and annually (when collected) through 10 years (e.g., mean effective orifice area, mean transvalvular gradient)
19. Aortic valve reintervention at 30 days, 12 months, and annually through 10 years
20. Prosthetic valve endocarditis at 12 months and annually through 10 years
21. Structural valve deterioration at 12 months and annually through 10 years
22. Non-structural valve dysfunction at 12 months and annually through 10 years
23. Successful coronary access as needed at 12 months and annually through 10 years
24. Clinically significant prosthetic valve thrombosis at 12 months and annually through 10 years

The two co-primary endpoints and three secondary endpoints will be tested for the primary analysis cohort. All event-based endpoints will be assessed from the index procedure unless otherwise noted.

5.0 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This clinical trial will enroll subjects of all genders who have symptomatic, severe AS and are determined to be at intermediate or low surgical risk except for subjects in the ViV cohort. Complete clinical investigation eligibility criteria are described in **Section 5.3**. Subjects must meet all general eligibility criteria and provide written informed consent prior to sites conducting any investigation-specific procedures not considered standard of care. Informed consent must occur prior to transmission of any subject data to the independent computed tomography (CT) and echocardiographic core laboratories, Screening Committee (SC) or Sponsor for screening purposes.

The operative risk determination of study candidates will be based on assessment by the local heart team and confirmation by the SC. 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.[3,26]

Subject case review will be conducted by the SC to determine primarily the final risk classification. The SC charter provides details of the SC process.

5.1.1 Intermediate Surgical Risk Classification

To be classified as intermediate surgical risk, the heart team's estimate of the subject's 30-day surgical mortality risk must be greater than or equal to 3% but less than 7%. This determination will include consideration of the surgical risk calculator but will not rely entirely on the surgical risk calculator as indices of frailty and other comorbidities will also be considered when making this overall surgical risk determination. The final risk classification of the subject will be determined by the SC.

5.1.2 Low Surgical Risk Classification

To be classified as low surgical risk, the heart team's estimate of the subject's 30-day surgical mortality risk must be less than 3%. This determination will include consideration of the surgical risk calculators and the absence of indices of frailty or other comorbidities that would elevate the overall surgical risk for the subject. The final risk classification of the subject will be determined by the SC.

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 CIP must evaluate patients for the general clinical investigation 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 clinical investigation.

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 clinical investigation.

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 EC. This process will include a verbal discussion with the patient on all aspects of the clinical investigation that are relevant to the patient's decision to participate, such as details of clinical investigation procedures, anticipated benefits, and potential risks of clinical investigation participation. Sites must inform patients about their right to withdraw from the clinical investigation at any time and for any reason without sanction, penalty, or loss of benefits to which the patient is otherwise entitled. Withdrawal from the clinical investigation 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. Patients may be compensated for travel directly related to the participation in the clinical investigation. 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 EC. 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 clinical investigation-specific procedures. The site will file the signed original in the patient's hospital or research charts and provide a copy to the patient. The dated signatures can be electronic. The site will follow local hospital and local EC provisions for documenting electronic informed consent form (ICF) signature.

Sites should report any failure to obtain informed consent from a patient to the Sponsor within 5 working days and to the reviewing center's EC according to the EC's reporting requirements.

If, during the clinical investigation, 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.

For information regarding obtaining the trial informed consent template, please see **Appendix VI**.

5.2.2.1 Special Circumstances for Informed Consent

Consistent with the study exclusion criteria listed in **Section 5.3.3**, this clinical investigation excludes individuals unable to make the decision to participate in a clinical investigation on their own or who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response. 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**.

For live or recorded cases to be broadcast at congresses, the subject needs to sign a specific Live Case ICF, approved by the EC and by the Sponsor, as well as by the Competent Authorities, as applicable. The investigator must obtain Sponsor approval prior to performing a Live Case.

Proctoring and/or observation of cases by other medical professionals (whether in-person or virtually) does not require special provisions for informed consent.

5.2.3 Subject Screening

Once a duly dated and signed Informed Consent form is obtained, sites will perform the below CIP-specific assessments as part of the clinical investigation screening process:

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, Grip Strength, 5-meter Walk Test, Albumin (collected with Laboratory Measurements))
7. Forced Expiratory Volume (FEV1) Test, if clinically indicated
8. 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)
9. Laboratory Measurements (including complete blood count (CBC) and platelet count, creatinine and estimated glomerular filtration rate (eGFR), and albumin)
10. 12 Lead Electrocardiogram (ECG)
11. 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, and determination of appropriate coaxial angles for optimizing the valve implantation procedure. CT covering at least systole is required for valve sizing (please refer to the CT Acquisition Protocol from the CT Core Laboratory). CT scan performed up to 12 months prior to consent will be acceptable.
12. Invasive coronary angiography or CT coronary angiography and aortic angiography (if clinically indicated or standard of care). Angiography performed up to 12 months prior to consent will be acceptable.
13. Adverse Event Assessment

Data available in the subject's medical record may be utilized to fulfill screening requirements and testing does not need to be repeated if performed within 90 days prior to Informed Consent. CT scan with coronary angiography or invasive coronary angiography and aortic angiography (if clinically indicated or standard of care) may be performed within 12 months prior to Informed Consent.

If any clinical and/or laboratory tests are required for patient screening and are not included in a site's standard tests, they must be completed after written informed consent is obtained.

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

Upon initial screening of eligibility of patients by the heart team, subject case reviews will be conducted by the SC to confirm a subject's eligibility for this trial per the SC Charter. If the SC does not approve the subject for study participation, the subject will be exited from the study as a screen failure and will not be counted toward the sample size. The Principal Investigator or the delegated clinical investigation personnel will record the screen failure in the hospital records and on the screening log.

Further details regarding methods used for subject screening can be found in **Appendix VII**.

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.

If any clinical and/or laboratory tests are required for patient screening and are not included in a site's standard tests, they must be completed after written informed consent is obtained.

5.3.2 Inclusion Criteria[D]

5.3.2.1 General Inclusion Criteria

1. Subject who is judged by a Heart Team, including a cardiac surgeon, to be appropriate for transcatheter heart valve intervention therapy, and is deemed to be at intermediate or low risk for open surgical aortic valve replacement (i.e., heart team estimates risk of surgical mortality < 7% at 30 days, considering the Society of Thoracic Surgeons (STS) risk score, overall clinical status, and other clinical co-morbidities unmeasured by the risk calculator). [#,E]
2. New York Heart Association (NYHA) Functional Classification of II, III, or IV [#]
3. Subject is of legal age for consent in the host country.
4. Subject has been informed of the nature of the trial, agrees to its provisions and has provided written informed consent as approved by the Ethics Committee (EC) of the respective clinical site.
5. Able and willing to return for required follow-up visits and assessments

5.3.2.2 Imaging Inclusion Criteria

6. Degenerative aortic valve stenosis with echo-derived criteria, defined as: aortic valve area (AVA) of ≤ 1.0 cm^2 (or indexed EOA ≤ 0.6 cm^2/m^2) AND either mean gradient ≥ 40 mmHg or peak jet

[D] Eligibility criteria labeled with "#" are not applicable for the ViV cohort. Sites in Switzerland will not participate in the ViV enrollment.
[E] In France and Switzerland, if a subject is deemed low surgical risk, the subject must be at age 75 or over to be included in this trial.

velocity ≥ 4.0 m/s or doppler velocity index (DVI) ≤ 0.25. The echocardiogram supporting the qualifying AVA baseline measurement must be performed within 90 days prior to informed consent) .[#]

7. Aortic annulus diameter of 19-30 mm and ascending aorta diameter of 26-44 mm for the specified valve size listed in the IFU, as measured by CT (systolic phase) conducted within 12 months prior to informed consent.

5.3.3 Exclusion Criteria

5.3.3.1 General Exclusion Criteria

1. Pregnant or nursing subjects and those who plan pregnancy during the clinical investigation follow-up period. A pregnancy test is required for all women of childbearing potential.
2. Need for emergency surgery for any reason
3. Life expectancy is less than 2 years in the opinion of the Investigator.
4. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical trial or to comply with follow up requirements, or impact the scientific soundness of the clinical trial results
5. Incapacitated individuals, defined as persons who are mentally ill, mentally handicapped, individuals with severe dementia or individuals without legal authority
6. Individuals who are unable to read or write
7. Currently participating in an investigational drug or device study that has not reached the primary endpoint or may confound the results of this trial
8. Evidence of an acute myocardial infarction [defined as ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI) with acute ischemia symptoms and troponin elevation] within 30 days prior to index procedure
9. Untreated clinically significant coronary artery disease requiring revascularization
10. Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior (except pacemaker or implantable cardioverter defibrillator (ICD) implant) to index procedure or planned within 30 days following the index procedure.
11. Blood dyscrasias as defined: leukopenia (WBC < 3000 mm^3), acute anemia (Hb < 9 g/dL), thrombocytopenia (platelet count < 50,000 cells/mm^3); history of bleeding diathesis or coagulopathy
12. Refuses blood products
13. Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support
14. Hemodynamic instability requiring inotropic support or mechanical heart assistance
15. Hypertrophic cardiomyopathy with obstruction

16. Active peptic ulcer or upper GI bleeding within 3 months prior to index procedure that would preclude anticoagulation
17. Known intolerance, hypersensitivity, or contraindication, including subjects that meet any of the following conditions:
    a. Subjects who cannot take any antiplatelets or anticoagulants*,
    b. Subjects who have sensitivity to contrast media which cannot be adequately premedicated,
    c. Subjects who have known hypersensitivity to nitinol (nickel or titanium), or
    d. Subjects who have clinical contraindication that precludes contrast CT imaging

    *Note: Subjects who can take either an antiplatelet or anticoagulant therapy post-procedure will be eligible.
18. Recent (within 6 months prior to index procedure date) cerebrovascular accident (CVA) or a transient ischemic attack (TIA)
19. Renal insufficiency (creatinine > 3.0 mg/dL or eGFR < 30 ml/min/1.73m^2) and/or end stage renal disease requiring chronic dialysis
20. Active bacterial endocarditis within 6 months prior to the index procedure
21. A positive COVID-19 test within 30 days prior to the index procedure
22. Liver failure (Child-Pugh class B or C)
23. Subjects with atrial fibrillation who are not on anticoagulants or who are not implanted with a left atrial appendage occlusion (LAAO) device
24. Symptomatic carotid or vertebral artery disease, significant carotid or vertebral artery disease requiring intervention, or successful treatment of carotid or vertebral stenosis within 30 days prior to index procedure
25. Severe pulmonary hypertension with pulmonary systolic pressure greater than two-thirds of systemic pressure
26. Severe lung disease (FEV1 < 50% predicted) or currently on home oxygen
27. Hostile chest or conditions or complications from prior surgery that would make the subject be considered high surgical risk (i.e., mediastinitis, radiation damage, abnormal chest wall, porcelain aorta, adhesion of aorta or internal mammary artery to sternum, etc.) #
28. Significant frailty as determined by the heart team (after objective assessment of frailty parameters) that would indicate high or extreme surgical risk #

5.3.3.2 Imaging Exclusion Criteria

29. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation 3-4+) #
30. Aortic valve is a congenital unicuspid or congenital bicuspid valve as verified by echocardiography or CT. #
31. Non-calcified aortic valve #
32. Severe ventricular dysfunction with LVEF < 30% as measured by resting echocardiogram

33. Pre-existing prosthetic heart valve or other implant (such as prosthetic ring or transcatheter edge-to-edge repair (TEER) clip) in any valve position [#] (Note: Subjects with a bioprosthetic aortic valve may be included in the ViV cohort.)
34. Severe circumferential mitral annular calcification (MAC) which is continuous with calcium in the left ventricular outflow tract (LVOT) [#]
35. Prohibitive left ventricular outflow tract calcification [#]
36. Severe (greater than or equal to 3+) mitral regurgitation or severe mitral stenosis with pulmonary compromise
37. Severe tricuspid regurgitation or severe right ventricle dysfunction
38. Echocardiographic or multi-slice computed tomography (MSCT) evidence of intracardiac mass, thrombus or vegetation
39. Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5.5 cm or greater or ascending aortic aneurysm defined as maximal luminal diameter 5 cm or greater
40. Marked aortic tortuosity (hyperacute bend) or severe “unfolding” and tortuosity of the thoracic aorta (applicable for transfemoral access only)
41. Aortic arch atheroma (thick [> 5 mm], protruding or ulcerated)
42. Significant narrowing (calcification and surface irregularities) of the abdominal or thoracic aorta
43. Aortic root angulation > 70°
44. Undue risk of coronary obstruction (e.g., low coronary ostia, narrow Sinus of Valsalva anatomy that would prevent adequate coronary perfusion, or bulky aortic valve leaflets in close proximity to coronary ostia)
45. Access vessel characteristics that would preclude safe insertion of the FlexNav Delivery System such as severe obstructive calcification, protruding thrombus or severe tortuosity
46. Minimum access vessel diameter of < 5.0 mm for small FlexNav Delivery System and < 5.5 mm for large FlexNav Delivery System
47. Ascending aorta anatomy that would preclude safe delivery of the valve to the native aortic annulus
48. Eccentricity ratio of the annulus < 0.73

Refer to country-specific addendums for other details.

5.4 Subject Enrollment, Subject Registration, and Study Cohorts

A patient is considered enrolled in the clinical trial from the moment the patient provides written informed consent.

Consented subjects who undergo study-specific testing and are found to have met exclusion criteria or not all inclusion criteria prior to the procedure (or if a site disagrees with and does not accept the Screening Committee’s final decision regarding risk classification) will be considered screen failures;

these subjects will not be counted toward the sample size of roll-ins, primary analysis subjects, or ViV subjects and will be exited from the study without further follow-up.

In addition, a consented (enrolled) subject is considered registered in the clinical investigation from the moment the FlexNav Delivery System (loaded with a Navitor Valve) is inserted into the subject's vasculature. Consented subjects who undergo trial-specific testing and meet trial criteria but do not undergo a Navitor implant attempt (defined as insertion of the FlexNav Delivery System into the vasculature) will not be registered in the trial. Reasons for enrolled but not registered may include screen failure, death, and withdrawal. This includes subjects in whom the implanting physician at the time of the procedure but before the insertion of the delivery system into the vasculature determines implantation of the Navitor Valve is either not feasible or not in the best interest of the subject. These subjects will not be counted toward the sample size of roll-ins, primary analysis subjects or ViV subjects and will be exited from the study without further follow up. Only registered subjects will be counted toward the sample size.

All subjects who undergo a Navitor attempt will be included in either the roll-in cohort as described in **Section 5.4.1**, the primary analysis cohort as described in **Section 5.4.2**, or the ViV cohort as described in **Section 5.4.3**. Subjects who undergo a Navitor attempt but are not implanted with the Navitor Valve will be followed for 30 days and then exited from the study **(Figure 4)**; similarly, any subject who undergoes explant of the Navitor Valve during the study follow-up period will be exited from the study 30 days following the explant procedure.

5.4.1 Roll-in Cohort

The requirement for roll-in cases will be determined based on experience of the implanting physicians. If neither of the implanting physicians have previous Portico or Navitor clinical experience, a minimum of one roll-in subject will be required. A maximum of [redacted] roll-in subjects will be allowed per implanting physician, and up to 40 roll-in subjects will be permitted in the study. Designation of roll-in or analysis subject will be determined by the Sponsor in consultation with the Study PI and communicated to the site in advance of the procedure.

5.4.2 Primary Analysis Cohort

The primary analysis cohort will include all registered subjects that are not designated as a roll-in subject or ViV subject. A maximum of 450 registered subjects will be included in this cohort.

If subjects receive a Navitor Valve without meeting all the conditions listed in **Section 5.3**, they should complete all follow-up requirements. These subjects are considered CIP deviations but will be included in the primary analysis cohort.

5.4.3 Valve-in-Valve (ViV) Cohort

Subjects who have documented failed aortic surgical valve prosthesis regardless of risk classification and are deemed eligible to receive a Transcatheter Navitor Valve into the existing bioprosthesis will be considered for eligibility in the ViV cohort. The ViV cohort will register up to 100 qualified subjects.

ViV subjects must meet all the applicable inclusion criteria and none of the applicable exclusion criteria with the following exceptions to **Section 5.3**. Criteria that may not apply include inclusion criterion numbers 1, 2 and 6 (the surgical bioprosthetic valve may be stenotic or require replacement due to other forms of structural valve deterioration), and exclusion criterion numbers 27, 28, 29, 30, 31, 33, 34, and 35. If the subject has a bioprosthetic valve in another location, the subjects will be excluded from this

trial. All risk levels will be included[F] and SC will assess surgical risk for demographic characterization and sub-analysis purposes.

ViV subjects' data will not be included in the primary data analysis; however, the data will be analyzed descriptively and presented separately.

5.5 Subject Discontinuation

Each subject meeting all general and screening eligibility criteria shall remain in the clinical investigation until completion of the required follow-up period; however, a subject's participation in any clinical investigation 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 voluntary withdrawal
- Subject lost-to follow-up as described below
- Subject's follow-up is terminated according to **Section 13.1**

Sites must notify the Sponsor of 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 clinical investigation, except for the status (deceased/alive).

However, if a subject withdraws from the investigation due to problems related to the safety or performance of the device under investigation, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical investigation.

In case of subject withdrawal of consent, the site should make attempts to schedule the subject for a final clinical investigation visit. At this final follow-up visit, the subject will undergo the following assessments:

- 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

Upon completion of trial-specified follow-up (regardless of how follow-up was completed, e.g., withdrawal, completion of required follow-up), subjects should be followed per standard of care for subjects with severe aortic stenosis that underwent transcatheter aortic valve implantation. Participation in this trial does not require subjects to have any unique follow-up requirements once trial participation is complete. Valve traceability and identification requirements for such follow-up are the same as for commercially approved transcatheter aortic valve implants.

<u>Lost-to-Follow-up</u>

[F] In Germany, only subjects at high or extreme surgical risk can be included in the ViV cohort. Sites in Switzerland will not participate in the ViV enrollment.

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 450 subjects will be included in the primary analysis cohort in order to analyze the primary endpoints and meet the requirement of 400 patient-years of follow-up to assess late adverse events per ISO 5840-3:2021. In addition, up to 100 subjects may be included in the ViV cohort and up to 40 subjects may be included in the roll-in cohort. No site may register more than 20% without prior approval from the Sponsor.

5.7 Total Expected Duration of the Clinical Investigation

The expected duration of enrollment in the primary analysis cohort is [redacted] months. The expected duration of each subject's participation is 10 years, including the scheduled visits and data collection for this clinical trial. Subjects will be exited from the trial at the conclusion of their 10-year follow-up visit. Therefore, the total duration of the clinical investigation is expected to be approximately [redacted] years, consisting of approximately [redacted] months of enrollment, 10 years of follow-up, and 0.5 years for final data cleaning, reporting and site close-out.

6.0 TREATMENT AND EVALUATION OF ENDPOINTS

For subjects that have successfully completed screening and been approved by the SC, scheduled visits will be performed in the following order: Baseline, Index Procedure, Discharge, 30 days,12 months, and annual follow-up assessments to 10 years.

This is an open-label clinical investigation. Investigators and subjects will not be blinded to treatment assignment.

6.1 Baseline

Subjects who are deemed eligible for implantation of a Navitor Valve using the FlexNav Delivery System will undergo a baseline visit prior to the procedure. (A separate baseline visit is not required if baseline assessments are performed during the screening visit per the site's practice.)

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 (Refer to **Appendix IX** for further details)
- Six Minute Walk Test (6MWT) (Refer to **Appendix VII** for further details)
- Quality of Life Assessment: KCCQ (Refer to **Appendix VIII** for further details)
- 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 study-related assessments.

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 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 Under Investigation

Please refer to IFU for instructions on handling and preparation of the Navitor Valve, FlexNav Delivery System, Navitor Loading System. If the devices were not used according to the IFU or other instructions in this CIP, 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 implants will be performed by experienced TAVI implanters that are board certified interventional cardiologist(s) and/or cardiac surgeon(s) and study investigators. Implanters must complete all required Navitor implant procedure training prior to their first Navitor case and be approved to implant by the Sponsor.

It is strongly recommended that the index procedure occur within 14 calendar days following SC approval.

A Navitor Valve may be implanted in a subject who has provided written informed consent and was approved by the SC. 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 (cine-angiogram, intra-procedure echocardiography to be stored and provided to the Sponsor for the first 5 procedures at each site and upon request thereafter)

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 study-specific guidelines for the assessment of aortic regurgitation and implant depth. Refer to **Appendix X** 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 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 Loading Systems) should be securely disposed as per hospital requirements for hazardous materials.

If there are any concerns noted with the Navitor Valve, FlexNav Delivery System, or the Navitor Loading System during the procedure, please notify the Sponsor and return these products to the Sponsor for evaluation if possible. See **Section 7.3.3** for Device Deficiency/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 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 10 years (± 60 days)

The only exceptions to the above follow-up requirements are subjects in the high or extreme risk category in the ViV cohort, who will be followed at 30 days, 12 months, and annually through 5 years. Subjects with a Navitor implant attempt (registered subjects) that did not have a Navitor Valve implanted will only be required to complete the 30-day follow-up visit prior to exiting the study.

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, except for remote follow-up at 6, 8, and 9 years. 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. Remote assessments should include telephone contact with the subject and/or a visit to a medical facility (i.e. non-investigational site) with all data that can be reasonably and legally collected remotely on the study subject. To aid in follow-up compliance, if necessary, an authorized health care representative (e.g. Hawthorne Effect) may be utilized to provide in-home visits for both the clinical and echocardiographic follow-up. Follow-up visits occurring at non-study sites will be limited to standard of care data collection only. Authorization for the release of medical records from non-study facility is the responsibility of the investigational site. Any missed testing will be considered a protocol deviation.

A registered subject may only be followed at another investigational site (e.g. subject moves closer to another investigational site) with prior agreement from that site's Investigator and from the Sponsor.

Each site will be responsible for performing and interpreting the follow-up echocardiograms for potential adverse events. Echocardiograms will be submitted to an independent Echocardiographic Core Laboratory for further analysis. Examinations should be recorded in DICOM format and should be de-identified prior to submitting to the Echocardiographic Core Laboratory. 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 Sponsor and/or appropriate core laboratory for analysis.

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. Modified Rankin Scale (mRS)
5. Six Minute Walk Test (6MWT)
6. 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)
7. Echocardiography (TTE)
8. Quality of Life Assessment (KCCQ)
9. Lab Measurements (INR if subject is on warfarin or other anticoagulants/vitamin K antagonists in lieu of warfarin)
10. 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. Modified Rankin Scale (mRS)
5. Six Minute Walk Test (6MWT)
6. 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)
7. Echocardiogram (TTE)
8. Quality of Life Assessment (KCCQ)
9. Lab measurements (INR if subject is on warfarin or other anticoagulants/vitamin K antagonists in lieu of warfarin)
10. Adverse events assessment

6.4.2.3 Annual Follow-up

The following data should be collected at years 2 through 10 years (± 60 days) post index procedure:

1. Cardiovascular medications
2. Adverse event assessment
3. Modified Rankin Scale (mRS)

The following are only required at years: 2, 3, 4, 5, 7, and 10

4. Physical Examination (including weight, resting heart rate, and blood pressure)
5. NYHA Functional Classification
6. Quality of Life Assessment (KCCQ)
7. Echocardiography (TTE)

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 must 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 must be performed at an unscheduled visit 90 days (± 14 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 Sponsor 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 according to the CIP requirements to assess whether the health of subjects has improved since enrollment in the clinical 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. Refer to **Appendix VIII** for the sample questionnaire.

6.4.5 Schedule of Events

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

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Table 5: Follow-up and Data Collection Requirements

Trial Activity	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[A]
Surgical Risk Assessment (STS & EuroSCORE II)	X						
NYHA Classification	X				X	X	X[A]
Frailty Index (Katz Index of ADLs, Grip strength, 5-meter walk, Albumin)	X						
Forced Expiratory Volume (FEV1) Test (if indicated)	X						
Cardiovascular Medications documentation		X		X	X	X	X
Invasive coronary angiography or CT coronary angiography and Aortic Angiogram (if clinically indicated or standard of care)	X						
Modified Rankin Scale (mRS)		X		X	X	X	X
Neurological Assessment	A neurological assessment and mRS must be performed at 90 days (±14 days) from the date of a suspected neurological event						
Six-Minute Walk Test		X			X	X	
Non-Invasive Tests							
12 lead Electrocardiogram (ECG) [B,C]	X		X[C]	X[B,C]	X[B]	X[B]	
Cardiac Rhythm			X				
2D Transthoracic Echocardiogram (TTE)	X		X[D]	X	X	X	X[A]
Angiogram			X				
CT Scan with Angiography of chest, abdomen and pelvis	X[E]						
Patient Reported Outcome Measure							
KCCQ		X			X	X	X[A]
Laboratory Measurements							
CBC and Platelet Count	X						
Creatinine	X[F]		X[G]	X			
INR (if subject is on Warfarin)		X			X	X	
Troponin *or* CK-MB			X[G]	X			
Albumin (for Frailty Index)	X						
Other							
Adverse Event Assessment [H]	X	X	X	X	X	X	X
Deviation	(X)	(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)	(X)

[A] Required at years 2, 3, 4, 5, 7, and 10; not required at years 6, 8, and 9. Subjects in the high or extreme risk category in the ViV cohort will be followed up to 5 years.

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[B] For subjects receiving a new permanent pacemaker, ECG should be completed showing the underlying rhythm as well as the current pacing programming.
[C] Record a 12-lead ECG following the implant of the valve and daily until day of discharge
[D] Copy of echocardiographic examination to be stored at the site and available to the Sponsor upon request.
[E] To be done within 12 months prior to consent; CT covering at least systole is required for valve sizing.
[F] Includes eGFR
[G] To be collected within 72 hours before index procedure
[H] Transesophageal echocardiogram (TEE) is also recommended after adverse events of ischemic stroke and myocardial infarction

(X) indicates if applicable

6.5 Requirement for Core Laboratories

Independent core laboratories will be utilized for evaluating CT scans and echocardiograms collected in the clinical study. Each investigational site will submit CT scans and echocardiograms to the respective core laboratories for evaluation. The core laboratories will provide the study required acquisition requirements and documentation of each data submission according to their Standard Operating Procedures and study specific charter.

Data obtained from the core laboratory readings will be used for study purposes only and not for clinical treatment of the subject. The Sponsor will use the data provided by the core laboratories in data analyses, where measurements were collected by the core laboratory. If the core laboratory determines that the imaging examination is unreadable, the site will be responsible for having the subject return for another assessment.

7.0 Adverse Events

To comply with worldwide standards and guidelines on clinical investigation adverse event reporting, the Sponsor has adopted uniform and worldwide applicable standard definitions and reporting timelines to be used and adhered to by the investigators.

7.1 Definition

7.1.1 Adverse Event

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational medical device and whether anticipated or unanticipated.

As part of ISO14155 Section 3.2, the Adverse Event definition has the following notes:

Note 1: This definition includes events related to the investigational medical device or the comparator.

Note 2: This definition includes events related to the procedures involved.

Note 3: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

7.1.2 Serious Adverse Event

Serious Adverse Event is an AE that leads to any of the following:

a) death,
b) serious deterioration in the health of the subject, that resulted in any of the following:
    1. life-threatening illness or injury,
    2. permanent impairment of a body structure or a body function,

3. hospitalization or prolongation of patient hospitalization,
4. medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function, or
5. chronic disease

c) fetal distress, fetal death or a congenital physical or mental impairment or birth defect.

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

7.1.3 Device Deficiency/Device Malfunction

Device deficiency is defined as any inadequacy in the identity, quality, durability, reliability, usability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in the information supplied by the manufacturer including labeling.

Note 1: The definition includes device deficiencies related to investigational medical device or the comparator.
Note 2: Cyber-security incidents related to the investigational product shall be reported as device deficiencies.

A device malfunction is the failure of an investigational medical device perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP or IB.

7.2 Device Relationship

Determination of whether there is a reasonable possibility that an investigational product or device under investigation caused or contributed to an AE is to be **determined by the Investigator** and recorded on the appropriate CRF form. Determination should be based on the assessment of temporal relationships, evidence of alternative etiology, medical/biologic plausibility and subject condition (pre-existing condition).

7.2.1 Unanticipated (Serious Adverse) Device Effect [U(S)ADE]

Unanticipated serious adverse device effect (USADE) refers to any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

7.3 Adverse Event and Device Deficiency/Device Malfunction Reporting

7.3.1 Adverse Event Reporting

Safety surveillance and reporting starts as soon as the subject is enrolled in the clinical investigation. Safety surveillance and reporting will continue until sites perform the last follow-up visit, the subject is deceased, the subject concludes participation in the clinical investigation, or the subject withdraws from

the clinical investigation. Sites will collect all adverse event data, including deaths and device deficiency data, throughout the period defined above and will report these events to the Sponsor on a CRF. Sites should update additional information regarding an adverse event on the appropriate CRF.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be reported.

Non-cardiac related abnormal laboratory values will not be considered AEs unless:

1. the investigator determined that the value is clinically significant,
2. the abnormal lab value required intervention, or
3. the abnormal lab value required subject withdrawal from the clinical investigation.

All adverse events will be collected on each subject through the 10-year follow-up visit.

SAE Reporting

The investigator must report all SAEs to the Sponsor as soon as possible but no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

Sites must record the date the site staff became aware that the event met the criteria of an SAE in the source document. The Investigator will further report the SAE to the local EC according to the institution's EC reporting requirements.

The Sponsor will provide an offline form to allow the investigator to report SAEs in the event the entry cannot be made in the electronic data capture system (EDC), and site must use this offline form to report SAEs by email to [redacted]. This does not replace the EDC reporting system. Sites must still enter all information in the EDC system as soon as feasible.

7.3.2 Unanticipated Serious Adverse Device Effect Reporting to Sponsor and EC

The Sponsor requires the Investigator to report any potential USADE to the Sponsor within 3 calendar days of the investigator's knowledge of the event, unless local requirements are more stringent, and to the EC per EC requirements.

7.3.3 Device Deficiency/Malfunction Reporting

All device deficiencies/malfunctions should be reported on the Device Deficiency CRF form.

The investigator must report all device deficiencies/malfunctions to the Sponsor as soon as possible but no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.
Sites must report device deficiencies/malfunctions to the EC per the investigative site's local requirements.

Sites should return the device, if not implanted or not remaining in the subject, to the Sponsor.

An offline form will be made available to allow the investigator to report device deficiencies/malfunctions in the event that the entry cannot be made in the EDC system, and sites must use this offline form to report device deficiencies/malfunctions by email to [redacted]. This does not replace the EDC reporting system. All information must still be entered in the EDC system as soon as feasible.

7.3.4 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

The Sponsor will report SAEs and reportable device deficiencies/malfunctions to the country regulatory authority, per local requirements.

The Sponsor's Clinical Safety Team will submit the clinical investigation SAEs and device deficiencies/malfunctions reportable per MedDEV 2.7/3 regulations to the European Competent Authorities (per MDCG 2020-10/1 after May 2021). Contact details are provided in **Appendix XII**.

Note: Reportable device deficiencies include device deficiencies that might have led to an SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

8.0 STATISTICAL CONSIDERATIONS

The following section describes the statistical methods for the primary analysis cohort (subjects with stenosis of the native aortic valve) unless otherwise specified. Data on roll-in and ViV cohorts will be descriptively summarized. The ViV cohort will be summarized relative to data from studies in which patients with a failed surgical bioprosthetic aortic valve were treated with TAVI for the valve-in-valve application. [27,28] Additional details on statistical analyses, including justification of clinical investigation design, sensitivity analyses, poolability analyses, subgroup analyses, and analysis of descriptive endpoints, will be maintained in a separate Statistical Analysis Plan (SAP).

8.1 Statistical Analyses

8.1.1 Primary Safety Endpoint Analysis

The primary safety endpoint is a composite of all-cause mortality or fatal stroke/stroke with disability at 12 months post index Navitor implantation procedure as adjudicated by the CEC per the VARC-3 event definitions.[G]

The hypothesis testing of the primary safety endpoint will be performed for the mixed-risk (mixed intermediate and low risk) group based on the attempted population described in **Section 8.1.1**. If the primary safety endpoint is met, the trial will have demonstrated that the Navitor TAVI System is safe in the intermediate and low risk populations.

Specifically, the following hypotheses will be tested:

H_{10}: $p_{Mixed} \geq PG_{Mixed}$
H_{1a}: $p_{Mixed} < PG_{Mixed}$

where p_{Mixed} is the primary safety endpoint event rate in the mixed intermediate and low risk group at 12 months and PG_{Mixed} is the performance goal for a mixed intermediate and low risk group. This hypothesis will be tested at a one-sided significance level of 0.025 and the null hypothesis will be rejected if the 97.5% upper confidence bound (UCB) for the event rate, p_{Mixed}, is less than the performance goal, PG_{Mixed}. The 12-month event rate will be estimated using the Kaplan-Meier (KM) method, and the standard error of KM estimate will be calculated using Greenwood method.

The performance goal for the mixed-risk group (PG_{Mixed}) is determined by the proportion of the study population registered in the trial that is intermediate risk ($prop_{Int}$) or low risk ($prop_{Low}$). The performance goals in the intermediate risk and low risk groups are PG_{Int} and PG_{Low}, respectively. The mixed-risk group performance goal is determined by:

$$PG_{Mixed} = (prop_{Int} * PG_{Int}) + (prop_{Low} * PG_{Low})$$

The 12-month primary safety endpoint event rates for the Navitor TAVI System in the intermediate and low risk groups are assumed to be [redacted], respectively, based on published data from other TAVI pivotal trials [redacted]. Per the recommendation of ISO 5840-3:2021, [redacted]

[G] A composite of all-cause mortality or fatal stroke/stroke with disability per VARC-3 is equivalent to a composite of all-cause mortality or disabling stroke per VARC-2 as previously mentioned in Section 4.1.

[redacted] the performance goals in the intermediate risk group (PG_{Int}) and low risk group (PG_{Low}) are set to be 16.6% and 5.4%, respectively. Assuming a 1:1 ratio between intermediate and low risk groups, with 262 registered subjects, there is 85% power at a one-sided 2.5% significance level [redacted] with the performance goal set at 11%, and an attrition rate of 10% at 12 months (due to withdrawal or loss to follow-up prior to 365 days). [redacted] The sample size of 262 subjects provides at least 85% power for all scenarios within the range of proportions of intermediate risk group between 50% and 70%. [redacted]

The first 262 consecutively registered subjects will be used to test this hypothesis.

8.1.2 Primary Effectiveness Endpoint Analysis

The primary effectiveness endpoint is moderate or greater PVL at 30 days post index Navitor implantation procedure, assessed by the echocardiographic core laboratory.

The hypothesis testing of the primary effectiveness endpoint will be performed based on the implanted population (described in **Section 8.1.2**) in whom a functional Navitor Valve remains implanted at 30 days. If the primary effectiveness endpoint is met, the trial will have demonstrated that the Navitor TAVI System is effective in the intermediate and low risk populations. Given TAVI devices have the same anatomical considerations regardless of a subject's surgical risk category, the expected event rate and performance goal for the primary effectiveness endpoint do not need to be adjusted according to the subject's risk classification. Based on published data from other TAVI pivotal trials [redacted], the [redacted] performance goal [redacted] is 6.6%.

Specifically, the following hypothesis will be tested:

H_{20}: $\pi \geq 6.6\%$
H_{2a}: $\pi < 6.6\%$

where π is the proportion of subjects who have moderate or greater PVL at 30 days. π will be estimated as a binomial proportion. The hypothesis will be tested at a one-sided significance level of 0.025, and the null hypothesis will be rejected if the 97.5% upper confidence bound (UCB) for the proportion, π, is less than the performance goal of 6.6%. The 97.5% UCB will be calculated by the Clopper-Pearson method for exact confidence intervals for binomial proportion.

With 390 subjects, there is approximately 85% power at a one-sided 2.5% significance level [redacted]. With an approximately 10% attrition rate at 30 days (due to death or withdrawal prior to the 30-day visit, missing echo images, or inability of echo core lab to assess PVL on echo image), the sample size needed is 434 subjects. [redacted]

All registered subjects with available 30-day PVL data will be used to test this hypothesis.

8.1.3 Secondary Endpoint Analyses

The following are secondary endpoints for the primary analysis cohort:

1. Mean change in mean transvalvular gradient between baseline and 12 months

   The null and alternative hypotheses are stated as:

   H_{30}: $\Delta\mu_{3,12\text{ months - Baseline}} \geq$ -10 mmHg
   H_{3a}: $\Delta\mu_{3,12\text{ months - Baseline}} <$ -10 mmHg

   where $\Delta\mu_{3,12\text{ months - Baseline}}$ is the mean paired difference in mean transvalvular gradient from baseline to 12 months.

   This secondary endpoint will be assessed in the implanted population in whom a functional Navitor Valve remains implanted at 12 months.

2. Mean change in effective orifice area between baseline and 12 months

   The null and alternative hypotheses are stated as:

   H_{40}: $\Delta\mu_{4,12\text{ months - Baseline}} \leq 0.4\ cm^2$
   H_{4a}: $\Delta\mu_{4,12\text{ months - Baseline}} > 0.4\ cm^2$

   where $\Delta\mu_{4,12\text{ months - Baseline}}$ is the mean paired difference in effective orifice area from baseline to 12 months.

   This secondary endpoint will be assessed in the implanted population in whom a functional Navitor Valve remains implanted at 12 months.

3. Mean change in KCCQ quality of life score between baseline and 12 months

   The null and alternative hypotheses are stated as:

   H_{50}: $\Delta\mu_{5,12\text{ months - Baseline}} \leq 5$
   H_{5a}: $\Delta\mu_{5,12\text{ months - Baseline}} > 5$

   where $\Delta\mu_{5,12\text{ months - Baseline}}$ is the mean paired difference in KCCQ quality of life score from baseline to 12 months.

   This secondary endpoint will be assessed in the attempted population.

All secondary endpoint hypothesis tests will be performed with one-sample *t*-test at one-sided significance level of 0.025.

8.2 Sample Size Calculations

The sample size (which includes attrition) required for evaluation of the primary safety endpoint and primary effectiveness endpoint are 262 and 434 subjects, respectively. The primary effectiveness endpoint requires a larger sample size (N=434) and therefore determines the overall sample size of the trial.

8.3 Timing of Analysis

The analysis in the primary analysis cohort for regulatory approval submission will be conducted after (1) the first 262 consecutively registered subjects have been followed for 12 months[H], (2) all registered subjects[I] have been followed for 30 days[J], and (3) 400 patient-years of follow-up have been completed. The first 262 consecutively registered subjects will be used for the hypothesis testing of the primary safety endpoint, and all registered subjects will be used for the hypothesis testing of the primary effectiveness endpoint.

8.4 Subgroup Analysis

Subgroup analysis will be performed to examine the consistency of the primary endpoints across baseline risk categories, specifically by risk group (intermediate vs low risk), and sex (male vs female). For each subgroup, KM estimates on the primary safety endpoint will be reported along with 95% confidence intervals, while proportional rate estimates on the primary effectiveness endpoint event will be reported along with 95% exact confidence intervals.

8.5 Multiplicity

The study will be successful if both primary safety and effectiveness endpoints are met. If both primary endpoints are met, fixed sequence procedure in the pre-specified order of secondary endpoints listed below will be used.

1. The secondary endpoint (#1) of change in mean transvalvular gradient between baseline and 12 months.
2. The secondary endpoint (#2) of change in mean effective orifice area between baseline and 12 months.
3. The secondary endpoint (#3) of change in KCCQ quality of life score between baseline and 12 months.

If one hypothesis test in the secondary endpoint sequence is not statistically significant, the subsequent tests will not be performed. Hence, no additional multiplicity adjustment is needed.

8.6 Pooling Strategy

Additional information regarding the planned pooling strategy in this clinical study will be maintained in a separate SAP.

8.7 Procedures for Accounting for Missing Data

Tipping point analyses will be performed to evaluate the impact of missing data on the primary safety and effectiveness endpoints analysis result. [redacted]

[H] This includes subjects who die, withdraw, or are lost to follow-up before 365 days.
[I] If more than 434 subjects are registered before enrollment completion for this cohort, all registered subjects will be included in the hypothesis testing of the primary effectiveness endpoint.
[J] This includes subjects who die, withdraw, or are lost to follow-up before the 30-day follow-up visit.

8.8 Planned Interim Analysis

No interim analyses are planned for this study.

8.9 Statistical Criteria for Termination

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

8.10 Success Criteria

The study will be considered successful if both the primary safety and effectiveness endpoints are met.

8.11 Deviations from Statistical Plan

The Sponsor will document any major changes to the statistical plan in an amendment to the statistical plan and any less significant changes to the planned analyses in the final report.

9.0 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 clinical investigation. This information may be shared with regulatory agencies; however, the Sponsor undertakes not to otherwise release the subject's personal and private information.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Selection of Clinical Sites and Investigators

The Sponsor will select investigators qualified by training and experience to participate in the clinical investigation. Sites will be selected based upon review of a recent site assessment, if applicable, and the qualifications of the investigators who will participate in the clinical investigation. A list of the participating sites will be provided upon request (refer to **Appendix XII**).

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 clinical investigation, as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation. The principal investigator shall support monitoring and reporting to EC and local Competent Authorities as necessary, throughout the conduct of the clinical investigation. 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 clinical investigation. 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 Clinical Investigation Finances and Agreements

Abbott will finance the clinical investigation and will compensate investigational sites for participation in the clinical investigation per the conditions of agreement between Abbott and the investigational site.

10.4 CIP Amendments

The Sponsor will provide approved CIP amendments to the Investigators prior to implementing the amendment. The Principal Investigator is responsible for notifying the EC or equivalent committee of the CIP amendment (administrative changes) or obtaining EC's approval of the CIP amendment (changes in subject care or safety), according to the instructions provided by the Sponsor with the CIP amendment.

Sites must document in writing acknowledgement/approval of the CIP amendment by the EC prior to implementation of the CIP amendment. Sites must also provide copies of this documentation to the Sponsor.

For a history of CIP Amendments please see **Appendix XI.**

10.5 Measures Taken to Avoid and Minimize Bias

The clinical trial will include the following measures to minimize bias in the conduct of the study and analysis of clinical data.

10.5.1 Screening by an Interdisciplinary Heart Team

At each investigational site, a heart team consisting of at least of one cardiac surgeon and one interventional cardiologist will be responsible for screening patients for surgical risk classification for participation in the clinical study. It is strongly recommended for the heart team to assess all available TAVI patients as potential candidates for the study.

10.5.2 Use of a Screening Committee

An independent Screening Committee (SC), consisting of interventional cardiologists and cardiac surgeons considered experts in the field of aortic valve replacement with a focus on TAVI, will be responsible for ensuring all subjects' clinical eligibility per the SC Charter. SC review and approval, with voting members independent of the implanting site and the Sponsor, are required prior to implanting a subject with the Navitor Valve. The SC ensures subjects' risk classification is done consistent with the trials used to derive the primary endpoint performance goal and therefore the hypothesis test is making a valid assessment. The Committee's decision on whether to include the subject in the study will be documented and communicated to the enrolling investigational site by the Sponsor. If the SC considers the subject ineligible for participation in the study, the subject will be exited from the study and the reason for exclusion will be documented in the reviewers' feedback form.

The composition, guiding policies, and operating procedures governing the SC in this clinical study are further defined in the SC Charter.

10.5.3 Ascertainment and Adjudication of Adverse Events

An independent Clinical Events Committee (CEC), consisting of, at a minimum, an interventional cardiologist, cardiothoracic surgeon, and a neurologist (for possibly neurological-related events only) will review and adjudicate pre-specified events reported by investigators in the clinical study as defined in the CEC Charter. Pre-specified clinical events defined in the primary and descriptive endpoints will be adjudicated in a consistent manner according to the VARC-3 definitions.[21] The CEC will have final adjudication responsibilities for subject outcomes related to primary and descriptive outcome measures which will be outlined in a CEC charter. The CEC reduces bias by consistently applying adverse event definitions following VARC-3. This consistency allows for the performance goal to be fairly assessed as it was derived from previous clinical trials. Also, the independent adjudication allows for the results of this study to be descriptively compared to other studies in intermediate and low surgical risk populations.

Adaptations for subsequent VARC definitions will also be captured in the CEC charter.

10.5.4 Review of Echocardiographic Images by an Independent Echocardiographic Core Laboratory

An independent Echocardiographic Core Laboratory will be utilized for the analysis of all study visit echocardiograms according to the echocardiographic protocol.

Echocardiograms collected post implantation will be assessed for hemodynamic performance and aortic regurgitation (total regurgitation and paravalvular leak (PVL)) according to the Echo Core Laboratory Standard Operating Procedure Manual. The independent echocardiogram assessment allows for the results of this study to be descriptively compared to other studies in intermediate and low surgical risk populations. Each site is responsible for performing the echocardiogram according to the core laboratory imaging protocol, forwarding the examination to the core laboratory for analysis and providing local interpretation of the echocardiogram for clinical assessment. The echocardiographic core laboratory will be responsible for submitting their data to the Sponsor.

10.5.5 Maintaining High Rates of Follow-Up Compliance

The Sponsor will work with investigational sites to maintain a high follow-up compliance as follows:

1. Site must clearly communicate the requirement for follow-up visits to the patient during the consenting process and obtain reasonable assurance that the patient has the intention and means to return for visits.
2. Sponsor will monitor each sites' subject follow-up compliance and communicate performance to the site as needed. Site should continue to communicate the importance of follow-up visits to each subject.
3. Sites will be informed to promptly reschedule any missed subject visits, and to reinforce the necessity of a follow-up visit to the subject.
4. Sites are advised to involve Sponsor if Sponsor assistance is needed to maintain high follow-up compliance. Example: To cover costs associated with alternate transportation if a scheduled visit may be missed due to transportation/travel issues.

5. Sites should document reasons for any missed visits and/or subject withdrawals from the study.
6. Sites should monitor their follow-up rates closely to promptly identify and address any issues.

Additionally, investigational sites will be educated on the importance of maintaining low rates of withdrawals and will be expected to make all effort to maintain low withdrawals during study conduct.

10.5.6 Standardized Administration of Patient-Reported Outcome Measures and Stroke Assessment Scales

A standardized script will be used when administering patient-reported outcome (PRO) measures to minimize bias and undue influence. All PRO measures must be completed by the subject or his/her legal representative (where allowed per local regulations). In the latter case, a note to file must be completed to document the inability of the subject to complete the measures(s).

The Modified Rankin Scale (mRS) must be completed by an assessor who has a current certificate that demonstrates completion of an accredited training program for this stroke scale. Standardized PRO measures and assessment scales minimize bias in the reporting of clinical events and perceived patient outcomes, thus allowing for a more robust comparison to results captured from other studies utilizing these same measures.

10.6 Training

10.6.1 Site Training

All Investigators and clinical investigation personnel are required to attend Sponsor training sessions [redacted].

10.7 Monitoring

Sponsor and/or designee will monitor the clinical investigation over its duration according to the CIP-specific monitoring plan which will include the planned extent of source data verification.

Prior to initiating any procedure, the Sponsor monitor (or delegate) will ensure that the following criteria are met:

- The investigator understands and accepts the obligation to conduct the clinical investigation according to the CIP and applicable regulations and has signed the Investigator Agreement or the Clinical Trial Agreement.

- The Investigator and his/her staff should have sufficient time and facilities to conduct the clinical investigation and should have access to an adequate number of appropriate subjects to conduct the clinical investigation.
- Sites must have source documentation (including original medical records) to substantiate proper informed consent procedures, adherence to CIP procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information.
- The Investigator/site will permit access to such records and will maintain a monitoring visit sign-in log at the site. The Investigator will agree to dedicate an adequate amount of time to the monitoring process. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator will provide the monitor with a suitable working environment for review of clinical investigation-related documents.

For instructions for obtaining the Monitoring Plan, please reference **Appendix XIII**.

10.8 Deviations from CIP

The Investigator should not deviate from the CIP 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 Sponsor immediately by phone or in writing.

The Sponsor will not grant any waivers for CIP deviations. Sites must report all deviations to the Sponsor using the Deviation CRF. The Sponsor will monitor the occurrence of CIP for evaluation of investigator compliance to the CIP and 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 CIP deviations in accordance with their specific EC or equivalent committee reporting policies and procedures.

In the event of repeated non-compliance, as determined by the Sponsor, a Sponsor's monitor or company representative will attempt to secure compliance by one or more of the following (and not limited to):

- Visiting the investigator and/or delegate
- Telephoning the investigator and/or delegate
- Corresponding with the investigator and/or delegate

Repeated non-compliance with the signed agreement, the CIP, or any other conditions of the clinical investigation may result in further escalation in accordance with the Sponsor's written procedures, including securing compliance or, at its sole discretion, the Sponsor may terminate the investigator's participation in the clinical investigation.

10.9 Quality Assurance Audit

A Sponsor representative or designee may request access to all clinical investigation records, including source documentation, for inspection during a Quality Assurance audit.

If an investigator is contacted by a Regulatory Agency in relation to this clinical investigation, the Investigator will notify Sponsor immediately. The Investigator and Research Coordinator must be available to respond to reasonable requests and audit queries made during the audit process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current clinical investigation (e.g., Form FDA 483, Inspectional Observations, Warning Letters, Inspection Reports, etc.). The Sponsor may provide any needed assistance in responding to regulatory audits.

10.10 Sponsor Auditing

Sponsor audits may be conducted for the clinical study in accordance with the below requirements:

1. The Sponsor shall prepare an audit plan as well as the operating procedures for the related duties and conduct audits in accordance with the audit plan and the operating procedures.
2. Individuals engaged in auditing (hereinafter referred to as "auditor") shall be different than those in charge of medical device development or monitoring.
3. The auditor shall prepare an audit report documenting the matters confirmed in the audit to certify and verify that the audit has been conducted and submit them to the Sponsor.

10.11 Committees

The clinical trial will utilize the following committees.

10.11.1 Steering Committee

The 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 CIP at individual centers, to review and act upon recommendations of the Data Monitoring Committee (DMC), to review operational issues that may arise and warrant a CIP amendment or other corrective action, and to determine policy regarding the primary results publication arising from data generated from the performance of the clinical investigation.

10.11.2 Screening Committee

Refer to **Section 10.5.2** for Screening Committee.

10.11.3 Clinical Events Committee (CEC)

The CEC is an independent adjudication body comprised of qualified physicians who are not participants in the clinical investigation. The CEC will review and adjudicate pre-specified events reported by investigators or identified by Safety personnel for the clinical investigation as defined in the CEC charter and according to definitions provided in this CIP.

10.11.4 Data Monitoring Committee (DMC)

The DMC is an independent multidisciplinary group restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. The DMC is typically composed of at least two physicians with experience relevant to the clinical investigation and a biostatistician.

The DMC will serve in an advisory role to the Sponsor to ensure safety by reviewing cumulative data from the clinical investigation at prescribed intervals for safeguarding the interests of enrolled subjects and those patients yet to be enrolled, as well as the continuing validity and scientific merit of the clinical investigation. The composition, frequency of the meetings, and the statistical monitoring guidelines are described in detail in the DMC charter.

The DMC may make a recommendation for modifications or termination of the clinical investigation based on any perceived safety concerns regardless of statistical significance. The recommendations of the DMC are not binding, and all final decisions related to clinical investigations modifications rest with the Sponsor.

10.11.5 Publications Committee

A Publication Committee shall be established to oversee clinical investigations publications, including publication planning and authorship determinations. Publication Committee membership may include members of the Steering Committee, Principal Investigators, a representative of the Sponsor, and a statistician. The Publication Committee will determine policy and strategies regarding individual presentations and/or publications arising from clinical investigation generated data. The committee will also review all external requests for accessing clinical investigation-related data and strategies aligning with the Sponsor's presentation and publication team expectations. The committee will also follow the Sponsor's applicable policies and Standard Operating Procedures.

11.0 DATA HANDLING AND RECORD KEEPING

Sponsor and/or its affiliates will maintain documentation of the systems and procedures used in data collection for the duration of the clinical investigation.

CRF data collection will be performed through a secure web portal 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 Sponsor.

At the end of the clinical investigation, 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 clinical investigation, the Investigator will maintain complete and accurate documentation including, but not limited to, medical records, clinical investigation progress records, laboratory reports, CRFs, signed ICFs, device accountability records (if applicable), correspondence with the EC and clinical investigation monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical investigation.

11.1 Protection of Personally Identifiable Information

The Sponsor respects and protects personally identifiable information collected or maintained for this clinical investigation.

The Sponsor implements technical and physical access controls 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.

The Sponsor requires the investigational sites to enter only pseudonymous Personal Information (key-coded) necessary to conduct the clinical investigation, such as the patient's medical condition, treatment, dates of treatment, etc., into Sponsor's data management systems. The Sponsor discloses as part of the clinical investigation informed consent process that some Sponsor representatives still may see Personal Information at the participating sites for technical support of the participating physicians on the device implant or procedures, monitoring and quality control purposes. 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 Sponsor data management systems and processes were designed, developed, and tested according to industry standards to appropriately safeguard Confidential Information (including any Personal Information) against unauthorized access and/or interference by third parties, intrusion, theft, destruction, loss or alteration. Clinical Investigation data are encrypted in transit and at rest.

The Sponsor maintains a Privacy Incident procedure that complies in all respects with Applicable Law and industry best practices.

11.2 Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data review, data cleaning, and issuing and resolving data discrepancies, and database locking. If appropriate, the Sponsor may update the DMP throughout the duration of the clinical investigation. The Sponsor will track and document control all revisions.

11.3 Source Documentation

Regulations and GCP require the Investigator to maintain information in the subject's original medical records that corroborates data collected on the CRFs. To comply with these regulatory requirements/GCP, sites should include the following information in the subject record at a minimum and if applicable to the clinical investigation:

- Medical history/physical condition of the subject before involvement in the clinical investigation sufficient to verify CIP entry criteria
- Dated and signed notes on the day of entry into the clinical investigation referencing the Sponsor, CIP number, subject ID number, and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of procedures and examinations)

- AEs reported and their resolution, including supporting documents, such as discharge summaries, catheterization laboratory reports, ECGs, and lab results including documentation of site awareness of SAEs and of investigator assessment of device relationship for SAEs.
- CIP-required laboratory reports and 12-lead ECGs, reviewed and annotated for clinical significance of out of range results (if applicable).
- Notes regarding CIP-required and prescription medications taken during the clinical investigation (including start and stop dates)
- Subject's condition upon completion of or withdrawal from the clinical investigation
- Any other data required to substantiate data entered into the CRF
- Patient reported outcome measures may be completed using CRF worksheets. This serves as source documentation.

11.4 Case Report Form Completion

Site research personnel trained on the CIP 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 to the Sponsor on the CRFs and in all required reports.

Sites will collect data on all subjects who sign an informed consent form, including subjects who may not meet all inclusion/exclusion criteria during screening at the index procedure.

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

For instructions for obtaining the trial case report forms, please see **Appendix XIV**.

11.5 Record Retention

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

11.6 Investigational Devices Accountability

The Sponsor ships investigational products only to the Principal Investigator (the responsible leader of the investigational site) or his/her legal designee of each site, after site activation and shipping authorization is complete.

The Investigator or an authorized designee must maintain adequate records of the receipt and disposition of each investigational device, including serial number, date received, date used, subject identification, and final device disposition.

Storage locations for the devices at investigational sites must be locked with access restricted only to investigators and authorized personnel.

Sites must return all investigational devices associated with a device failure or device deficiency immediately to the Sponsor in biohazard or protective packaging.

The clinical investigation will use the electronic Device Accountability Log supplied by the Sponsor for device accountability. The electronic Device Accountability Log documents the disposition of all investigational devices used as reported by Device case report form and unused product that have been returned to Sponsor.

12.0 ETHICAL CONSIDERATION

12.1 Institutional Review Board/Medical Ethics Committee Review and Approval

The Principal Investigator at each investigational site will obtain EC approval for the CIP 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 Sponsor.

Sites will submit any amendments to the CIP 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 CIP or ICF or other written information provided to the patient without appropriate approvals, including EC, the Sponsor, and the regulatory agencies (if applicable).

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

Sites will not perform any investigative procedures, other than those defined in this CIP, on the enrolled subjects without the written agreement of the EC and the Sponsor.

13.0 CLINICAL INVESTIGATION CONCLUSION

The clinical investigation will be concluded when:

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

The Sponsor will submit the clinical investigation report within one year of the end of the investigation to the investigational sites, Competent Authorities, and reviewing ECs.

13.1 Suspension or Early Termination of the Clinical Investigation

While no formal statistical rule for early termination of the clinical investigation for insufficient effectiveness of the device under investigation is defined, the Sponsor reserves the right to discontinue the clinical investigation 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:

- Unanticipated ADE event occurs and it presents an unreasonable risk to the participating subjects
- 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 sponsor.
- Further product development is cancelled.

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

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

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

The investigator will be requested to return all clinical investigation materials (including devices) to the Sponsor and provide a written statement to the EC (if applicable). All applicable clinical investigation document shall be subject to the same retention policy as detailed in **Section 11.0** of the CIP.

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.

14.0 PUBLICATION POLICY

[redacted]

The Sponsor will be responsible for registering this clinical investigation on ClinicalTrials.gov website, in accordance with the International Committee of Medical Journal Editors guidelines, or any other applicable guidelines. The Sponsor shall be responsible for any such registration and results posting as required by the ClinicalTrials.gov website. Institution and/or Principal Investigator(s) shall not take any action to register the clinical investigation. A full report of the pre-specified outcomes, regardless of the results, will be made public through the ClinicalTrials.gov website no later than 12 months after clinical investigation completion, as required by section 801 of the FDA Amendments Act. If this clinical investigation is terminated early, the Sponsor will make every effort to hasten the release of the pre-specified outcomes through the ClinicalTrials.gov website.

15.0 RISK ANALYSIS

15.1 Anticipated Clinical Benefits

[redacted]

15.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

Risks associated with the specified device and procedure, together with their likely incidence, are described in **Appendix XV**. There may be risks related to the device under investigation that are unknown at present. Likewise, the exact frequency of the risk may be unknown.

Commercially available models of the Navitor TAVI system may be used in VANTAGE in geographies where an approval has been obtained from the applicable Competent Authority and/or EC. Since the commercial units and the clinical units are physically identical and the procedures involved are also the same, there are no additional risk concerns associated with the use of the commercial units in VANTAGE.

APPENDIX I: ABBREVIATIONS AND ACRONYMS

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

Abbreviation	Term
6MWT	Six Minute Walk Test
ACT	Activated Clotting Time
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AHA	American Heart Association
AMI	Acute Myocardial Infarction
AP	Attempted Population
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)
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
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	Hypoattenuated Leaflet Thickening
HVD	Hemodynamic Valve Deterioration
IB	Investigator's Brochure
ICF	Informed Consent Form
IDC	Implantable Cardioverter Defibrillator
IDE	Investigational Device Exemption
IFU	Instructions For Use

Clinical Investigation Plan

INR	International Normalized Ratio
IP	Implanted Population
IRB	Investigational Review Board
KCCQ	Kansas City Cardiomyopathy Questionnaire
KM	Kaplan-Meier
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
SAP	Statistical Analysis Plan
SAVR	Surgical Aortic Valve Replacement
SC	Screening Committee
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)
TEER	Transcatheter Edge-to-Edge Repair
TIA	Transient Ischemia Attack
TTE	Transthoracic Echocardiogram
UADE	Unanticipated Adverse Device Effect
UCB	Upper Confidence Bound
USA	United States of America (same as US)
VARC	Valve Academic Research Consortium
ViV	Valve-in-Valve
WBC	White Blood Cell

Clinical Investigation Plan

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 CIP 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

ADVERSE EVENT [32]

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device under investigation and whether anticipated or unanticipated.

1. **SERIOUS ADVERSE EVENT**
   Serious Adverse Event (SAE) is an AE that led to any of the following:
   - death,
   - serious deterioration in health of the subject, that either resulted in any of the following:
     - life-threatening illness or injury
     - permanent impairment of a body structure or a body function
     - hospitalization or prolongation of patient hospitalization
     - medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function.
     - chronic disease
   - fetal distress, fetal death or a congenital abnormality or birth defect.

   Note: A planned hospitalization for a pre-existing condition, or a procedure required by the CIP without a serious deterioration in health, is not considered a SAE.
2. **ADVERSE DEVICE EFFECT (ADE)**

An adverse event related to the use of an investigational medical device.

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

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

3. **SERIOUS ADVERSE DEVICE EFFECT (SADE)**
   Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

4. **UNANTICIPATED ADVERSE DEVICE EFFECT (UADE)**
   As defined in 21 CFR §812.3, unanticipated adverse device effects (UADE) are defined as any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the CIP or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

5. **ANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (ASADE)**
   A serious adverse device effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

6. **UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE)**
   A serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

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

BLEEDING AND TRANSFUSION[21]
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**
   - **<u>Procedure-related or Valve-related Hospitalization</u>**
     - **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

MYOCARDIAL INFARCTION[21]

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 criteria[33]

- 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[21]

	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 days 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

Clinical Investigation Plan

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.
3	Severe hemodynamic valve deterioration	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)

Timing

- 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

Clinical Investigation Plan

APPENDIX III: CIP SUMMARY

Clinical Investigation Name and Number	VANTAGE Trial [redacted]
CIP Name	VANTAGE
Title	Evaluation of TAVI Using the Navitor™ Valve in a Global Investigation
Objective	The objective of the proposed clinical trial is to evaluate the safety and effectiveness of the Navitor TAVI System in patients with severe, symptomatic native aortic stenosis who are at intermediate or low risk of surgical mortality. This trial will also evaluate the safety and effectiveness of the Navitor TAVI System in a valve-in-valve application in patients with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve across all surgical risk categories.
Device Under Investigation	• Navitor Transcatheter Aortic Valve (23 mm, 25 mm, 27 mm, 29 mm, and 35 mm sizes) • Navitor Loading System (small, large, and LG+) • FlexNav Delivery System (small and large)
Number of Subjects Required for Inclusion in Clinical Investigation	Navitor Valve implantation is expected in Australia, Europe, and Israel (1) Primary Analysis Cohort: up to 450 registered subjects (2) Roll-in Cohort: Up to 40 registered subjects (3) Valve-in-valve (ViV) Cohort: Up to 100 registered subjects
Clinical Investigation Design	The VANTAGE trial is a prospective, single-arm, multi-center, international, premarket clinical trial designed in accordance with ISO standard 14155:2020. To be eligible for participating in the primary analysis and roll-in cohorts, a patient must have symptomatic, severe native aortic stenosis and have intermediate or low risk for surgical valve replacement. To be eligible for participating in the ViV cohort, a patient must have symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve, and the patient can be in any risk category.[K] Subjects will be enrolled and treated with the Navitor Valve at up to 40 experienced TAVI implant centers across Australia, Europe, and Israel and followed for 10 years. All sites must have prior Navitor TAVI system experience or must complete roll-in cases.
Primary Endpoint(s)	The primary safety endpoint is a composite of all-cause mortality or fatal stroke/stroke with disability at 12 months post index Navitor Valve implantation procedure. The primary effectiveness endpoint is moderate or greater

[K] In Germany, only subjects at high or extreme surgical risk can be included in the ViV cohort. Sites in Switzerland will not participate in the ViV enrollment.

Clinical Investigation Plan

	paravalvular leak at 30 days post index Navitor Valve implantation procedure. Both of the primary endpoints will be evaluated in a mixed-risk group including both intermediate and low risk subjects and will be tested against literature-derived performance goals.
Subject Follow-up	For subjects that have successfully completed screening and been approved by the Screening Committee, scheduled visits will be performed at: Baseline, Index Procedure, Discharge, 30 days,12 months, and annual follow-up assessments to 10 years. Echocardiograms are required at 30 days, 12 months and 2, 3, 4, 5, 7, and 10 years. Note: Subjects in the high or extreme risk category in the ViV cohort will be followed up to 5 years.
Key Inclusion Criteria	• Subject who is judged by a Heart Team, including a cardiac surgeon, to be appropriate for transcatheter heart valve intervention therapy, and is deemed to be at intermediate or low risk for open surgical aortic valve replacement (i.e., heart team estimates risk of surgical mortality < 7% at 30 days, considering the Society of Thoracic Surgeons (STS) risk score, overall clinical status, and other clinical co-morbidities unmeasured by the risk calculator) # (Note: In France and Switzerland, if a subject is deemed low surgical risk, the subject must be at age 75 or over to be included in this trial. Refer to country-specific addendums for other details.) • New York Heart Association (NYHA) Functional Classification of II, III, or IV # • Degenerative aortic valve stenosis with echo-derived criteria, defined as: aortic valve area (AVA) of ≤ 1.0 cm^2 (or indexed EOA ≤ 0.6 cm^2/m^2) AND either mean gradient ≥ 40 mmHg or peak jet velocity ≥ 4.0 m/s or doppler velocity index (DVI) ≤ 0.25. The echocardiogram supporting the qualifying AVA baseline measurement must be performed within 90 days prior to informed consent. # • Aortic annulus diameter of 19-30 mm and ascending aorta diameter of 26-44 mm for the specified valve size listed in the IFU, as measured by CT (systolic phase) conducted within 12 months prior to informed consent.
Key Exclusion Criteria	• Untreated clinically significant coronary artery disease requiring revascularization • Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior (except pacemaker or ICD implant) to index procedure or planned within 30 days following the index procedure. • Blood dyscrasias as defined: leukopenia (WBC < 3000 mm^3), acute anemia (Hb < 9 g/dL), thrombocytopenia (platelet count < 50,000 cells/mm^3); history of bleeding diathesis or coagulopathy • Active peptic ulcer or upper GI bleeding within 3 months prior to index procedure that would preclude anticoagulation • Known intolerance, hypersensitivity, or contraindication, including subjects that meet any of the following conditions:

	a. Subjects who cannot take any antiplatelets or anticoagulants*, b. Subjects who have sensitivity to contrast media which cannot be adequately premedicated, c. Subjects who have known hypersensitivity to nitinol (nickel or titanium), or d. Subjects who have clinical contraindication that precludes contrast CT imaging *Note: Subjects who can take either an antiplatelet or anticoagulant therapy post-procedure will be eligible. • Recent (within 6 months prior to index procedure date) cerebrovascular accident (CVA) or a transient ischemic attack (TIA) • Renal insufficiency (creatinine > 3.0 mg/dL or estimated GFR < 30 ml/min/1.73m^2) and/or end stage renal disease requiring chronic dialysis • Active bacterial endocarditis within 6 months prior to the index procedure • Liver failure (Child-Pugh class B or C) • Subjects with atrial fibrillation who are not on anticoagulants or who are not implanted with a left atrial appendage occlusion (LAAO) device • Symptomatic carotid or vertebral artery disease, significant carotid or vertebral artery disease requiring intervention, or successful treatment of carotid or vertebral stenosis within 30 days prior to index procedure • Severe pulmonary hypertension with pulmonary systolic pressure greater than two-thirds of systemic pressure • Severe lung disease (FEV1 < 50% predicted) or currently on home oxygen • Hostile chest or conditions or complications from prior surgery that would make the patient be considered high surgical risk (i.e., mediastinitis, radiation damage, abnormal chest wall, porcelain aorta, adhesion of aorta or internal mammary artery to sternum, etc.) # • Significant frailty as determined by the heart team (after objective assessment of frailty parameters) that would indicate high or extreme surgical risk # • Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation 3-4+) # • Aortic valve is a congenital unicuspid or congenital bicuspid valve as verified by echocardiography or CT • Non-calcified aortic valve # • Severe ventricular dysfunction with LVEF < 30% as measured by resting echocardiogram • Pre-existing prosthetic heart valve or other implant (such as prosthetic ring or transcatheter edge-to-edge repair (TEER) clip) in any valve position # (Note: Subjects with a bio-prosthetic aortic valve may be included in the ViV cohort.) • Severe circumferential mitral annular calcification (MAC) which is continuous with calcium in the left ventricular outflow tract (LVOT) # • Prohibitive left ventricular outflow tract calcification #

	• Severe (greater than or equal to 3+) mitral regurgitation or severe mitral stenosis with pulmonary compromise • Echocardiographic or multi-slice computed tomography (MSCT) evidence of intracardiac mass, thrombus, or vegetation • Significant aortic disease, including abdominal aortic or thoracic aneurysm defined as maximal luminal diameter 5.5cm or greater or ascending aortic aneurysm defined as maximal luminal diameter 5cm or greater. • Marked aortic tortuosity (hyperacute bend) or severe “unfolding” and tortuosity of the thoracic aorta (applicable for transfemoral access only) • Aortic arch atheroma ([> 5 mm], protruding or ulcerated) • Significant narrowing (calcification and surface irregularities) of the abdominal or thoracic aorta • Aortic root angulation > 70° • Undue risk of coronary obstruction (e.g., low coronary ostia, narrow Sinus of Valsalva anatomy that would prevent adequate coronary perfusion, or bulky aortic valve leaflets in close proximity to coronary ostia) • Access vessel characteristics that would preclude safe insertion of the FlexNav Delivery System such as severe obstructive calcification, protruding thrombus or severe tortuosity • Minimum access vessel diameter of < 5.0 mm for small FlexNav Delivery System and < 5.5 mm for large FlexNav Delivery System • Ascending aorta anatomy that would preclude safe delivery of the valve to the native aortic annulus • Eccentricity ratio of the annulus < 0.73

[#] Criterion not applicable for ViV cohort

Note: The ViV subjects can be in any risk category except in Germany, where only subjects at high or extreme surgical risk can be included in the ViV cohort.

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APPENDIX IV: LITERATURE REVIEW

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APPENDIX V: LABELS

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APPENDIX VI: INFORMED CONSENT FORM

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APPENDIX VII: SCREENING AND ASSESSMENT TOOLS

1. SURGICAL RISK ASSESSMENT

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

1. The Society of Thoracic Surgeons' (STS) Short-term / Operative Risk Calculator, Adult Cardiac Surgery Database STS ACSD Operative Risk Calculator (https://acsdriskcalc.research.sts.org)
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.

The frailty assessment consists of four evaluations:

I. Katz Index of Independence in Activities of Daily Living
II. Grip Strength
III. 5 Meter walk test
IV. Nutritional Deficiency (Albumin)

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

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

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FEEDING Points: _____	(1 POINT) Gets food from plate into mouth without help. Preparation of food may be done by another person.	(0 POINTS) Needs partial or total help with feeding or requires parenteral feeding.
TOTAL Points:_____		

II. Grip strength

Subjects elbow should be at a 90 degree angle without arm supported or resting on table or against chest wall. Each grasp should be completed with the dynamometer in the dominant hand.

Grasp 1_____ Grasp 2_____Grasp3_____ Average_____

Grip Strength, stratified by gender and body mass index (BMI) quartiles

Gender	BMI	Cutoff for grip strength (Kg) criterion for frailty
Male	≤24	≤29
	24.1–26	≤30
	26.1–28	≤31
	>28	≤32
Female	≤ 23	≤17
	23.1–26	≤17.3
	26.1–29	≤18
	>29	≤21

III. 5-Meter Walk Time

This examination should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The walking course must be 5 meters in length (15 feet). The time to walk this distance is to be recorded.

_____seconds

Walk Time, stratified by gender and height

Gender	Height	Cutoff values for Time to Walk 5 meters criterion for frailty
Male	≤ 173 cm	≥ 7sec
	> 173 cm	≥ 6sec
Female	≤159 cm	≥ 7sec
	> 159 cm	≥ 6sec

IV. Nutritional Deficiency

A blood albumin level is measured. Frailty is defined as a level < 3.5 mg/ml. Albumin lab values performed ≤ 90 days prior to informed consent, per standard of care, may be utilized.

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.

4. QUESTIONNAIRES

The KCCQ and mRS questionnaires will be provided under separate cover (**Appendices VIII and IX**).

5. Six Minute Walk Test

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

SAFETY ISSUES

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

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

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

CONTRAINDICATIONS

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

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

LOCATION

The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. If the weather is comfortable, the test may be performed outdoors. The walking course must be 30 m in length. A 100-ft hallway is, therefore, required. The length of the corridor should be marked every 3 m. The turnaround points should be marked with

a cone (such as an orange traffic cone). A starting line, which marks the beginning and end of each 60-m lap, should be marked on the floor using brightly colored tape.

PROCEDURE

REQUIRED EQUIPMENT

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

PATIENT PREPARATION

- Comfortable clothing should be worn.
- Appropriate shoes for walking should be worn.
- Patients should use their usual walking aids during the test (cane, walker, etc.).
- The patient's usual medical regimen should be continued.
- A light meal is acceptable before early morning or early afternoon tests.
- Patients should not have exercised vigorously within 2 hours of beginning the test.
- This test should be performed about the same time of day for each interval to minimize intraday variability.
- A "warm-up" period before the test should not be performed.
- The patient should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate. Complete the first portion of the worksheet.

Baseline Measurements

1. Set the lap counter to zero and the timer to 6 minutes. Assemble all necessary equipment (lap counter, timer, clipboard, Borg Scale, worksheet) and move to the starting point.

Instruct the patient as follows:

"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

Start now, or whenever you are ready."

Position the patient at the starting line. You should also stand near the starting line during the test. Do not walk with the patient. As soon as the patient starts to walk, start the timer.

Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the patient. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

After the first minute, tell the patient the following (in even tones):
"You are doing well. You have 5 minutes to go."

When the timer shows 4 minutes remaining, tell the patient the following:
"Keep up the good work. You have 4 minutes to go."

When the timer shows 3 minutes remaining, tell the patient the following:
"You are doing well. You are halfway done."

When the timer shows 2 minutes remaining, tell the patient the following:
"Keep up the good work. You have only 2 minutes left."

When the timer shows only 1 minute remaining, tell the patient:
"You are doing well. You have only 1 minute to go."

Do not use other words of encouragement (or body language to speed up).

If the patient stops walking during the test and needs a rest, say this:
"You can lean against the wall if you would like; then continue walking whenever you feel able."

Do not stop the timer. If the patient stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

When the timer is 15 seconds from completion, say this:
"In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."

When the timer rings (or buzzes), say this: **"Stop!"**

Walk over to the patient. Consider taking the chair if they look exhausted. Mark the spot where they stopped.

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APPENDIX VIII: KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE (KCCQ)

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APPENDIX IX: MODIFIED RANKIN SCALE QUESTIONAIRE

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APPENDIX X: PERI-PROCEDURAL GUIDELINES

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APPENDIX XI: REVISION HISTORY

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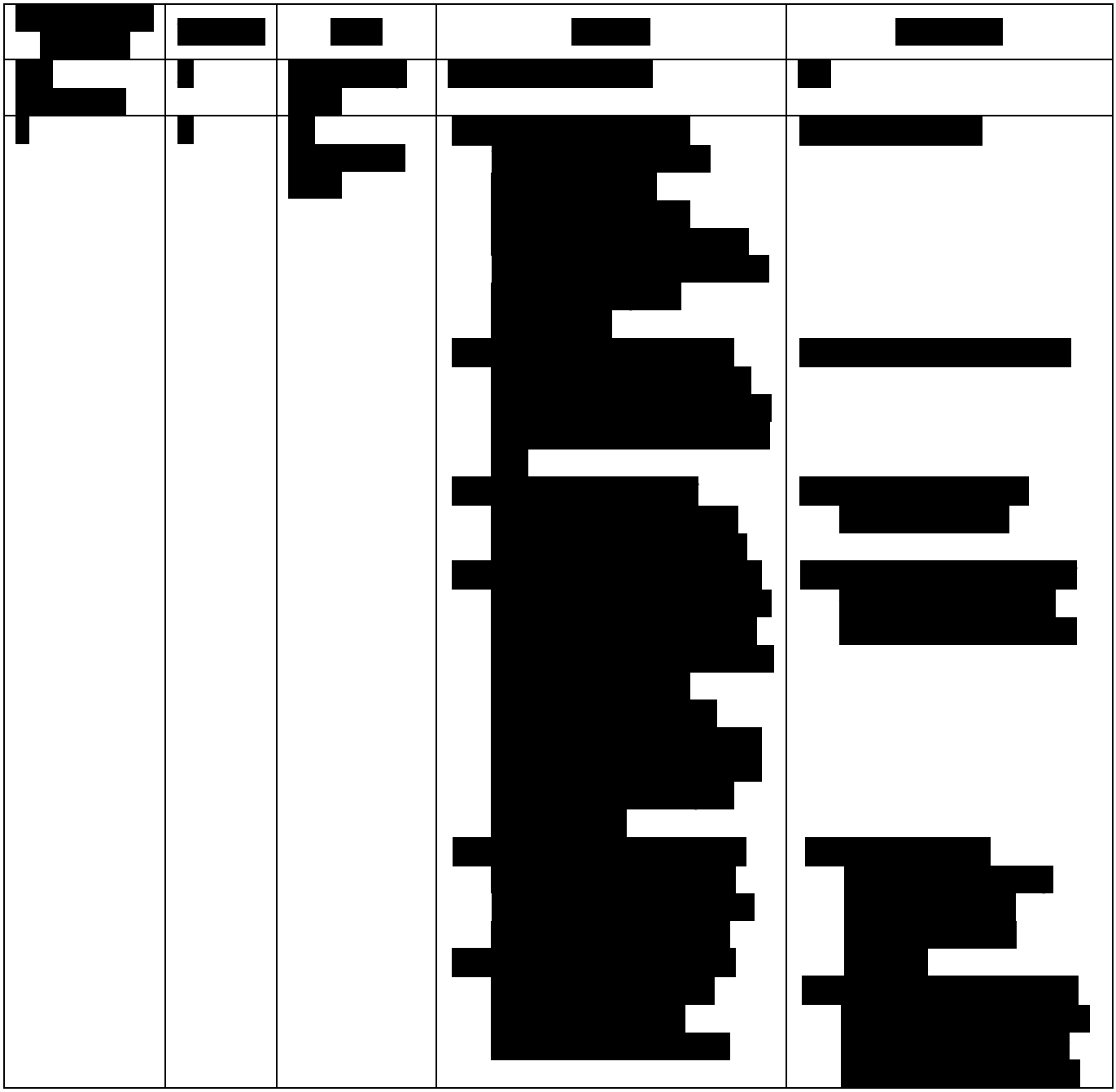

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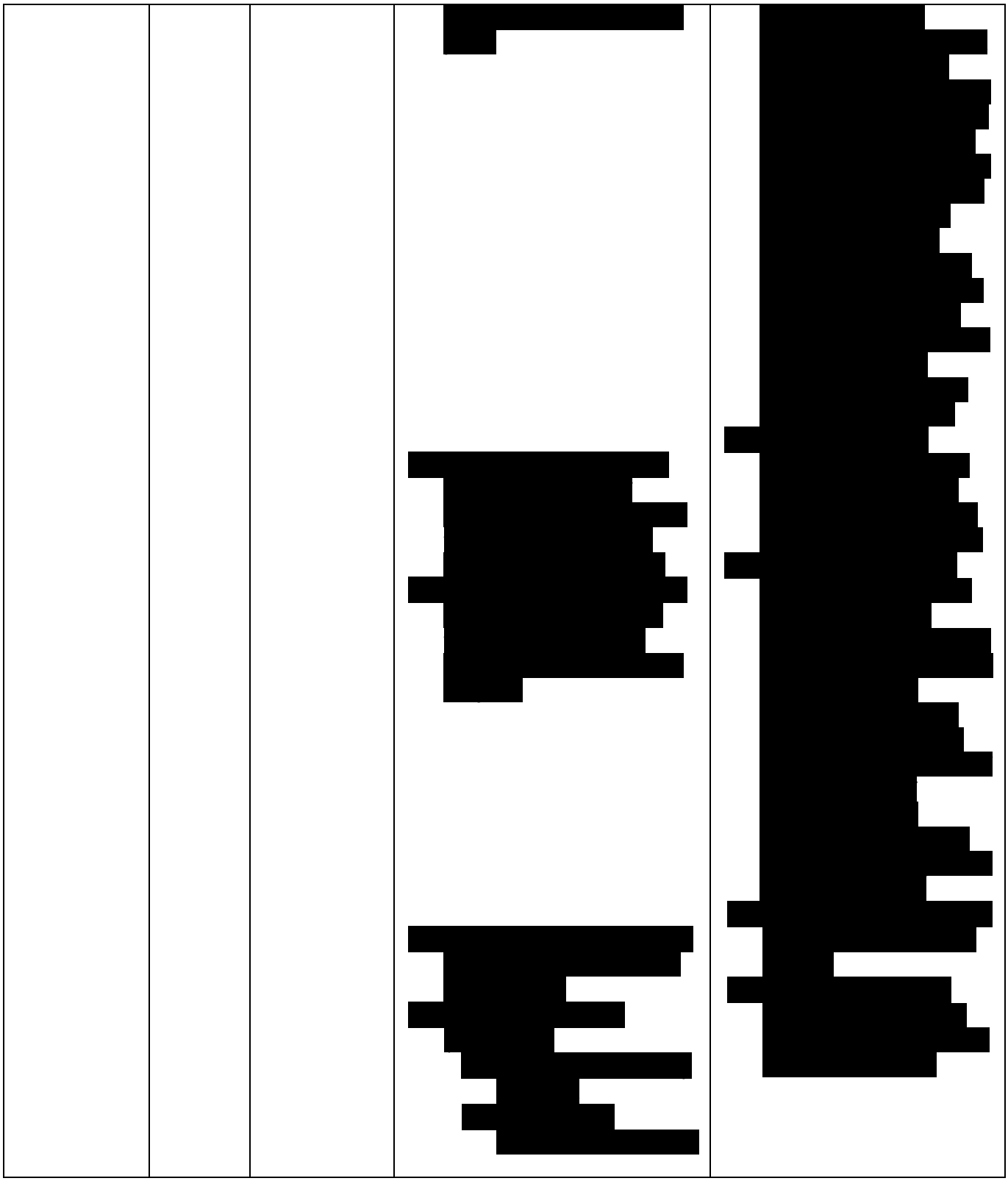

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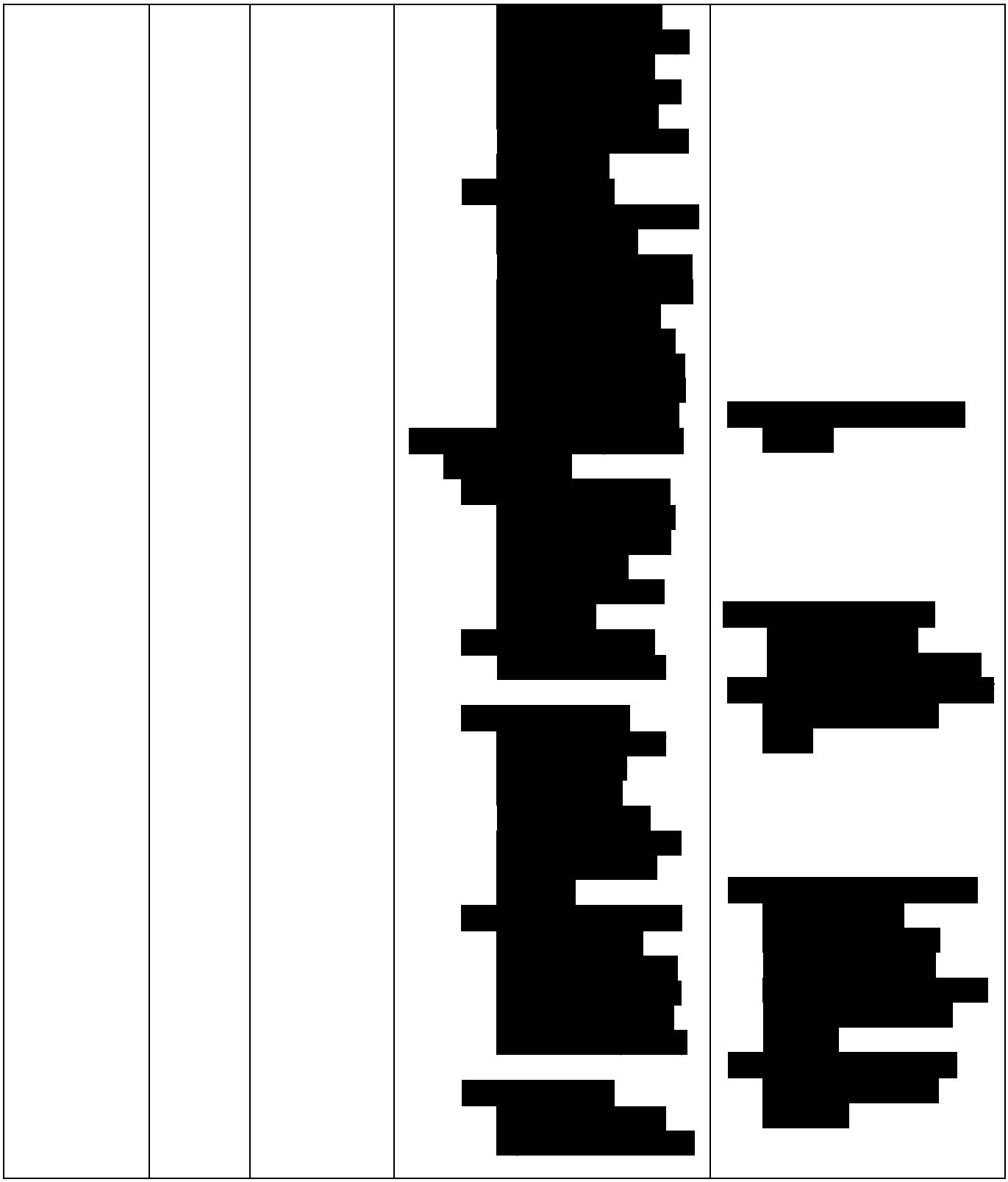

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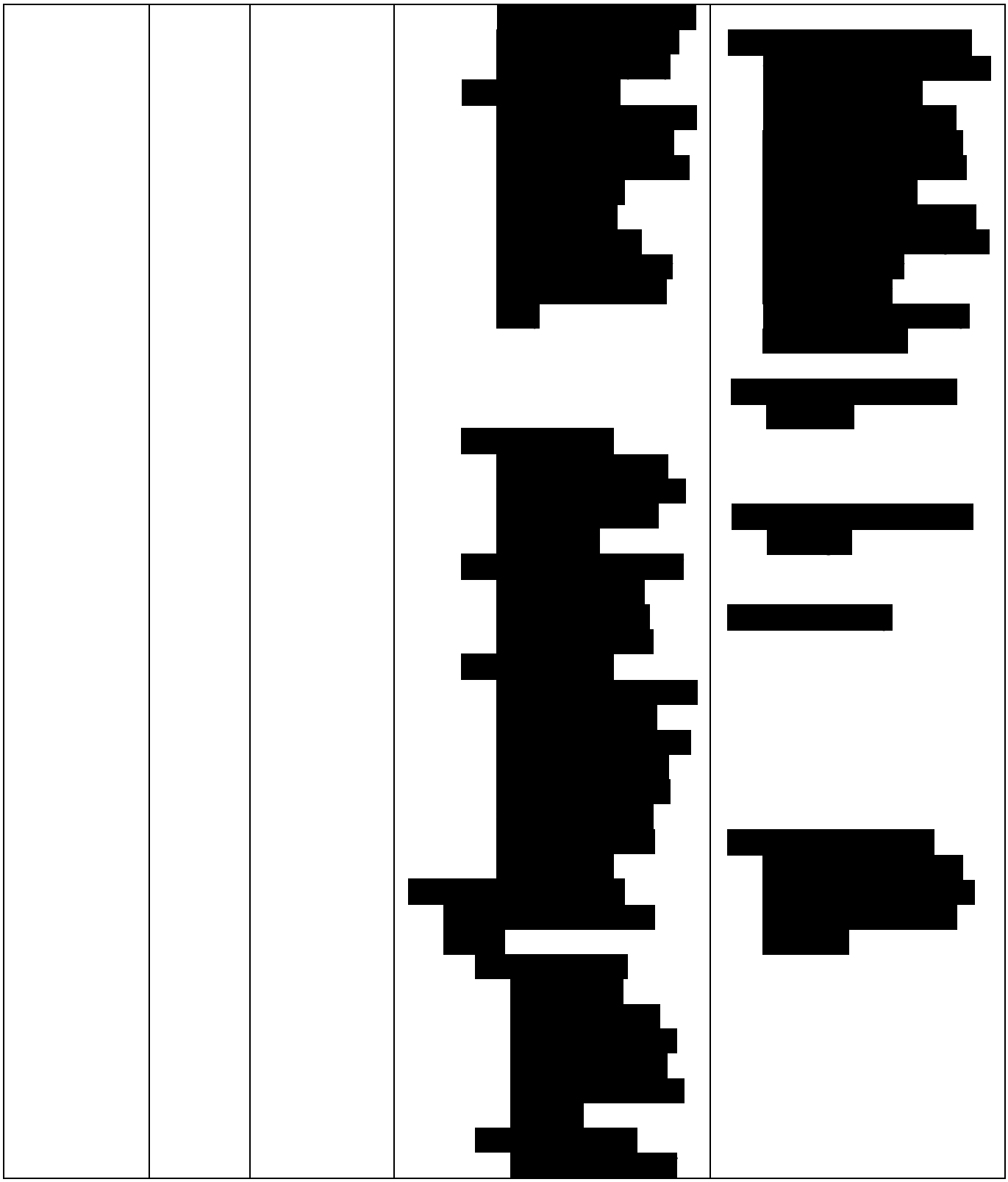

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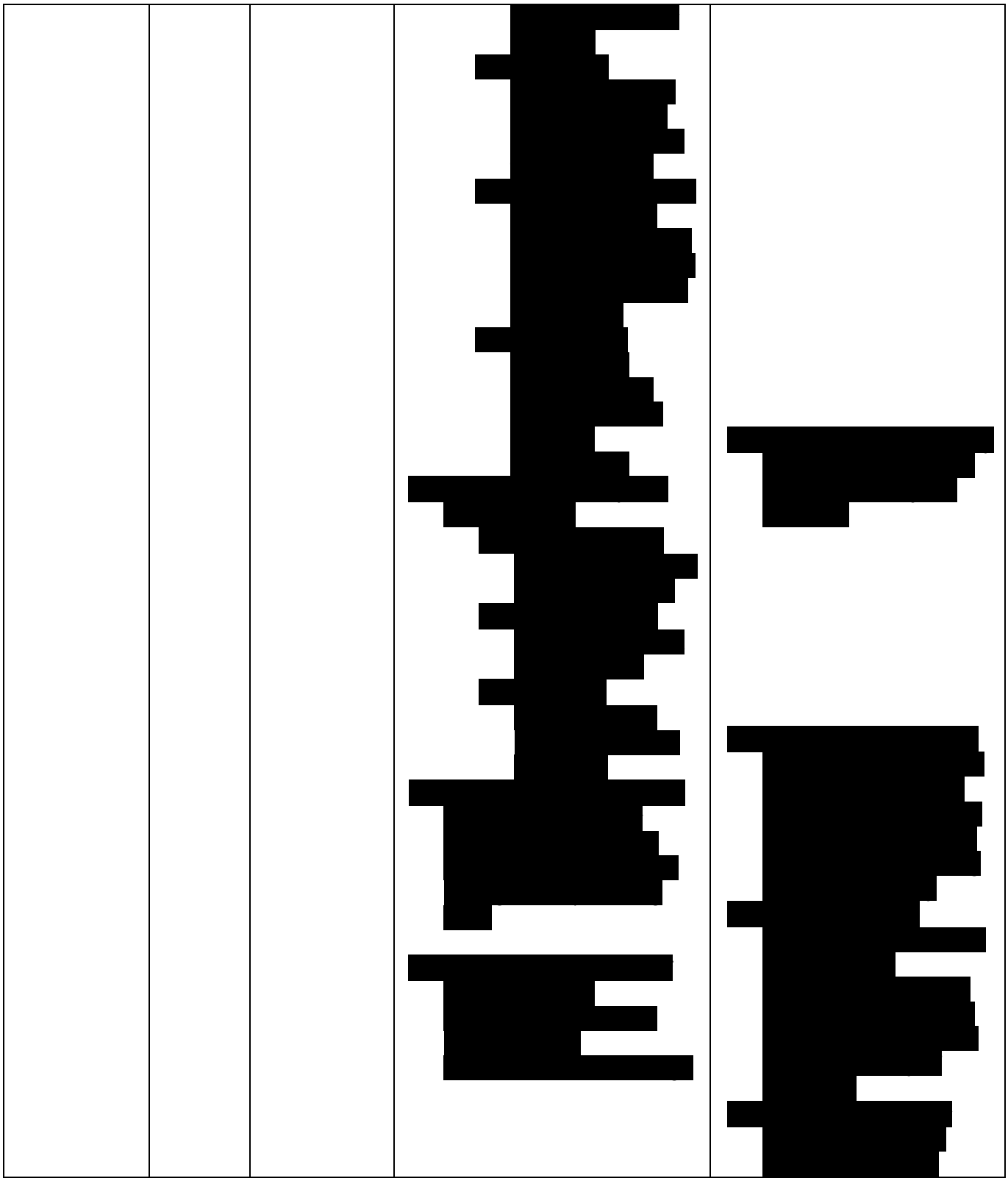

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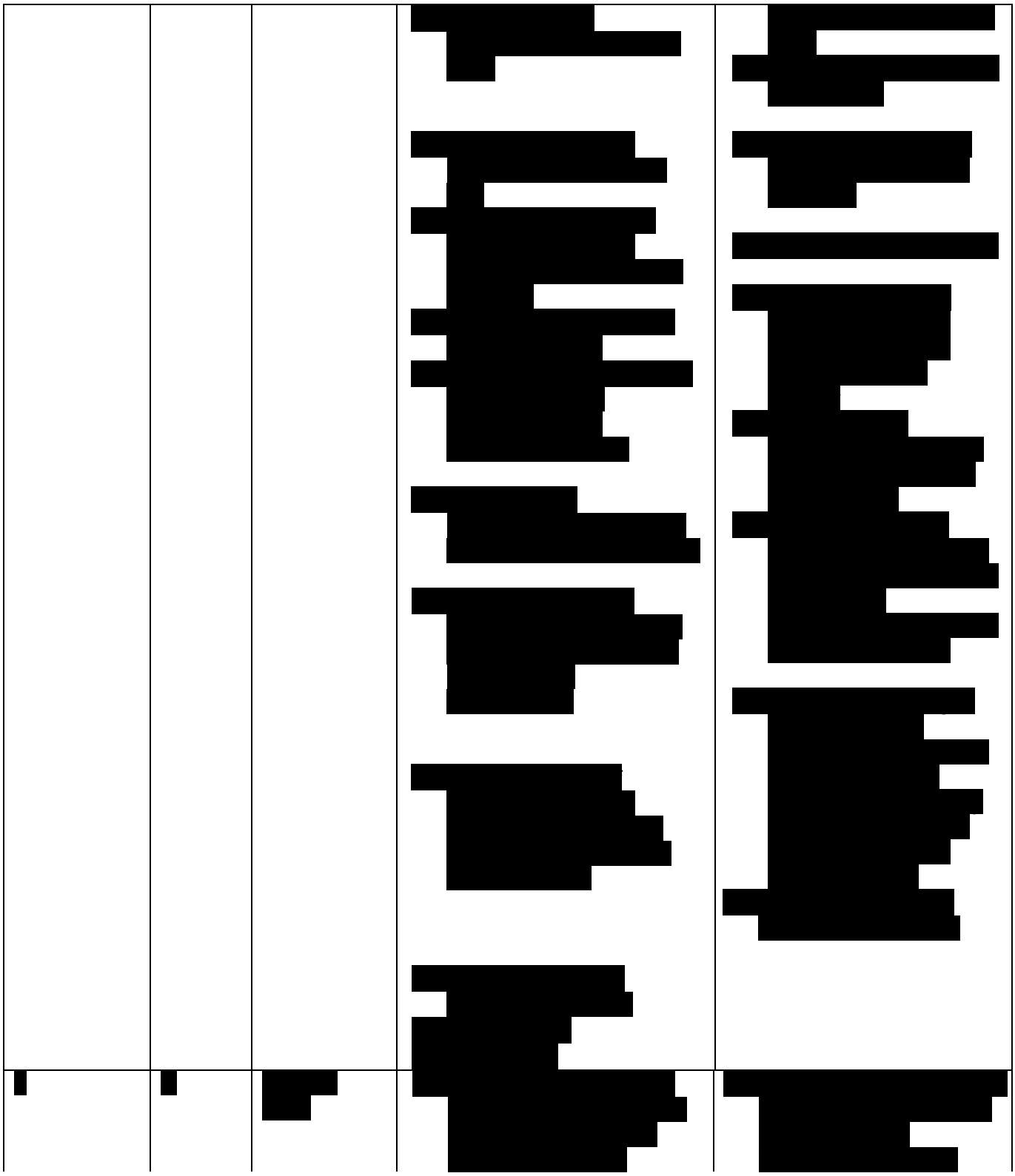

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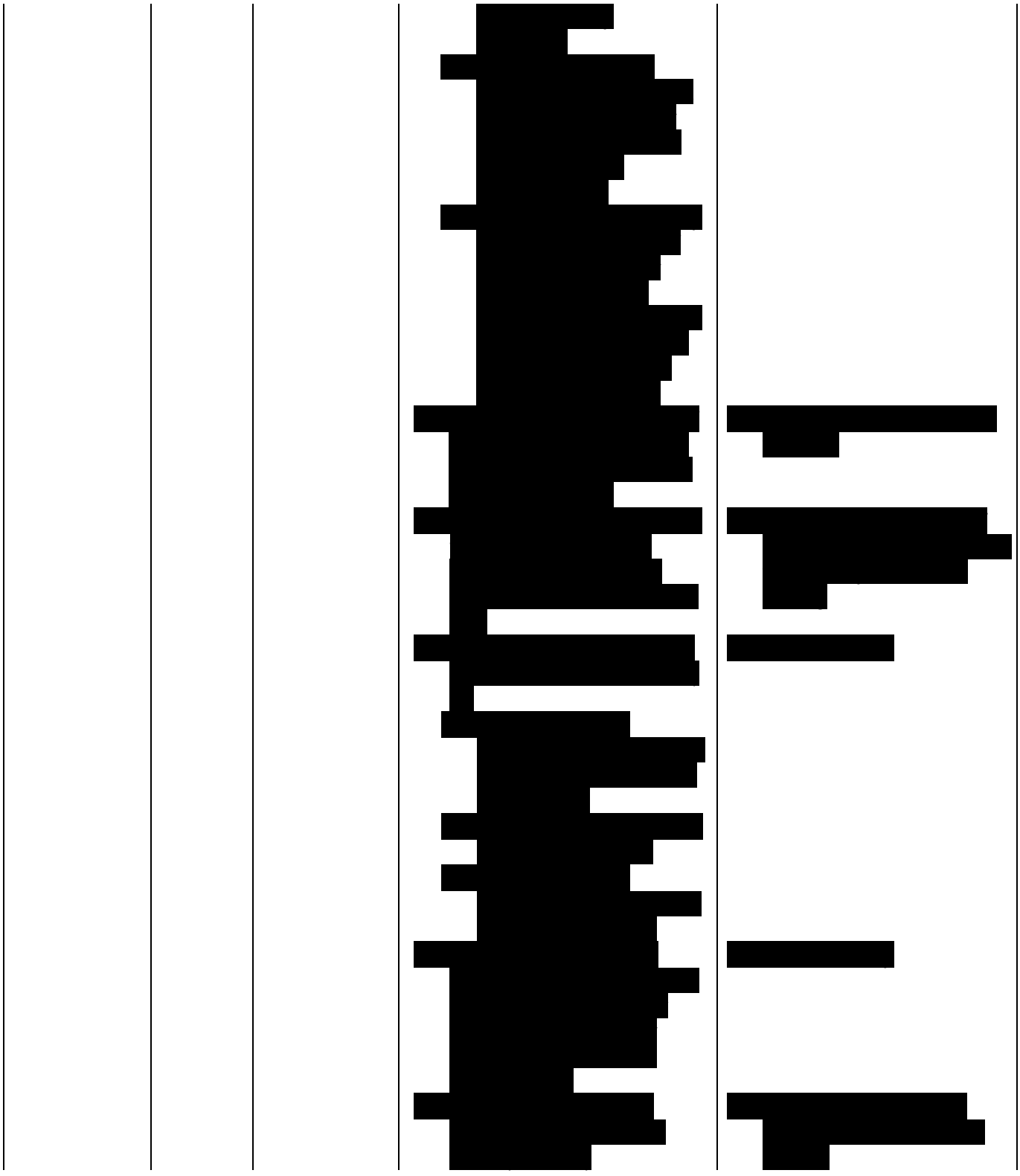

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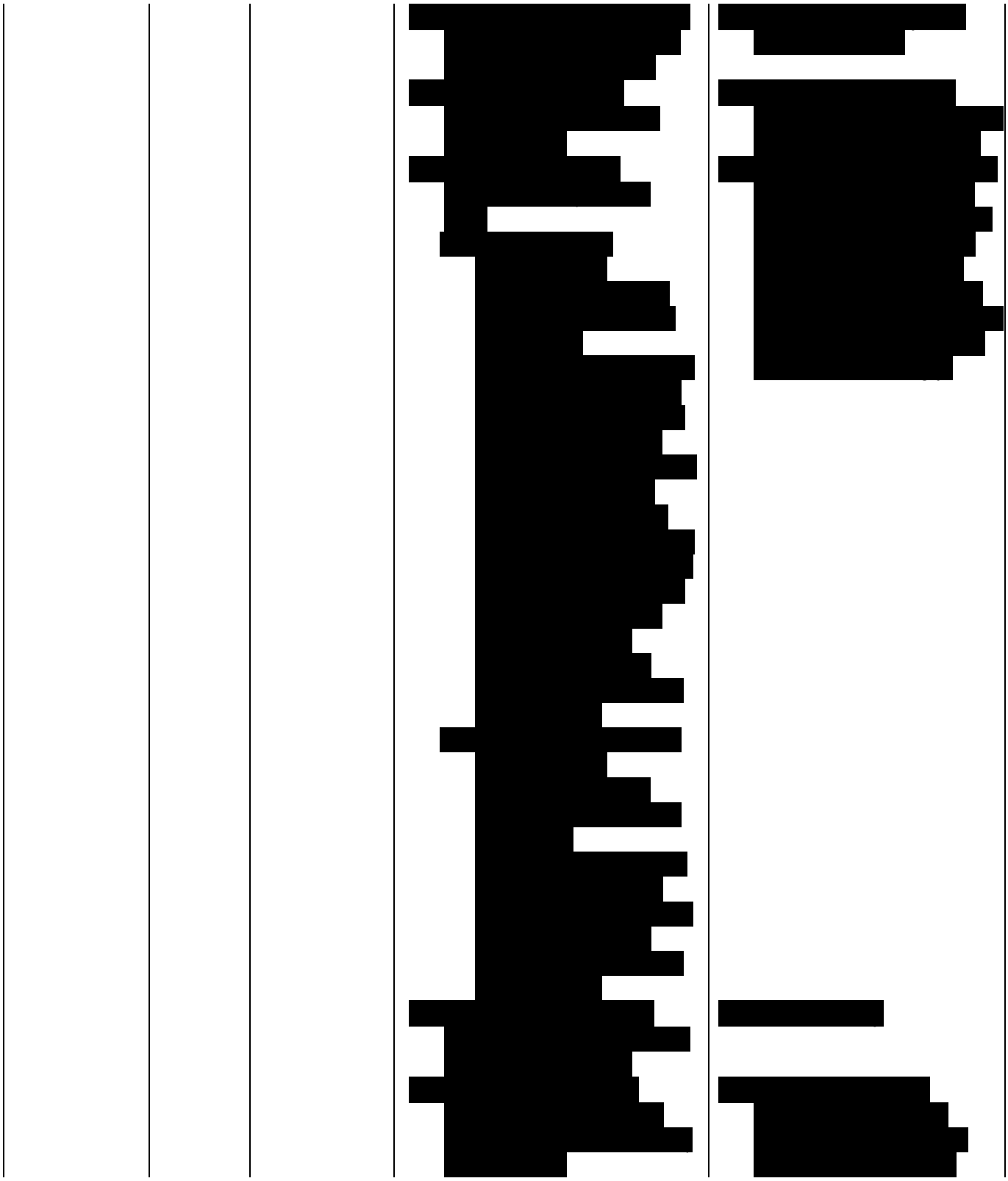

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APPENDIX XII: SITE CONTACT INFORMATION

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APPENDIX XIII: MONITORING PLAN

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APPENDIX XIV: CASE REPORT FORMS

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APPENDIX XV: FORESEEABLE ADVERSE EVENTS AND ASSOCIATED FREQUENCY CATEGORIES

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