STUDY CODE: APR002 STUDY NAME: BELIEVE

STUDY TITLE:

BEhavior of valve Leaflets and the Incidence of rEduced mobility post-surgical aortic valVE implant

CLINICAL INVESTIGATION PLAN

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BEhavior of valve Leaflets and the Incidence of rEduced mobility post-surgical aortic valVE implant

CLINICAL INVESTIGATION PLAN

Version N° B **Date: 05 December 2018**

Investigational Device: *Commercially approved LivaNova Perceval bioprosthetic aortic heart valve*

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DOCUMENT HISTORY

Version	Date	Section	Description of modifications
A	06/MAR/2017	N/A	Clinical Investigation Plan Initial Release
B	21/DEC/2018	ALL	Removal of Crown PRT and Solo Smart references Minor editorial changes applied to increase CIP clarity
		10	Study sample size reconsidered on the basis of the following changes: • Study cohort changed from three to one. • The study is descriptive in nature, aiming at describing the risk of reduced leaflet motion as such it is considered non-confirmative and no multiplicity adjustment will be applied to the inferential statistical methods that will be presented. • Confidence levels updated to 90% rather than 95%. • Expected acceptable confidence interval width updated to be 13% rather than 8.3%. • Statistical two-sided confidence interval calculation to compute the sample proportion (Reduced Leaftlet Mobility) updated to be based directly on the Exact Binomial Distribution rather than Normal approximation (Wald). Analysis sets have been updated: • It has been clarified that Safety population will coincide with the enrolled population, • Removal the of the following specification "No Per Protocol population will be defined". Subgroups analysis updated to remove the classification by valve.
		1	Language changed in Blinding of CT Scan Imaging to clarify that the site does not need to be blinded to their own results, only the core lab results
		6	Point of enrollment clarified Language changed to clarify the Secondary Endpoint of RLM
		7	Language added to clarify when it is not required for a patient visit to be done with the surgeon Language added to confirm that all patients are to be followed to the 1 year visit Language added to clarify when unblinding may occur
		13.3	Updated events that will be adjudicated

INVESTIGATOR SIGNATURE PAGE

The Sponsor is required by regulations to obtain a signed agreement from each participating Principal Investigator (PI) for any used version of the Clinical Investigation Plan (CIP).

By signing the CIP, the PI certifies he/she reviewed the document and agrees to its content.

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First name:	
Name of institution:	

Signature **Date:**

D	D	M	M	M	Y	Y	Y	Y

One copy for the PI and one copy for the Sponsor.

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1. SYNOPSIS

Clinical Investigation Plan date	05 / DEC / 2018
Revision number	B
Title of study	**BE**havior of valve **L**eaflets and the **I**ncidence of r**E**duced mobility post-surgical aortic val**VE** implant (BELIEVE) *Clinical investigation of leaflet motion in commercially approved LivaNova Perceval bioprosthetic aortic heart valve*
Coordinating Investigators	Niv Ad, M.D. Federico Asch, M.D.
Study duration	Enrollment phase: approximately 24 months (2 years) Follow up phase: 1 year Total duration time: approximately 3 years
Planned study period	The study started in Q4-2017, after the regulatory and ethical requirements of the regulations/guidelines were completed. Planned completion is Q1-2020 after the 1-year follow-up of the last subject.
Number of study centers planned	Approximately 11 sites
Study type	Single-arm, interventional study
Study design	Prospective, multi-center study
Primary objective:	The purpose of this study is to report on the overall incidence of reduced leaflet motion identified by CT imaging in the LivaNova Perceval bioprosthetic aortic heart valve up to 1 year post- implant in subjects that are off anticoagulation/dual antiplatelet therapy (ACT/DAPT) for at least 30 days.
Secondary objectives:	The main secondary objective is to assess all relevant device and subject demographics, procedural events through hospital discharge and short-term outcomes, as described in the secondary endpoints section.

Primary endpoint	The primary endpoint is the incidence of reduced leaflet motion measured by 4D volume-rendered CT-imaging, as assessed by an independent Core Laboratory (Core Lab) at minimum 1 month after the end of anticoagulation (ACT) or dual antiplatelet therapy (DAPT) (expected within 1 to 6 months post-implant, preferably 3 months).
Secondary endpoints	1. Incidence of reduced leaflet motion in symptomatic and asymptomatic subjects, based on CT outcomes up to 1 year post-implant 2. Incidence of reduced leaflet motion through 4D volume-rendered CT imaging with contrast up to 1 year post-implant, in subjects in which reduced leaflet motion was previously detected 3. Incidence and relationship of reduced leaflet motion to the device, procedure, or other causes up to 1 year post-implant 4. Freedom from valve safety events (all-cause mortality, valve re-intervention, myocardial infarction, structural valve deterioration, moderate or severe valve regurgitation, valve endocarditis, valve thrombosis, thromboembolic events, hemolysis and major bleeding) up to 1 year post-implant 5. NYHA classification at 1 year post-implant 6. Hemodynamic performance up to 1 year post-implant through transthoracic echocardiogram (TTE) assessed by a Echocardiographic Core Lab
Study population	All subjects who have been successfully implanted with the LivaNova Perceval bioprosthetic aortic heart valve.

Study population criteria	**Inclusion Criteria** 1. The subject has been successfully implanted with the commercially approved LivaNova Perceval bioprosthetic valve 2. The subject has signed the informed consent. 3. The subject is at least 18 years of age at the time of implant and consent signature 4. The subject will be available for post-operative follow-up through one year **Exclusion Criteria** 1. The subject has a planned concomitant cardiac surgical procedure (other than CABG or septal myectomy) including MAZE procedures, atrial fibrillation surgery, and left atrial appendage exclusion or resection, or has a prosthetic heart valve or annuloplasty ring in any position 2. The subject has any medical condition requiring long term (> 6 months) anticoagulation or dual antiplatelet therapy 3. The subject has any clinical condition precluding the use of CT imaging with contrast 4. The subject had a stroke or myocardial infarction (STEMI and NSTEMI) within 30 days of the planned valve implant surgery 5. The subject has active endocarditis, myocarditis, or sepsis 6. The subject is in cardiogenic shock manifested by low cardiac outputrequiring hemodynamic support 7. The subject is included in another clinical study that could confound the results of this clinical investigation
Number of subjects to be enrolled	A sufficient number of subjects will be enrolled in this study to allow a minimum of 75 evaluable CT scans at 1-6 months post-surgery for the primary endpoint (evaluable scans are those where a determination of normal/abnormal leaflet motion is possible). Taking attrition into account, it is expected that approximately 88 subjects will be enrolled.
Investigational devices	Perceval

Assessment schedule	• Subject inclusion (subject demography, implant data, hospital discharge) • 4D CT scan to be obtained at minimum of 1 month after the discontinuation of the anticoagulation or dual antiplatelet therapy (expected within 1 to 6 months post-implant). A transesophageal echocardiogram (TEE) will be performed in instances where CT imaging is not possible at follow-up. • Second 4D CT scan within 1 year post-implant for all subjects (both symptomatic and asymptomatic) in which reduced leaflet motion was previously detected during the first CT assessment. The timeframe will be as outlined in Table 4 Schedule of Study Procedures. • 1 year post-implant

Statistical considerations	A sample size of 75 evaluable CT scans is required to produce an Exact two-sided 90% CI with a width lower than 13% when the sample proportion is lower than 10%. All main outcomes, including demographic, clinical and surgical characteristics, incidence of reduced leaflet motion, NYHA class and echocardiography data shall be summarized using descriptive statistics. Survival data will be evaluated using Kaplan-Meier method. Nonparametric estimates at 1 year post-implant of the survivor function and instantaneous hazard rate will be reported by time-intervals for the main mortality and morbidity events.Number of events and number of subjects with at least one event will be presented in each group broken down by serious adverse event (SAE) type. Number of events, as well as number and percentage of subjects, will be tabulated by timing. Linearized rates (90% CIs) will be calculated as number of late (> 30 days) events divided by late patient-years.Subject improvement after valve implant will be determined by comparison of preoperative and postoperative NYHA functional classifications.Statistical analysis shall be performed using SAS (Release 9.4 or newer, by SAS Institute Inc., Cary, NC, USA).

Blinding of CT Scan Imaging	The Core Lab will be blinded to subject status. For asymptomatic subjects, PIs and subjects will be blinded from the CT imaging results from the Core Lab. Symptomatic subjects and the PI can be unblinded to CT imaging results. For all subjects (symptomatic and asymptomatic), the PI will receive notification that a reduced leaflet follow-up visit, including a 2nd CT scan, is required to be scheduled. To limit access and visibility of the CT images they will be sent directly to the Core Lab, which will be responsible for the assessment. Core Lab findings will not be sent to the site or accessible to sites in the electronic data capture (EDC) system. Subjects inadvertently unblinded will remain in the study and continue to be followed. Investigators will be requested to not alter relevant antiplatelet or anticoagulation drug therapies for asymptomatic subjects. The need for and use of antiplatelet or anticoagulation drug therapy will be assessed at each follow-up visit.

2. JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

2.1. INTRODUCTION

Surgical aortic-valve replacement (SAVR) is the gold standard for the management of aortic valve stenosis. Recent innovations in therapeutic intervention, most notably transcatheter aortic valve replacement (TAVR), have been studied in several randomized clinical studies.[1,2,3] The efficacy and safety of both treatment modalities are well established. Recently, findings of reduced leaflet motion in the Portico Re-sheathable Transcatheter Aortic Valve System U.S. Investigational Device Exemption (PORTICO IDE) study, the RESOLVE registry, and SAVORY registry have been reported in the literature.[4,5] Further evaluation revealed that the reduced leaflet motion phenomenon is not isolated to TAVR devices. In fact, reduced leaflet motion was observed in subjects after both TAVR (10-40%) and SAVR (8-12%).[6] with a bioprosthetic valve.

The Makkar et al report is the most comprehensive publication to date on reduced leaflet motion after AVR. Makker reported results from the PORTICO IDE study showing the overall incidence of reduced leaflet mobility to be 40% (22 of 55 subjects with evaluable 4D CT scans), 43% with Portico valves (16/37), 43% with Sapien XT valves (6/14), and 0% with CoreValve (0/9). Data from 132 subjects pooled from RESOLVE and SAVORY registries showed that the overall incidence was 13%; 14% after TAVR and 7% after SAVR. Among subjects with SAVR (27), the incidence was 9.1% (1/11) with Edwards Perimount, 11.1% with Perimount Magna (1/9); and 0% for the 6 subjects with Trifecta (3), Mitroflow (1), and Perceval (2) valves. Reduced motion was detectable by CT and transesophageal echocardiography with 100% concordance, but was undetected by transthoracic echocardiography, which is commonly used to evaluate bioprosthetic valve performance after implant. More importantly, the subjects were found to be hemodynamically stable at the time of detection, with aortic-valve gradients that were statistically similar to those with normal leaflet motion. The study also found that subjects on therapeutic anticoagulation had a lower rate of occurrence than among those receiving sub-therapeutic or no anticoagulation. In addition, the authors reported that full or partial

recovery of motion was observed among TAVR and SAVR subjects who were treated with anticoagulation (11 of 21 subjects who underwent follow-up CT) using therapeutic doses of aspirin or warfarin. The median clinical follow up was 169-183 days and outcomes between subjects with reduced leaflet motion and those with normal motion were the same for death and MI. There was a higher incidence of stroke among the subjects in the pooled registries. Based on the echocardiography / CT findings of attenuated hypo-echoic opacities on the leaflets and the impact of anticoagulation, the hypothesized etiology of reduced leaflet motion is the development of leaflet thrombosis.

The incidence of reduced leaflet motion has not been previously evaluated in the Perceval valve in clinical studies. The objective of this study is to examine the incidence of reduced leaflet motion in the LivaNova commercially approved bioprosthetic aortic valve, Perceval, as assessed by four-dimensional, volume-rendered CT (4D CT), in both symptomatic* and asymptomatic subjects.

**Symptomatic subjects are those subjects with clinical symptoms, (such as, but not limited to shortness of breath, fatigue, or signs of thromboembolic events) and determined by the treating physician.*

2.2. PRE-CLINICAL TESTING

The LivaNova biological prosthesis (Perceval) is a commercial device available at the chosen participating sites. Please refer to the Instructions for Use (IFU) for device related information.

2.3. AVAILABLE CLINICAL DATA

2.3.1. PERCEVAL Clinical Data

From April 2007 to February 2008, a Pilot study was conducted to demonstrate the safety of the Perceval valve at 30 days post implant in 30 subjects affected by aortic valve disease requiring valve replacement. Female subjects were 73% of the enrolled population and the mean age was 80.4±3.8 years. The subjects were followed for 5 years and at the latest follow up a total of 22 subjects were alive with a freedom from death of 71.31%. No incidence of stroke, dislodgment or structural valve deterioration was reported. At 5 years, overall mean gradient was 9.3 mmHg and the overall effective orifice area was 1.7cm^2.

Based on the Pilot preliminary results, the "PERCEVAL Pivotal Study – V10801" was designed to confirm the safety and performance results of the first study in a larger subject population at 3-6 months post-implantation. From January 2009 to January 2010 a total of 150 consecutive subjects (mean age: 80.0 ± 3.8 years, 76.7% were female) with symptomatic aortic valve stenosis or steno-insufficiency underwent AVR with the Perceval valve in eight European centers.

In 2010, the CAVALIER study was started. The study was designed to evaluate the safety and effectiveness of the Perceval valve with an extended indication in terms of subject age and preoperative mortality risk score. From February 2010, through September 2013, 658 subjects (mean age 78.3 years; 40% octogenarians; 64.4% females; mean STS score 7.2) underwent sutureless AVR in 25 European centers. The data of the CAVALIER study were used to obtain Perceval FDA approval. The study showed that the rates for all valve-related morbidity with the Perceval valve were less than two-times the OPCs, despite the advanced age, high STS scores, and the performance of concomitant cardiac procedures in this study population. There was no incidence of valve thrombosis or valve-related hemolysis reported in the study subjects. The hemodynamic performance of the Perceval valve was excellent with resultant salutary effects on the ventricular myocardium. Stable reduction of mean and peak pressure gradients was observed for all valve sizes. Corresponding to the observed reduction in gradients, subjects demonstrated an increase in the valve effective orifice area from preoperatively to discharge and remained stable through 3 years follow up. The assessment of functional status demonstrated marked and stable improvement in NYHA class for the majority of subjects throughout the study period.

The pooled results of the three studies were published by Shrestha et al. The three studies recruited a total of 756 subjects (mean age 78.5 years; 68.1% female) in 25 European sites. In the early period, the overall mortality rates were 3.4%; stroke events occurred in 1.2% of the subjects; major PVL occurred in 1.4%. Late events were reported as: all-cause mortality 7.0%, stroke 0.8% and major PVL 0.3%. No cases of valve thrombosis, SVD or valve migration were reported.

The safety and performance of the Perceval valve are also extensively documented in the scientific literature.

2.4. STATEMENT OF COMPLIANCE & ETHICAL PRINCIPALS

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice described in ISO 14155, and the applicable regulatory requirement(s). This CIP, informed consent forms, other information to be completed by participants, such as survey instruments or questionnaires, and any proposed advertising/recruitment materials will be submitted to the Institutional Review Board (IRB) for written approval. Any additional requirements imposed by the IRB or regulatory authority shall be followed. The PI will assure that no planned deviation from the CIP will take place except where necessary to eliminate an immediate hazard to the study participants. The PI will promptly report to the IRB and the Sponsor any changes in research activity and all unanticipated problems involving risk to human subjects, or others.

3. PURPOSE

3.1. PRIMARY OBJECTIVES

The purpose of this study is to report the overall incidence of reduced leaflet motion identified by CT imaging in the LivaNova Perceval bioprosthetic aortic heart valve up to 1 year post implant in subjects that are off anticoagulation for at least 30 days.

The primary objectives will be assessed using primary endpoint described in Section 6.3.6.

3.2. SECONDARY OBJECTIVES

The main secondary objective is to assess all relevant device and subject demographics, procedural and hospital discharge, short-term data, as described in the secondary endpoints in Section 6.3.6.

4. CLINICAL INVESTIGATIONAL PLAN (CIP)

4.1. STUDY DESIGN

This is a prospective, interventional, multi-center study. A minimum of 75 subjects with evaluable 4D CT scans will be enrolled at approximately 11 investigational sites where the Perceval device is commercially available. For asymptomatic subjects, PIs and subjects will be blinded from the CT imaging results, and from the Core Lab findings. Symptomatic subjects and the PI can be unblinded to CT imaging results. For all subjects (symptomatic and asymptomatic), the PI will receive notification that a reduced leaflet follow-up visit, including a 2nd CT scan, is required to be scheduled.

4.2. EXPECTED DURATION OF EACH SUBJECT'S PARTICIPATION

Subjects are expected to remain in the study from the time of enrollment (defined below) through one (1) year follow-up. Full assessment details for each time point follow.

4.3. TOTAL EXPECTED DURATION OF THE CLINICAL INVESTIGATION

The study plans for an inclusion period of approximately 24 months at approximately 11 sites. Subjects will be followed for 1 year, so a total duration of approximately 3 years is expected.

4.4. NUMBER OF SUBJECTS REQUIRED TO BE INCLUDED IN THE CLINICAL INVESTIGATION

A sufficient number of subjects shall be enrolled so as to result in the study with 75 subjects having evaluable CT scans. It is expected that approximately 88 subjects shall be enrolled to account for attrition (around 15%). In the event that the attrition rate may be higher than expected, the study will continue to enroll additional subjects to ensure that the goal of 75 evaluable CT scans is achieved.

5. IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

5.1. DESCRIPTION OF THE DEVICE AND ITS INTENDED PURPOSE

5.1.1. PERCEVAL (PMA P150011)

The Perceval sutureless aortic heart valve (Perceval valve) is a bioprosthesis manufactured with bovine pericardium and assembled on a Nitinol stent. The Perceval valve is designed to offer an alternative to standard surgically implanted prostheses (stented and stentless biological valves) that requires suturing to the aortic annulus. A special feature of the device is that it is self-anchoring and does not require sutures to be fixed to the implant site.

The Perceval valve is supplied un-mounted along with all accessories necessary for implantation. Prior to implantation, the prosthesis diameter is collapsed onto the dedicated delivery system. The valve is then positioned and released in the aortic root, where the stent design and its ability to apply a radial force to the annulus provides stable anchoring of the device. To achieve final stable seating and deployment, the valve is then dilated using an appropriately sized balloon. A detailed description of the device features and implantation technique is included in the product IFU.

5.2. MANUFACTURER DETAILS

The Perceval valve is manufactured by:

- **LivaNova Canada Corp.**
  5005 North Fraser Way, Burnaby – British Columbia V5J 5M1 CANADA

The accessories intended for use with the Perceval valve are manufactured by **Sorin Group Italia S.r.l.** in the facility identified below. **Sorin Group Italia S.r.l.** and **LivaNova Canada Corp.** are sister companies and part of LivaNova plc.

- **Sorin Group Italia S.r.l.**
  Via Crescentino, sn – 13040 Saluggia (VC) ITALY

5.3. MODEL AND TYPE

5.3.1. BIOPROSTHETIC VALVE

The Perceval valve is available in four (4) sizes: size S (small), size M (medium), size L (large) and size XL (extra-large). Each size is identified by a catalogue number (**Table 1**).

Table 1 Perceval valve available sizes and catalogue numbers (REF)

Size	S	M	L	XL
Catalogue number (REF)	PVS21	PVS23	PVS25	PVS27
Aortic annulus size [mm]	S (19-21)	M (21-23)	L (23-25)	XL (25-27)

5.3.2. VALVE ACCESSORIES

The information related to the accessories to be used in association with the LivaNova Perceval valve can be found in the product's IFU.

5.3.3. Device Traceability

Specific information about the valves used in the study that will be collected and documented by the sites includes at least the following:

- Valve size
- Valve serial number

5.4. DETAILED DESCRIPTION OF THE INVESTIGATIONAL DEVICE AND IMPLANT PROCEDURE

5.4.1. INVESTIGATIONAL DEVICE DESCRIPTION

The Perceval (PMA P150011) heart valve is a bioprosthesis manufactured with bovine pericardium and assembled on a Nitinol stent. The Perceval heart valve was designed to offer an alternative to surgically implanted flexible prostheses (stented and stentless biological valves). A special feature of the device is that it does not require sutures to be fixed to the implant site.

Description of the device features and implantation technique are detailed in the product IFU.

5.4.2. SURGICAL PROCEDURE

Surgical procedure for implantation is detailed in the respective product IFU.

6. DESIGN OF THE CLINICAL INVESTIGATION

6.1. STUDY TYPE

This is a prospective, interventional, multi-center study. A minimum of 75 subjects with evaluable 4D CT scans will be enrolled at approximately 11 investigational sites where the device is commercially available. For asymptomatic subjects, PIs and subjects will be blinded from the CT imaging results and from the Core Lab findings. Symptomatic subjects and the PI can be unblinded to CT imaging results. For all subjects (symptomatic and asymptomatic), the PI will receive notification that a reduced leaflet follow-up visit, including a 2nd CT scan, is required to be scheduled.

6.2. CT SCAN

All acquisition protocols enabling the formal assessment of leaflet motion and thickening will employ contrast 4D CT with retrospective gating. The acquisition protocol is detailed in Appendix 3.

The valve leaflets will be assessed using 4D-VR (volume-rendered) CT imaging. Leaflet motion in all leaflets will be defined as normal, mildly reduced (<50% reduction in leaflet opening), moderately reduced (50-70% reduction in leaflet motion), severely reduced (>70% reduction in leaflet motion) and immobile (no or negligible leaflet motion).

6.3. SUBJECTS POPULATION

6.3.1. INTENDED POPULATIONS AND INDICATIONS IN THE PROPOSED CLINICAL INVESTIGATION

All subjects undergoing AVR and having been successfully implanted with the commercially available LivaNova Perceval bioprosthetic heart valve (according to the product's IFU) are the intended population for inclusion in this study. Subjects should be willing to sign the informed consent and to undergo a 4D CT scan (with contrast) during the follow-up time period (1 year). Subjects unable to undergo a contrast CT scan at follow-up will receive a TEE.

*6.3.2. **INCLUSION CRITERIA***

Subjects who meet all the following criteria will be included:

1. The subject has been successfully implanted with a commercially approved LivaNova Perceval bioprosthetic valve according to the IFU.
2. The subject has signed the informed consent.
3. The subject is of at least 18 years of age at the time of implant and consent signature.
4. The subject will be available for post-operative follow-up through one year.

*6.3.3. **EXCLUSION CRITERIA***

Subjects who meet any of the following criteria will be excluded:

1. The subject has a planned concomitant cardiac surgical procedure (other than CABG or septal myectomy) including MAZE procedures, atrial fibrillation surgery, and left atrial appendage exclusion or resection, or has a prosthesis in any other valvular position.
2. The subject has any medical condition requiring long term anticoagulation or dual antiplatelet therapy.
3. The subject has any clinical condition precluding the use of CT imaging with contrast.
4. The subject had a stroke or myocardial infarction (STEMI and NSTEMI) within 30 days prior to the planned valve implant surgery.
5. The subject has active endocarditis, myocarditis, or sepsis.
6. The subject is in cardiogenic shock manifested by low cardiac output and needing hemodynamic support.
7. The subject is already included in another clinical study that could confound the results of this clinical investigation.

The PI shall be responsible for ensuring all potential subjects meet the inclusion/exclusion criteria and are an appropriate subject for this clinical study.

Individuals who are screened but do not satisfy the inclusion and exclusion criteria will not be considered for enrollment in the study. Logs will be maintained for screening and consenting subjects.

6.3.4. Point of Enrollment

Patients that sign consent will be considered a study candidate; however, he/she will only be included into the study upon meeting the inclusion and exclusion criteria detailed in Section 6.3 and the criteria listed below.
Study candidates will be considered enrolled in the study when all the criteria below have been met:

- successfully implanted with a commercially approved LivaNova Perceval bioprosthetic aortic heart valve
- all inclusion and exclusion criteria were met, and
- an informed consent was obtained (including date and signature)

The date of the enrollment will be the later of either the date the Informed Consent was signed, or the date of the implant of the valve.

6.3.5. Criteria for Subject Termination

All enrolled subjects will be followed until the end of the study except upon premature discontinuation in the study. Participation of a subject in the study should be discontinued when:

- The exclusion from the study is required for the subject's safety,
- Relevant IRB and/or regulatory authority withdraw approval(s),
- The subject decides to withdraw from the study,
- The surgeon decides it is no longer in the subjects best medical interest to continue, or
- The subject is lost to follow up.

The subject may withdraw his/her consent or cooperation (i.e. the subject refuses to participate further in the study) at any time without jeopardizing the normal standard of care.

6.3.6. STUDY ENDPOINTS DEFINITIONS AND ASSESSMENTS

The primary endpoint will be evaluated with statistical hypothesis tests formally defined in Section 10.

- **Primary endpoint**

  The primary endpoint is the incidence of reduced leaflet motion identified through 4D volume-rendered CT imaging at minimum 1 month after the end of the anticoagulation or dual antiplatelet therapy (expected within 1 to 6 months post-implant, preferably 3 months), as assessed by an independent Core Lab. Enrolled subjects not receiving anticoagulation or antiplatelet therapy at discharge will be assessed via 4D volume-rendered CT imaging at a minimum of 30 days after hospital discharge.

- **Secondary endpoints**

  The secondary endpoints are as follows:

  1. Incidence of reduced leaflet motion (thrombus) with subanalysis in symptomatic and asymptomatic subjects, based on CT outcomes, and anticoagulation and dual antiplatelet treatment modalities, up to 1 year post-implant.
  2. Incidence of reduced leaflet motion on 2nd 4D volume-rendered CT scan with contrast up to 1 year post-implant, in subjects in which reduced leaflet motion was previously detected.
  3. Incidence and relationship of reduced leaflet motion to the device, procedure, or other causes up to 1 year post-implant.
  4. Freedom from valve safety events (all-cause mortality, valve re-intervention, myocardial infarction, structural valve deterioration, moderate or severe valve regurgitation, valve endocarditis, valve thrombosis, thromboembolic events, hemolysis and major bleeding) up to 1 year post-implant.
  5. NYHA classification at 1 year post-implant.
  6. Hemodynamic performance up to 1 year post-implant through TTE assessed by Echocardiographic Core Lab.

6.3.7. CORE LAB

- **CT Scan**

  The MedStar Health Research Institute, located at MedStar Washington Hospital Center, Washington D.C., USA will serve as the Core Lab for CT for this clinical study. Gaby Weissman, MD will serve as the Core Lab PI. All CT scans, and TEEs done in place of a CT scan, will be sent to the Core Lab for analysis.

- **Echocardiography**

  The MedStar Health Research Institute, located at MedStar Washington Hospital Center, Washington D.C., USA will serve as the Core Lab for echo for this clinical study. Neil J. Weissman, MD will serve as the Core Lab principal PI. All echoes, except the pre-implant TTE and the implant TEE, will be sent to the Core Lab for analysis. If there is an echo performed with an unscheduled visit, it may be sent to the Core Lab for analysis.

Each postoperative TTE should include all the views and measurements specified in the echocardiographic protocol (Appendix 2). A copy of the examination will be recorded and provided to the Core Lab for analysis.

The Core Lab will conduct a full analysis of the acquisitions and perform the required analysis. The Core Lab will discuss any discrepancies or data quality problems through the Sponsor or with the clinical site as necessary.

7. STUDY PROCEDURES

7.1. CLINICAL STUDY RELATED PROCEDURES

All qualified personnel performing selection, enrollment and/or follow-up procedures must be trained on applicable study material and procedures (e.g. protocol & appendices). The study devices should be used in accordance with the respective IFU.

Detailed instructions on the type of data to be collected and on the process of data to be followed for the completion of the eCRFs will be provided to the PIs during dedicated meetings or trainings.

Follow-up evaluations are expected to be conducted in an office, hospital or clinic setting and are to be performed by the PI or his/her designee. If the subject has moved, the site is to make every effort to obtain the data required for the study (including copies of source documents) from the subject's physician in the new location.

7.2. SCREENING & ENROLLMENT

Subjects shall be provided with relevant information about the study, including the potential risks and benefits, prior to enrollment. Only those subjects who voluntarily provided written informed consent to participate will be eligible for enrollment.

The following activities shall be completed BEFORE subjects will be considered enrolled in the study:

- Successfully implanted with a commercially approved LivaNova Perceval bioprosthetic aortic heart valve (according to the IFU)
- All inclusion and exclusion criteria were met
- An informed consent was obtained (including date and signature)

The following activities must be conducted AFTER inclusion of the subject in the study

- Obtain subject medical history and preoperative clinical conditions, including cardiac rhythm and NYHA class
- Operative details as per below

7.3. PRE-IMPLANT & IMPLANT DATA

Pre-implant information will be collected. These data will include:

- Subject characteristics and vitals (date of birth, sex, measured height and weight, blood pressure)
- Medical history (including previous cardiovascular surgery)
- Physical evaluation (including cardiac rhythm and NYHA functional classification)
- Medications
- Hemodynamic data

Information collected during the implant will be recorded on an eCRF and will include the following information:

- Implant details including surgical approach and valve information
- Surgical procedural data
- Valve lesion type, pathology, and etiology
- Concomitant procedures
- Hemodynamic data
- SAEs
- Subject outcome
- Cardiac rhythm
- Medications

7.4. INTRAOPERATIVE TEE IS A ROUTINE PART OF THE STANDARD OF CARE IN MANAGEMENT OF VALVE SUBJECTS. THE RESULTS OF THE TEE SHALL BE RECORDED IN THE HOSPITAL SUBJECT FILES AND DEDICATED ECRF. HOSPITAL DISCHARGE

The hospital discharge data shall be collected and entered in the eCRF before the subject is discharged. The following data listed below shall be collected at hospital discharge or within 30 days of implant:

- Subject status
- Physical evaluation (including cardiac rhythm and NYHA functional classification)
- Medications
- Hemodynamic data or echocardiographic examination measured at investigational site (MPG; PPG, EOA, aortic regurgitation with severity and location)
- SAEs
- Transthoracic echocardiogram (TTE)

7.5. ANTICOAGULATION / DUAL ANTIPLATELET DISCONTINUATION (OR PLANNING) VISIT

This visit may be done by the subject's primary care physician as part of the standard of care for the subject. If done at a location other than the research location, the documentation of the visit will need to be obtained, reviewed by the site PI, and filed in the subject's research records. The visit details may then be entered in the EDC

system and made available for monitoring/source data review. Any part of the evaluation not completed will be considered a protocol deviation.

For subjects discharged with anticoagulation or dual antiplatelet therapy, (see Appendix 4 for American College of Cardiology guidelines for anticoagulation therapy[11]) an additional visit shall be performed to assess the possibility to stop the anticoagulation or antiplatelet therapy and plan the CT scan. The discontinuation of anticoagulation or antiplatelet therapy is usually around 3 months after surgery in subjects without a further clinical need for this treatment. This additional visit shall evaluate the following information:

- Subject status
- Physical evaluation (including cardiac rhythm and NYHA functional classification)
- Medications
- SAEs

Subjects which are not able to come off ACT/DAPT treatment will remain in the study and followed through the 1-year evaluation.

7.6. 1ST CT SCAN VISIT (1 TO 6 MONTHS FOLLOW-UP VISIT)

This visit is intended to be done a minimum of 30-days after the initial discontinuation of anti-coagulation or dual antiplatelet therapy; usually between 1-6 months post-implant, or at least one month after discharge for subjects discharged without anti-coagulation therapy. Follow-up evaluations are to be conducted in an office, hospital or clinic setting and are to be performed by the PI or his/her designee.

The following data listed below shall be collected:

- Subject status
- Physical evaluation (including cardiac rhythm and NYHA functional classification)
- Medications
- Hemodynamic data from TTE examination measured at investigational site (MPG; PPG, EOA, aortic regurgitation with severity and location)
- CT Scan

- TEE only in subjects that are unable to undergo CT scan at the time of follow-up
- Medications
- SAEs

7.7. UNSCHEDULED VISITS

Unscheduled visits in symptomatic subjects (subjects with symptoms of reduced leaflet function) and any other subjects needing a study related follow-up visit that is not covered by the standard visit schedule. The following items may be captured:

- Subject status
- Physical evaluation (including cardiac rhythm and NYHA functional classification)
- Medications
- Transthoracic echocardiogram (TTE) (if available)
- SAEs

7.8. 2ND CT SCAN VISIT/REDUCED LEAFLET VISIT (AFTER THE 1ST CT SCAN, BUT PRIOR TO 1-YEAR FOLLOW-UP VISIT)

This visit is intended provide a 2nd follow-up 4D CT scan if the 1st CT scan showed reduced leaflet motion. This second CT scan visit is expected at approximately 6-10 months, but prior to 1 year follow-up. This follow-up evaluation shall be conducted in an office, hospital or clinic setting by the PI or his/her designee, at a time designated by the PI.

If the 1st CT scan showed no signs of reduced leaflet motion, a repeat 4D CT is not mandated and will only be done if it becomes clinically indicated. For subjects unable to undergo a contrast CT scan (e.g. inadequate renal function), a TEE may be performed.

The following data listed below shall be collected if this visit is required:

- Subject status
- Physical evaluation (including cardiac rhythm and NYHA functional classification)
- Medications

- Hemodynamic data from TTE examination measured at investigational site (MPG; PPG, EOA, aortic regurgitation with severity and location)
- CT scan with contrast
- TEE only in subjects that are unable to undergo CT scan at the time of follow-up
- Medications
- SAEs

7.9. 1-YEAR FOLLOW-UP VISIT

This visit is intended as a clinic visit at 1 year ± 1 month after the day of the surgery. Follow-up evaluations shall be conducted in an office, hospital or clinic setting and are to be performed by the PI or his/her designee. **All efforts should be made to ensure that the subject comes to the clinic.**

The following data listed below shall be collected:

- Subject status
- Physical evaluation (including cardiac rhythm and NYHA functional classification)
- Medications
- Hemodynamic data from TTE examination measured at investigational site (MPG; PPG, EOA, aortic regurgitation with severity and location)
- Medications
- SAEs

The information collected during these follow-up evaluations, including serious adverse events, will be recorded on eCRFs in the electronic data capture (EDC) system according to the schedule of procedures **(Table 4)**

7.10. VISIT WINDOW GUIDE

Visit Name	Calculate from:	Window Start Day	Window Stop Day
Pre-Implant / Implant Data	Enrollment date	- 90	0
Hospital Discharge (completed prior to actual discharge)	Implant date	0	30
ACT / DAPT Discontinuation or Planning Visit	Implant date *90 days after Implant date preferred*	30	180
1st CT-scan Follow-up Visit (no ACT/DAPT)	Hospital Discharge date *30 days after Hospital Discharge preferred*	30	90
1st CT-scan Follow-up Visit (DC on ACT/DAPT)	ACT / DAPT Discontinuation date	60	240
2nd CT-scan (if needed) *A minimum of 6 weeks after 1st CT-scan*	Implant date	180	300
1 year follow-up	Implant date	335	395

7.11. BLINDING OF CT IMAGING RESULTS

Blinding of CT imaging results, for the purpose of evaluation of reduced leaflet motion, has been implemented to minimize the PI's exposure to imaging information that would typically not be obtained through standard of care practices. This blinding is intended to

prevent influence of the subject's (medical) treatment based on the possible findings of the CT scan.

To limit access and visibility of the CT images they will be sent directly to the Core Lab, which will be responsible for the assessment. Core Lab findings will not be sent to the site or accessible to sites in the EDC system. If, through assessment of the CT scan, the Core Lab becomes aware of findings that would potentially jeopardize subject safety (i.e. thrombus), the PI will be notified. Any medical circumstance requiring the PI's access to the CT scan or imaging results will lead to unblinding of the PI, possible unblinding of the subject, and may result in an adjustment of the subject's treatment (including medication) based on the PIs discretion.

For asymptomatic subjects, PIs and subjects will be blinded from the CT imaging results and from the Core Lab findings. Investigators will be requested to not alter relevant antiplatelet or anticoagulation drug therapies for asymptomatic subjects. The need for and use of antiplatelet or anticoagulation drug therapy will be assessed at each follow-up visit.

Symptomatic subjects and the PI can be unblinded to CT imaging results based on any treatment deemed necessary by the PI or treating physician. In this case, the PI can request CT scan results from the Core Lab as they will not be automatically sent to the site. Symptomatic subjects are those with clinical symptoms, such as, but not limited to shortness of breath, fatigue, or signs of thromboembolic events, as assessed by the treating physician. Asymptomatic subjects with reduced leaflet mobility on their 1st CT scan, and who have an increase in valve gradients, may be unblinded. This determination will be made by the Core Lab and/or Coordinating Investigators, and revealed to the study site through the LivaNova Project Manager or designee.

For all subjects (symptomatic and asymptomatic), the PI will receive notification that a reduced leaflet follow-up including a 2nd CT scan is required to be scheduled within 6 to 10 months post implant. Unblinding may be performed after the second (2nd) CT Scan is completed if the findings from the Core Lab suggest continued reduced leaflet mobility, or any finding that may be determined to put the subject at risk.
During the site initiation visit, sites will be trained and provided with instructions regarding the flow of CT scan data between the site imaging department, Core Lab, and the site to preserve the blind. These instructions will be maintained in the site study file. Subjects inadvertently unblinded will remain in the study and continue to be followed.

8. SCHEDULE OF STUDY PROCEDURES

Subject data will be collected on electronic Case Report Forms (eCRFs) provided by the Sponsor for all subjects giving informed consent. Subjects will be considered enrolled only after a successful implant of the Perceval aortic heart valve. Data, including SAEs, will be collected and recorded on eCRFs in the electronic data capture (EDC) system for the required study visits according to the following **Table 4: Schedule of Study Procedures**. After the data is entered onto the eCRFs, it will be checked for consistency and completeness. Inconsistent or incomplete data will be clarified by the study site through a query process.

8.1. TABLE 2 SCHEDULE OF STUDY PROCEDURES

Procedure	Pre-Implant / Implant Data	Hospital Discharge	ACT / DAPT Discontinuation (or Planning) Visit	1st CT-Scan Follow-up Visit	Reduced Leaflet Follow-Up (2nd CT-Scan)	1 Year Follow-Up	Unscheduled Visits
Applicable Subjects	All Subjects	All Subjects	Subjects on ACT / DAPT	All Subjects	Subjects with Reduced Leaflet Motion on 1st CT Scan	All Subjects	Subjects with reduced leaflet function symptoms or other condition needing study related Follow-up
Timing	After Successful Implant	≤ 30 days of Implant (before the subject is discharged)	1 – 6 mo. Post-Implant (3 mo. preferred)	Non-ACT/DAPT Pts. 30 days after Hospital Discharge (+ 60 day window) ACT/DAPT Pts. 30 days after ACT/DAPT Therapy discontinuation (+ 60 day window)	6 – 10 mo. Post-Implant	1 year after the day of surgery (± 30 day window)	At Discretion of Investigator
Informed Consent	**X◆**						
Inclusion / Exclusion (confirmed Post-Implant)	**X**						
Subject Characteristics	**X**						
Medical History (including previous cardiovascular procedures)	**X**						
Surgical Details	**X**						
Concomitant Procedures	**X**						
Physical Evaluation (Vitals / ECG± / NYHA Classification)	**X#**	**X**	**X**	**X**	**X**	**X**	**X±**
Post-operative ECG	**X**						
Transesophageal	**X**						

echocardiogram (TEE) (SOC)							
Transthoracic echocardiogram (TTE)	X#	X		X	X	X	X±
CT scan 4 D (with contrast)				X*	X*		
Medications Assessment	X#	X	X	X	X	X	X±
Serious Adverse Events and Outcomes	X	X	X	X	X	X	X±

*A transesophageal echocardiogram (TEE) may be performed in subjects that are unable to undergo CT scans.
Collected from Pre-Implant Data. NYHA classification will be collected from pre-implant history. TTE should be done within 3 months of implant.
◆ May occur prior to implant if the PI & subject have already determined a LivaNova Perceval bioprosthetic valve will be implanted.
± If available as standard of care procedure

8.2. HANDLING OF STUDY DISCONTINUATIONS

8.2.1. Handling of Subject Temporary Treatment Discontinuation or Termination

For all subjects reaching the end of the study (completed 1 year visit, death, or explants) or in case of premature withdrawal as described in Section 6.3.5 (lost-to-follow-up, or subject's decision) a study termination form will be filled out in order to document the date and reason for discontinuation.

Every attempt must be made to have all subjects complete the follow-up visit schedule. A subject will be considered lost to follow-up when all efforts to obtain information are unsuccessful. At a minimum, the effort to obtain information must include at least two (2) attempts to make contact via phone, and a certified letter should be sent to the subject's last known address. Both phone contacts and copy of the letter must be documented/available in the subject's medical record and recorded in the eCRF. For subjects discontinued by the PI for a safety reason, the PI shall document the reasons for the decision.

8.2.2. Handling of Study Temporary or Definitive Discontinuation

The Sponsor, regulatory authorities, or IRBs may decide to temporarily suspend or definitively terminate the study. In this case, the Sponsor shall promptly inform the PIs and IRB of the termination or suspension, providing the reasons and an action plan (including a description of what measures were or will be taken to ensure the safety, the rights and welfare of the currently enrolled subjects).

8.2.3. Handling of Site Participation: Temporary or Definitive Discontinuation

The Sponsor may decide to temporarily suspend or definitely terminate a site, or terminate site enrollment and remove all applicable study material from the study site for the following reasons:

1. Subject enrollment is unsatisfactory as to the quality (violations of inclusion or exclusion criteria) or enrollment rate
2. Completion of the eCRFs is inaccurate, incomplete or considerably late
3. Repeated, uncorrected protocol or GCP deviations

4. Data quality or quantity is not sufficient
5. Upon recommendation of the regulatory authorities or IRB

If an investigational site is suspended or prematurely terminated, the Sponsor shall promptly inform the PI(s) of the termination or suspension and the reason(s). Also, the reviewing IRB (and Regulatory Authorities, if required) will be informed. The decision will be documented and the PI will be informed. For all subjects a study termination form needs to be completed.

If a PI voluntarily decides to suspend or terminate participation in the study, the reviewing IRB and regulatory authorities shall be notified of the termination and of the reasons, including a description of what measures were or will be taken to ensure the safety, the rights and welfare of the currently enrolled subjects.

9. RISKS AND BENEFITS OF THE DEVICE AND CLINICAL INVESTIGATION

9.1. RISKS ASSOCIATED WITH PROTOCOL-REQUIRED CT SCAN

A CT scan is a low risk procedure. However, similar to x-rays, there is a small possibility to increase the risk of cancer. The doctors will minimize the subjects' exposure to radiation as much as possible. Additionally, there is a possibility that a subject may have a reaction to the contrast dye used during the CT scan. These allergic reactions can range from mild to serious. Mild reactions usually are associated with hives, rash or pruritus. Serious reactions can be life threatening and in rare instances can result in toxicity to the kidneys. The physician/investigator can take measures to reduce the potential for these reactions in their subjects, if needed.

9.2. RISKS ASSOCIATED WITH SURGICAL AORTIC VALVE REPLACEMENT

The risks associated with the use of the LivaNova valve are not expected to exceed the frequency or severity of those reported with the implant of other aortic bioprosthetic valves. The Perceval valve is an approved commercial device in the United States and Canada. Therefore, all anticipated adverse device effect and risk analysis have been submitted to regulatory bodies as part of standard registration processes. The potential Adverse Events and risks are described in the product's Instructions For Use.

9.3. ANTICIPATED ADVERSE DEVICE EFFECTS AND RISK MITIGATION

To protect the welfare of subjects, IRB approval of the investigation will be obtained for each site prior to the first enrollment at that site. Training will be provided to all PIs and their staff to ensure that the protocol and all relevant (study) processes are understood and applied.

Risks can also be minimized through compliance with the protocol, using the device in accordance with its respective IFU, performing the procedures following recommended standard practices/guidelines, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's status, and by promptly supplying the Sponsor with all pertinent information required by this protocol.

Unanticipated Adverse Device Effects can occur and will be handled as described in Section12.

9.4. POTENTIAL BENEFIT

In a subject with symptomatic severe aortic stenosis, the benefit from undergoing implantation of a bioprosthetic valve is the overall improvement in the subject's aortic valve function, general condition (improvement in NYHA classification) and quality of life as a result of improved heart valve function. Additional benefit to subjects that are receiving specific monitoring of leaflet motion in this study related to early detection of reduced leaflet mobility is not determined.

9.5. RISK-TO-BENEFIT ANALYSIS

Subjects that agree to participate in this study will have already been selected to be implanted with the commercially approved LivaNova Perceval bioprosthetic valve. Additional benefits associated with participation in this study related to specific monitoring for reduced leaflet motion, is not determined, although they will receive more consistent visits with their health care provider, which may allow for detection of symptoms more quickly than they would receive outside of the study.

10. STATISTICAL CONSIDERATIONS

The statistical analyses will be performed as summarized in this protocol and detailed in the Statistical Analyses Plan. The study is descriptive in nature, aiming at

describing the risk of reduced leaflet motion as such it is considered non-confirmative and no multiplicity adjustment will be applied to the inferential statistical methods that will be presented.

10.1. STATISTICAL DESIGN, METHOD AND ANALYTICAL PROCEDURES

Statistical analysis will be performed using SAS (Release 9.4 or higher, by SAS Institute Inc., Cary, NC, USA).

Protocol Amendment Version No. B: The study was initially designed with three cohorts of valve types to be analyzed: Perceval, SOLO Smart, and CROWN PRT. In an effort to focus the research to the Perceval device, the other cohorts (SOLO/CROWN) are being removed from the research study. The subjects that have received one of the two devices prior to removal from the study will be followed and presented as a sub-category in safety tables, but will not be included in the endpoint analysis. Additionally, with this change the total number of subjects required for the study is approximately 88 which should yield 75 evaluable CT Scans.

10.1.1. Summary Statistics

Standard summary statistics will be calculated for all study variables.

For continuous variables, statistics will include means, Standard Deviation, median, quartiles and range values. Categorical variables will be summarized using count and frequency distributions.

Survival data will be evaluated using Kaplan-Meier method. The degree of uncertainty will be expressed with 90% confidence limits. The 90% CI bounds for the cumulative freedom will be calculated per the method proposed by Greenwood. Comparison of curves among subjects groups (if any) will be performed with the log-rank test at the 0.10 two-sided level of significance. Nonparametric estimates at 1-year post-implant of the survivor function and instantaneous hazard rate will be reported by time-intervals.

The following outcomes will be evaluated by summary statistics at each available assessment:

- Demographic, clinical and surgical characteristics

- Incidence of reduced leaflet motion, overall and in symptomatic and asymptomatic subjects
- NYHA functional classification data
- Hemodynamic performance
- Valve regurgitation

10.1.2. Time to Event Analysis

A Cox's proportional hazards regression model will be performed. The model will include demographic and preoperative/operative characteristics (including but not limited to age class, gender, concomitant procedures, and surgical approach). Hazard rates (90% CI) will be reported. The assumptions of proportionality will also be investigated with a time-dependent exploratory variable. In case of non-proportional hazards, a Weibull model will be assumed as parametric form of the distribution of survival times.

The following mortality and morbidity events will be evaluated by time-to-event analysis:

- death
- reoperation
- structural valve deterioration
- moderate or severe valve regurgitation
- valve endocarditis
- valve thrombosis
- thromboembolic events
- hemolysis
- major bleeding

10.1.3. Primary Endpoint Analysis

Since the primary study objective is to estimate the incidence of the reduced leaflet motion, the primary analysis of the primary endpoint will not provide any formal test of hypothesis confirmatory in nature, but will focus on the 90% CI. Accordingly, the sample size calculation is based on the precision (width) of the desired 90% CI rather than desired power and hypothesized effect size.

A 2-sided 90% CI will be calculated by means of Exact confidence limits based on the Binomial Distribution of the the proportion ($\overline{p}$) of subjects with reduced leaflet motion within the specified time period divided by the size of the population at risk..

10.1.4. Secondary Endpoint

The secondary endpoints are defined in **Section 6.3.6**. Analysis of the secondary endpoint will be detailed in the Statistical Analysis Plan.

The incidence proportion of reduced leaflet motion up to 1 year post-implant will be evaluated using the same method described for the evaluation of the primary endpoint. The analyses will be done:

- in symptomatic and asymptomatic subjects, based on CT outcomes and anticoagulation or dual antiplatelet therapy modalities, and
- considering relationship to device, procedure, or other causes

Moreover, in subjects in which reduced leaflet motion was previously detected, the proportion of reduced leaflet motion detected through 4D volume-rendered CT-scan with contrast up to 1 year post-implant will be evaluated.

Number of AEs and number of subjects with at least one event will be presented in each group broken down by SAE type. Number of events, as well as number and percentage of subjects, will be tabulated by timing. Linearized rates (90% CIs) will be calculated as number of late (> 30 days) events divided by late subject-years, defined as the subject-years accumulated starting from the 31st day after surgery.

Subject improvement after valve implant will be determined by comparison of preoperative and postoperative NYHA functional classifications.

10.2. SAMPLE SIZE

A sufficient number of subjects will be enrolled in this study to allow a minimum of 75 evaluable CT scans for the primary endpoint (evaluable scans are those where a determination of normal/abnormal leaflet motion is possible). Considering an attrition rate of 15% of subjects, the sample size targeted for enrollment is approximately 88 subjects.

A sample size of 75 evaluable CT scans produces an Exact two-sided 90% CI with a width lower than 13% when the sample proportion is lower than 10% (evaluation calculated using PASS software, version 13).

10.3. SPECIFICATION OF ANALYSIS SETS

The "Enrolled population" will include all enrolled subjects.

All enrolled subjects will be analyzed under the intention-to-treat (ITT) principle, such that subjects will be analyzed according to the final implant attempt to place an aortic Perceval valve.

A safety population will be defined as all enrolled subjects with a successful implant of the Perceval aortic valve. The safety population will coincide with the enrolled population and will be used for efficacy, performance and safety summaries.

Some specific populations will be defined according scientific relevance.

10.4. PROCEDURES FOR REPORTING ANY DEVIATION(S) FROM THE ORIGINAL STATISTICAL PLAN

Any relevant change to the statistical analysis requested after protocol approval must be defined and approved through a protocol amendment or must be clearly mentioned in the statistical plan of the study in a section 'Changes in the conduct of analyses from protocol', including the rationale of changes.

Deviations from the original statistical plan will be reported in the final study report.

10.5. TREATMENT OF MISSING DATA

If applicable, the management/replacement of missing data will be defined in the Statistical Analysis Plan, to be finalized before the database lock.

10.6. SPECIFICATION OF SUBGROUPS FOR ANALYSIS

Primary and secondary endpoints will be evaluated by the following subgroups:

- Subject implanted with or without a concomitant procedure performed.
- Asymptomatic or symptomatic symptoms.
- Subjects on or off ACT/DAPT at hospital discharge (or 30-days after implant).
- Core Lab evaluation by CT scan or TEE.

10.7. MINIMUM AND MAXIMUM NUMBER OF SUBJECTS TO BE INCLUDED PER CENTER

This study will in principle apply the rule of competitive enrollment. Depending on timelines and total number of sites participating, enrollment may be stopped at an implanting center if a certain level of subjects included.

10.8. TIMING OF ANALYSES

The "main statistical analysis" shall be performed after all evaluable subjects have completed the CT-scan at expected 1-6 months post-implant. The "final statistical analysis" will be performed after all enrolled subjects have completed the 1 year visit.

11. DATA MANAGEMENT

11.1. DATA REVIEW, CLEANING, AND QUERIES RESOLVING PROCEDURES

Data management activities will be described in the Data Management Plan in order to ensure that data processing is complete, consistent and logical and all data as described in the clinical investigational plan are included in the study database.

Site staff will need to enter study data using Electronic Data Capture (EDC) application, which has edit checks programmed to trigger queries at the time of entry or immediately after submitting the data. Clinical data management activities (e.g. data review and query management) are conducted within the EDC system.

The PI is responsible for reviewing all eCRF entries for completion and correctness. Changes to the CRFs will be made electronically and an audit trail of the changes will be kept by the system. The PI, or his designee, is also responsible for addressing queries. The Sponsor is responsible for reviewing queries to support the source data verification and resolution.

Data management will perform data reviews using listings and reports according to the Data Management Plan, to fully ensure data are complete, consistent, and logical.

After resolution of all inconsistencies and discrepancies, a global data review will be performed in order to prepare the final study database. The final locked database will be provided for the statistical analysis.

11.2. VERIFICATION, VALIDATION AND SECURING OF ELECTRONIC CLINICAL DATA SYSTEM

Database and systems are stored in a secure environment. The EDC application is qualified (verification and validation) and hosted by the system vendor having a technical infrastructure to support high-bandwidth access to the server with 24/7 availability and high quality security (21 CFR part 11 compliant) and emergency planning. Access to data is limited to authorized individuals.

12. SAFETY REPORTING

The Sponsor is responsible for the ongoing safety evaluation of the study device, review of reported SAEs, investigation of UADEs, and notification of regulatory authorities per applicable requirements (For this study, only SAEs will be reported.). The Sponsor is also responsible for training the investigational staff prior to start the study on any study-related procedures, including reporting of SAEs. The Sponsor, through the Clinical Safety Office, will provide oversight of general SAE handling procedures for the clinical study and can assist the PIs and various committees in conducting a medical review of reported SAEs.

The PI is responsible for ensuring the safety and well-being of the subjects enrolled in their clinical site and should report events to the Sponsor, IRB, and regulatory bodies as described in this Section.

12.1. PRINCIPAL INVESTIGATOR'S RESPONSIBILITIES IN SAE REPORTING

The PI is required to report all SAEs to the Sponsor including mortality, valve re-intervention, myocardial infarction, structural valve deterioration, moderate or severe valve regurgitation, valve endocarditis, valve thrombosis, thromboembolic events, hemolysis, major bleeding and other clinical endpoints.

Table 5 SAE Reporting to the Sponsor

	Subject Visit			
	Discharge	**Early Post-op (1-6 Mo.)**	**Late Post-op (6-9 Mo.)**	**1 Year (11-13 Mo.)**
All Deaths, UADEs, and SAEs	X	X	X	X

The following timelines for reporting should be followed (**Table 6**):

- UADEs should be reported to the Sponsor immediately within 24 hours of awareness of the event(s) by notifying the Clinical Project Manager (or designee) and by entering the information in the EDC. These events require urgent investigation by the Sponsor and reporting to regulatory authorities, as applicable.
- SAEs should be reported as soon as possible but no later than 10 calendar days of awareness. The PI should enter all available information in the SAE section of the EDC system.

Table 6 Timelines and Communication Methods for Reporting SAEs

Event Classification	Communication Method	Communication Timeline
SAEs including deaths and Adverse Device Effects	Complete the AE eCRF page with all available information. Provide all relevant source documentation (unidentified) for the reported event.	Within 10 calendar days of first becoming aware of the event or as per local/regional regulations. Reporting of any updated information required through the end of the study When documentation is available.
UADE	Contact the Clinical Project Manager (or designee). Complete the SAE eCRF page with all available information.	Within 24 hours of awareness.

a) The PI should perform the following assessments for each reported SAE:

- Identify the clinical event term or description
- Seriousness/severity of the event
- Relationship of the event to the device, procedure, and/or medications

b) The PI should provide all the information needed to complete the AE eCRF.

c) The PI is responsible for informing the IRB of SAEs as required by local/regional regulations and IRB.

d) The PI is expected to assist in clinical review and supply the Sponsor with relevant source documents and results of ancillary procedures required in the protocol.

12.2. SPONSOR REPORTING RESPONSIBILITIES

The Sponsor is responsible for reporting SAE information to all participating PIs, IRB and regulatory authorities, as applicable following local regulations. UADE investigation results will be reported to FDA, all IRB, and all participating PIs within 10 working days of the Sponsor's first notice of the effect. The Sponsor will also notify the FDA, all IRBs, and all participating PIs of any IRB withdrawal of approval within 5 working days of receipt of the approval withdrawal.

If the Sponsor determines an UADE to be an unreasonable risk to subjects, all parts of

the investigation presenting that risk will be terminated or suspended as soon as possible, no later than 5 working days after said termination and no later than 15 working days after the Sponsor's first notice of the UADE. All SAEs must be reported to IRB following the IRB's safety reporting guidelines. The suspended study may not resume until the study has received both IRB and regulatory approval, where required.

12.2.1. Contact Details for Reporting SAEs and UADEs

In case of questions for reporting of SAEs and/or SADEs, please contact the Clinical Project Manager of the study or the monitor responsible for your site.

13. INDEPENDENT CLINICAL STUDY COMMITTEES

13.1. STEERING COMMITTEE

A Steering Committee (SC) will be established to assist the Sponsor in designing and managing the study based upon scientific, medical and technical experience and expertise and providing advice on modifications or amendments to the protocol. The committee is comprised of at least two coordinating investigators; one with expertise in the diagnosis and management of cardiovascular disease and one with expertise in imaging. The SC will provide oversight of the study and recommend processes and procedures to ensure timely and accurate data collection and data quality. The SC will also support the site selection process and make recommendations about participating centers. A named member of the Sponsor's Clinical Affairs department will be part of the SC as a non-voting member, along with the coordinating investigators.

13.2. DATA SAFETY MONITORING BOARD (DSMB)

A Data Safety Monitoring Board (DSMB) will not be established for this study. As noted in Section 12.2 of the protocol Unanticipated Adverse Device Effects will be reported to the FDA and Institutional Review Board in accordance with FDA & IRB regulation. LivaNova will review the study data for subject safety throughout the life of the study and collect all serious adverse events once a subject is enrolled in the study until the end of their participation.

13.3. CLINICAL EVENTS COMMITTEE

A Clinical Events Committee (CEC) will be established for this study. The members of the CEC will be independent of the Sponsor and the PIs. The committee will be composed of physicians with expertise in the following fields, but not limited to: cardiothoracic surgery, cardiology (echocardiography), and neurology. The details of operations and activities are described in the CEC Charter.

The CEC activities will be coordinated by the Sponsor. This committee will adjudicate the following related to the clinical events cited in the primary and secondary endpoints:

- Endpoints or event type according to clinical study protocol definitions: valve re-intervention, myocardial infarction, all-cause mortality, structural valve deterioration, moderate or severe valve regurgitation, valve endocarditis, valve thrombosis, thromboembolic events, hemolysis, major bleeding and other clinical endpoints according to clinical study protocol definitions.
- Relationship of the event to the device and/or procedure
    - Not related: The SAE is clearly not or doubtfully related to the device/procedure.
    - Likely related: The SAE may be related to the device/procedure.
    - Definitely related: There is a clear and documented relationship or causality between the SAE and the device or the procedure.
    - Unknown if related: The relationship between the SAE and the device/procedure cannot be assessed or there is insufficient information available to perform this assessment.
- Review and provide clinical input to a site-reported Unexpected (Serious) Adverse Device Effect (UADE).
- Other SAEs as requested by the Sponsor.

14. TRAINING

The Clinical Project Manager (or designee) will ensure that the participating sites will receive the necessary training needed for appropriate study conduction. This training may include GCP training if not required and documented at the site level, and can only be provided by dedicated and experienced staff.

15. ADMINISTRATIVE REQUIREMENTS

15.1. INSTITUTIONAL REVIEW BOARD

The PI must provide the Sponsor with documentation that the study has been approved by an Institutional Review Board (IRB) prior to study initiation. Approval must also be maintained per IRB requirements. A suspended study may not resume until it has received a new approval from the IRB. The PI must report to the Sponsor withdrawal of IRB approval within five (5) working days. Appropriate submissions to relevant IRBs will be performed according to local regulations. The study will not begin until necessary approvals have been obtained. Any additional requirements imposed by the IRB or regulatory authority will be followed, as appropriate.

15.2. INFORMED CONSENT PROCESS

The subject's informed consent form should contain all relevant aspects pertaining to the clinical investigation in writing and in native, non-technical and understandable language.

The subject's informed consent must be obtained and documented according to the principles of informed consent in the current version of the Declaration of Helsinki for Protection of Human Subjects, 21 CFR 812 part 50 and any local regulations, as applicable. Failure to obtain subject informed consent will be reported to the applicable regulatory authority according to the requirements of either the site or the Sponsor.

15.2.1. Process for Obtaining Informed Consent

The site is encouraged to use the study-specific Informed Consent Form supplied by Sponsor. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. Any changes to the ICF document must be reviewed by Sponsor and approved by the appropriate IRB to ensure that it meets all requirements before use by the center.

The person conducting the informed consent shall verbally explain the study to the potential subject, providing all pertinent information (e.g., purpose, procedures, risks, benefits, alternatives to participation, etc.), and must allow the potential subject ample opportunity to ask questions. The potential subject shall be provided with a written consent form and afforded sufficient opportunity to consider whether or not to participate in the research. After allowing the potential subject time to read the consent form, the patient should be given the opportunity to meet with an Investigator listed on the delegation of authority log to answer any additional questions he/she may have. Once a patient has had all his/her questions answered and has agreed to participate in the clinical investigation, the person conducting the informed consent shall ask the patient to personally date and sign the informed consent form. A copy of the signed informed consent form must be given to the subject and the original filed at the investigational site. The PI must ensure that the requirements for obtaining informed consent are met. The date in which the subject signature is obtained should be also reported in the source documentation (e.g. subject hospital chart). The consent form should be updated or amended whenever new information becomes available that may be relevant to the subject. In such case, the subjects shall be re-consented to the latest version.

Any violations of the informed consent process must be reported as deviations to the Sponsor and local regulatory authorities.

15.3. SITE AND INVESTIGATOR SELECTION CRITERIA

Sites will be selected to participate in this study if they have demonstrated sufficient experience with the implantation of the Perceval valve and are able to implement the requirements of the study protocol. In order to ensure appropriate physician and site participation, the criteria outlined in the Section 15.3.1 shall be met.

15.3.1. Site Selection Criteria

Sites selected to participate in this study shall meet the following criteria:

- Must have sufficient infrastructure to conduct a clinical study (including 4D CT-scan capabilities as specified by the Core Lab requirement).
- Must have experience with Electronic Data Capture system (EDC)

15.3.2. PI selection criteria.

The PIs selected to participate in this study:

- Must be experienced in the implantation of the LivaNova Perceval bioprosthetic aortic valve.
- Must have experience in clinical studies execution and knowledge of GCP.

Before participating in the study, all PIs must agree to respect and fulfill the terms of this investigational plan and sign an Investigator Agreement.

15.4. CIP ADHERENCE / CIP AMENDMENT

Except under emergency circumstances, the PI is not allowed to deviate from the protocol. Deviations to the investigational plan that are decided by the PIs to protect the rights, safety and well-being of human subjects, or are as a result of an incorrect application of the protocol, shall be documented and reported by the PI to the Sponsor as soon as possible.

Deviations affecting subject's safety and/or well-being will be promptly reported to the IRB. Any deviation from the investigational plan to protect life, or physical well-being of a subject in an emergency shall be reported within 5 days to the site's IRB and the Sponsor.

Any amendment to the protocol will be submitted to appropriate authorities for authorization or information depending on the nature of the change. Moreover, any administrative updates, not requiring a submission to the IRB will be documented. Administrative updates are defined as changes that will not impact the safety and well-being of the subjects nor the scientific value of the study. Examples include the following: change in the name of staff responsible for the study conduction as defined in the section "names and addresses", possible change in the legal entities or name of the Sponsor, and formatting or grammar edits.

15.4.1. Protocol Deviations

Principle Investigators of the study are not allowed to deviate from the protocol requirements. In particular, it is recommended to make every effort to avoid introduction of biases caused by protocol deviations. If a deviation still occurs, it shall be listed and reported in the appropriate eCRF.

The Sponsor will assess the seriousness of the deviation, classifying these as major or minor; and will present the list of the deviations to the SC. The final decision about the seriousness of the deviation will be assessed by the SC.

Major deviations are defined as departures from the protocol that may potentially compromise the subject's rights, safety, and well-being, or the completeness, accuracy, reliability, or scientific integrity of the data. Major and minor deviations will be validated before data lock and prior to the statistical analysis being performed.

15.4.2. Corrective and Preventive Actions, Investigator Disqualification Criteria

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions may be investigated and put in place by the SC and/or Sponsor.

If a site fails to implement a corrective action, or in case of repeated non-compliance, the Sponsor may decide to discontinue enrollment at that site or to prematurely disqualify the site from the study.

15.5. MONITORING PROCEDURES, AUDITS AND INSPECTIONS

15.5.1. Study Monitoring

Study monitoring will be performed during the study by appropriately trained and qualified monitors to assess continued compliance with the protocol and applicable regulations. In addition, the monitors verify that study records are adequately maintained, that data are correctly reported (source data verification) with respect to timeliness, adequacy, and accuracy, and that the PI continues to have sufficient staff and facilities to conduct the study safely and effectively.

The PI guarantees the Sponsor's personnel, their designees, and any appropriate regulatory authorities direct access to original source documents.

The Sponsor monitoring procedures will be defined in a specific monitoring plan referring to responsibilities related to the study, including but not limited to site initiation, routine monitoring, in-house quality control, study close-out and securing compliance. The monitoring plan will describe the frequency and extent of monitoring, including the amount of source data verification required for the study.

15.5.2. Sponsor Audits and Inspections by Regulatory Agencies

The study may be subject to quality assurance audits by the Sponsor or designee, as well as inspection by appropriate regulatory authorities, in which case the Sponsor should be immediately notified. In case of a site audit, either by the Sponsor or legal authorities, the PI must allow the inspection. It is important that the PI and relevant study personnel are available during audits and that sufficient time is devoted to the process.

15.6. ROLE OF SPONSOR REPRESENTATIVES

Sponsor personnel can provide support to the PI as needed during the study, testing required by the protocol, follow-ups, and on-site troubleshooting if necessary. Support may include Investigative site training, addressing questions, or providing clarifications to investigative sites.

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

- Reviewing collected data and study documentation for completeness and accuracy
- On-site troubleshooting if necessary

Sponsor personnel will not do the following:

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject without the approval and presence of the PI
- Independently collect study data (defined as safety or effectiveness endpoint data)
- Enter data in the investigative site electronic data capture systems

15.7. CURRICULUM VITAE

The PI will provide updated curriculum vitae with current position and evidence of required qualifications through education, training and experience.

15.8. INVESTIGATOR REPORTS

The PI must provide the following reports to a Sponsor or designee in a timely manner (for safety reports, refer to Section 12.1)

Table 8 Investigator Reporting Requirements

Report Type	Timeframe for Reporting	Report to:
Withdrawal of IRB approval	5 Working Days	Sponsor
Progress reports	At least Annually	Sponsor, IRB
Other reports	Upon Request	Sponsor, FDA, IRB, and/ or other regulatory agencies

15.9. DATA RETENTION

15.9.1. Investigator

The PI must retain all study records, including study case report forms, data clarification forms, and other supporting documentation. These records will be filed and archived at the Principal Investigator and Sponsor locations. Data will be retained at least 15 years after study closure, starting from the signature date of the study report.

15.9.2. Sponsor

It is the Sponsor's responsibility to inform the PI when documents no longer need to be maintained. The PI will take measures to ensure that these essential documents are not accidentally lost, damaged, or destroyed. If for any reason the PI withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and the Sponsor must receive written notification of this custodial change.

The Sponsor will maintain, organize and archive study documentation prior, during and after the study in accordance with established processes and procedures. Throughout the study and after, measures will be taken to prevent accidental or premature destruction of study documentation. Electronic data will be stored on the Sponsor's servers. For some EDC studies, raw data will be stored on the EDC provider servers.

16. CONFIDENTIALITY

Confidentiality of subjects' data and identity will be maintained for the length of the study and beyond.

All information and data sent to the Sponsor concerning study subjects or their participation in this study will be considered confidential by the Sponsor. Only authorized personnel of the Sponsor or an authorized representative shall have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Data collected during this study may be used by the Sponsor for the purposes of this study, for publications, to support future research, or for other business purposes. All data used in the analysis and reporting of this study shall include no identifiable reference to specific subject name.

17. PROPERTY RIGHTS

This protocol is property of the Sponsor. It should not be altered, used or disclosed to a third party without prior written consent.

18. DATA PROTECTION

The Sponsor is committed to uphold the local regulation relating to data management and data protection in biomedical research.

19. SUBJECTS' INSURANCE AND POTENTIAL COMPENSATION

Providing the present protocol is respected, the civil liability of the Sponsor and all its agents is underwritten by a policy taken out the Sponsor with CHUBB Insurance.

20. CLINICAL STUDY RESULTS

Clinical study results will be communicated to appropriate scientific communities at the appropriate timelines as well to the authorities according to local laws after completion or termination of the study.

The study will be registered on the ClinicalTrials.gov website and updated on a regular basis.

21. PUBLICATION POLICY

Study results will be pooled across all sites participating in the study for the purpose of preparing a single, multi-site publication that will be coordinated by the Sponsor. Preparation of the comprehensive publication will occur at study end, but the Sponsor may, at its discretion, coordinate an additional, interim publication. The order of authorship will be determined by the Sponsor and will be based in part on the number of CIP compliant subjects at each site.

The agreement of the Sponsor is mandatory before any publication.

- Authors will be selected based on participation and the quality of the data provided (deviations)
- Number of co-authors in the Authorship will be submitted to each Journal Authorship specific requirements.
- Sponsor must be cited in all publication and the Sponsor will have at least one name of the project team members in the list of primary authors.
- Any named author must meet all of the following standard criteria for authorship:
  - Substantial contributions to the conception or design of the work; or the acquisition, analysis , or interpretation of data; AND
  - Drafting the work or revising it critically for important intellectual content, AND
  - Final approval of the version to be published, AND
  - Agreement to be accountable for all the aspects of the work in ensuring that questions related to the accuracy of integrity of any part of the work are appropriately addressed and resolved.

A PI intending to publish results of the study must provide the Sponsor with a copy of any proposed publication, abstract, or presentation at least 60 days prior to submission for publication or presentation. The Sponsor shall have the right to object to the publication, abstract, or presentation if in the Sponsor's reasonable opinion such publication (i) contains Confidential Information; or (ii) will adversely affect any intellectual property or proprietary right of the Sponsor. In the event of an objection by the Sponsor the PI must either modify or delay the publication, abstract, or presentation for a period requested by the Sponsor not to exceed ninety to one hundred-twenty (90 to 120) days to permit the Sponsor to protect its interests.

22. LIST OF INVESTIGATORS

An updated list of PIs, investigation sites and potential institutions will be maintained by the Clinical Project Manager (or designee). The definitive list will be provided with the final clinical study report.

23. REFERENCES

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11. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD, 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease, *Journal of the American College of Cardiology* (2014), doi: 10.1016/j.jacc.2014.02.536.

24. APPENDICES

Appendix 1 – ABBREVIATIONS & DEFINITIONS
Appendix 2 – ECHOCARDIOGRAPHIC PROTOCOL
Appendix 3 – CT SCAN PROTOCOL
Appendix 4 – American College of Cardiology Guidelines for Anticoagulation Therapy

APPENDIX 1:

ABBREVIATIONS & DEFINITIONS

Note: This Appendix is versioned independent of the Investigational Plan. Document included in this Appendix is current as of the version date of this Investigational Plan.

APPENDIX 2:
ECHOCARDIOGRAPHIC PROTOCOL

Note: This Appendix is versioned independent of the Investigational Plan. Document included in this Appendix is current as of the version date of this Investigational Plan.

APPENDIX 3:
CT SCAN PROTOCOL

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APPENDIX 4:

American College of Cardiology Guidelines for Anticoagulation Therapy

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