Type of document **Clinical Investigational Plan**			
Project **Perceval valve**	*Department:* **Clinical Affairs**	*Original stored in:* **Saluggia**	*Department Internal Ref:* **TPS003**

Trial Title	***Per**ceval **S**utureless **I**mplant Vs **St**andard **A**ortic **V**alve **R**eplacement* *A Controlled Randomized Trial in the surgical treatment of Aortic Valve disease*	*Filed in .MasterControl. on: as per InfoCard* *By: as per InfoCard*

TRIAL CODE: TPS003 TRIAL NAME: PERSIST-AVR

Version N° 3.0

CLINICAL INVESTIGATION PLAN

(NCT02673697)

DOCUMENT HISTORY

Version	Date	Section(s)	Description of modifications
1.0	16JUL2015	N/A	Initial Release
2.0	28JUL2015	4.2	Added TTE and NIHSS as procedure in table
	28JUL2015	2	Removed surgeon affiliation
	28JUL2015	Whole document	Typo corrections
	28JUL2015	Appendix 1	Patient informed consent changed from version 1.0 15july2015 to version 1.0 27july 2015.
3.0	27FEB2018	Whole document	typo and editorial correction
	27FEB2018	Name and addresses	Updated contact details
	27FEB2018	2	Updated version and date; update Statistical consideration. Introduction of adaptive design feature.
	27FEB2018	4.1.	removed number of patients in the flow chart
	27FEB2018	4.2.	Specified inclusion of troponin as cardiac biomarker for MI detection; Added as per protocol NIHSS assessment at discharge, medication assessment added at 2and 4 years follow up
	27FEB2018	5.2	Updated names, due to legal entity and company name change
	27FEB2018	8.1	Update to include adaptive design
	27FEB2018	8.5.7	Editorial change and updated crosslink fro paragraph
	27FEB2018	8.6	Updated to introduce adaptive design
	27FEB2018	8.7	Section updated to align to the section 4.2
	27FEB2018	10	Update to include adaptive design of the study
	27FEB2018	11	Remove name of Steering committee members who resign
	27FEB2018	13.1	Add specification on data management for interim analysis
	27FEB2018	18.1	Reworded definition of lost to follow up
	27FEB2018	19.3.1	Reworded to add the need to have patient informed consent process documented.
	27FEB2018	Appendix	Added appendix 8 and 9

CLINICAL INVESTIGATION PLAN AMENDMENT

Former CIP version: 2.0

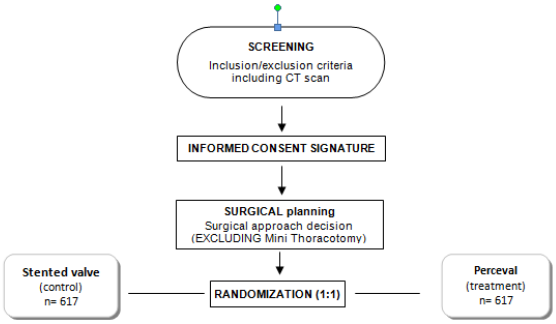
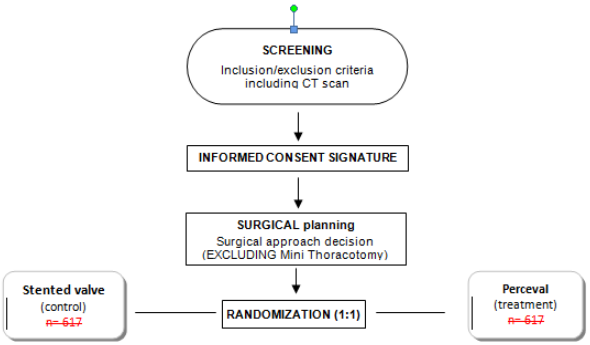
New CIP version: 3.0

Date of amendment: 27/FEB/2018

The following sections have been revised in order to update the Clinical Investigational Plan (CIP).

Change 1	
CIP Section	Names and addresses, Trial Management
Justification	Change of email address due to new name of organization. Updated phone number of trial management to enter mobile phone rather than a ground line number.
Old Text	**TRIAL MANAGEMENT** **Name:** Michele Nozza **Address:** Sorin Group Italia Srl Via Benigno Crespi, 17 20159 Milan Italy **Tel** 0039 0161 487 959 **Fax:** 0039 0161 487636 **E-mail:** Michele.nozza@sorin.com
New Text	**TRIAL MANAGEMENT** **Name:** Michele Nozza **Address:** Sorin Group Italia Srl Via Benigno Crespi, 17 20159 Milan Italy **Tel** 0039 346 744 11 32~~0161 487 959~~ **Fax:** 0039 0161 487636 **E-mail:** Michele.nozza@livanova.com~~sorin.com~~

Change 2	
CIP Section	2.
Justification	Synopsis has been modified to introduce the adaptive design in the statistical section. Editorial changes have been done in other sections of the synopsis.
Old Text	See Appendix 9
New Text	

Change 3	
CIP Section	4.1
Justification	Due to the adaptive design the number of enrolled patients is not fixed, so the number has been removed from the flow chart of the study
Old Text	**4.1 GRAPHICAL STUDY DESIGN** 
New Text	**4.1 GRAPHICAL STUDY DESIGN** 

Change 4	
CIP Section	4.2
Justification	Troponin is mentioned in the VARC-2 as cardiac enzyme, but not specifically reported into the study procedure table. To avoid question from sites, troponin has been added in the table and in the foot note (not reported here in the images) NIHSS test has been added in the table. This was already mentioned on section 8.7 of the CIP, but not reported in this table. Medication assessment can be performed at each early follow-up not only at 3 and 5 year follow-up. This was already reported on section 8.7 of the CIP.
Old Text	

Procedure	Prior to Implant	Intra-operative	Hospital discharge	1 month	1 - 3 months	1 Year	Yearly Follow-up
Screening	X						
Informed Consent	X						
Medical History	X						
Chest CT-scan	X						
Surgical Details		X					
Universal sizer measurement		X					
Transesophageal Echocardiogram (TEE)		X					
Cardiac rhythm		X					
CKMB§	X		X (post operative up to discharge)				
Platelet count**	X		X (post operative up to discharge)				
NIHSS	X				X	X	
QOL (EQ5D) Questionnaire	X			X (self administered)	X	X	
NYHA Assessment	X				X	X	X
Transthoracic Echocardiogram (TTE)	X		X		X	X	X (for 3 and 5 year follow up only)
Modified Rankin Scale	X		X		X	X	X (for 3 and 5 year follow up only)
Physical Exam	X		X		X	X	X (for 3 and 5 year follow up only)
Medications Assessment	X		X		X	X	X (for 3 and 5 year follow up only)

New Text

Procedure	Prior to Implant	Intra-operative	Hospital discharge	1 month	1 - 3 months	1 Year	Yearly Follow-up
Screening	X						
Informed Consent	X						
Medical History	X						
Chest CT-scan	X						
Surgical Details		X					
Universal sizer measurement		X					
Transesophageal Echocardiogram (TEE)		X					
Cardiac rhythm		X					
CKMB/troponin§	X		X (post operative up to discharge)				
Platelet count**	X		X (post operative up to discharge)				
NIHSS	X		X		X	X	
QOL (EQ5D) Questionnaire	X			X (self administered)	X	X	
NYHA Assessment	X				X	X	X
Transthoracic Echocardiogram (TTE)	X		X		X	X	X (for 3 and 5 year follow up only)
Modified Rankin Scale	X		X		X	X	X (for 3 and 5 year follow up only)
Physical Exam	X		X		X	X	X (for 3 and 5 year follow up only)
Medications Assessment	X		X		X	X	X (for 3 and 5 year follow up only)

Change 5	
CIP Section	5.2
Justification	Name of the manufacturer has been updated due to legal entity and company name changes.
Old Text	**5.2 MANUFACTURER DETAILS** The Perceval valve is manufactured by: • **Sorin Group Italia S.r.l.** Via Crescentino, sn – 13040 Saluggia (VC) ITALY • **Sorin Group Canada Inc.** 5005 North Fraser Way, Burnaby – British Columbia V5J 5M1 CANADA **Sorin Group Italia S.r.l** and **Sorin Group Canada Inc.** are sister companies and part of Sorin Group. For increased manufacturing flexibility, the Perceval valve is manufactured in the two above mentioned manufacturing sites, with the same design, manufacturing process, sterilization method and intended use, as well as the same product codes identifying the device. The accessories intended for use in association with the Perceval valve are manufactured by **Sorin Group Italia S.r.l.** in the facility identified above. For this trial, the Perceval valve can be used from both manufacturing facilities.
New Text	**5.2 MANUFACTURER DETAILS** The Perceval valve is manufactured by: • **Sorin Group Italia S.r.l.** Via Crescentino, sn – 13040 Saluggia (VC) ITALY • ~~**Sorin Group**~~**LivaNova Canada** ~~**Inc.**~~ **Corp.** 5005 North Fraser Way, Burnaby – British Columbia V5J 5M1 CANADA **Sorin Group Italia S.r.l** and ~~**Sorin Group**~~**LivaNova Canada** ~~**Inc**~~**Corp.** are sister companies and part of ~~Sorin Group~~LivaNova PLC. For increased manufacturing flexibility, the Perceval valve is manufactured in the two above mentioned manufacturing sites, with the same design, manufacturing process, sterilization method and intended use, as well as the same product codes identifying the device. The accessories intended for use in association with the Perceval valve are manufactured by **Sorin Group Italia S.r.l.** in the facility identified above. For this trial, the Perceval valve can be used from both manufacturing facilities.

Change 6	
CIP Section	8.1
Justification	Change to introduce adaptive design
Old Text	**8.1 TRIAL TYPE** This is a prospective, randomized, stratified non blinded multi-center, international, post market trial assessed in a non-inferiority study. A minimum of 1234 subjects will be enrolled at approximately 60 worldwide investigational sites where the device is commercially available.
New Text	**8.1 TRIAL TYPE** This is a prospective, randomized, stratified non blinded multi-center, international, post market trial assessed in a non-inferiority study. ~~A minimum of 1234~~The trial has a flexible sample size that will be determined adaptively. The trial will enroll up to 1234 subjects, but accrual may stop after 900, 1050, or 1234 subjects (see section 10.2). These subjects will be enrolled at approximately 60 worldwide investigational sites where the device is commercially available. Regardless of the sample size selected, follow up of subjects will continue annually up to 5 years. The primary endpoint will be reached at 1 year FU and, consequently, the planned primary analysis will be performed 12 months following the end of accrual.

Change 7	
CIP Section	8.5.7
Justification	Editorial change and change of paragraph number
Old Text	**8.5.7 RANDOMIZATION** Only subjects who have undergone standard chest CT-scan to determine if the aortic stenosis can be replaced with an available Perceval valve (size) and is potentially suitable for mini-sternotomy . For each subject the randomization will be performed based on the randomization list after enrollment and before valve operation, specifically after CT scan and surgical approach ("full sternotomy" or "mini-sternotomy") to minimize bias.
New Text	**8.5.7 RANDOMIZATION** Only subjects who have undergone standard chest CT-scan to determine if the aortic stenosis can be replaced with an available Perceval valve (size~~)~~), and is potentially suitable for mini-sternotomy~~.~~, may be randomized. For each subject the randomization will be performed based on the randomization list after enrollment and before valve operation, specifically after CT scan and surgical approach ("full sternotomy" or "mini-sternotomy") has been determined, to minimize bias.

Change 8	
CIP Section	8.6
Justification	Introduction of adaptive design will have an impact on the study population (8.6.3) so this paragraph has been updated. Section 8.6.1 has been updated to reflect new study timelines.
Old Text	
New Text	**8.6 SUBJECTS NUMBER AND TRIAL PERIOD** **8.6.1 TOTAL EXPECTED DURATION OF THE CLINICAL INVESTIGATION** The trial plans for an inclusion period of approximately ~~24~~30 months at approximately 60 international sites where the Perceval is commercially available. Subjects will be followed for 5 years~~, so a total~~. Total study duration of approximately 7.5 years is expected. **8.6.2 EXPECTED DURATION OF EACH SUBJECT'S PARTICIPATION** Subjects will be evaluated at screening, at discharge visit following prosthesis implant, between one and three months, at 1 year, and annually up to 5 years. **8.6.3 NUMBER OF SUBJECTS REQUIRED TO BE INCLUDED IN THE CLINICAL INVESTIGATION** The number of subjects to be enrolled in the trial ~~is~~will be adaptively determined. Accrual may stop after approximately 900, 1050, or 1234 subjects, including an attrition rate between enrolled and per-protocol population of 10%.

Change 9	
CIP Section	8.7
Justification	The section has been updated in order to align the table in section 4.2 (flow chart) with the procedures reported in this section. Some of them were reported in the table, but not in the section 8.7.
Old Text	See Appendix 9
New Text	

Change 10	
CIP Section	10
Justification	Complete revision of the chapter to introduce adaptive design.
Old Text	See Appendix 9
New Text	

<table>
<tr><td colspan="2">Change 11</td></tr>
<tr><td>CIP Section</td><td>11.1</td></tr>
<tr><td>Justification</td><td>A member of the Steering Committee resigned on June 2017; the name has been deleted from the table.</td></tr>
<tr><td>Old Text</td><td>
Table 7 Named members of Steering Committee
<table>
<tr><td>Theodor Fischlein, M.D.</td><td>Steering committee Chairman and Principal investigator</td></tr>
<tr><td>Roberto Lorusso, M.D.</td><td>Co-Principal Investigator</td></tr>
<tr><td>Pieter Kappetein, M.D.</td><td></td></tr>
<tr><td>Thierry Folliguet, M.D</td><td></td></tr>
<tr><td>Malakh Shrestha, M.D.</td><td></td></tr>
<tr><td>Bart Meuris. M.D</td><td></td></tr>
<tr><td>Eric Roselli, M.D.</td><td></td></tr>
<tr><td>Sara Gaggianesi, DMV</td><td>Sponsor nonvoting member</td></tr>
</table>
</td></tr>
<tr><td>New Text</td><td>
Table ~~7~~8 Named members of Steering Committee
<table>
<tr><td>Theodor Fischlein, M.D.</td><td>Steering committee Chairman and Principal investigator</td></tr>
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<tr><td>Sara Gaggianesi, DMV</td><td>Sponsor nonvoting member</td></tr>
</table>
</td></tr>
</table>

Change 12	
CIP Section	13.1
Justification	Since interim analyses have been added to the CIP, specifications on how the data are handle for these analyses have been added.
Old Text	**13.1 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 trial database. Site staff will need to enter trial 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. The EDC is linked to a Clinical Data Management System (CDMS). The investigator is responsible for reviewing all CRF 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 investigator 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 trial database. The final locked database will be provided for the statistical analysis.
New Text	**13.1 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 trial database. Site staff will need to enter trial 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. The EDC is linked to a Clinical Data Management System (CDMS). The investigator is responsible for reviewing all CRF 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 investigator 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. At the time of each interim analysis (see section 10.1.2), an interim soft lock will be performed by the Clinical Data Manager: the data exported from the EDC system will be accessible only to the Clinical Data Manager and to the ISU delegated by the Sponsor to perform the interim analysis.

Change 13	
CIP Section	18.1
Justification	Definition of "lost to follow up patient" has been re-worded
Old Text	**18.1 HANDLING OF SUBJECTS' TEMPORARY TREATMENT DISCONTINUATION OR TERMINATION** For all subjects reaching the end of the trial (completed 5 year visit, death, or explant) or in case of premature withdrawal as described in section 8.5.5 (lost-to-follow-up, or subject's decision) a trial termination form will be filled out in order to document the date and reason for discontinuation. Subjects who had their valves explanted will still have to be followed at least till 1 year primary endpoint. 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 attempts to make contact via phone, and/or 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.
New Text	**18.1 HANDLING OF SUBJECTS' TEMPORARY TREATMENT DISCONTINUATION OR TERMINATION** For all subjects reaching the end of the trial (completed 5 year visit, death, or explant) or in case of premature withdrawal as described in section 8.5.5 (lost-to-follow-up, or subject's decision) a trial termination form will be filled out in order to document the date and reason for discontinuation. Subjects who had their valves explanted will still have to be followed at least till 1 year primary endpoint. 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 attempts to make ~~contact~~ three contacts via phone, ~~and/or a~~ one certified letter should be sent to the subject's last known address. ~~Both phone~~Phone contacts and copy of the letter must be documented/available in the subject's medical record ~~and recorded in the eCRF.~~

Change 14	
CIP Section	19.3.1
Justification	Introduction of the need to have the process of patient consent documented in the source documentation of the hospital
Old Text	**19.3.1 PROCESS FOR OBTAINING INFORMED CONSENT** The Investigator is encouraged to use the trial-specific Informed Consent Form (Appendix 1) supplied by Sponsor, eventually translated in local language. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. If an investigating center chooses to use an alternatively worded written consent document, the document must be reviewed by Sponsor to ensure that it meets all requirements before use by the center. The EC/IRB at each center must also approve the consent. An Investigator (or other trial staff who are conducting the informed consent interview) have to explain the trial to the potential subject verbally, 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 should 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, an Investigator listed on the delegation of authority list should meet with the potential subject and answer any additional questions s/he may have. Once an individual has had all his/her questions answered and has agreed to participate in the clinical investigation, the investigator shall ask the subject to personally date and sign all required copies of the informed consent form. It may be appropriate for the Investigator to sign after the subject if the Investigator needs to verify that basic eligibility criteria have been met.
New Text	**19.3.1 PROCESS FOR OBTAINING INFORMED CONSENT** The Investigator is encouraged to use the trial-specific Informed Consent Form (Appendix 1) supplied by Sponsor, ~~eventually~~ translated ~~in~~into local language. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. If an investigating center chooses to use an alternatively worded written consent document, the document must be reviewed by Sponsor to ensure that it meets all requirements before use by the center. The EC/IRB at each center must also approve the consent. An Investigator (or other trial staff who are conducting the informed consent interview) have to explain the trial to the potential subject verbally, 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 should be provided with a written consent form and afforded sufficient ~~opportunity~~time to consider whether or not to participate in the research. After allowing the potential subject time to read the consent form, an Investigator listed on the delegation of authority list should meet with the potential subject and answer any additional questions s/he may have. Once an individual has had all his/her questions answered and has agreed to participate in the clinical investigation, the investigator shall ask the subject to personally date and sign all required copies of the informed consent form. It may be appropriate for the Investigator to sign after the subject if the Investigator needs to verify that basic eligibility criteria have been met. Patients participation to the study should be documented in the source documentations.
Change 15	

CIP Section	29
Justification	A paper has been added in the bibliography.
Old Text	24. Matilde Sanchez, M. and X. Chen, *Choosing the analysis population in non-inferiority studies: per protocol or intent-to-treat.* Stat Med, 2006. **25**(7): p. 1169-81. 25. Konig, K.C., et al., *Sutureless Perceval aortic valve in comparison with the stented Carpentier-Edwards Perimount aortic valve.* J Heart Valve Dis, 2014. **23**(2): p. 253-8. 26. Mohr, F.W., et al., *The German Aortic Valve Registry: 1-year results from 13 680 patients with aortic valve diseasedagger.* Eur J Cardiothorac Surg, 2014. **46**(5): p. 808-16.
New Text	24. Matilde Sanchez, M. and X. Chen, *Choosing the analysis population in non-inferiority studies: per protocol or intent-to-treat.* Stat Med, 2006. **25**(7): p. 1169-81. ~~25~~25. Kalbfleisch, J.D.a.P., R. L. , *The Statistical Analysis of Failure Time Data*, ed. J.W. Sons. 1980, New York. 26. Konig, K.C., et al., *Sutureless Perceval aortic valve in comparison with the stented Carpentier-Edwards Perimount aortic valve.* J Heart Valve Dis, 2014. **23**(2): p. 253-8. ~~26~~27. Mohr, F.W., et al., *The German Aortic Valve Registry: 1-year results from 13 680 patients with aortic valve diseasedagger.* Eur J Cardiothorac Surg, 2014. **46**(5): p. 808-16.

Change 16	
CIP Section	Appendices
Justification	Appendix 8 (Adaptive Design) and Appendix 9 (to reflect changes 2, 9 and 10) have been added.
Old Text	N/A
New Text	See new appendices

Change 17	
CIP Section	Whole document
Justification	Revision of the document for typo corrections and editorial changes.

NAMES AND ADDRESSES

STEERING COMMITTEE CHAIRMAN	**Name:**	Theodor Fischlein, M.D
	Address:	*Department of Cardiac Surgery Cardiovascular Center* *Paracelsus Medical University (PMU)* Klinikum Nürnberg Breslauer Str. 201 90471 Nürnberg
	Tel:	+49 911 398-5441
	Fax:	
	E-mail:	Theodor.Fischlein@klinikum-nuernberg.de
TRIAL MANAGEMENT	**Name:**	Michele Nozza
	Address:	Sorin Group Italia Srl Via Benigno Crespi, 17 20159 Milan Italy
	Tel	0039 346 744 11 32
	Fax:	0039 0161 487636
	E-mail:	Michele.nozza@livanova.com
SPONSOR	**Company:**	Sorin Group Italia Srl
	Address:	Via Crescentino s/n 13040 Saluggia (VC) Italy
	Tel:	0039 0161 487975
	Fax:	0039 0161 487636

TABLE OF CONTENTS

1 LIST OF ABBREVIATIONS

ADE	Adverse Device Event
AE	Adverse Event
AI	Aortic Insufficiency
AS	Aortic Stenosis
AVR	Aortic Valve Replacement
CABG	Coronary Artery Bypass Graft
CCT	Cross Clamp Time
CCU	Cardiac Care Unit
CEC	Clinical Event Committee
CFR	Code of Federal Rules
CKMB	Creatine Kinase - MB
CPB	Cardio Pulmonary Bypass
CRF	Case Report Form
CT-Scan	Computerized Tomography Scan
DSMB	Data Safety Monitoring Board
DVI	Doppler Velocity Index
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EOA	Effective Orifice Area
EROA	Effective Regurgitant Orifice Area
FDA	Food and Drug Administration
GCP	Good Clinical Practices
IABP	Intra Aortic Balloon Pump
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IFU	Instructions For Use
IRB	Institutional Review Board
ISU	Independent Statistical Unit
ITT	Intention To Treat
LDH	Lactate DeHydrogenase
LVEF	Left Ventricle Ejection Fraction
LVOT	Left Ventricle Outflow Tract
MACCE	Major Cerebral And Cardiovascular Event
MAE	Major Adverse Event
MDR	Medical Device Reporting
MICS	Minimal Invasive Cardiac Surgery
MPG	Mean Pressure Gradient
mRS	modified Rankin Scale
NIHSS	NIH Stroke Scale/Score
NSTEMI	Non St-Elevation Myocardial Infarction
NYHA	New York Heart Association
OR	Operating Room
PP	Per Protocol
PPG	Peak Pressure Gradient
PPM	Patient Prosthesis Mismatch
PVL	Para Valvular Leak
QOL	Quality Of life Questionnaire
RBC	Red Blood Cell
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SC	Steering Committee
STEMI	ST-Elevation Myocardial Infarction
STS	Society of Thoracic Surgeons
SVD	Structural Valve Deterioration
TAVI	Transcatheter Aortic Valve Implantation
TEE	Trans Esophageal Echocardiogram
TTE	Trans Thoracic Echocardiogram
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
VARC	Valve Academic Research Consortium
WBC	White Blood Cell

2 STUDY EXTENDED SYNOPSIS

Clinical Investigation Plan date	27 February 2018
Revision number	3.0
Title of trial	**Per**ceval **S**utureless **I**mplant Vs **St**andard Aortic Valve Replacement (**PERSIST-*AVR)*** *A Controlled Randomized Trial in the surgical treatment of Aortic Valve disease*
Principal investigators	Theodor Fischlein, M.D., Roberto Lorusso, M.D., Ph.D.
Trial duration	Inclusion phase: from approximately 24 months to 30 months (2.5 years) according to sample size selection. Follow up phase: 5 years. Total duration time: from 7 to 7.5 years, depending on inclusion phase.
Planned trial period	The trial is expected to start in Q4-2015, once the relevant (inter)-national regulations/guidelines are fulfilled, including signed research agreements between the sites and Sponsor. The trial shall be completed after the 5-year follow-up of the last subject enrolled.
Number of trial centers planned	Approximately 60 sites worldwide
Study type	Non-inferiority post-market study
Trial design	Prospective, randomized (1:1), stratified, non blinded, multi-center, international
Primary objective:	The primary objective of this trial is to test the safety and efficacy of Perceval valve versus standard sutured stented bioprosthetic aortic valves among the intended trial population.
Secondary objectives:	To compare all relevant device and subject demographics, procedural and hospital discharge, short and long-term data, as described in the secondary endpoints section

Primary endpoint	The primary endpoint is freedom from MACCE (composite endpoint of all cause death, myocardial infarction, stroke, and valve re-intervention) at one year based on CEC adjudication
Secondary endpoints	1. Surgical time a. Cross clamp time during index procedure b. Cardiopulmonary bypass time during index procedure 2. Normalized Consumption Index and reduced Normalized Consumption Index, including resource consumption items such as (but not limited to): a. Operative room time, b. Duration of ICU/CCU and total hospital stay c. Incidence of specific serious adverse events as defined in Appendix 3 d. Blood transfusion(s) 3. Quality of life questionnaire b. At 1 month and 1 year post surgery 4. Intraprocedural and periprocedural serious adverse events regardless of relationship with the device within 72 hours 5. All valve and procedure relevant serious adverse as specified in VARC-2 guidelines [1] a. Early safety at 30 days b. Clinical efficacy after 30 days c. Time related valve safety: SVD, endocarditis, thrombosis, thromboembolic events (excluding stroke), and bleeding annually up to 5 years 6. Serious device related adverse events up to 5 years 7. Freedom from MACCE at 2, 3, 4 and 5 years of follow up 8. Pacemaker implantation and cause up to 1 year 9. Valve hemodynamics (PPM, PPG, MPG; DVI, EOA, LVOT, AI, PVL,EROA) assessed by site-reported echocardiographic parameters preoperatively, at discharge, between 1-3 month, 1 year, 3 year and 5 year. 10. Valve hemodynamics (PPM, PPG, MPG; DVI, EOA, LVOT, AI, PVL,EROA) in a reduced cohort of patients assessed by core lab echocardiographic parameters preoperatively, at discharge, between 1-3 month, 1 year, 3 year and 5 year.
Trial population	All subjects with severe symptomatic aortic stenosis or steno-insufficiency who are candidates for surgical replacement of their native aortic valve according to established guidelines [2, 3] in current medical practice and as specified in the Perceval valve IFU.
Trial population criteria	**<u>Inclusion criteria</u>** 1. The subject has an indication for treatment by valve replacement with a bioprosthesis according to the IFU, through either full sternotomy or mini-sternotomy.

	2. The subject has aortic valve disease that can be treated with a commercially available Perceval valve size, based on preoperative CT-scan. 3. The subject has: a) critical aortic valve area defined as an initial aortic valve area of ≤1.0 cm^2 or aortic valve area index < 0.6 cm^2/m^2 AND b) Mean gradient > 40mmHg or Vmax > 4m/sec by resting echocardiogram or simultaneous pressure recordings at cardiac catheterization [or with dobutamine stress, if subject has a left ventricular ejection fraction (LVEF) <55%] or velocity ratio < 0.25; 4. The subject is symptomatic due to aortic stenosis with functional class of NYHA II or higher. 5. The subject has signed the informed consent. 6. The subject is of legal minimum age. 7. The subject will be available for postoperative follow-up beyond one year. **<u>Exclusion criteria</u>** 1. The subject has a contraindication for treatment by the Perceval valve or by a bioprosthetic aortic valve as stated in the IFU. 2. The subject has aneurysmal dilation or dissection of the ascending aortic wall. 3. The subject is scheduled for concomitant procedures other than CABG, myectomy with or without aortic annulus enlargement. 4. The subject has congenital bicuspid (i.e. Sievers type 0) or unicuspid aortic valve. 5. Anatomical structures not suitable for Perceval valve such as: aortic root enlargement, where the ratio between the diameter of the sino-tubular junction and the annulus diameter is > 1.3. 6. The subject has a prosthetic heart valve in any position, including mitral valve repair. 7. The subject had a stroke or myocardial infarction (STEMI and NSTEMI) within 30 days prior to the planned valve implant surgery. 8. The subject has active endocarditis, myocarditis, or sepsis. 9. The subject is in cardiogenic shock manifested by low cardiac output and needing hemodynamic support. 10. The subject is allergic to nickel alloys. 11. The subject is already included in another clinical trial that could confound the results of this clinical investigation.
Number of subjects to be enrolled	A maximum of 1234 patients are planned to be enrolled, but accrual may stop earlier at approximately 900 or 1050 subjects.
Investigational device	Perceval sutureless aortic heart valve
Assessment schedule	• Subject inclusion (subject demography, surgery, hospital discharge)

	• 1-3 month post implant • 1 year post implant • Yearly up to 5 years
Statistical considerations	The study includes an adaptive approach for the determination of the study sample size. **Primary analysis** The primary study objective will be investigated by the primary analysis comparing the primary endpoint between the two randomized groups on PP population defined as all subjects without major protocol deviations and attending the scheduled follow-up visits up to 1 year at minimum. A one-sided non-inferiority test will compare the two arms on the proportion of subjects that are event-free at one year. The null hypothesis is that the 1-year freedom from MACCE in the Perceval arm is inferior to the 1-year freedom from MACCE in the Control arm: - H_0: $MACCE_{CONTROL} - MACCE_{PERCEVAL} \geq 0.05$ - H_1: $MACCE_{CONTROL} - MACCE_{PERCEVAL} < 0.05$ where $MACCE_j$ is the one-year event-free rate for arm j. The primary analysis will use the Bayesian posterior probability that the difference (CONTROL – PERCEVAL valve) in 1 year MACCE event-free rates is lower than 0.05: $$Pr(MACCE_{CONTROL} - MACCE_{PERCEVAL} < 0.05 \mid Data)$$ The null hypothesis will be rejected, and non-inferiority concluded, if the Bayesian posterior probability exceeds 0.9775 at the final analysis. This threshold was selected to control the Type I error rate at 2.5% (one-sided). Non-inferiority will be assessed in the Per Protocol population as primary analysis. Sensitivity analyses on the primary endpoints will be performed using different assumptions and populations. **Interim Analysis and sample size determination** Total sample size for this trial will be adaptively determined through interim analyses to be performed when 900 and 1050 subjects will be enrolled. Accrual may stop earlier if there is at least 99.6% and 99.3% posterior probability of non-inferiority at the first and second interim analysis, respectively. The interim analysis will be conducted by an external Independent Statistical Unit (ISU) not involved in the study

	conduct who will communicate to the Sponsor the decision on the continuation of enrollment. Assuming a 91% event-free rate in both arms (based on blinded data review) this trial has 80.5% probability of success with a mean sample size of approximately 1129. As the interim analysis objective simply focuses on patient recruitment, it will have no impact on subsequent study milestones. Therefore primary analysis will be performed at 12 months after last patient implanted and subject follow up will continue up to 5 years. **Other statistical analysis** Each component of the MACCE composite endpoint will be analyzed as proportion of subjects event-free at one year (95% C.I.) as well as using time-to-event methods. For Cox regression models, the stratification factors (country and surgical approach) and pre-operative variables (including demographic, medical history, and concomitant procedures) will be taken into account. All data collected up to cutoff date (eg. 12 months after last patient implanted) will be used for the time-to-event analysis. Surgical times and Normalized Consumption Index endpoints will be analyzed in a superiority context. A one-sided superiority test will be conducted comparing the treatment and control group at discharge using appropriate regression models to account for stratification factors. Number of serious adverse events and number of patients with at least one event will be presented in each group broken down by AE type. Number of events, as well as number and percentage of patients will be tabulated by timing (before / on or after intervention according to VARC-2 definitions).

3 INTRODUCTION

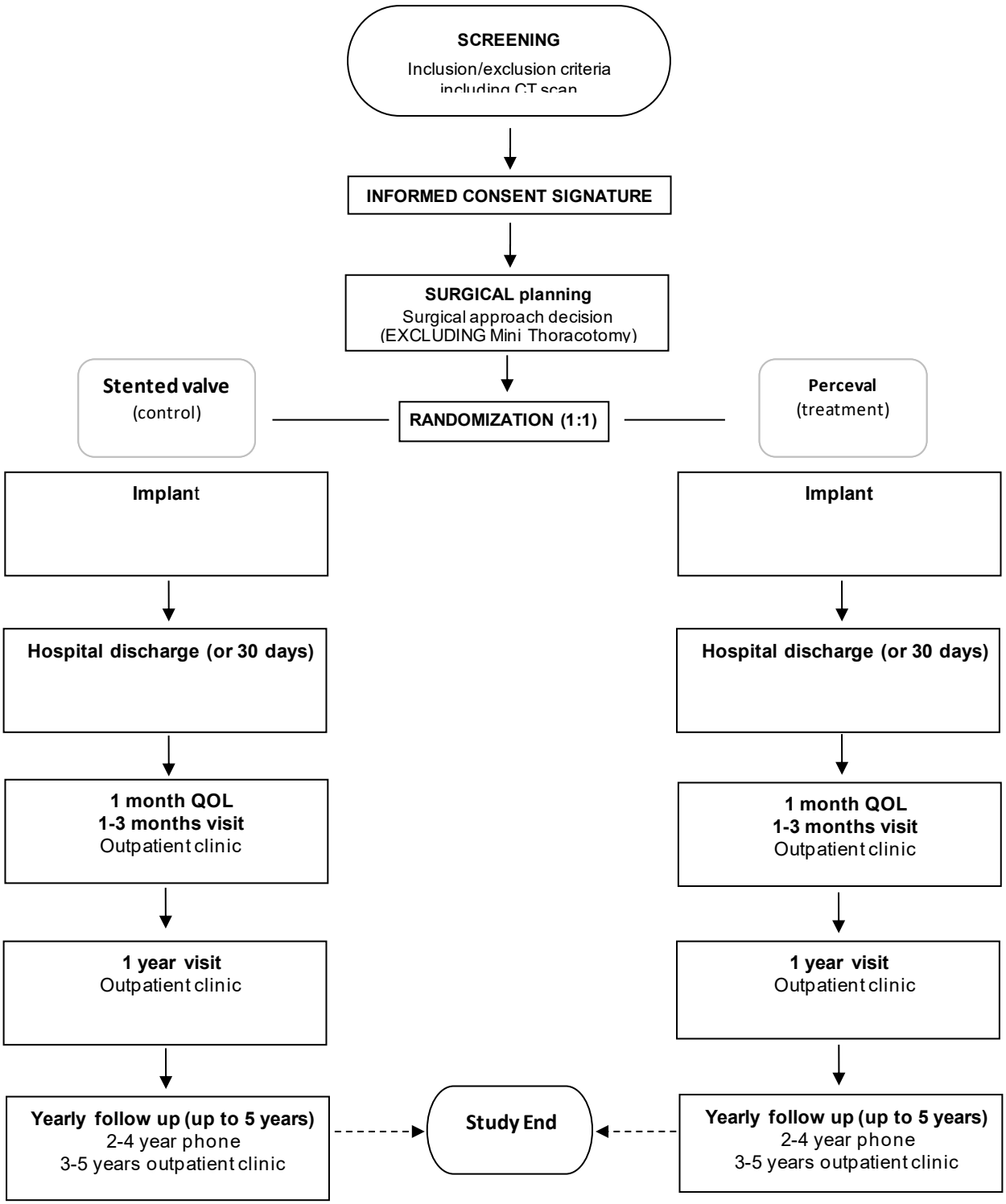
The field of heart valve replacement began in the 60's with the use of first generation mechanical valves (the ball-cage design) and has undergone few changes through time. Mechanical valves improved over the years with the introduction of the tilting-disc design, until the late 70's when the bileaflet valve was made available to the market. Mechanical prosthesis proved to be satisfactory in terms of durability, but require life-long anticoagulation treatment, increasing the risk of hemorrhagic and/or thromboembolic episodes. As far as biological artificial valve is concerned, in 1961, Heimbecker attempted the first use of homograft to replace a cardiac valve in Toronto [4], followed by the first investigations of heterologous artificial valves, which led to the first porcine valve implantation at aortic position, as implanted in 5 patients in 1965 by Binet, Carpentier, Duran and Langlois [5]. In the 70's, the first generation of animal- derived prostheses enabled a wider clinical use of heterologous tissue valves. These valves were made from bovine pericardium or porcine aortic root. Despite the advantage of not requiring anticoagulation treatment, the first generation of biological valve prostheses had the pitfall of early failures. The current generation of bioprosthesis provides better outcomes in terms of durability compared to earlier generations, thanks to improvements in the valve design and tissue preservation treatments. Aortic valve replacement with biological or mechanical valves is the gold standard for the treatment of the severe symptomatic aortic stenosis [2]. Long-term clinical data available in the literature confirm the validity of using pericardial valves, and today, according to several authors, pericardial prostheses represent the best choice of replacement in the aortic position in elderly patients with very low gradients and improved long-term durability. [6-9]. In an effort to improve the outcomes of patients with stented biological valves, stentless valves were introduced into clinical practice in the early 1990s. These valves were designed to be less obstructive, resulting in lower transvalvular gradients at the expense of longer cross-clamp times as implantation is more complicated, frequently requiring additional suture lines [10].

Older patients with other significant co-morbidities, requiring complex procedure, will benefit from less invasive approach to diminish the operative risk [11]. Thus, recent advances in technologies have led to the introduction of alternative treatment modalities including sutureless AVR. These valves allow surgeons to implant without the need for sutures, thereby reducing the cross clamp time and facilitating a minimally invasive surgical approach. To assess the clinical outcome of this new prosthesis, studies [12-14], have been conducted with a propensity matched cohorts, of patients receiving a standard bioprosthesis with patients receiving a sutureless valve. The results demonstrated decreased cross clamp time in patients receiving a sutureless valve and similar clinical outcome between the two groups in the short to mid-term period. A meta-analysis confirmed these findings for sutureless valve technology with shortened of cross-clamp time and facilitation of the minimally invasive approach as well as concomitant cardiac surgery for high-risk patients [11]

Due to the lack of prospective, randomized comparison data between sutureless valve and standard aortic valve, this randomized study is planned to demonstrate, as primary endpoint, the non inferiority of Major Adverse Cardiac and Cerebrovascular (MACCE) events at one year while showing superiority in resource consumptions at hospital discharge in patients treated with a sutureless valve (Perceval sutureless aortic heart valve), when compared to standard aortic valve replacement. The patients will be recruited according to valve's instruction for use and randomized 1:1 between the sutureless and standard AVR groups.

4 STUDY FLOW CHART

4.1 GRAPHICAL STUDY DESIGN



4.2 FLOW CHART

Procedure	Prior to Implant	Intra-operative	Hospital discharge	1 month	1 - 3 months	1 Year	Yearly Follow-up
Screening	X						
Informed Consent	X						
Medical History	X						
Chest CT-scan	X						
Surgical Details		X					
Universal sizer measurement		X					
Transesophageal Echocardiogram (TEE)		X					
Cardiac rhythm		X					
CKMB/troponin§	X		X (post operative up to discharge)				
Platelet count **	X		X (post operative up to discharge)				
NIHSS	X		X		X	X	
QOL (EQ5D) Questionnaire	X			X (self administered)	X	X	
NYHA Assessment	X				X	X	X
Transthoracic Echocardiogram (TTE)	X		X		X	X	X (for 3 and 5 year follow up only)
Modified Rankin Scale	X		X		X	X	X (for 3 and 5 year follow up only)
Physical Exam	X		X		X	X	X (for 3 and 5 year follow up only)
Medications Assessment	X		X		X	X	X
Routine Blood tests †	X		X		X	X	X (recommended for 3 and 5 year follow up only)
12-Lead Electrocardiogram (ECG) with rhythm strip	X		X		X	X	X (for 3 and 5 year follow up only)
Serious Adverse Events and Outcomes		X	X		X	X	X

† Blood evaluations will include WBC, RBC, hemoglobin (Hgb), hematocrit (Hct), platelet count, serum LDH, haptoglobin, reticulocyte, plasma free hemoglobin, serum creatinine (pre-operatively and early post-operative visit only) and coagulation data. Plasma free hemoglobin will be collected only at sites that have the local capabilities of performing the evaluation.

** Platelet count should be collected before and at the time of surgery up to discharge as per standard hospital practice.

§ CKMB/troponin should be collected according to VARC-2 recommendations [1st at baseline prior to implantation, twice post procedure (starting at 12 -24 hours after, separated 6-8 hours apart) for 2nd and 3rd determination; and the 4th test should be at 72 hours post procedure or at hospital discharge whichever comes first] If post-procedure values are elevated, the test should be done daily until the values are declining) [1].

5 IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

5.1 SUMMARY DESCRIPTION AND INTENDED PURPOSE

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 surgically implanted flexible prostheses (stented and stentless biological valves). 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 reduced to a suitable size by loading it 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.

5.2 MANUFACTURER DETAILS

The Perceval valve is manufactured by:

- **Sorin Group Italia S.r.l.**
  Via Crescentino, sn – 13040 Saluggia (VC) ITALY
- **LivaNova Canada Corp.**
  5005 North Fraser Way, Burnaby – British Columbia V5J 5M1 CANADA

Sorin Group Italia S.r.l and **LivaNova Canada Corp.** are sister companies and part of LivaNova PLC. For increased manufacturing flexibility, the Perceval valve is manufactured in the two above mentioned manufacturing sites, with the same design, manufacturing process, sterilization method and intended use, as well as the same product codes identifying the device.

The accessories intended for use in association with the Perceval valve are manufactured by **Sorin Group Italia S.r.l.** in the facility identified above.

For this trial, the Perceval valve can be used from both manufacturing facilities.

5.3 MODEL AND TYPE

5.3.1 PERCEVAL HEART 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

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

5.3.2 PERCEVAL VALVE ACCESSORIES

The catalogue numbers (REF) of the accessories to be used in association with the Perceval valve are reported in **Table 2**

Table 2 Perceval valve accessories catalogue numbers

	PVS21 (size S)	**PVS23 (size M)**	**PVS25 (size L)**	**PVS27 (size XL)**
Sizer set	ICV1219			
Dual Collapser base	ICV1232			
Dual Collapser	ICV1235		ICV1236	
Dual Holder (1)	ICV1242		ICV1243	
Dual MICS Holder (2)	ICV1244		ICV1245	
Smart Clip	ICV1268			
Post-dilation catheter (1)	ICV1148	ICV1149	ICV1170	ICV1234
MICS Post-dilation catheter (2)	ICV1216	ICV1217	ICV1218	ICV1241

(1) Indicated for sternal approaches
(2) Specifically indicated for Minimally Invasive Cardiac Surgery

The Perceval valve single-use accessories (Dual Collapser, Dual Holder/Dual MICS Holder with Smart Clip, Postdilation catheter/MICS Postdilation catheter) are also supplied as accessory kits, as detailed in the **Table 3** below.

Table 3 Single-Use Accessory Kit Table

Single Use Accessory Kits REF	Single Use Accessory Kits Content	PVS21	PVS23	PVS25	PVS27
ICV1345(1)	ICV1235 Dual Collapser ICV1242 Dual Holder ICV1148 Post-dilation Catheter	X			
ICV1346(1)	ICV1235 Dual Collapser ICV1242 Dual Holder ICV1149 Post-dilation Catheter		X		
ICV1347(1)	ICV1236 Dual Collapser ICV1243 Dual Holder ICV1170 Post-dilation Catheter			X	
ICV1348(1)	ICV1236 Dual Collapser ICV1243 Dual Holder ICV1234 Post-dilation Catheter				X
ICV1349(2)	ICV1235 Dual Collapser ICV1244 Dual MICS Holder ICV1216 MICS Post-dilation Catheter	X			
ICV1350(2)	ICV1235 Dual Collapser ICV1244 Dual MICS Holder ICV1217 MICS Post-dilation Catheter		X		
ICV1351(2)	ICV1236 Dual Collapser ICV1245 Dual MICS Holder ICV1218 MICS Post-dilation Catheter			X	
ICV1352(2)	ICV1236 Dual Collapser ICV1245 Dual MICS Holder ICV1241 MICS Post-dilation Catheter				X

(1) Indicated for sternal approaches
(2) Specifically indicated for Minimally Invasive Cardiac Surgery

5.4 DEVICE TRACEABILITY

Information about valves that will be used per randomization assignment and/or the actual valve implanted for the enrolled subjects will be collected and documented by the sites including all the following, but not limited to:

- Valve manufacturer
- Valve size
- Valve serial number

5.5 DETAILED DESCRIPTION OF THE INVESTIGATIONAL DEVICE AND IMPLANT PROCEDURE

5.5.1 INVESTIGATIONAL DEVICE DESCRIPTION

Perceval valve is a bioprosthetic heart valve made of bovine pericardium, stabilized in a buffered glutaraldehyde solution and assembled on a nitinol stent. The device is indicated for the replacement of a damaged or malfunctioning native heart valve in humans via traditional surgery.

The product is designed to be anchored to the implant site without the use of sutures. This sutureless technique is achieved by the nitinol stent, which has the dual role of valve support and anchoring to the aortic root. The stent has two cylindrical ring elements on the distal (outflow ring) and proximal (inflow ring) ends, with a double set of struts connecting the two rings. The first set comprises straight struts to support the valve. The second set comprises sinusoidal struts protruding from the cylindrical section to anchor the prosthesis to the aortic root in the sinus of Valsalva. The nitinol stent is coated with a thin film of turbostratic carbon (Carbofilm™).

The design of the Nitinol stent allows compression of the device to a reduced diameter in the pre-positioning phase. As a result, positioning is simplified and a-traumatic. Subsequent release allows the nitinol stent to self-expand to a final diameter conforming to the aortic root.

The stent is sized to allow coupling to the aortic root, from the native annulus area to the sinotubular junction, and is designed so that the various structural elements do not interfere with blood flow. The ability of the released stent to apply a moderate radial force to the internal wall of the implant site allows stable anchoring of the device to surrounding tissue.

The functional component is made of two pericardium sheets shaped according to a patented process. The pericardium tissue is selected and then fixed in a glutaraldehyde-based process in which the stabilizing agent reacts under dynamic conditions. The first functional sheet has the form of three valvular cusps arranged to allow the blood to flow in only one direction. The second sheet is the connecting element between the leaflets of the first sheet and the stent.

The valve is set into the nitinol stent by overstitching the valve tissue to the inflow ring around the circumference and axially to the straight struts. The thread used to assemble the bioprosthesis is also coated with Carbofilm™.

The inflow ring of the valve is designed with an external bovine pericardium collar encouraging adaptation to the aortic annulus. In correspondence with each valve sinus, the inflow ring has three button holes through which guide threads are passed to aid prosthesis positioning.

The prosthesis is treated for the elimination of aldehyde residues to minimize calcium deposition and stored in a buffered solution without aldehydes.

5.5.2 SURGICAL PROCEDURE

Surgical procedure for implantation of Perceval valve is detailed in the IFU (Appendix 2).

5.6 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 trial protocol. The study will only be executed in those countries where the valve has obtained regulatory approval and is commercially available. In order to ensure appropriate physician and site participation the following criteria have to be met

5.6.1 SITE SELECTION CRITERIA

Sites selected to participate in this trial

- Preoperative CT-Scan done as routine practice
- Must have at least 2 physicians proficient with Perceval valve implant
- Capability to have trained people to perform basic neurological assessment preoperatively, postoperative and at follow up.
- Must have sufficient infrastructure to conduct a clinical trial

- Must have capability and proficiency to use Electronic Data Capture system (EDC)

5.6.2 INVESTIGATOR SELECTION CRITERIA

The selected investigators to participate in this trial:

- Must be experienced in the implantation of a stented aortic bioprosthetic valve and Perceval valve
- Must have implanted a minimum of 25 to 50 Perceval valves at the time of trial start
- Must be experienced in thoracic and cardiovascular surgical approaches (e.g. mini-sternotomy)
- Must have experience in clinical trials execution and knowledge of GCP

Before participating in the trial, all investigators must agree to respect and fulfill the terms of this investigational plan and sign off the Investigator Agreement.

6 JUSTIFICATION FOR THE DESIGN OF THE CLINICAL INVESTIGATION

6.1 PRE-CLINICAL TESTING

The Perceval valve is an approved commercial device in the chosen participating sites. Thus, all the pre-clinical testing both in-vitro and in-vivo have been submitted to regulatory bodies as part of registration process.

6.2 AVAILABLE CLINICAL DATA

From April 2007 to February 2008 a Pilot trial 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 patients were 73% of the enrolled population and the mean age was 80.4±3.8 years. The patients were followed for 5 years and at the latest follow up 22 patients were alive with a freedom from death of 71.31%. No incidence of stroke, dislodgment or structural valve deterioration were reported [15]. 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 Trial – V10801" was designed to confirm the safety and performance results of the first trial in a larger patient population at 3-6 months post-implantation. From January 2009 to January 2010 a total of 150 consecutive patients (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. The one year data was presented at the 63rd International Congress of the European Society of Cardiovascular and EndoVascular Surgery (ESVCS), in 2014. At 3-6 months, mean trans-valvular systolic gradients were 9.3 and 9.1 mmHg, with EOA of 1.60±0.45 and 1.64±0.39 cm2 respectively. At 12 months, 93% of the patients were in NYHA class I or II. Three early, non-valve related deaths (2.1%) were reported. Two cases of neurological stroke occurred, one of them in the early period. No postoperative migration or dislodgement of the valve occurred. The one year freedom from reoperation and from endocarditis was 94.7% and 96.7% respectively. In 2010, the CAVALIER trial was started. The trial was designed to evaluate the safety and effectiveness of the Perceval valve with an extended indication in terms of patient age and preoperative mortality risk score. From February 2010, through September 2013, 658 patients (mean age 78.3 years; 40% octogenarians; 64.4% females; mean STS score 7.2) underwent sutureless AVR in 25 European centers. The one year data of the CAVALIER trial were presented at 95th annual meeting of the American Association for Thoracic Surgery (AATS) in April 2015. The trial showed that the overall 1-year cardiac mortality, stroke and valve-related reoperation occurred in 4.5% (28), 3.0% (19), and 1.9% (12) patients, respectively. Endocarditis occurred in 1.4 % (9) patients and major paravalvular leak in 0.6% (4) patients. No valve thrombosis, migration or structural valve deterioration occurred.

The pooled results of the three trials have been published by Shrestha et al. [16]. The three studies recruited 756 patients (mean age 78.5 years; 68.1% female) in 25 sites among Europe. In the early period, overall mortality rate were 3.4%; stroke events occurred in 1.2% of the patients; 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.

A European Multicenter trial on 314 patients (mean age 77.9 years; 60.2% female) was published by Rubino et al. [14] with a mean follow-up of 1.1 years. The authors reported that Perceval valve was successfully implanted in

all but 1 patient (99.7%). Severe paravalvular leak occurred in 2 patients (0.6%). In-hospital mortality was 3.2% (1.4% after isolated procedure, and 7.4% after concomitant coronary surgery). One-year survival was 90.5%. Freedom from valve-related mortality, stroke, endocarditis, and reoperation was 99.0%, 98.1%, 99.2%, and 98.3%, respectively.

Dalén et al. [17] reported a multicenter trial comparing aortic valve replacement trough full sternotomy with stented valve and minimally invasive approach using Perceval valve. Propensity score based matching resulted in 171 pairs with similar baseline characteristics. The 30-day mortality was 1.8% in the mini-sternotomy sutureless group and 2.3% in the full sternotomy stented group (P = 0.706). Aortic cross-clamp and cardiopulmonary bypass time were shorter in the mini-sternotomy sutureless group. Two-year survival was 91% in patients who underwent mini-sternotomy with sutureless bioprosthesis, and 93% in patients who underwent full sternotomy with stented bioprosthesis.

In a German single center trial published by Pollari et al. [13], 82 patients receiving a Perceval valve were compared through propensity score match with patients receiving traditional valve. Among the two groups there were no differences in terms of hospital death. Aortic cross-clamp, cardiopulmonary bypass, and operation times were significantly shorter in the sutureless group ($p < 0.001$). Patients in the sutureless group required blood transfusion less frequently, shorter intensive care unit stay, hospital stay, and intubation time. Overall survival was 96.8%, and freedom from valve-related death was 99.4%. No differences were observed in sutureless compared with the stented population in survival, whereas freedom from valve-related death was 100% vs. 98.7% (p=0.31), freedom from stroke was 98.8% vs. 97.5% (p=0.55), freedom from endocarditis was 100% vs. 98.7% (p= 0.31), and freedom from reoperation was 100% vs. 98.7% (p =0.31).

Finally, a metanalysis performed by Phan at al. [11] reported that AVR with sutureless valves resulted in shortened CPB and cross-clamp times, thereby facilitating minimally invasive approaches as well as concomitant cardiac surgery for high-risk patients. Current short-term clinical evidence indicates similar mortality and complication rates compared to standard AVR, with satisfactory hemodynamic performance.

6.3 HEALTHCARE ECONOMICS

Perceval is a bioprosthetic valve designed to replace a diseased native or malfunctioning prosthetic aortic valve via open heart surgery with the unique characteristic of allowing sutureless anchoring at the implant site.

For this reason Perceval is thought as a possible cost-saving treatment compared with standard aortic valve replacement in adult population with severe aortic stenosis and in adult patients with moderate AS in a concomitant CABG operation: a quicker and easier implant which reduces cross clamping time would limit drawbacks associated to longer surgical operations with a positive impact on OR utilization and reduced hospitalization length of stay, rehabilitation and incidence of adverse events. Even complexity associated with Minimally Invasive Cardiac Surgery, poor visualization and difficult deployment of the valve, seem offset by Perceval Sutureless valve which would allow a facilitated and fast positioning of the valve. These advantages improve patients' health and limit the resource use which has a relevant impact on costs savings from Hospitals, local authorities and National Health System's perspective.

Literature shows the positive impact of reduced CCT [18], [19]. The relatively easy and quick implantation allowed by Perceval valve, by reducing the CCT, would in turn lead to:

1. Reduction of OR utilization
2. Shorter ICU hospital length of stay
3. Quicker rehabilitation period

Economic benefits of Perceval, when compared to traditional valves seem to originate from two value levers:

1. Reduction of cross-clamp time. Al-Sarraf et al. [18] and Ranucci et al. [19] have identified cross-clamp time as an independent predictor of cardiac morbidity.
2. Delivery of Perceval in a Minimally Invasive setting. Studies that have assessed the clinical advantages of using MICS versus conventional AVR can also be used to make an economic argument. Economic benefits of MICS originate from fewer complications and faster recovery time that are reflected in reduced time in intensive care and reduced overall hospital stay

Concerning delivery of Perceval in a Minimally Invasive setting, studies that have assessed the clinical advantages of using MICS versus standard AVR can also be used to make an economic argument. Economic benefits of MICS originate from fewer complications and faster recovery time that are reflected in reduced time in intensive care and reduced overall hospital stay.

Starting from these findings, a model (Pradelli *et al. [20])* was developed to calculate the impact of adding the benefits of MICS to the benefits of reducing cross clamp time in AVR using Perceval. The adopted perspective is the hospital perspective and the valve acquisition costs have not been considered in the following analysis.

This model relies on the effects on the outcomes that were significantly influenced by cross clamp times according to Al-Sarraf et al [18] and by the technique according to different MICS studies:

- ICU length of stay
- Total hospital length of stay
- Renal complication rate
- Blood loss and bleeding
- Ventilation time

The usage of Perceval shows consistent savings both for isolated and concomitant AVR. Savings are mainly originated by shorter ICU and hospital length of stays and by shorter surgery time.

The model results show that the incremental cost due to the adoption of new technology can be offset by savings from a reduced resources consumption of the other most relevant key cost drivers: ICU length of stay and ward length of stay. The additional clinical benefits of a reduced risk of severe complications and the additional value of a faster and easier implant will be sustainable for the health care systems and will potentially allow a more efficient use of resources for the hospital.

In line with the predictions of the model, empirical evidence suggests relevant cost savings of Perceval compared with traditional AVR from a hospital payer perspective:

- A retrospective observational study was carried out to compare Perceval compared with traditional AVR in a hospital in Nuremberg, Germany (Pollari *et al [13]).* The authors highlight that not only the resource consumption profile is favorable for Perceval, but as well the hospital costs per patient are lower for Perceval vs. the traditional valves. Perceval showed 25% costs savings compared with traditional AVR.
- A further observational retrospective study is available in favor of Perceval from a costs-savings perspective. In particular a retrospective comparative study (Laborde *et al [21]).* has been implemented with 65 patients implanted with traditional aortic valves (T) and 65 patients treated with the sutureless aortic prosthesis Sorin Group Perceval (P). Data were collected in the period between January 2010 and December 2012. Sutureless aortic valves present shorter procedural times and lower hospital costs compared with traditional valves, with higher cost savings at increased age and risk. More precisely, the mean cardiopulmonary bypass and aortic cross-clamp times in the T group were 80±41 min and 58±26 min vs. in the P group 39±16 min and 26±10 min ($p < 0.0001$). When adjusted for the imbalance in patient characteristics, mean costs savings of P compared with T are €3350 ($p=0.13$), mainly driven by the hospital stay costs. Savings between the P group and the T group increased with age: €4992 in patients aged 70-79 and €9326 in patients aged 80+ years old and with risk (€4296 for high risk patients).
- Another retrospective observational study was carried out to compare Perceval with traditional AVR in a hospital in Leuven, Belgium (Bart Meuris M.D. *[22])* The authors conclude that, in spite of a cohort with higher risk patients, *"As a result of a less invasive surgery for the patient, Perceval has shown a consistent and solid optimization of resources (Operating Room utilization, transfusions, ICU and ward stay)"*. A more recent extended analysis[144] concluded that *"In a population of elderly intermediate-risk patients, the shortened cross-clamp times and CPB-times, as obtained with the sutureless Perceval S bioprosthesis, result in a favorable effect on the postoperative recovery and use of resources when compared to a standard bioprosthesis"*. Identified savings of Perceval when compared with traditional AVR have been of 27%

Despite health economic simulation and real world evidence shows the cost savings associated to Perceval compared with traditional AVR, the limited number of patients involved in the analysis would require a stronger evidence with a larger number of patients involved in the comparison between Perceval and traditional AVR such as this current trial.

To be able to confirm the cost-minimization profile of Perceval, when compared to standard traditional valves, a resource consumption index has been developed within the frame of this study: such index, which could predict the total cost of aortic valve replacement, is independent from unit costs specific to each country/hospital. This index, called Normalized Consumption Index – together with its reduced version, the reduced Normalized Consumption Index - and the details of calculation and validations are described in Appendix 3.

7 OBJECTIVES AND HYPOTHESES OF THE CLINICAL INVESTIGATION

7.1 PRIMARY OBJECTIVE

The primary objective of this trial is to test the safety and efficacy of Perceval versus standard sutured stented bioprosthetic aortic valves among the intended trial population. The primary objectives will be assessed using the primary endpoint described in section 8.5.8.

7.2 SECONDARY OBJECTIVE

The main secondary objective is to compare all relevant device and subject demographics, procedural and hospital discharge, short and long term follow-up data as described in the secondary endpoints section (§ 8.5.8).

8 DESIGN OF THE CLINICAL INVESTIGATION

8.1 TRIAL TYPE

This is a prospective, randomized, stratified non blinded multi-center, international, post market trial assessed in a non-inferiority study.

The trial has a flexible sample size that will be determined adaptively. The trial will enroll up to 1234 subjects, but accrual may stop earlier at approximately 900 or 1050 subjects (see section 10.2). These subjects will be enrolled at approximately 60 worldwide investigational sites where the device is commercially available. Regardless of the sample size selected, follow up of subjects will continue annually up to 5 years. The primary endpoint will be reached at 1 year FU and, consequently, the planned primary analysis will be performed 12 months following the end of accrual.

8.2 RATIONALE FOR USE OF COMPARATORS

Aortic valve replacement is considered the gold standard for treatment of severe symptomatic aortic valve stenosis [2, 3]. For this clinical trial, the comparator will be other commercially approved standard biological sutured stented valves, both bovine and porcine. The choice of the comparator tissue valve will be at the discretion of the participating investigators. Mechanical valves required life-long anticoagulation treatment, increasing the risk of hemorrhagic and/or thromboembolic events. Thus, to avoid the introduction of a bias this prosthesis has been excluded.

8.3 PREOPERATIVE CT-SCAN

In current contemporary cardiac surgery practices, preoperative cardiac CT-scan is routinely done in the majority of cases to aid an appropriate surgical planning (including TAVI) for aortic valve replacement [2]. This standard diagnostic imaging modality allows optimal patient preparation and evaluation of anatomical characteristics such as the position of the aorta, measurement of the annulus, and presence of calcification [2]. Moreover CT-Scan will allow preoperative determination of the presence of aneurismal dilation, dissection of the ascending aortic wall, and presence of congenital bicuspid valve. All this information allows the surgeon to choose the appropriate valve size and surgical approach (i.e. appropriateness of minimally invasive approach). CT-scan will be performed in order to plan a possible mini-sternotomy in order to visualize the anatomical position of the aortic valve which will

influence the length of the mini-sternotomy (3rd or 4th intercostal space) and also the anatomical position of the aorta (midline or displaced to the right side). Detecting the presence of extensive calcification of the aorta can influence the site of aortic cross-clamping and whether a median sternotomy will be more appropriate.
For this randomized trial the included population will undergo a standard cardiac CT-scan prior to randomization. The minimum required measurement to be collected and reported are, but not limited to: aortic annulus diameter (short axis and long axis), LVOT diameter, STJ diameter, sinus of Valsalva diameter, ascending aorta diameter, aortic root height. In case of renal insufficiency a non-contrast injected CT-scan of the aorta can be performed. Standardized CT manufactured software for dimension measurement software tolls can be used or generally available software like (i.e. 3-Mensio) is recommended

8.4 PREOPERATIVE AND POSTOPERATIVE NEUROLOGICAL EXAMINATIONS

8.4.1 NATIONAL INSTITUTE OF HEALTH STROKE SCALE (NIHSS)

The National Institutes of Health Stroke Scale (NIHSS) is a systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit. The NIHSS was originally designed as a research tool to measure baseline data on patients in acute stroke clinical trials. Now, the scale is also widely used as a clinical assessment tool to evaluate acuity of stroke patients, determine appropriate treatment, and predict patient outcome. The NIHSS is a 15-item neurologic examination stroke scale used to evaluate the effect of acute cerebral infarction on the levels of consciousness, language, neglect, visual-field loss, extraocular movement, motor strength, ataxia, dysarthria, and sensory loss. A trained observer rates the patient's ability to answer questions and perform activities. Ratings for each item are scored with 3 to 5 grades with 0 as normal, and there is an allowance for untestable items. A NIHSS of zero indicates a normal evaluation whereas higher numbers indicate increasing impairment and severity. Trained clinical personnel (e.g. neurologist, qualified health care professional) will be asked to determine whether there is a change in the NIHSS from the baseline discharge and up to one year visit and if this change is because a suspected stroke. The use of this score will allow a more objective assessment of the incidence of stroke as part of primary endpoint of this trial.

8.4.2 MODIFIED RANKIN SCALE

The modified Rankin Scale is a commonly used scale for measuring the degree of disability or dependence in the daily activities of people who have suffered a stroke or other causes of neurological disability. The scale runs from 0-6, running from perfect health without symptoms to death. Trained clinical personnel (e.g. neurologist, qualified health care professional) will be asked to determine the status of the patient and report the value of the scale. The use of this score will allow assessment of the grade of stroke according to the proposed guidelines [1]

8.5 SUBJECTS POPULATION

8.5.1 INTENDED POPULATIONS AND INDICATIONS IN THE PROPOSED CLINICAL INVESTIGATION

All subjects with severe symptomatic aortic stenosis or steno-insufficiency who are candidates for surgical replacement of their native aortic valve according to established guidelines [2, 3] in current medical practice and as specified in the Perceval valve IFU (Appendix 2) are the intended population for inclusion in this randomized

trial. Right mini-thoracotomy is not allowed as a surgical approach due to limited experience within the surgical community and/or suitability with the comparator standard valve.

8.5.2 INCLUSION CRITERIA

Subjects who meet all the following criteria will be included:

1. The subject has an indication for treatment by valve replacement with a bioprosthesis according to the IFU, through either full sternotomy or mini-sternotomy.
2. The subject has aortic valve disease that can be treated with a commercially available Perceval valve size, based on preoperative CT-scan.
3. The subject has:
   a) critical aortic valve area defined as an initial aortic valve area of ≤1.0 cm2 or aortic valve area index < 0.6 cm^2/m^2

   AND

   b) Mean gradient > 40mmHg or Vmax > 4m/sec by resting echocardiogram or simultaneous pressure recordings at cardiac catheterization [or with dobutamine stress, if subject has a left ventricular ejection fraction (LVEF) <55%] or velocity ratio < 0.25;
4. The subject is symptomatic due to aortic stenosis with functional class of NYHA II or higher.
5. The subject has signed the informed consent.
6. The subject is of legal minimum age.
7. The subject will be available for postoperative follow-up beyond one year.

8.5.3 EXCLUSION CRITERIA

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

1. The subject has a contraindication for treatment by the Perceval valve or by a bioprosthetic aortic valve as stated in the IFU.
2. The subject has aneurismal dilation or dissection of the ascending aortic wall.
3. The subject is scheduled for concomitant procedures other than CABG, myectomy with or without aortic annulus enlargement
4. The subject has congenital bicuspid (i.e. Sievers type 0) or unicuspid aortic valve.
5. Anatomical structures not suitable for Perceval valve such as: aortic root enlargement, where the ratio between the diameter of the sino-tubular junction and the annulus diameter is > 1.3.
6. The subject has a prosthetic heart valve in any position, including mitral valve repair.
7. The subject has a stroke or myocardial infarction (STEMI and NSTEMI) within 30 days prior to the planned valve implant surgery.
8. The subject has active endocarditis, myocarditis, or sepsis.
9. The subject is in cardiogenic shock manifested by low cardiac output and needing hemodynamic support.
10. The subject is allergic to nickel alloys.
11. The subject is already included in another clinical trial that could confound the results of this clinical investigation.

8.5.4 CRITERIA FOR SUBJECT RANDOMIZATION

Randomization will occur once

a) subject has met all inclusion criteria without any exclusion criteria
b) subject has been determined eligible for the trial through preoperative CT-scan and echocardiographic assessment,
c) subject has received the appropriate and mandatory information about the trial,
d) informed consent form has been obtained and signed.

8.5.5 CRITERIA FOR SUBJECT TERMINATION

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

- The exclusion from the trial is required for the subject's safety;
- Relevant Ethics Committee and/or regulatory authority withdraw approval(s)
- The subject decides to withdraw from the trial
- The subject is deemed lost to follow up

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

8.5.6 POINT OF ENROLLMENT

Subjects will be considered enrolled in the trial after all inclusion and exclusion criteria have been met and informed consent has been obtained (informed consent form dated and signed). The investigator is responsible for screening all potential subjects and selecting the ones meeting the inclusion/exclusion criteria.
All screened subjects should be recorded in a screening log, including the reason why the subjects were not deemed eligible for the trial.

For subjects who have been enrolled but who do not undergo randomization or do not undergo the protocol-required procedures, the signed informed consent and documentation must be maintained in the site files. No follow-up is needed.

Only those subjects with an assigned randomization code (through the electronic randomization process) will be included in the randomized trial.

8.5.7 RANDOMIZATION

Only subjects who have undergone standard chest CT-scan to determine if the aortic stenosis can be replaced with an available Perceval valve (size), and is potentially suitable for mini-sternotomy, may be randomized. For each subject the randomization will be performed based on the randomization list after enrollment and before valve operation, specifically after CT scan and surgical approach ("full sternotomy" or "mini-sternotomy") has been determined, to minimize bias.

Subjects will be randomly assigned in equal numbers (1:1) to one of two treatment arms. The blocked randomization list will be performed before the study start .The randomization will be stratified with 2 stratification factors, by country and by surgical approach (full sternotomy" or "mini-sternotomy").

8.5.8 TRIAL ENDPOINTS DEFINITION AND ASSESSMENTS

The primary endpoint will be evaluated in a non-inferiority setting, with statistical hypothesis tests formally defined in section 10.

Primary endpoint

The primary endpoint is freedom from MACCE (composite endpoint of all cause death, myocardial infarction, stroke, and valve re-intervention) at one year based on CEC adjudication.

The definitions of each component endpoint are reported in the **Table 4** below, complete definitions can be found in Appendix 4.

Table 4 Definitions of the single endpoint of MACCE

Endpoint	Definition
All cause of death	Total number of deaths regardless of cause (cardiovascular mortality + non cardiovascular mortality)
Myocardial infarction	Myocardial injury as specified in VARC-2 [1]
Stroke	Stroke is defined as an acute episode of focal or global neurological dysfunction caused by the brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. A stroke may be classified as ''undetermined" if there is insufficient information to allow the categorization as ischemic or hemorrhagic.
Valve Re-intervention	Any re-intervention, including a transcatheter valve implant, on the implanted aortic valve bioprosthesis after surgical closure of the chest.

Secondary endpoints

1. Surgical time
    a. Cross clamp time during index procedure
    b. Cardiopulmonary bypass time during index procedure
2. Normalized Consumption Index and reduced Normalized Consumption Index, including resource consumption items such as (but not limited to):
    a. Operative room time,
    b. Duration of ICU/CCU and total hospital stay
    c. Incidence of specific serious adverse events as defined in Appendix 3
    d. Blood transfusion(s)
3. Quality of life questionnaire
    a. At 1 month and 1 year post surgery
4. Intraprocedural and periprocedural serious adverse events regardless of relationship with the device within 72 hours.
5. All valve and procedure relevant serious adverse events as specified in VARC-2 guidelines [1] (Appendix 7)
    a. Early safety at 30 days
    b. Clinical efficacy after 30 days
    c. Time related valve safety: SVD, endocarditis, thrombosis, thromboembolic events (excluding stroke), and bleeding annually up to 5 years
6. Serious device related adverse events up to 5 years
7. Freedom from MACCE at 2, 3, 4 and 5 years of follow up
8. Pacemaker implantation and cause up to 1 year
9. Valve hemodynamics (PPM, PPG, MPG; DVI, EOA, LVOT, AI, PVL, EROA) assessed by site-reported echocardiographic parameters preoperatively, at discharge, between 1-3 month, 1 year, 3 year and 5 year.
10. Valve hemodynamics (PPM, PPG, MPG, DVI, EOA, LVOT, AI, PVL, EROA) in a reduced cohort of patients assessed by core lab echocardiographic parameters preoperatively, at discharge, between 1-3 month, 1 year, 3 year and 5 year.

8.5.9 SUB STUDIES

CT-scan

The collection of the data with the preoperative CT-scan for surgical planning will allow a direct comparison of the measurement done using this imaging system and the measurement done with dedicated valve sizers. Once the aorta of the subject is exposed, the aortic annulus is measured by a standard universal sizers (e.g. Hegar dilator) and the valve's specific sizers. These measurements will allow assessment of the concordance of the aortic annulus size determined by CT-scan with the valve size implanted; and allow a comparison of hemodynamic parameters based on the true annulus size independent of the prosthetic size.

Echocardiography sub-study (Participating Centers Only)

In addition to the echo parameters collected for all the subjects, one fourth (approximately 300 patients) of the trial population will have a complete echocardiographic examination that will be sent to a Core Lab for independent evaluation of the hemodynamic performance in the two treatment groups. At selected centers all patients will be recruited with the agreement to perform the echocardiographic assessment as required by the study guidelines.

The MedStar Health Research Institute, located at MedStar Washington Hospital Center, Washington D.C., USA will serve as the echo Core Laboratory for this clinical trial. Neil J. Weissman, MD and Federico Asch, MD will serve as the Core Laboratory principal investigators.

For this subgroup of subjects the echocardiographic examination is planned at hospital discharge, at the 1-3 month visit, and at the 1, 3 and 5 years visits.

The Core lab may request for the submission of a test echo performed according to the TTE protocol to verify completeness and ensure compatibility, readability prior to enrolling the first subject.

Each postoperative TTE should include all the views and measurements specified on the Site Echo Case Report Form and the echocardiographic protocol (Appendix 5). A copy of the examination will be recorded and will be sent to the Echo Core Laboratory.

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

Pacemaker evaluation

A sub-study is established for all the patients who will have received a permanent pulse generator, defined as permanent pacemaker or defibrillator, implanted. All the available ECGs of these patients will be collected and evaluated by an independent Core Lab analyzing the cause of the implant. The following variables at minimum, will be collected: clinical indication and relationship with the device, timing from heart valve surgery, correlation of clinical indication with ECGs findings by the Core Lab and pulse generator functionality (e.g. evolution and percentage of pacing) at one year.

8.6 SUBJECTS NUMBER AND TRIAL PERIOD

8.6.1 TOTAL EXPECTED DURATION OF THE CLINICAL INVESTIGATION

The trial plans for an inclusion period of approximately 30 months at approximately 60 international sites where the Perceval is commercially available. Subjects will be followed for 5 years. Total study duration of approximately 7,5 years is expected.

8.6.2 EXPECTED DURATION OF EACH SUBJECT'S PARTICIPATION

Subjects will be evaluated at screening, at discharge visit following prosthesis implant, between one and three months, at 1 year, and annually up to 5 years.

8.6.3 NUMBER OF SUBJECTS REQUIRED TO BE INCLUDED IN THE CLINICAL INVESTIGATION

The number of subjects to be enrolled in the trial will be adaptively determined. Accrual may stop after approximately 900, 1050, or 1234 subjects, including an attrition rate between enrolled and per-protocol population of 10%.

8.7 PROCEDURES

8.7.1 CLINICAL TRIAL RELATED PROCEDURES

All qualified personnel performing selection, implantation and/or follow-up procedures must be trained on the trial protocol. The trial devices should be used in accordance with the corresponding instructions for use.

Detailed instructions on the type and process of data to be collected for the study and how to fill in the eCRFs will be provided to the Investigators during dedicated meetings.

Screening & enrolment

Subjects must be informed about the study including the potential risks and benefits prior to enrollment. Only those subjects who voluntarily provided written informed consent to participate, in a timely manner will be eligible for enrollment.

The following procedures must be conducted BEFORE inclusion:

- Determination of patient eligibility for biological standard surgical aortic valve replacement.
- Echo examination to asses severity of aortic stenosis (e.g. blood flow velocity, EOA)
- CT-scan
- Evaluate subject eligibility based on the inclusion and exclusion criteria. The source documents that demonstrate conformance with all inclusion and no exclusion criteria must be retained at the investigational site in order to allow Source Data Verification (SDV) during the monitoring process.
- Obtain the subject's medical history
- Perform relevant physical examination
- Obtain the subject's current medications

- Determine subject's NYHA classification
- Obtain a written informed consent

The following procedures must be conducted AFTER inclusion (informed consent) of the subject in the trial

- Collect blood sample if not standard of care
- 12-lead Electrocardiogram (ECG) if not standard of care
- Questionnaire for quality of life (EQ5D)
- Determine subject's STS score and EuroSCORE II if not standard of care
- Determine modified Rankin scale and NIHSS scores

Operative evaluation

The Perceval valve is designed to be anchored in the native annulus using a sutureless technique. The IFU of the Perceval valve is provided in Appendix 2
Information collected during the implant will be recorded on the Operative Case Report Form. These data will include (but not limited to) and will be collected within the eCRF:

- Implant details including surgical approach and valve information
- Surgical procedure including insertion and sizing
- Valve lesion type, pathology, and etiology
- Surgical procedural information
- Concomitant procedures
- Subject outcome
- Cardiac rhythm

It is required that a transesophageal echocardiogram (TEE) be performed to verify the performance of the valve after implantation. Intraoperative TEE is a routine part of the standard of care in management of valve patients. The results of the TEE should be recorded in the hospital patient files and dedicated eCRF.

Hospital Discharge

The hospital discharge data will be collected and entered in the eCRF preferably before the subject is discharged. The following data listed below will be collected:

- ICU information
- Subject status
- Physical evaluation
- Modified Rankin Scale and NIHSS assessments
- Medications
- Blood sample (including WBC, RBC, hemoglobin, hematocrit, platelet count, serum LDH, haptoglobin, reticulocyte count, plasma free hemoglobin, serum creatinine, serial cardiac marker enzymes (CK-MB/Troponin) and coagulation data)

- All available platelet counts should be collected from surgery day to hospital discharge per hospital standard practice.
- Serial cardiac markers are to be collected in the perioperative (72 hour) time frame.

- 12-lead electrocardiogram (ECG)
- Echocardiographic examination (TTE) measured at investigational site (MPG; PPG, EOA, DVI, PVL)
- Serious adverse events as defined in section 17

1 month (QOL questionnaire - EQ5D)

The Quality of Life questionnaire should be completed out by the subject at 30 days ± 7 days. This timeline is intended to ensure that the completion of QOL questionnaire will be performed by the subject himself. The information should be submitted to the site during the 1-3 months visit.

1 to 3 months Follow up visit

Follow-up evaluations are to be conducted in an office, hospital or clinic setting and are to be performed by the Principal Investigator or designee between 30 and 90 days. If the subject has been seen at another health care facility, the site is to make every effort to obtain the data required for the trial (including copies of source documents) from the subject's physician (referring or General Practitioner) in the offsite location. All efforts should be made to ensure that the subject returns to the outpatient clinic.

- Subject status (including NYHA functional classification)
- Physical evaluation
- Medications
- 12-lead electrocardiogram (ECG)
- Modified Rankin Scale and NIHSS assessments
- Blood sample (including WBC, RBC, hemoglobin, hematocrit, platelet count, serum LDH, haptoglobin, reticulocyte count, plasma free hemoglobin, serum creatinine and coagulation data)
- Echocardiographic examination (TTE) measured at investigational site (MPG; PPG, EOA, DVI, PVL)
- Serious adverse events (as reported in section 17) including all hospitalizations

1 year FUP visit

This visit is for the evaluation of the primary endpoint and is intended to be done as a clinic visit at 1 year ± 1 month after the day of the surgery. Follow-up evaluations are to be conducted in an office, hospital or clinic setting and are to be performed by the Principal Investigator or designee. If the subject has been seen at another health care facility, the site is to make every effort to obtain the data required for the trial (including copies of source documents) from the subject's offsite physician. All efforts should be made to ensure that the subject comes to the outpatient clinic.

The following data listed below are to be collected:

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

- 12-lead electrocardiogram (ECG)
- Modified Rankin Scale and NIHSS assessments
- Blood sample (including WBC, RBC, hemoglobin, hematocrit, platelet count, serum LDH, haptoglobin, reticulocyte, plasma free hemoglobin, serum creatinine and coagulation data)
- Questionnaire for quality of life (recommended)
- Echocardiographic examination (TTE) measured at investigational site (MPG; PPG, EOA, DVI, PVL)
- Serious adverse events (as reported in section 17) including all hospitalizations

2 year FUP visit

This visit is intended to be done between 2 years ± 1month after the day of the surgery. Follow-up evaluations are to be conducted in an office, hospital or clinic setting and are to be performed by the Principal Investigator or designee. If the subject has been seen at another health care facility, the site is to make every effort to obtain the data required for the trial (including copies of source documents) from the subject's offsite physician. For this visit telephone follow up is acceptable to collect the clinical information.

The following data listed in **Table 5** below are to be collected according to the type of visit:

Table 5 Data to be collected at 2 year visit according to the type of visit.

Data to be collected	Phone call visit	Outpatient visit
Subject status (including NYHA functional classification)	X	X
Medications	X	X
Blood sample (including WBC, RBC, hemoglobin, hematocrit, platelet count, serum LDH, haptoglobin, reticulocyte, plasma free hemoglobin, serum creatinine and coagulation data)		X
Modified Rankin Scale		X
12-lead electrocardiogram (ECG)		X
Serious adverse events (as reported in section 17) including all hospitalizations	X	X

3 year FUP visit

This visit is intended to be done as clinic visit between 3 years ± 1month after the day of the surgery. Follow-up evaluations are to be conducted in an office, hospital or clinic setting and are to be performed by the Principal Investigator ordesignee. If the subject has been seen at another health care facility the site is to make every effort to obtain the data required for the trial (including copies of source documents) from the subject's offsite physician. All efforts should be made to ensure that the subject comes to the outpatient clinic.

The following data listed below are to be collected:

- Subject status (including NYHA functional classification)
- Physical evaluation
- Medications
- Modified Rankin Scale

- Blood sample (including WBC, RBC, hemoglobin, hematocrit, platelet count, serum LDH, haptoglobin, reticulocyte, plasma free hemoglobin, serum creatinine and coagulation data) – recommended
- 12-lead electrocardiogram (ECG) – recommended
- Echocardiographic examination (TTE) measured at investigational site (MPG; PPG, EOA, DVI, PVL)
- Serious adverse events (as reported in section 17) including all hospitalizations

4 year FUP visit

This visit is intended to be done between 4 years ± 1month months after the day of the surgery. Follow-up evaluations are to be conducted in an office, hospital or clinic setting and are to be performed by the Principal Investigator or designee. If the subject has been seen at another health care facility, the site is to make every effort to obtain the data required for the trial (including copies of source documents) from the subject's offsite physician. For this visit telephone follow up is acceptable to collect the clinical information. .

The following data listed in **Table 6** below are to be collected according to the type of visit:

Table 6 Data to be collected at 4 year visit according to the type of visit.

Data to be collected	Phone call visit	Outpatient visit
Subject status (including NYHA functional classification)	X	X
Medications	X	X
Blood sample (including WBC, RBC, hemoglobin, hematocrit, platelet count, serum LDH, haptoglobin, reticulocyte, plasma free hemoglobin, serum creatinine and coagulation data)		X
Modified Rankin Scale		X
12-lead electrocardiogram (ECG)		X
Serious adverse events (as reported in section 17) including all hospitalizations	X	X

5 year FUP visit

This visit is intended to be done as clinic visit between 5 years ± 1month after the day of the surgery. Follow-up evaluations are to be conducted in an office, hospital or clinic setting and are to be performed by the Principal Investigator or designee. If the subject has been seen at another health care facility moved, the site is to make every effort to obtain the data required for the trial (including copies of source documents) from the subject's offsite physician. All efforts should be made to ensure that the subject comes to the outpatient clinic.

The following data listed below is to be collected:

- Subject status (including NYHA functional classification)
- Physical evaluation
- Medications
- Modified Rankin Scale
- Blood sample (including WBC, RBC, hemoglobin, hematocrit, platelet count, serum LDH, haptoglobin, reticulocyte, plasma free hemoglobin, serum creatinine and coagulation data) – recommended
- 12-lead electrocardiogram (ECG) – recommended

- Echocardiographic examination (TTE) measured at investigational site (MPG; PPG, EOA, DVI, PVL)
- Serious adverse events (as reported in section 17) including all hospitalizations

9 RISKS AND BENEFITS OF THE INVESTIGATIONAL DEVICE AND CLINICAL INVESTIGATION

9.1 ANTICIPATED CLINICAL BENEFITS

In a subject with symptomatic severe aortic stenosis, the most obvious 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. The use of a sutureless valve is expected to result in a reduced aortic cross-clamp and perfusion times. Reduction in cross clamp time is expected to translate into other clinical benefits such as less bleeding, less incidence of renal failure, and lower in-hospital MACCE; as well as lower cost of in-hospital and procedural resources.

9.2 ANTICIPATED ADVERSE DEVICE EFFECTS AND RESIDUAL RISK

The risks associated with the use of the Perceval valve are not expected to exceed the frequency or severity of those reported with the implant of other aortic bioprosthetic valves. The Perceval valve has been an approved commercial device in the Countries of the chosen participating sites. Therefore all the anticipated adverse device effect and risk analysis have been submitted to regulatory bodies as part of standard registration processes.

Unanticipated adverse device effects can occur and will be handled as described in Paragraph 17.2.

9.3 RISKS ASSOCIATED WITH PARTICIPATION IN THE CLINICAL INVESTIGATION

There are no foreseen additional risks to the enrolled subjects since this is a post market trial evaluating commercially approved devices in both arms using standard of care clinical practice.

9.4 STEPS THAT WILL BE TAKEN TO CONTROL OR MITIGATE THE RISKS

To protect the welfare of subjects, ethics committee and/or competent authority approval of the investigation will be obtained for each site prior to the first implant at that site following local regulatory rules.

Training will be provided to the investigators and their staff to ensure that the protocol and all relevant (study) processes is understood and applied.

Each investigator must have signed an Investigator Agreement stating his/her responsibility to conduct this trial according to this investigational plan, to adhere to the records and reporting requirements, and to supervise use of the investigational device.

An independent Data Safety Monitoring Board (DSMB) will be established to monitor the safety of the subjects, and the overall conduct of the trial. This board could give recommendations to the Sponsor regarding stopping/continuing enrollment in the trial as warranted.

Risks can also be minimized through compliance with the protocol, using the devices in accordance with their applicable Instructions for Use, 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.

9.5 RISK-TO-BENEFIT RATIONALE

Subjects randomized to the investigational arm may have the benefits associated with a shortened cross-clamp time due to Perceval valve implantation. The trial will allow for an investigation of these benefits in comparison to standard aortic valve prosthesis, which has not been done before in a randomized fashion.

10 STATISTICAL CONSIDERATIONS

The study statistical design includes an adaptive sample size.
The study plans for the following statistical analyses:

- Interim analyses for accrual stopping: these analyses will be conducted by an Independent Statistical Unit (ISU) composed by external statistical personnel not involved in the study conduct at the time when approximately 900 and 1050 patients are enrolled in the study;
- Primary statistical analysis: this analysis will be performed by Sponsor personnel once all the subjects complete their 12 month follow-up and the study database will be locked;
- Follow-up statistical analyses: these analyses will be performed by Sponsor personnel once per year once all the subjects complete their 2, 3, 4, and 5 year follow-up and the study database will be locked;
- Analyses for the Data Safety and Monitoring Board (DSMB): these analyses will be produced according to the DSMB charter (Section 11.3).

The statistical analyses will be performed as mentioned in this protocol and detailed in the Statistical Analyses Plan (SAP). The SAP will be finalized prior to any interim analyses for sample size selection.

10.1 STATISTICAL DESIGN, METHOD AND ANALYTICAL PROCEDURES

10.1.1 PRIMARY ANALYSIS

The primary endpoint to assess the safety and efficacy of Perceval valve versus standard sutured stented valves is the freedom from MACCE (composite endpoint of all cause death, myocardial infarction, stroke, and valve re-intervention) at one year based on CEC adjudication (see section 11.4).

The primary analysis will compare Perceval valve (Treatment arm) vs. standard sutured stented valve (Control arm) on the Per Protocol population.

A one-sided non-inferiority test, using the non-inferiority margin Δ=0.05, will be performed to compare the two arms on the proportion of subjects that are event-free at one year (primary analysis). The null hypothesis is that the Perceval arm is inferior to the Control arm in the primary endpoint:

- H_0: $MACCE_{CONTROL} - MACCE_{PERCEVAL} \geq \Delta$
- H_1: $MACCE_{CONTROL} - MACCE_{PERCEVAL} < \Delta$

where $MACCE_j$ is the one-year event-free rate for arm j.
The primary analysis will calculate the Bayesian posterior probability that the difference (CONTROL – PERCEVAL valve) in the primary endpoint is lower than 0.05 (predetermined non inferiority margin):

$$Pr(MACCE_{CONTROL} - MACCE_{PERCEVAL} < 0.05 \mid Data)$$

The null hypothesis will be rejected, and non-inferiority concluded, if the posterior probability exceeds 0.9775 at the final analysis. This threshold was selected based on simulations (see Appendix 8) to control the Type I error rate at 2.5% (one-sided).
The arms are modeled independently on the log-odds scale:

$$\theta = \log\left(\frac{p}{1-p}\right)$$

with θ ~ Normal(1.99, 3^2) and p the proportion of subjects that are event-free at one year. When converted back to the probability scale, this prior is centered at 0.88, the expected event-free rate for the control arm. Full details of the adaptive design, including simulations, are described in the separate Appendix 8.

Superiority will be tested if non-inferiority is met. This superiority test is nested hierarchically within the non-inferiority comparison and is a closed-testing procedure, thus no alpha adjustment is required. The Bayesian posterior probability of superiority Pr($MACCE_{CONTROL}$ < $MACCE_{PERCEVAL}$ | Data) will be assessed in the Per Protocol population will be provided. Superiority will be claimed if:

$$Pr(MACCE_{CONTROL} < MACCE_{PERCEVAL} \mid Data) > 0.9775.$$

Non-inferiority will be assessed in the Per Protocol population as primary analyses [23, 24]. Sensitivity analyses on the primary endpoints will be performed using different assumptions and populations (section 10.1.4)

10.1.2 INTERIM ANALYSES FOR SAMPLE SIZE SELECTION

Two interim analyses will be performed to select the sample size. These interims will be triggered when the number of subjects enrolled will be approximately 900 and 1050 (interim analyses cut-off dates). The study will stop accrual for expected success if the posterior probability of non-inferiority in the Per Protocol population is sufficiently high. The threshold varies by interim with the earliest interim having highest threshold versus the second one. Thus, accrual will stop if the posterior probability exceeds 0.996 at N=900 or 0.993 at N=1050.
The analysis will be conducted by the external Independent Statistical Unit who will communicate to the Sponsor the result of the interim analysis and the consequent decision on the continuation of enrollment (i.e. “Stop enrolment for predicted success”, “Continue enrolment”).
As the interim analyses will only determine whether accrual needs to be stopped, then the interim analyses decisions have no impact on the subsequent study conduct. Therefore subject follow up will continue up to 5 years and the primary analysis will take place at the 12-month primary analysis.

10.1.3 INTERIM ANALYSIS IMPUTATION MODEL

At the time of each interim analysis, there will be subjects eligible for Per Protocol analysis population whose one-year outcome is unknown (e.g. ongoing subjects not having yet reached the one-year visit). For this reason at the interim analysis an imputation model will be used for their final PP status according to these rules:

- Any subjects that are missing the one-year outcome, but are known to have a MACCE event at an intermediate visit, will have their one-year outcome imputed as “not MACCE-free”.
- Any subjects that are missing the one-year outcome but have not had a MACCE event at an intermediate visit will have their one-year outcome imputed, using multiple imputation. The probability that a subject remains MACCE-free at one year, conditional on being MACCE-free as of their last known visit, follows a Beta-Binomial distribution. A non-informative Beta(1,1) priors, separately within each arm is going to be applied. Additional details are provided in the separate Appendix 8.

10.1.4 SENSITIVITY ANALYSES

The primary analysis will be assessed in sensitivity analyses using different assumptions and populations:

- the proportion of subjects that are event-free at one year will be estimated by means of a logistic regression model including as covariates the implanted valve groups (Perceval or standard sutured stented valves) and the stratification factors (country and surgical approach). This method allows to assess the sensitivity of non-inferiority results to possible confounding impact of the stratification factors.
  A 97.5% one-sided upper confidence limit will be computed from the logistic model for the difference ($MACCE_{CONTROL} - MACCE_{PERCEVAL}$). The non-inferiority of Perceval to the Control will be confirmed if the upper confidence limit is lower than 0.05. This sensitivity analysis of non-inferiority will be assessed in the Per Protocol Population.
- the one-year freedom from MACCE will be evaluated using the Kaplan-Meier estimates for cumulative freedom from MACCE and the Greenwood standard errors for each arm (as originally planned). A 97.5% one-sided upper confidence limit will be computed for the difference ($MACCE_{CONTROL} - MACCE_{PERCEVAL}$) where $MACCE_j$ is the survival estimated by the Kaplan-Meier algorithm for arm j. The Perceval arm will be confirmed not inferior to the Control if the upper confidence limit is lower than 0.05 (Δ).
  The test statistic is

$$\frac{\mathrm{MACCE}_{\mathrm{PERCEVAL}} - \mathrm{MACCE}_{\mathrm{CONTROL}} + \Delta}{\sqrt{\mathrm{VAR}(\mathrm{MACCE}_{\mathrm{PERCEVAL}}) + \mathrm{VAR}(\mathrm{MACCE}_{\mathrm{CONTROL}})}}$$

  where VAR()s are the variances estimated by Greenwood's formula [25]. The null hypothesis will be rejected if the test statistic is greater than 1.96. This sensitivity analysis of non-inferiority will be assessed both in Per Protocol and modified Intention To Treat populations in order to confirm the robustness of results to statistical method and protocol deviations.

10.1.5 SECONDARY ANALYSIS

Each component of the MACCE composite endpoint will be analyzed as proportion of subjects event-free at one year and their 95% C.I. will be reported. In addition, the primary endpoint will be analyzed by means of time-to-event methods (see section 10.1.6) as secondary analysis. For the Cox regression model, the stratification factors (country and surgical approach) and pre-operative variables (including demographic, medical history, and concomitant procedures) will be taken into account. All data collected up to cutoff date will be used for the time-to-event analysis.

Surgical times and Normalized Consumption Index endpoints will be analyzed in a superiority context. A one-sided superiority test will be conducted comparing the treatment and control group at discharge using appropriate regression models to account for stratification factors.

The serious adverse events will be assessed using descriptive statistics. Number of events and number of patients with at least one event will be presented in each group broken down by AE type. Number of events, as well as number and percentage of patients will be tabulated by timing (before / on or after intervention according to VARC-2 definitions). In case of some adverse events occur before intervention, they will be listed separately.

Number of events, as well as number and percentage of patients with at least one event will be reported overall and by treatment group in the Enrolled population, ITT population and Safety population.

Analysis on the secondary endpoint (section 8.5.8) will be detailed and defined in the Statistical Analysis Plan.

10.1.6 SUMMARY STATISTICS

Descriptive statistics will be calculated using as reference the number of subjects in the relevant analysis population (any exception will be specified) according to the nature of each parameter as follows:

- For quantitative (continuous) parameters: Number of subjects with available and missing data, mean, standard deviation (SD), median, quartiles (Q1-Q3) and extreme values [Minimum; Maximum];
- For qualitative (discrete) parameters: Number of subjects and frequency (percentage);
- For Time-to-event variables: Cumulative freedom from events will be evaluated using the method of Kaplan-Meier. The degree of uncertainty in each actuarial analysis will be expressed with 95% confidence limits. The 95% confidence interval bounds for the cumulative freedom will be calculated per the method proposed by Greenwood [25]. Comparison of curves among arms will be performed with the log-rank test. Kaplan-Meier graphs will be presented along with the number of patients-at-risk at exact time points. Covariate analyses will be based on the proportional hazards model. Arms will be compared using multivariate Cox proportional hazards regression. The hazard ratio (95% C.I.) will be presented.
- For Bayesian analyses: posterior means, standard deviations, and 95% credible intervals will be reported.

10.2 SAMPLE SIZE, LEVEL OF SIGNIFICANCE AND POWER

Total sample size for this trial will be adaptively determined through interim analyses. The sample size will be approximately 900, 1050, or 1234 subjects.

The sample size is based on the analysis of primary endpoint: assessing non-inferiority of Perceval valve arm compared to the control in terms of one year freedom from MACCE (composite endpoint of all cause death, myocardial infarction, stroke, and valve re-intervention) based on CEC adjudication,

Based on CAVALIER experience, propensity score matched studies [12, 13, 17, 26] and, GARY registry [27] the freedom from MACCE composite endpoint is expected to be similar for both arms.

The original sample size of 1234 patients was based on CAVALIER experience which reported a freedom form MACCE at 1 year equal to 88%.

Blinded review of the data for the ongoing current trial (database snapshot December 2017) estimated the pooled one year MACCE-free rate across arms at 91%, showing an overall primary endpoint higher than originally assumed. Due to this reason, 1234 patients may lead to an overpowered study and a smaller sample size may be required to demonstrate study objectives. In order to adapt the sample size to the real study performance an adaptive design has been included in the study protocol.

Table 7 summarizes the overall operating characteristics of the design over a range of assumptions for the true underlying MACCE-free rate on control ($MACCE_{ctrl}$) and treatment ($MACCE_{PERCEVAL}$). Pr(success) is the proportion of simulated trials achieving success at the final analysis. Thus, when the truth is that the treatment arm is exactly at the non-inferiority margin, Pr(success) is the Type I error. Otherwise Pr(success) is the power. E[N] represents

the mean sample size across simulated trials, reflecting an average over some trials that stop with N = 900, some at N = 1050, and others at N = 1234.

Simulations indicate that the adaptive design is able to control the Type I error and Power of the study while looking for the most appropriate sample size. In fact, under the expected assumption of equivalent arms with 91% MACCE-free rate, the trial has approximately 80% power, the type I error rate is controlled to 2.5% one-side and the average sample size is reduced to approximately 1129.

The adaptive design is fully described in Appendix 8 along with additional summaries of the operating characteristics.

Table 7 Overall operating characteristics

True $MACCE_{ctrl}$	True $MACCE_{PERCEVAL}$	True Effect	Pr(success)	E[N]
0.88	0.83	−0.05	0.025	1228.7
	0.88	0.00	0.704	1148.9
0.91	0.86	−0.05	0.023	1228.8
	0.91	0.00	0.805	1128.7

The level of significance of tests performed on secondary endpoints will be set at 0.05 two-sided.

10.3 EXPECTED DROP-OUT RATES

The considered attrition rate from enrollment to Per Protocol population will be 10% of subjects, which may include, but is not limited to subjects with failure to implant, lost to follow-up and discontinued subjects.

10.4 SPECIFICATION OF ANALYSIS SETS

The “Enrolled population” will include all enrolled subjects.

10.4.1 INTENTION-TO-TREAT (ITT) POPULATION

Intention-to-treat (ITT) population will include all randomized subjects. Subjects will be allocated to treatment group based on the treatment to which they were randomized (“as randomized” principle).

10.4.2 MODIFIED ITT

The “modified Intention-To-Treat Population” (mITT) will include all randomized subjects (corresponding to the ITT population) who receive a study valve (Perceval or standard sutured stented valve). All the efficacy analyses will be performed on this population as key sensitivity analysis. Subjects will be allocated to treatment group based on the treatment to which they were randomized (“as randomized” principle).

10.4.3 SAFETY POPULATION

Safety population will include all randomized and implanted subjects evaluated based on the treatment actually received.

10.4.4 PER-PROTOCOL (PP) POPULATION

Per-protocol (PP) population consists of subjects without major protocol deviations and attending the scheduled follow-up visits up to 1 year at minimum. The PP population will be evaluated in terms of primary and secondary objectives.

10.5 TERMINATION CRITERIA ON STATISTICAL GROUNDS

In case of, (but not limited to)

- Unanticipated Adverse Device Effect (UADE) presents an unreasonable risk to subjects
- Recommendation from DSMB (e.g. significant safety concerns)

The Sponsor based on a Steering Committee recommendation may take the necessary steps including the revision of the sample size, which may have an impact on the trial duration, suspension or premature termination of the trial.

If the trial is terminated early, the Sponsor will provide a written statement to the Investigators to enable prompt notification of the ECs/IRB. If the trial enrollment is terminated, the follow-up visits will continue for all enrolled subjects.

10.6 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 trial in a section 'Changes in the conduct of analyses from protocol', including the rationale of changes.
Deviations from the original statistical plan are unlikely. However, should they occur, they would have to be reported in the final study report.

10.7 SPECIFICATION OF SUBGROUPS FOR ANALYSIS

Any sub-group analysis will be defined before the execution of statistical analysis is performed and will be defined in the Statistical Analysis Plan.

10.8 TREATMENT OF MISSING DATA

Primary analysis is planned on PP population, so no missing data are expected.
During the interim analyses for sample size selection, missing data for subjects that are ongoing will be handled as described in Section 10.1.3.
For other statistical analysis, the missing data for prematurely withdrawal purpose could be replaced by an appropriate method and described in the SAP. These statistical analyses with an estimation of missing data could be performed as additional supportive analyses and could be conducted on some endpoints if relevant to assess the effect of missing data on the statistical analysis.

10.9 MINIMUM AND MAXIMUM NUMBER OF SUBJECTS TO BE INCLUDED PER CENTER

This trial will in principle apply the rule of competitive enrollment. A minimum number of around 8 patients by center is recommended. No maximum number is defined but a balanced number of patients is required to avoid over representation of a few centers. Depending on timelines and total number of sites participating a including center might be stopped enrolment if a certain level of patients included.

11 CLINICAL TRIAL COMMITTEES

11.1 STEERING COMMITTEE

A Steering Committee will be established to assist the Sponsor in designing and managing the trial based upon scientific, medical and technical experience and expertise and providing advice on modifications or amendments to the protocol. The committee is comprised of recognized experts in cardiac surgery, including the principal investigators, investigators from participating sites and/or clinical experts not directly involved in the clinical trial operating committee. The Steering Committee will provide oversight of the study and recommend processes and procedures to ensure timely and accurate data collection, data quality. The Steering Committee will also support site selection process and make recommendations about participating centers. A named member of the Sponsor's clinical affairs department will be part of the Steering Committee as a nonvoting member. The named members of the Steering Committee are listed in **Table 8**

Table 8 Named members of Steering Committee

Theodor Fischlein, M.D.	Steering committee Chairman and Principal investigator
Roberto Lorusso, M.D.	Co-Principal Investigator
Thierry Folliguet, M.D	
Malakh Shrestha, M.D.	
Bart Meuris. M.D	
Eric Roselli, M.D.	
Sara Gaggianesi, DMV	Sponsor nonvoting member

11.2 OPERATING COMMITTEE

An Operating Committee will be established as a selected group of the Steering Committee and will provide more day to day recommendations to the Sponsor (maximum 4 members). The committee will comprise at minimum the Steering Committee chairman and 3 other Steering Committee members. The Operating Committee will meet more frequently as the Steering Committee and convene (likely by conference call) on a regular basis to provide recommendations on day-to-day decision needed for efficient operation of the trial.

11.3 DATA SAFETY MONITORING BOARD

A Data Safety Monitoring Board (DSMB) will be established for this trial. The members of the DSMB will be independent from the Sponsor and the trial investigators. This board will be blinded to the actual treatment arms and will consist of at least three members including but not limited to: a cardiothoracic surgeon, a cardiologist with an expertise in echocardiography, and a biostatistician. The DSMB is responsible for monitoring the safety and well-being of the subjects participating in the trial, ensuring the scientific integrity of the trial, and recommending action items based on safety issues including trial termination as warranted. The DSMB is independent form the SC and CEC.

The general operating procedures are outlined in the DSMB Charter.

11.4 CLINICAL EVENTS COMMITTEE

A Clinical Events Committee (CEC) will be established for this trial. The members of the CEC will be independent of the Sponsor, the trial investigators, and the DSMB. The committee will be composed of physicians with expertise in the following fields, but not limited to: cardiothoracic surgery, cardiology, echocardiography, and neurology. 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:

- Endpoint event: deaths, stroke, myocardial infarction, valve re-intervention and explantation for any cause, and other clinical endpoints according to clinical trial 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 (USADE)
- Other serious adverse events as requested by the Sponsor.

The definitions and classifications for the major primary endpoint are summarized in the **Table 9** below:

Table 9 Primary endpoint definitions and classifications

Clinical Endpoint	Definition /Classification [1]
Death cardiovascular	Any of the following criteria: a) Death due to proximate cardiac cause (e.g., myocardial infarction, cardiac tamponade, worsening heart failure) b) Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease c) All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure d) All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related events e) Sudden or un-witnessed death f) Death of unknown cause
Death non-cardiovascular	Any death other than cardiovascular death

Table 9 Primary endpoint definitions and classifications

Clinical Endpoint	Definition /Classification [1]
Stroke	An acute episode of focal or global neurological dysfunction caused by the brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. The diagnostic criteria and classifications per VARC-2 [1] criteria and subsequent VARC recommendations will be applied: **Stroke classification by cause:** ○ Ischemic Stroke ○ Hemorrhagic stroke ○ Undetermined
Ischemic Stroke	An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue
Hemorrhagic stroke	An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage
Myocardial infarction	**Periprocedural MI (72 h after the index procedure)** ○ New ischemic symptoms (e.g., chest pain or shortness of breath), or new ischemic signs (e.g., ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q-waves in at least 2 contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality) AND ○ Elevated cardiac biomarkers (preferable CK-MB) within 72 h after the index procedure, consisting of at least 1 sample postprocedure with a peak value exceeding 153as the upper reference limit for troponin or 53 for CK-MB.* If cardiac biomarkers are increased at baseline (>99th percentile), a further increase in at least 50%postprocedure is required AND the peak value must exceed the previously stated limit **Spontaneous MI (>72 h after the index procedure):** ○ Detection of rise and/or fall of cardiac biomarkers (preferably Troponin) with at least 1 value above the 99th percentile URL, together with myocardial ischemia as evidenced by at least 1 of the following: ○ Symptoms of ischemia ○ ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)] or New pathological Q-waves in at least 2 contiguous leads ○ Imaging evidence of a new loss of viable myocardium or new wall motion abnormality ○ Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. ○ Pathological findings of an acute myocardial infarction"

Table 9 Primary endpoint definitions and classifications

Clinical Endpoint	Definition /Classification [1]
Valve reintervention	Any surgical or percutaneous interventional catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted prosthesis or repaired valve (i.e. after surgical closure of index valve implantation). Note: Additional interventions performed during the index valve implantation procedure before surgical closure are not considered re-interventions.

Every effort will be made to blind the CEC to the treatment arms. The detailed operating procedures are outlined in the CEC Charter. A system and process will be put in place to ensure timely adjudication of the events.

12 TRAINING

The Clinical Project Manager or his designee will ensure that the participating sites will receive the necessary training needed for appropriate trial conduction. This training may include GCP training if necessary and can only be provided by dedicated and experienced staff. This might be Sponsor or Sponsor delegated staff. The training materials will be filed at the site and in the trial master file. Training forms must be completed.

13 DATA MANAGEMENT

13.1 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 trial database.

Site staff will need to enter trial 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. The EDC is linked to a Clinical Data Management System (CDMS).

The investigator is responsible for reviewing all CRF 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 investigator 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.

At the time of each interim analysis (see section 10.1.2), an interim soft lock will be performed by the Clinical Data Manager: the data exported from the EDC system will be accessible only to the Clinical Data Manager and to the ISU delegated by the Sponsor to perform the interim analysis.

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

13.2 PROCEDURES FOR VERIFICATION, VALIDATION, 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.

14 TRIAL MONITORING

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

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

The Sponsor monitoring procedures will be defined in a specific monitoring plan referring to responsibilities related to the trial, including but not limited to site initiation, routine monitoring, in-house quality control, trial 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 trial.

The monitoring plan will be available under separate cover.

15 PROCEDURES RELATED TO AMENDMENTS TO THE CLINICAL INVESTIGATIONAL PLAN

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 competent authorities or ethical committee will be documented. Administrative update is defined as changes that will not impact the safety and well-being of the subjects nor the scientific value of the trial. Examples include the following but not limited to: change in the name of people responsible for the trial conduction as defined in section "names and addresses", possible change in the legal entities or name of the Sponsor, and formatting or grammar edits.

16 DEVIATIONS FROM CLINICAL INVESTIGATION PLAN

Except under emergency circumstances, the investigator is not allowed to deviate from the protocol. Deviations to investigational plan that are decided by the investigators to protect the rights, safety and well-being of human subjects shall be documented and reported to the Sponsor as soon as possible.

16.1 PROTOCOL DEVIATIONS

Investigators of the trial 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 should occur 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 Steering Committee (SC). The final decision about the seriousness will be taken by the SC.
Major deviations are defined as changes in the conduct of the trial different from what is specified in the protocol that may potentially compromise the subject's rights, safety, and well-being, or the completeness, accuracy, reliability, or scientific integrity of the trial data. Accrual of major deviations by a site may lead to no further participation within the study as reported in section 18.3.

Major and minor deviations will be validated before data lock and prior to the statistical analysis being performed.

16.2 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 will be put in place by the Sponsor.
If the site fails to implement corrective actions or in case of continued non-compliance, the Sponsor may decide to discontinue enrollment at the site or prematurely discontinue the site from the trial.

17 ADVERSE EVENTS, ADVERSE DEVICE EFFECTS AND DEVICE DEFICIENCIES

The Sponsor is responsible for the ongoing safety evaluation of the investigational device, review of reported adverse events, investigation of unanticipated serious adverse device effects, and notification of regulatory authorities per applicable requirements. The Sponsor is also responsible for training the investigational staff prior to start the trial on any trial-related procedures, including reporting of Serious Adverse Events.
The Sponsor, through the Clinical Safety Office, will provide oversight of general AE handling procedures for the clinical trial and can assist the investigators and various committees in conducting a medical review of reported serious adverse events.

The investigator is responsible for ensuring the safety and well-being of the subjects enrolled in their clinical sites and should report events to the Sponsor, Ethics Committees, and regulatory bodies as described in this section.

17.1 DEFINITIONS

Adverse events definitions are derived from ISO 14155, 2011 - Clinical investigation of medical devices for human subjects. The definitions of the following terms can be found in Appendix 4

- Major Adverse Cardiac and Cerebrovascular event - MACCE
- Serious Adverse Event – SAE
- Serious Adverse Device Event - SADE
- Unanticipated Serious Adverse Device Effect – USADE
- Unanticipated Adverse Device Effect – UADE
- Adverse Event – AE
- Adverse Device Event - ADE
- Device deficiencies

17.2 INVESTIGATOR'S RESPONSIBILITIES IN AE REPORTING

a) The Principal investigator is required to report the following serious adverse events to the Sponsor:
   - All MACCE (deaths, MI, Stroke and valve re-intervention) and USADEs throughout the trial duration up to 5 years.
   - All other serious adverse events up to 5 years including: structural valve deterioration, non-structural valve dysfunctions, endocarditis, thromboembolic events, and valve thrombosis.

Table 10 Adverse Events Reporting to the Sponsor

	Subject Visit					
	Point of enrollment	**Implant**	**Discharge**	**Late Post-op (1-3 Mo.)**	**1 Year (11-13 Mo.)**	**Annual Follow-up**
All Deaths, USADE, SAE	x	X	X	X	X	X

The following timelines for reporting should be followed (**Table 11**):

- Unanticipated Serious Adverse Device Effects (USADE) should be reported to the Sponsor immediately within 24 hours by notifying the Sponsor Clinical Project Manager and by entering the information in the EDC. These events require urgent investigation by the Sponsor and reporting to regulatory authorities, as applicable.
- Serious adverse events should be reported as soon as possible but no later than 3 calendar days upon awareness. The investigator should enter all available information in the SAE section of the EDC system.
- Device deficiencies should be reported within 3 calendar days of awareness. Deficiencies of the Sorin study device should be reported in the EDC. The investigator must return the device, if possible, to the Sponsor. Deficiencies of the non-Sorin study device should be reported following the commercial reporting procedure for that device.

Table 11 Timelines and Communication Methods for Reporting Serious Adverse Events

Event Classification	Communication Method	Communication Timeline
USADE	Contact Clinical Project Manager Complete AE eCRF page with all available information.	Within 24 hours of awareness
Serious Adverse Event including deaths and SADE Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities including labeling and packaging issues)	Complete AE eCRF page with all available information.	Within 3 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 trial
	Provide all relevant source documentation (unidentified) for reported event	When documentation is available
	Return device with deficiency, if possible.	Within 2 weeks of occurrence of deficiency.

b) The investigator should perform the following assessments for each reported serious adverse event:
   - Identify the clinical event term or description
   - Seriousness of the event
   - Relationship of the event to the device and/or procedure

c) The investigator should provide all the information needed to complete the AE CRF.

d) The Principal Investigator is responsible for informing the Ethics Committee, and regulatory authorities of serious adverse events as required by local/regional regulations.

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

17.3 EMERGENCY CONTACT DETAILS FOR REPORTING SAE AND SADE

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

17.4 SPONSOR REPORTING RESPONSIBILITIES

The Sponsor is responsible for reporting serious adverse event information to all participating investigators, Ethics Committee and regulatory authorities, as applicable following local regulations.

18 HANDLING OF TRIAL DISCONTINUATIONS

18.1 HANDLING OF SUBJECTS' TEMPORARY TREATMENT DISCONTINUATION OR TERMINATION

For all subjects reaching the end of the trial (completed 5 year visit, death, or explant) or in case of premature withdrawal as described in section 8.5.5 (lost-to-follow-up, or subject's decision) a trial termination form will be filled out in order to document the date and reason for discontinuation. Subjects who had their valves explanted will still have to be followed at least till 1 year primary endpoint.

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 attempts to make three contacts via phone, one certified letter should be sent to the subject's last known address. Phone contacts and copy of the letter must be documented/available in the subject's medical record .

18.2 HANDLING OF TRIAL TEMPORARY OR DEFINITIVE DISCONTINUATION

The Sponsor or regulatory authorities/EC may decide to suspend or prematurely terminate the trial. In this case, the Sponsor shall promptly inform the clinical investigators, the competent authorities and EC of the termination or suspension, the reason(s) why and the management (including a description of what measures were or will be taken to ensure the safety and the rights and welfare of currently enrolled subjects).

18.3 HANDLING OF SITE PARTICIPATION: TEMPORARY OR DEFINITIVE DISCONTINUATION

The Sponsor may decide to suspend or prematurely terminate the trial or terminate enrollment and remove all appropriate trial materials from the study site for the following reasons:

1. It becomes apparent that subject enrollment is unsatisfactory as to quality (violations of inclusion or exclusion criteria) or enrollment rate;
2. The completion of the CRFs is inaccurate, incomplete or considerably delinquent; and
3. There are repeated, uncorrected protocol deviations
4. Data quality or quantity not sufficient.
5. Upon recommendation of the DSMB or regulatory authorities/EC

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

If an investigator voluntarily decides to suspend or terminate participation in the trial, the reviewing EC and Competent Authorities must be notified of the termination, the reasons for the termination, including a description of what measures were or will be taken to ensure the safety and the rights and welfare of currently enrolled subjects.

18.4 CONSEQUENCES

18.4.1 SUBJECTS' DATA MANAGEMENT

In case of early trial/investigational site/subject suspension or termination, the Sponsor will consult with the Steering Committee but ultimately determine whether the enrolled subjects should be followed according to the clinical investigational plan or not. The decision will be documented and the investigator will be informed. For all randomized subjects, a study termination form will be completed. Subject's data will be collected and statistically treated according to the data-management plan defined previously.

19 ETHICAL AND REGULATORY STANDARDS

19.1 ETHICAL PRINCIPLES

This trial will be conducted in accordance with the latest version of the Declaration of Helsinki (Appendix 6), Good Clinical Practices defined in ISO 14155:2011 and data protection laws and pertinent individual country laws and regulations.

19.2 LAWS AND REGULATIONS

Appropriate submissions to relevant Ethics Committees and/or health authorities will be performed according to local regulations. The trial will not begin until necessary approvals have been obtained. Any additional requirements imposed by the EC or regulatory authority will be followed, as appropriate.

19.3 INFORMED CONSENT PROCESS

The patient's informed consent form contains 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, ISO 14155:2011, and any local regulations, as applicable. Date and time (if requested) must be clearly documented and must be before the patient was randomized.

Failure to obtain subject informed consent needs to be reported to the applicable regulatory authorities according to their requirements by either the site or the Sponsor

19.3.1 PROCESS FOR OBTAINING INFORMED CONSENT

The Investigator is encouraged to use the trial-specific Informed Consent Form (Appendix 1) supplied by Sponsor, translated into local language. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative. If an investigating center chooses to use an alternatively worded written consent document, the document must be reviewed by Sponsor to ensure that it meets all requirements before use by the center. The EC/IRB at each center must also approve the consent.

An Investigator (or other trial staff who are conducting the informed consent interview) have to explain the trial to the potential subject verbally, 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 should be provided with a written consent form and afforded sufficient time to consider whether or not to participate in the research. After allowing the potential subject time to read the consent form, an Investigator listed on the delegation of authority list should meet with the potential subject and answer any additional questions s/he may have. Once an individual has had all his/her questions answered and has agreed to participate in the clinical investigation, the investigator shall ask the subject to personally date and sign all required copies of the informed consent form.

It may be appropriate for the Investigator to sign after the subject if the Investigator needs to verify that basic eligibility criteria have been met. Patients participation to the study should be documented in the source documentations.

The Investigator's signature means that the informed consent process has taken place and the subject met the requirement to be recruited in the clinical investigation.

One copy of the signed informed consent form must be given to the subject and the other one filed at the investigational site.

The investigator 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 diary).

The consent form should be updated or amended whenever new information becomes available that may be relevant to the subject.

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

20 ADMINISTRATIVE RULES

20.1 CURRICULUM VITAE

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

20.2 DATA RETENTION PROCEDURES

The investigator will maintain, at the investigational site, in original format all essential trial documents and source documentation that support the data collected on the trial subjects in compliance with ICH/GCP guidelines. Data will be retained at least 15 years after trial closure, starting from the signature date of the trial report.

These documents will be retained for a longer period of time by agreement with the Sponsor or in compliance with other local regulations. It is the Sponsor's responsibility to inform the Investigator when these documents no longer

need to be maintained. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. If for any reason the Investigator 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.

21 CONFIDENTIALITY

Confidentiality of subjects' data and identity will be maintained throughout the trial and after.
All information and data sent to the Sponsor concerning subjects or their participation in this trial will be considered confidential by the Sponsor. Only authorized personnel of the Sponsor or a representative will have access to these confidential records. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this trial. Trial data collected during this trial may be used by the Sponsor for the purposes of this trial, publication, and to support future research and/or other business purposes. All data used in the analysis and reporting of this trial will be without identifiable reference to specific subject name.

22 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.

23 DATA PROTECTION

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

24 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 Company of Europe S.A.

25 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

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

26 CLINICAL TRIAL RESULTS

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

27 PUBLICATION POLICY

27.1 TRIAL RESULTS PUBLICATION

A separate publication plan will be issued which may be regularly updated according to the trial advancement.

27.2 PUBLICATION CONDITIONS

The agreement of the Sponsor is mandatory before any publication.

- Authors will be chosen among the Steering Committee and top recruiting centers based on the quality of the data provided (deviations)
- In case of co-investigators participating in the trial and belonging to the same center, only the Principal Investigator of the center is responsible to designate the name of the author (Principal Investigator or co-investigators) who will finally be included in the Authorship.
- 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.

28 LIST OF INVESTIGATORS

An updated list of investigators, investigation sites and potential institutions will be maintained by the Clinical Project Manager. The definitive list will be provided with the final clinical trial report.

29 BIBLIOGRAPHY

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30 APPENDICES

Appendix 1 - PATIENT INFORMED CONSENT FORM

Appendix 2 - INSTRUCTION FOR USE

Appendix 3 - NORMALIZED CONSUMPTION INDEX

Appendix 4 - DEFINITIONS

Appendix 5 - ECHOCARDIOGRAPHIC PROTOCOL

Appendix 6 - HELSINKI DECLARATION

Appendix 7 - VARC-2 PAPER

Appendix 8 - ADAPTIVE DESIGN: STATISTICAL METHODOLOGY AND OPERATING CHARACTERISTICS

Appendix 9 - CHANGE TO SYNOPSIS, PARAGRAPH 8.7, CHAPTER 10

APPENDIX 1:

PATIENT INFORMED CONSENT FORM

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ECHOCARDIOGRAPHIC PROTOCOL

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