ACURATE *neo*™ Aortic Bioprosthesis for Implantation using the ACURATE *neo*™ TA Transapical Delivery System in Patients with Severe Aortic Stenosis

Clinical Investigation Plan

Protocol Number: 2015-01

Version Number: 2

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08 SEP 2015

Statement of Compliance

INVESTIGATOR ENDORSEMENT PAGE

I, the undersigned, am responsible for the conduct of the study at this site and agree to the following:

- I understand and will conduct the study according to the protocol, approved protocol amendments, ICH, GCP and all applicable regulatory authority requirements and national laws;
- I will not deviate from the protocol without prior written permission from the Sponsor and prior review and written approval from the local and independent Ethics Committees, except where necessary to prevent any immediate danger to the subject;
- I have read and understand fully the Clinical Investigator Brochure, and I am familiar with the ACURATE *neo*™ Aortic Bioprosthesis and ACURATE *neo*™ TA Transapical Delivery System and their use according to this protocol;
- I have sufficient time to properly conduct and complete the trial within the agreed trial period, and I have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely;
- I will ensure that site personnel who are involved in the study conduct are adequately trained regarding ACURATE *neo*™ Aortic Bioprosthesis and ACURATE *neo*™ TA Transapical Delivery System, the present protocol and their responsibilities.

Name _____

Signature _____ *Date of Signature* _____

Signature Page

STUDY PRINCIPAL INVESTIGATOR SIGNATURE APPROVAL

I have read this protocol and I approve the design of this study:

Name: Prof. Dr. med. Thomas Walther 10.9.15

Signature *Date of signature*

SPONSOR SIGNATURE APPROVAL

I have read this protocol and I approve the design of this study:

Name: Pedro Eerdmans, CMO, Symetis S.A. 08 Sept 2015

Signature *Date of signature*

DATA MANAGEMENT SIGNATURE APPROVAL

I have read this protocol and I approve the design of this study:

Name: Charlene Braun, CPM, Symetis S.A. 08 sep 15

Signature *Date of signature*

SAFETY COORDINATOR SIGNATURE APPROVAL

I have read this protocol and I approve the design of this study:

Name: Kristine Dean, SO, Symetis S.A. 08 sep 2015

Signature *Date of signature*

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List of Abbreviations

AAn	Aortic Annulus
AAo	Ascending Aorta
AE	Adverse Event
aPTT	Activated Partial Tromboplastine Time
ASA	Aspirin
AS	Aortic Stenosis
AVA	Aortic Valve Area
AVR	Aortic Valve Replacement
BSA	Body Surface Area
CAD	Coronary Artery Disease
CBC	Complete Blood Count
CIB	Clinical Investigator's Brochure
CIP	Clinical Investigation Plan
CK	Creatine Phosphokinase
CK-MB	Creatine Phosphokinase – myoglobin (mitochondrial bands)
COPD	Chronic Obstructive Pulmonary Disease
Cr	Creatinine
CRF	Case Report Form
CRT	Creatinine
CSA	Clinical Study Agreement
CT	Computational Tomography
CV	Cardiovascular
D	Day
DAPT	Dual Antiplatelet Therapy
DC	Discharge
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
EOA	Effective Orifice Area
GCP	Good Clinical Practice
GI	Gastrointestinal
H	Hour
Hb	Hemoglobin
HOCM	Hypertrophic Obstructive Cardiomyopathy
IABP	Intra-aortic Balloon Pump
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICU	Intensive Care Unit
IFU	Instruction For Use
INR	International Normalized Ratio
LDH	Lactate Dehydrogenase

LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
M	Month
MI	Myocardial infarction
MMSE	Mini Mental State Exam
mRS	modified Ranking Scale
NIH	National Institute of Health
NIHSS	NIH Stroke Scale
NYHA	New York Heart Association
PCI	Percutaneous Coronary Intervention
PI	Principal Investigator
PIC	Patient Informed Consent
PO	Per Os (by mouth)
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RBC	Red Blood Count
QA	Quality Assurance
QC	Quality Control
QD	Each Day
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
STS*	Society of Thoracic Surgery
TA	Transapical
TA-AVI	Transapical Aortic Valve Implantation
TAVI	Transcatheter Aortic Valve Implantation
TAVR	Transcatheter Aortic Valve Replacement
TEE	Transeosophageal Echocardiogram
TF	Transfemoral
TF-AVI	Transfemoral Aortic Valve Implantation
TIA	Transient Ischemic Attack
TTE	Transthoracic Echocardiogram
UADE	Unexpected Adverse Device Effect
VARC 2	Valve Academic Research Consortium 2
VHD	Valvular Heart Disease
WBC	White Blood Count
Y	Year

* STS Predicted Risk of Mortality Score Calculator is available on line at www.STS.org

Clinical Investigation Plan Summary

Title:	ACURATE *neo*™ Aortic Bioprosthesis for Implantation using the ACURATE *neo*™ TA Transapical Delivery System in Patients with Severe Aortic Stenosis
Protocol #:	2015-01
Phase:	Pivotal study
Design:	A single arm, prospective, multicenter trial
Study Device:	ACURATE *neo*™ Aortic Bioprosthesis and ACURATE *neo*™ TA Transapical Delivery System
Population:	Patients with severe aortic stenosis where conventional aortic valve replacement (AVR) via open-heart surgery is considered to be high risk
Enrolment:	60 implanted patients. Up to 10 clinical sites in Germany and Switzerland
Study Duration:	Initial enrolment: Q4 2015 Last enrolment: Q3 2016 Last follow-up visit: Q3 2017 Last telephone check: Q3 2021
Patient follow-up:	Patient follow-up at 7 Days or discharge (whichever occurs first) and at 30 Days, 6 Months and 12 Months post-procedure Telephone annually up to 5 years post-procedure
Objectives:	To evaluate the safety and performance of the study device in patients presenting with severe aortic stenosis (AS) considered to be high risk for surgery
Endpoints:	*Primary safety:* Freedom from all-cause mortality at 6 Months *Primary device performance:* procedure success in absence of MACCE at 30 Days post procedure *Secondary:* Procedure success, device success at 7 Days/ Discharge, 30 Days, and at 6 Months and 12 Months follow-up, incidence of all cause mortality at 30 Days and 12 Months, the rate of clinical endpoints per VARC 2[1] at 30 Days, freedom from MACCE at 30 Days, 6 Months, 12 Months, functional improvement per NYHA classification and ECHO assessment of valve performance at 7 Days/ Discharge, 30 Days and at 6 and 12 Months follow-up.

[1] European Heart Journal (2012) 33, 2403–2418 doi:10.1093/eurheartj/ehs255

1 BACKGROUND INFORMATION & SCIENTIFIC RATIONALE

1.1 Purpose

The purpose of this investigation is to collect data pertaining to the safety and performance of the ACURATE *neo*™ Aortic Bioprosthesis as implanted with the ACURATE *neo*™ TA Transapical Delivery System. This device is intended for treatment of subjects with severe aortic stenosis (AS) who have high risk for conventional aortic valve replacement (AVR) surgery. The ACURATE *neo*™ Aortic Bioprosthesis is intended for use via minimally-invasive transapical implantation in a well-defined population.

The data of this investigation will be used to obtain market approval in Europe (CE mark) and Japan. The number of patients evaluated has been calculated taking into account the requests of the Notified Body.

1.2 Background Information / Literature Overview

1.2.1 Aortic Valve Stenosis: Prevalence & Etiology

Since the first descriptions of acquired calcified Aortic Stenosis (AS) by Stokes in 1845 and by Monckeberg in 1904, this disease has undergone a dramatic increase in incidence. It is the third most common cardiovascular disease after hypertension and Coronary Artery Disease (CAD) and the most common valve lesion, being present in 43% of all patients with valvular heart disease in the Euro Heart Survey on Valvular Heart Disease (VHD) [5]. AS is also the most common cause for Aortic Valve Replacement (AVR), accounting yearly for about 40’000 valve operations in Europe and 95’000 in the United States [1].

The abnormalities of aortic valve morphology and function represent the most common cardiac valve lesion, with relevant implications both for medical and surgical treatment. Particularly, aortic valve sclerosis (aortic valve thickening and calcification without pressure gradient) seems to affect about one fourth of adults over 65 years of age, while the AS is present in 2–9% of the general population over 65 years of age; an increased prevalence of both sclerosis and stenosis with ageing (respectively 48% and 14% in those over 85 years) is observed [2]. In the past, valvular heart diseases were typically caused by rheumatic heart disease, which remains a major burden in developing countries. However, in industrialized countries, rheumatic disease has fallen substantially [3] and residual valvular diseases are now mostly degenerative [4].

In the Euro Heart Survey on VHD [5] conducted at 92 centers in 25 countries, 5’000 adult patients were included with moderate to severe native VHD, infective endocarditis, or previous valve intervention. Enrolled patients were hospitalized in cardiology (43%) and surgical (19%) departments, or visited the outpatient clinic (38%).

AS was the most common valve abnormality (33.9% and 46.6% in the overall group and surgical subgroup, respectively). The etiology of AS was degenerative-calcific in the majority of patients (81.9%), while it was rheumatic in 11.2%, congenital in 5.6% and post-endocarditic in the remaining 1.3%. Among the 512 AS patients who underwent AVR, 54.3% were elderly (more than 70 years), 80% had a preserved left ventricular systolic function (left ventricular ejection fraction >60%) and 85% had symptoms of heart failure (NYHA class II-IV).

1.2.2 Aortic Valve Stenosis: Clinical Management

After the appearance of symptoms, AS is associated with a high rate of death if left untreated [1-5]. Surgical Aortic Valve Replacement (sAVR) is the reference treatment for symptomatic AS associated with symptoms or objective consequences such as LV dysfunction [6, 7]. Surgical AVR is proven to decrease symptoms and prolong survival in patients with severe, symptomatic AS. Low-risk patients at high volume centers show mortality at ~1% for isolated AVR. The average perioperative mortality reported from the recent Society of Thoracic Surgery (STS) database is 4.0% to 5.7% for isolated AVR and up to 6.8% for AVR combined with coronary bypass surgery. Recent publications from the STS database have shown that surgical mortality increases to 9.4% in patients >70 years old and 14.5% in patients >90 years old [8, 9].

Few therapies in cardiovascular medicine have become as accepted and standardized as this treatment. Indications for AVR are well defined in guidelines and there is a consensus that intervention should be advised in patients with severe, symptomatic AS [6]. The recently published “American College of Cardiology / American Heart Association (ACC/AHA) Guidelines for the management of patients with VHD” list four Class I recommendations for AVR in patients with severe AS: the presence of cardiac symptoms; concomitant coronary artery bypass graft surgery; concomitant surgery of the aorta or other heart valves; and left ventricular systolic dysfunction (ejection fraction less than 50%) [10].

However, even if AVR is the treatment of choice for symptomatic patients with severe AS, the decision to operate raises specific problems in the elderly, because of the increase in operative mortality and morbidity and today a considerable number of these patients (more than 30%) do not undergo surgery for reasons not well known [11]. In the Euro Heart Survey [5], 216 patients aged 75 or older had severe AS (valve area ≤ 0.6cm²/m² body surface area or mean gradient ≥50mmHg) and angina or dyspnea with a NYHA Class III or IV. A decision “not to operate” was taken in 72 of these patients (33%). In multivariable analysis, older age and left ventricular dysfunction were the most obvious characteristics of patients who were denied surgery, whereas comorbidity played a less important role. Neurological dysfunction was the only comorbid condition significantly related to the decision not to operate.

Recent publication from STS database have shown that surgical mortality increases with age from 9.4% in patients older than 70 years to 14.5% for patients older than 90 years [8, 9]. In other series, risk factors such as female gender, pulmonary hypertension, triple vessel disease, low body surface area, previous cardiac surgery,

severely depressed LV function, and NYHA class III or IV heart failure have increased mortality up to 21%.

Although surgical AVR improves symptoms and survival, numerous patients (i.e., elderly, poor ventricular function and multiple co-morbidities) who are at high surgical risk remain untreatable by AVR [12]. So far, there is no recognized or approved medical treatment available to palliate or prevent the disease from worsening or to reduce the aortic valve calcification burden and balloon valvuloplasty has a temporary effect only and can be considered as a bridge to further extensive therapies.

Therefore, for these patients who are at high surgical risk, a minimal invasive aortic valve treatment with suitable long-term clinical outcomes, is a desirable alternative. Consequently, Transcatheter Aortic Valve Implantation (TAVI) was developed as a viable alternative to conventional open-heart surgery in selected high-risk patients with severe symptomatic AS.

1.2.3 Transcatheter Aortic Valve Implantation (TAVI)

Since 2002, when the first TAVI procedure was performed [13], there has been rapid growth in its use throughout the world for the treatment of severe aortic stenosis in patients who are at high surgical risk. Transcatheter aortic-valve replacement (TAVR) treats aortic stenosis by displacing and functionally replacing the native valve with a bioprosthetic valve delivered on a catheter. As presented in several clinical studies, two specific pathways are currently practiced with regards to the delivery approach; antegrade implantation employing direct transapical access, and retrograde implantation using either transfemoral or, alternatively, trans-aortic or trans-subclavian access.

Today many TAVI technologies are used in clinical practice and become commercially available devices:

- Balloon-expandable technologies for both antegrade and retrograde approach (Edwards-SAPIEN™, Sapien XT™ and Sapien 3 bioprosthesis.
- Self-expandable technologies for antegrade approach (Medtronic Engager™, Symetis ACURATE TA™, JenaValve TA system).
- Self-expandable technologies for antegrade approach (Medtronic CoreValve®, Medtronic Evolut R, Symetis ACURATE *neo*™, St. Jude Medical Portico™)
- Other expandable devices for retrograde approach (Direct Flow Medical bioprosthesis, Boston Scientific Lotus™ Valve System).

The results from the landmark multicenter randomized trial PARTNER (Placement of Aortic Transcatheter Valves, NCT00530894) have confirmed that TAVI is the treatment of choice for patient with severe AS who are too sick for conventional surgery [14].

In Germany and considering the early clinical results, the German Cardiac Society (DGK) and the German Society of Thorax, Heart and Vessel Surgery (DGHTG), had already issued a position paper in 2009 to highlight that TAVI should be considered

as the standard of care for patients with AS deemed as unsuitable surgical candidates due to high risk of preoperative mortality [15].

Therefore, after more than 20 years of clinical development and clinical evaluation, TAVI is the treatment of choice for patients with symptomatic aortic stenosis and with a high-risk for conventional aortic valve replacement. [

TAVI is also recommended in the guidelines of international medical societies:

- The guidelines on the management of valvular heart disease edited in 2012 by the European Society of Cardiology ESC [17], TAVI is recommended as in patients with severe symptomatic aortic stenosis who are, according to the heart team, considered unsuitable for conventional surgery because of severe co-morbidities.
- The guidelines on the management of valvular heart disease edited in 2014 by the American Heart Association and American College of Cardiology [18], TAVI is recommended as in patients with severe symptomatic aortic stenosis who are, according to the heart team, considered inoperable or high-risk for conventional surgery because of severe co-morbidities.

1.2.4 Transapical Approach: Clinical Experience

Over the last years, TAVI with an antegrade or transapical approach has become a well-established procedure [19, 20].

Comparable clinical outcomes from the transapical approach versus other TAVI approaches have been established in studies [21, 22] and in real-practice registries [23].

Clinical experience Symetis ACURATE TA™ Transapical Bioprosthesis have been reported [24, 25] in the literature. Single-center comparisons have shown comparable and to some extent superior outcomes [26] versus other 2nd-generation transapical TAVI systems.

Further progresses in transapical delivery system development and valve manufacturing are expected especially in view of compatibility with apical closure devices and enhanced ease of use from earlier generation TAVI devices [20].

The ACURATE *neo*™ Aortic Bioprosthesis using the ACURATE *neo*™ TA Transapical Delivery System have been developed to fulfill these expectations of the medical community.

1.3 General Overview of Symetis ACURATE *neo*™ Technology

The ACURATE *neo*™ Aortic Bioprosthesis is designed for minimally invasive transcatheter implantation. It is self-aligning and self-expandable facilitating positioning in the diseased aortic valve thereby reducing the risk of coronary occlusion.

1.3.1 Product Description

The product is composed of two separately packed components: a single use aortic bioprosthetic implant, the ACURATE *neo*™ Aortic Bioprosthesis, designated hereafter as “ACURATE *neo*™”, and a single use delivery system, the ACURATE *neo*™ TA Transapical Delivery System, designated hereafter as “Delivery System”.

A detailed description as well as the history of development and previous clinical experience of the ACURATE *neo*™ and its Delivery System for transapical implantation is presented in the Clinical Investigator’s Brochure.

1.3.2 ACURATE *neo*™ Aortic Bioprosthesis Components

The ACURATE *neo*™ (Fig. 1 and 2) is composed of the following three elements:

- A porcine pericardium valve which regulates blood flow between the left ventricle (LV) and the ascending aorta (AAo);
- A self expandable nitinol stent acting as an anchoring structure within the native aortic annulus (AAn) for the porcine pericardium valve which is sutured onto it;
- A double porcine pericardium skirt sutured on the inner and outer surface of the stent to prevent paravalvular leak.

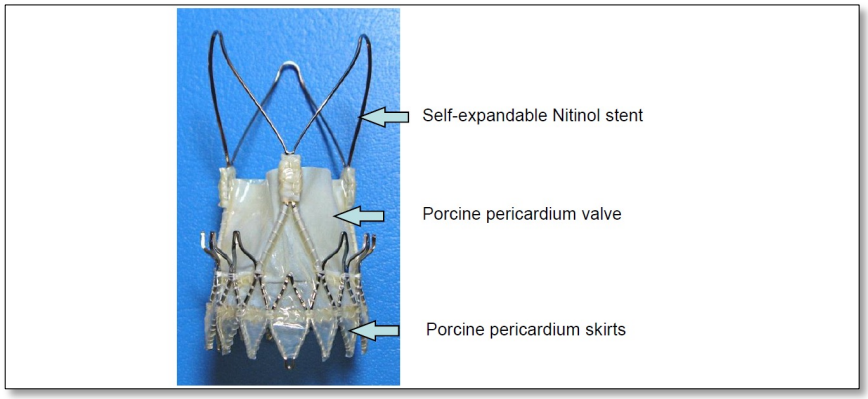


Figure 1: ACURATE *neo*™ Aortic Bioprosthesis

1.3.3 Porcine Pericardium Valve

The valve leaflets and skirts are composed of porcine pericardium. All biological tissue components are processed according to ISO22442-2:2007 - Medical devices utilizing animal tissues and their derivatives - Part 2: Controls on sourcing, collection and handling. The thread utilized for the final assembly is a braided polyester suture with a long history in cardiovascular surgery. All components are sterile.

1.3.4 Nitinol Stent

The aortic stent is composed of nitinol and complies with the ASTM F2063-05 - Standard specification for wrought nickel-titanium shape memory alloys for medical devices and surgical implants. Nitinol supports large deformations and recovers its original geometry upon removal of the force or constraint. The super-elastic property of nitinol at body temperature makes it the material of choice for numerous medical applications as an implant and especially for intravascular stents such as coronary and carotid stents, femoral stents and aortic stent grafts.

The uniqueness of the product mainly relies on the stent design (Fig. 2) and its five sections that are specifically optimized for their respective functions:

1. The stabilization arches to orient the bioprosthesis within the AAo during deployment and to avoid its tilting
2. The commissural totems that affix the pericardium valve to the stent frame
3. The upper anchoring crown which serves to avoid migration of the implant towards the LV during diastole
4. The lower anchoring crown which serves to avoid migration of the implant toward the AAo during systole.
5. The inflow-edge fixation loops that serve to attach the bioprosthesis to the stent holder during the release procedure.

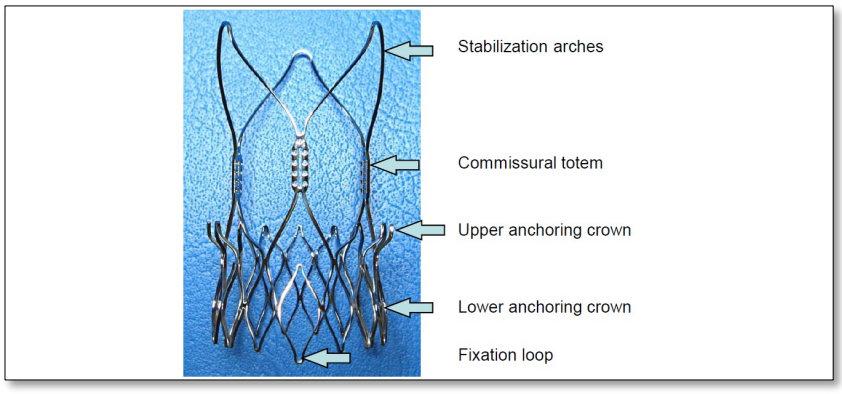


Figure 2: Self-expandable nitinol stent

The arrangement of the upper and lower crowns forming a diabolo shape is a key feature of the stent design, which facilitates self-alignment of the ACURATE *neo*™ after its release from the Delivery System. This feature ensures very tolerant positioning of the ACURATE *neo*™ prior to its full release within the native annulus.

Furthermore, anchoring of the ACURATE *neo*™ within the native calcified aortic annulus relies on two different aspects:

- Form-based fitting due to the diabolo shape of the stent
- Friction-based fitting due to radial force applied by the self-expandable stent

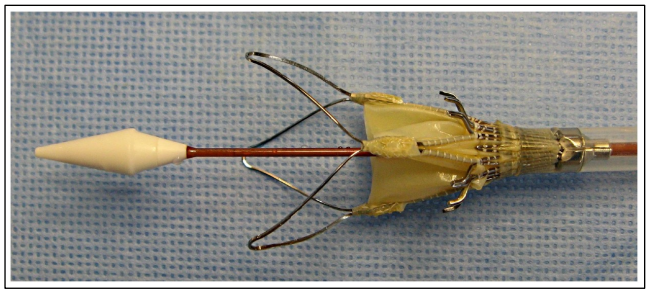


Figure 3: Partial release of the ACURATE *neo*™ Aortic Bioprosthesis

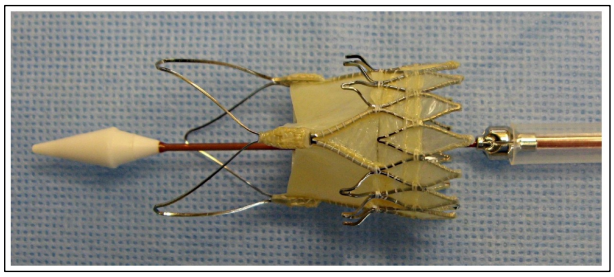


Figure 4: Full release of the ACURATE *neo*™ Aortic Bioprosthesis

1.3.5 Porcine Pericardium Skirt

The outer pericardium skirt is sutured on the outer surface of the stent and follows its in-flow edge. The inner pericardium skirt reinforces the valve in the area where stitches fix the valve to the stent struts. The outer and inner pericardium skirts shall contribute to the leak-tightness of the implant and presents a specific atraumatic design which prevents direct contact of the stent struts with the surrounding tissue within the left ventricular outflow tract.

1.3.6 ACURATE *neo*™ TA Transapical Delivery System

The Delivery System (Fig. 5) is used to position and release the ACURATE *neo*™ at the intended location over the patient's native, calcified aortic valve via transapical access. The delivery system is composed of the following components (Fig. 6):

1. A flexible inner member that contains a guidewire lumen bonded proximally onto a female luer lock and distally to a radio-opaque atraumatic tip, a stent holder to avoid premature release of the ACURATE *neo*™ Aortic Bioprosthesis during the implantation procedure and a radio-opaque markerband for the accurate positioning of the bioprosthesis (Figure 6). A further asymetric radio-opaque markerband indicates the position of one of the bioprosthesis commissural posts when loaded onto the delivery system (Fig. 7). The inner member is fixed proximally to the release handle.
2. A flexible outer member that contains distally the loaded bioprosthesis and is fixed proximally to the release handle.

3. A release handle (Fig. 8) providing an ergonomic fit to the physician's hand facilitating the precise two-step deployment of the ACURATE *neo*™. The release handle has the following features:
   - A check valve for flushing of the annular space between the inner and outer member;
   - A rotating knob for the two-step controlled release of the bioprosthesis from the delivery system;
   - A safety button to avoid premature and uncontrolled release of the bioprosthesis.

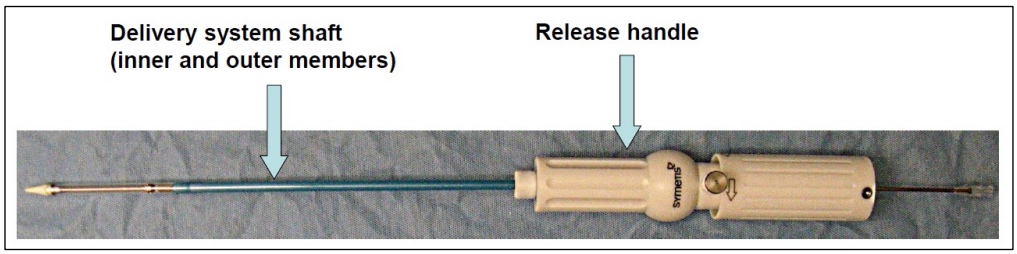


Figure 5: ACURATE *neo*™ TA Transapical Delivery System

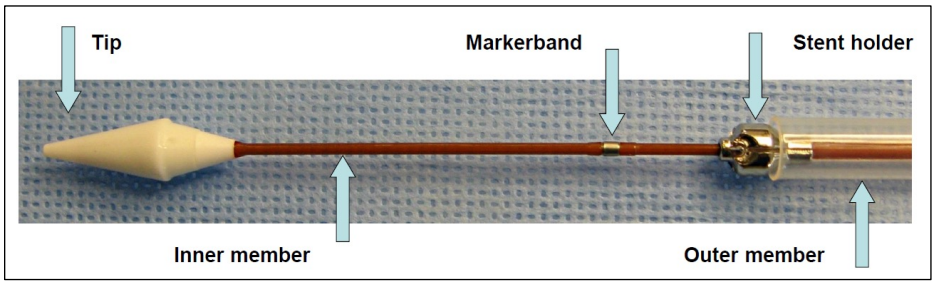


Figure 6: Distal section of ACURATE *neo*™ TA Transapical Delivery System

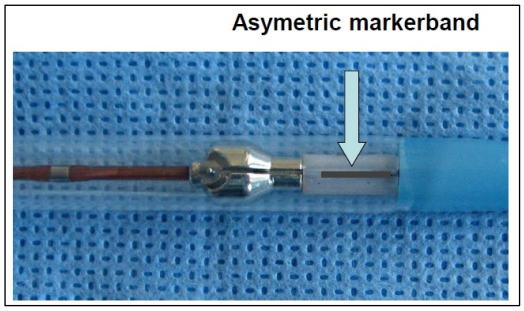


Figure 7: Asymetric markerband on inner member

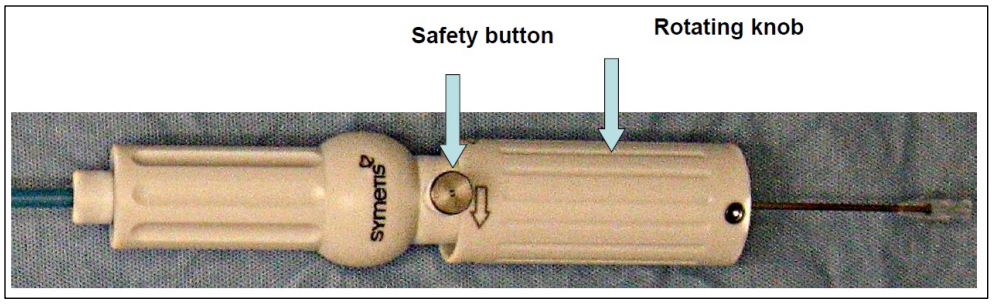


Figure 8: Release handle of the ACURATE *neo*™ TA Transapical Delivery System

1.3.7 Medical Devices Classification

The ACURATE *neo*™ is a Class III product following the rule 17 of the Annex IX of the MDD 93/42/EEC (implantable device utilizing animal tissues).

The ACURATE *neo*™ has received the CE mark in June 2014 for implantation using the ACURATE TF™ Transfemoral Delivery System through a transfemoral access.

The ACURATE *neo*™ TA Transapical Delivery System is a Class III product following the rule 6 of the Annex IX of the MDD 93/42/EEC (cardiovascular, surgically invasive device intended for transient use) and is not CE mark approved.

1.3.8 Dimensions/Sizes

The ACURATE *neo*™ is available in three different sizes (S-small, M-medium and L-large with respectively 23mm, 25mm and 27mm nominal diameter at waist level) for native annulus diameter range between 21 and 27mm. The following table summarizes the product part numbers, denomination and native aortic annulus diameters:

Part No.	Denomination	Native Aortic Annulus Ø
SYM-SV23-002	ACURATE *neo*™ Aortic Bioprosthesis S	21mm ≤ annulus Ø ≤ 23mm
SYM-SV25-002	ACURATE *neo*™ Aortic Bioprosthesis M	23mm < annulus Ø ≤ 25mm
SYM-SV27-002	ACURATE *neo*™ Aortic Bioprosthesis L	25mm < annulus Ø≤ 27mm

Table 1: ACURATE *neo*™ Aortic Bioprosthesis product range

The Delivery System has a crossing profile of 22F, a minimum usable length of 320mm and is compatible with 0.035” guidewires and can be used with all three sizes of the ACURATE *neo*™.

Part no.	Denomination
SYM-DS-004	ACURATE *neo*™ TA Transapical Delivery System

Table 2: ACURATE *neo*™ TATransapical Delivery System product range

All Symetis manufacturing activities are provided by ISO13485:2012 certified suppliers.

1.3.9 ACURATE *neo*™ Aortic Bioprosthesis Manufacture

The ACURATE *neo*™ is manufactured by Acurate Industria e Comercio Ltda (a subsidiary of Labcor Laboratorios located in Belo Horizonte, Brazil) which has received the ANVISA authorization to produce biological medical devices and is certified to ISO13485:2012.

1.3.10 Stent Manufacture

The nitinol self-expandable stent is manufactured by Admedes, an international leader of stent manufacturing. Admedes is certified according to ISO9001:2008 and ISO13485:2012. Their Quality Management System covers FDA requirements such as the current GMP QSR guidelines (21CFR Part 820). Admedes is also a FDA registered facility.

1.3.11 ACURATE *neo*™ TA Transapical Delivery System Manufacture

The ACURATE *neo*™ TA Transapical Delivery System is manufactured by Symetis SA in its own, certified clean room fulfilling the class ISO 7 requirements located in Ecublens, Switzerland. Symetis is certified according to EN ISO 13485:2012 for the design, manufacture and distribution of Percutaneous Tissue Heart Valve Prostheses and related Delivery Catheters, Introducers and Surgical Instruments.

1.3.12 Sterilization

The ACURATE *neo*™ Aortic Bioprosthesis is sterilized in its primary packaging filled with a 0.65% glutaraldehyde sterilant solution for 18h at 37°C. The sterilant solution is replaced by a 0.25% glutaraldehyde preserving solution upon sterilization. A sterility test of the sterilant solution and of bioprosthesis samples is performed for each sterilization batch prior to releasing the products for clinical use. The bioprosthesis and the preserving solution are sterile as long as the bottle and the sealed screw cap are intact. The external surface of the bottle / sealed screw cap is unsterile. The sterilization process complies with the ISO 14160:2011 standard.

The ACURATE *neo*™ TA Transapical Delivery System is sterilized by gamma irradiation at a minimum dose of 25kGy in its external packaging at Synergy Health, Däniken in Switzerland as contract sterilizator certified according to ISO 13485:2012 and ISO 9001:2008. The Delivery System is sterile as long as the breather bag is intact. The sterilization process complies with the EN ISO 11137-1:2006, EN ISO 11137-2:2012, EN ISO 11737-1: 2006 and EN ISO 11737-2: 2009 standards.

1.3.13 Storage Information

The ACURATE *neo*™ shall be stored in dry and cool area between 5°C and 25°C thereby avoiding direct contact with sunlight. Storage temperatures outside of the

mentioned range may potentially damage the biological tissue and compromise the product performances. The temperature sensor affixed to the bottle shall be checked prior use. If previous storage conditions have caused the activation of the temperature sensor the bioprosthesis shall not be used.

The Delivery System shall be stored in a dry area at room temperature thereby avoiding direct contact with sunlight. Storage at elevated temperatures may potentially damage the polymeric components and adhesives thus compromising product performance.

1.4 Pre-Clinical/Clinical Experience

A risk analysis according to ISO 14971 Application of risk management to medical devices has also been conducted. The risks associated with this device have been identified by performing Failure Mode and Effect Analysis (FMEA) / Risk Analysis. Risks have been proven, minimized or eliminated through appropriate design control, confirmed by pre-clinical bench, laboratory and animal testing. A summary of preclinical results is disclosed in the Clinical Investigator's Brochure. The present clinical study (Study 2015-01) is a prospective human clinical evaluation of the ACURATE *neo*™ Aortic Bioprosthesis for implantation using the ACURATE *neo*™ TA Delivery System, following a first-in-man study. The data of the present clinical study will be used to obtain market approval (CE mark).

However, clinical experience related to the device used in this study is based from the previous clinical investigations and registry based on:

- Clinical experience for the ACURATE *neo*™ Aortic Bioprosthesis is based on clinical studies that have evaluated the ACURATE *neo*™ Aortic Bioprosthesis (previously named as ACURATE TF™ Aortic Bioprosthesis) for implantation with its transfemoral delivery system.
- Clinical experience for the ACURATE *neo*™ Aortic Bioprosthesis and ACURATE *neo*™ TA delivery system is based on the TA LP FIM study performed in 15 patients.

The ACURATE *neo*™, was previously evaluated (while named the ACURATE TF™ Transfemoral Aortic Bioprosthesis) in a pre-market clinical trial performed in Brazil and Germany (Study 2011-03) and in a small Japanese study. The ACURATE *neo*™ and the ACURATE TF™ Transfemoral Delivery System were granted CE mark in June 2014. The average age of the population treated was 83.7 ± 4.3 years with a pre-operative predicted risk of mortality assessed by STS Score of 7.5 ± 8.2% and Logistic EuroSCORE of 26.6 ± 7.7%. All patients suffered severe aortic stenosis and 94.4% presented in NYHA Functional Class III/IV. The ACURATE *neo*™ was implanted successfully in 94.4% of cases and results at 30 days are favourable. At 30-day follow-up, an all-cause mortality rate of 3.4% is reported, a rate comparable to, if not improved, to other commercial TAVI devices. The mean aortic gradient improved from 43.6 ± 17.1 mmHg at baseline to 8.0 ± 2.9 mmHg and 95.1% of patients exhibit a paravalvular leak grade of ≤ Grade 1 at 30 days follow-up. Only 9.0% of patients

required a permanent pacemaker after implantation with the ACURATE *neo*™ as reported at 30 days. Further data is disclosed in the Clinical Investigator's Brochure and supports the CE mark approval of the ACURATE *neo*™ and its transfemoral Delivery System.

Furthermore, the ACURATE TA™ Transapical Aortic Biorprosthesis and the Delivery System, was granted a CE mark in September 2011 and is commercially available in several countries and was evaluated in the post-market surveillance SAVI registry. Follow-up at 12 months showed an all-cause mortality rate of 18.8% with a stroke rate of 4.0%, rates comparable if not improved to other commercial TAVI devices. The mean aortic gradient improved from 43.2 ± 17.4 mmHg at baseline to 12.9 mmHg at 12 months with 95.1% of returning patients exhibiting paravalvular leak of ≤ Grade 1. Additionally, 83.7% of returning patients at 12 months demonstrated NYHA Class I/II.

1.5 Potential Risks & Benefits for Participating Patients

1.5.1 Methods of Assessment

The inclusion and exclusion criteria of the present study (see §3) indicate that participating patients must have severe aortic stenosis, and at high risk for surgical aortic valve replacement. As previously reported (see Section 1.2.3 Transcatheter Aortic Valve Implantation), TAVI is now considered the standard of care for this population.

As a consequence, the risks & benefits of patients participating in the present clinical study have been assessed in comparison to other approved TAVI devices. The detailed analysis is disclosed in the Clinical Investigator's Brochure.

1.5.2 List of Residual Risks

A detailed product risk analysis is provided in the Clinical Investigator Brochure and the residual risks are also listed in Section 6.3 Known & Anticipated Risks of the present Clinical Investigation Plan. This risk analysis concludes that all risks have been sufficiently mitigated for a clinical investigation.

1.5.3 Risk/Benefit Assessment

The Risk/Benefit Assessment concludes that it is reasonable to expect that the risk for the patient enrolled in this study will not be higher than those they would be exposed to should they were receiving an alternative treatment. It is also reasonable to expect that these patients will experience all established clinical benefits from the TAVI procedure. The present study will confirm these assumptions.

1.6 Rationale

The ACURATE *neo*™ and the ACURATE *neo*™ TA Delivery System have the potential to become a new treatment alternative that would benefit the medical community.

The ACURATE *neo*™ has a lower crossing profile which makes it possible to significantly reduce the diameter of the delivery system required to deploy the aortic bioprosthesis at the intended location using the transapical approach.

The benefits are multiple:

- Smaller access incision (mini-thoracotomy) and therefore a decreased incidence of potential access-related complications;
- Usage of newly designed percutaneous access and closure systems which combine the advantages of minimally-invasive access using an antegrade approach;
- Optional usage of soft-tissue access instead of the more traditional use of rib-spreaders (retractors);
- Patient oriented decision-making by the Heart Team to choose either the transfemoral (retrograde) or transapical (antegrade) access route depending upon the patient's risk profile and anatomic characteristics as the same supraannular aortic bioprosthesis, the ACURATE *neo*, can be loaded onto either a transapical (ACURATE *neo*™ TA Delivery System) or transfemoral (ACURATE TF™ Delivery System) delivery system.

The scientific rationale for conducting this clinical trial is to prove the safety and feasibility of use of the device in a well-defined population at a small number of investigation sites providing transcatheter treatment of AS with a second-generation, low profile TA-AVI device.

2 STUDY OBJECTIVES

The goal of the study is to evaluate the ACURATE *neo*™ Aortic Bioprosthesis using the low profile transapical Delivery System, in patients with severe aortic stenosis. The objectives are to evaluate safety and performance and adverse event at follow-up.

Data of this study will be used to obtain market approval in Europe and Japan.

2.1 Endpoints

2.1.1 Primary Safety Endpoint

The primary safety endpoint is freedom from all-cause mortality at 6 Months

2.1.2 Primary Device Performance Endpoint

The primary device performance endpoint is defined as procedure success in absence of MACCE at 30 Days post procedure

2.1.3 Secondary Endpoints

Secondary endpoints are defined as below:

1. Rate of clinical endpoints (VARC 2[2]) at 30 Days
    - Mortality
    - Stroke
    - Myocardial infarction
    - Bleeding complication
    - Acute kidney injury
    - Vascular complication
    - Conduction disturbances and arrhythmia
    - Other TAVI-related complications
2. Incidence of all cause mortality at 30 Days and 12 Months
3. Freedom from MACCE at 30 Days, 6 Months and 12 Months
4. Procedural success defined as ACURATE *neo*™ at intended location with:
    - Aortic Insufficiency/ Regurgitation < Grade 3
    - Mean aortic gradient < 20 mmHg
    - EOA ≥ 1.0 cm^2
    - No further re-intervention performed on the ACURATE *neo*™ implant
    - No intra- procedure mortality

[2] European Heart Journal (2012) 33, 2403–2418 doi:10.1093/eurheartj/ehs255

5. Device success at 7 days/ Discharge, 30 Days, 6 Months and at 12 Months follow-up defined as:
    - Single study device implanted at intended location
    - No impingement of the mitral valve
    - Normal coronary blood flow
    - Aortic Insufficiency/ Regurgitation < Grade 3
    - Mean aortic gradient < 20mmHg
    - EOA ≥ 1.0 cm^2
    - No further re-intervention performed on the ACURATE *neo*™ implant
6. Functional improvement from baseline as per NYHA Functional Classification at 30 Days, 6 Month and at 12 Months follow-up.
7. Echocardiographic assessment of valve performance (at 7 Days or Discharge, 30 Days, 6 Months, 12 Months) using the following measures:
    a. Transvalvular mean gradient
    b. Effective Orifice area
    c. Aortic Valve Insuficiency/ Regurgitation (paravalvular and transvalvular)
    d. Left Ventricular Ejection Fraction

2.2 Study Design

This is a prospective, multicenter, open, single arm safety study of the treatment of severe symptomatic AS for patients presenting with high surgical risk to undergo conventional AVR. All patients will be followed up to 12 Months after the intervention and survival status will be collected annually by phone up to 5 years. The study will be divided into three periods:

1. Baseline eligibility evaluation (screening to enrolment if study criteria are met)
2. Implantation procedure (immediately pre-implant to 24 hours post-procedure)
3. Follow-up period (Discharge/ 7 Days - whichever occurs first - to study exit)

Evaluation of subjects will be documented in Case Report Forms (CRF).

2.2.1 Estimated Timeline

- Study start date Q3 2015 (Ethics Committee submission)
- Enrolment start Q4 2015
- Enrolment end Q3 2016
- Interim study report Q4 2016 (30 Days interim analysis)
- Study visit completion Q3 2017 (12 Months follow-up)
- Final study report Q3 2017 (primary and secondary endpoints)
- Last telephone check Q3 2021

2.2.2 Study Centers

Up to ten (10) investigation sites is planned to enrol a total of a sixty (60) patients in Europe. All selected investigation sites will have significant experience in transcatheter

treatment therapies - specifically TA-AVI. All investigation sites will be trained before any implantation occurs. The initial cases at each new clinical site are proctored by an expert ACURATE *neo*™ TA physician end user or qualified Symetis personnel.

3 STUDY POPULATION

The ACURATE *neo*™ Aortic Bioprosthesis is indicated for the treatment of patients suffering from severe symptomatic AS and for whom a conventional AVR represents a high surgical risk. These patients will possibly benefit from a transcatheter valve replacement procedure performed on the beating heart without cardiopulmonary bypass assistance, which furthermore has the potential to shorten the recovery time.

Sixty (60) patients with severe symptomatic AS and considered at high-risk for conventional AVR will be implanted. To be evaluable for analysis each patient must:

- Meet ALL inclusion criteria
- Not meet ANY exclusion criteria

The analysis population has been described in the section 7.2.

3.1 Subject Inclusion Criteria

Subjects must fulfil all following inclusion criteria in order to be eligible for the study:

1. Subject must be at least 18 years old
2. Severe aortic stenosis defined as:
    - Mean aortic gradient > 40 mmHg *or*
    - Peak jet velocity > 4.0 m/s *or*
    - Aortic valve area of < 0.8 cm^2
3. High risk patient determined by a multidisciplinary heart team consensus (cardiologist and cardiac surgeon) that patient is not a surgical candidate for conventional AVR due to risk factors[3] such as STS Score (8% or higher) or other co-morbid conditions unrelated to aortic stenosis such as severe chronic obstructive pulmonary disease (COPD), chest deformities and irradiated mediastinum.
4. NYHA Functional Class > II
5. Multidisciplinary heart team (cardiologist and cardiac surgeon) consensus that the transapical approach is the most suitable access route for TAVI due to the presence of the following anatomic conditions:
    - porcelain aorta *or*
    - severely calcified or highly tortuous peripheral vasculature not appropriate for transfemoral transcatheter aortic valve implantation *or*
    - vessels too small for retrograde approach *or*
    - other anatomical conditions making transapical approach more suitable
6. Aortic annulus diameter from ≥ 21mm up to ≤ 27mm by CT or TEE
7. Patient willing to participate in the study and provides signed informed consent

[3] Nishimura et al. 2014 AHA/ACC Guideline for Management of Patients with Valvular Heart Disease ; JACC Vol.63 ; No.22 ;2014

3.2 Subject Exclusion Criteria

Subjects will be excluded from the study if presenting any of the following:

1. Congenital unicuspid or bicuspid aortic valve or non-calcified
2. Extreme eccentricity of calcification
3. Severe mitral or aortic regurgitation (> Grade 3)
4. Pre-existing prosthetic heart valve in any position and / or prosthetic ring
5. LV apex is not accessible via transapical access due to severe chest deformity
6. Previous surgery of the LV using a patch, such as the Dor procedure
7. Presence of apical LV thrombus
8. Calcified pericardium
9. Septal hypertrophy unacceptable for transapical procedure
10. Transesophageal echocardiogram (TEE) or angiography is contraindicated
11. ECHO evidence of intracardiac mass, thrombus, or vegetation
12. LVEF < 20% by ECHO
13. Need for emergency intervention for any reason within 30 Days of scheduled procedure
14. Any percutaneous intervention, except for balloon valvuloplasty (BAV) within 1 month prior to implant procedure
15. Untreated clinically significant coronary artery disease requiring revascularization within 30 days before or after the study procedure
16. Acute myocardial infarction within 1 month prior to implant procedure
17. Previous TIA or stroke within 6 months prior to implant procedure
18. Active gastrointestinal (GI) bleeding within 3 months prior to implant procedure
19. Scheduled surgical or percutaneous procedure to be performed prior to 30 day visit
20. History of bleeding diathesis, coagulopathy, refusal of blood transfusions or severe anemia (Hb < 8 g/dL)
21. Systolic pressure <80mmHg, cardiogenic shock, need for inotropic support or IABP
22. Primary hypertrophic obstructive cardiomyopathy (HOCM)
23. Active infection or endocarditis
24. Hepatic failure (> Child B)
25. Chronic renal dysfunction with serum creatinine > 3.0 mg/dL or renal dialysis
26. Neurological disease severely affecting ambulation, daily functioning, or dementia
27. Life expectancy < 12 months due to co-morbid conditions
28. Intolerance to aspirin, clopidogrel, contrast media, or porcine tissue and allergy to nickel
29. Pregnant or breast-feeding women
30. For other severe illnesses of the patient (e.g. active carcinoma), the investigator shall decide on an individual basis whether the patient is not to be included in the study
31. Currently participating in an investigational drug or another device study

4 STUDY PROCEDURES

4.1 Study Methods & Evaluations

4.1.1 Study Conduct

See Appendix A "Schedule of Procedures/Evaluations". The last expected study visit duration for each subject is 360 ± 45 Days. Survival status is collected via telephone check annually at 2 to 5 years post-implantation.

4.1.2 Screening Period

Patients presenting with severe AS and considered high risk for conventional AVR may be candidates for the study procedure and will be provided with information about the study by the Investigator. Prior to performing any study activities/evaluations, except the standard assessments for this population, the subject **must be thoroughly informed** about all aspects of the study, including scheduled study visits and activities, and **must have signed the informed consent**. A signed copy of the informed consent should be given to the subject. Patients will be assigned a unique identifier during the screening process. This identifier will include the study number (2015-01) and consecutively assigned patient numbers (001, 002, 003) determined for each clinical site (e.g. 201501001, 201501002, 201501303).

Below are the pre-treatment baseline (screening) procedures that must be completed no more than 30 Days before the implant procedure:

- Demographic data
- Medical history including cardiac medications and antiplatelet regimen, as well as recording any comorbidity
- Disease history, including date of diagnosis, disease state, treatment and response
- Physical examination including NYHA functional classification (see Appendices E)
- 12-lead electrocardiogram (ECG)
- Transthoracic (TTE) or transeosophageal echocardiography (TEE)
- CT angiography scan or invasive angiography of the ilio-femoral vasculature, aortic valve and entire aorta, coronary arteries and cardiac anatomy for assessing appropriateness of TA procedure
- Logistic EuroSCORE I and II and STS Predicted Risk of Mortality Score (see Appendices C & D)
- NIH stroke scale, MMSE neurologic examinations and mRS (see Appendix B)

Below are the pre-treatment baseline (screening) procedures that must be completed no more than 24 hours before the scheduled procedure:

- Start dual antiplatelet regimen (DAPT)
- CBC with differential (red and white cell counts)
- Creatinine (Cr) and lactate dehydrogenase (LDH)
- Cardiac Enzymes; troponin I or T and/or CK/CK-MB
- Coagulation Profile (PT, PTT or aPTT, INR)

All patients screening data have to be sent to the screening committee for review. The screening committee will give the final decision of patient's eligibility after review of patient screening data.

4.1.3 Implantation Procedure

If the subject is found to be eligible, and has signed informed consent, he/she can undergo implantation of the ACURATE *neo*™. Please refer to the Clinical Investigator Brochure in the "Description of Intended Use" section to get more recommendations on the procedure and use of the study device.

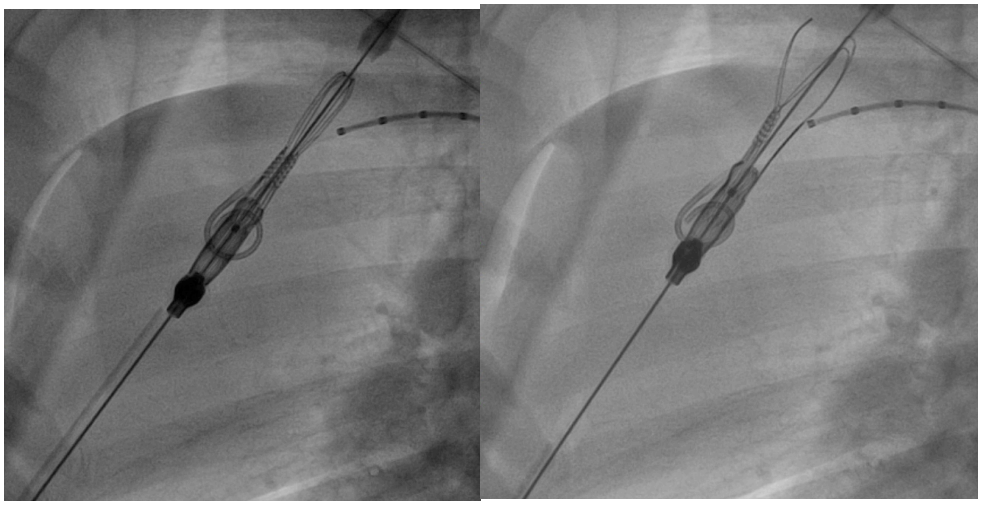
Information related to this known standard procedure for TAVI is found in appropriate literature and medical journals. The patient will be prepared according to the recommendations of the ESC "Guidelines on the Management of Valvular Heart Disease". However, the preparation of the access site, the preliminary balloon dilatation, the post-implantation procedures and access site closure are not described within this document. The implanting physician will follow usual practice since he/she will have experience in TA-AVI procedures. A TEE must be used during the procedure.

Additionally, the physician will follow the usual practice regarding administration of concomitant medication, antibiotics and anticoagulation therapy before and during the procedure. Dual antiplatelet medications, to begin within 24 hours of procedure, are recommended as specified here: 100mg daily of ASA for life and prescribed daily dose of Clopidogrel for 6 months post-implant.

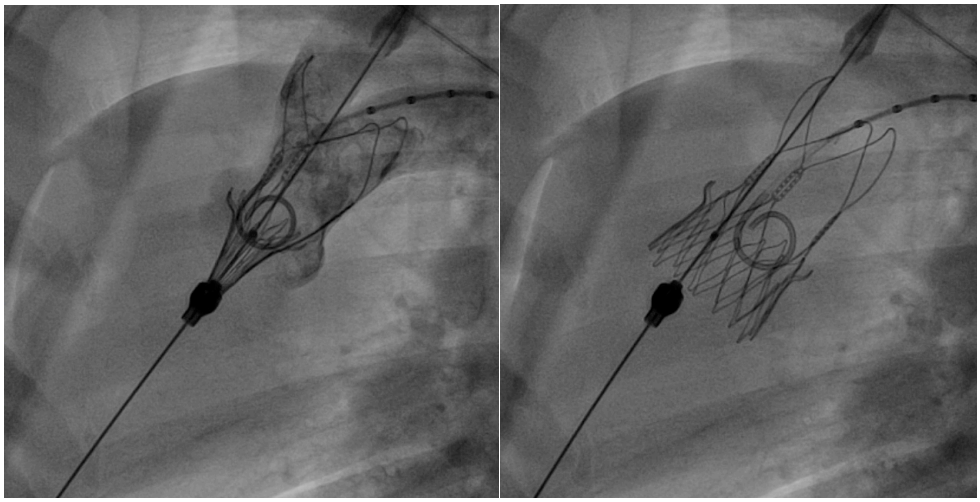
The ACURATE *neo*™ TA Delivery System containing the ACURATE *neo*™, loaded within its distal section, is introduced under fluoroscopic control transapically into the LV over a guidewire, preliminarily positioned across the calcified native aortic valve into the ascending aorta (Fig. 9 / Pos. 1). By pulling back the outer sheath of the delivery system, the stabilization arches start to deploy and enter into contact with the ascending aorta, thereby orientating the system towards the longitudinal direction of the aorta – "anatomical orientation" (Fig. 9 / Pos. 2).

Upon further retraction of the outer sheath, the upper anchoring crown of the ACURATE *neo*™ begins to deploy and engages the cusps of the native valve leaflets (Fig. 9 / Pos. 3). It is recommended to position the implant slightly above the aortic annular plane.

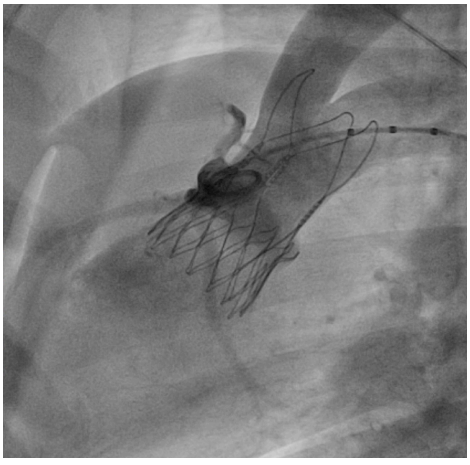
Upon final retraction of the outer sheath, the ACURATE *neo*™ automatically detaches from the delivery system due to its self-expandable properties thereby leaving the lower crown fully expanded (Fig. 9 / Pos. 4) within the left ventricle.



Position 1. *Position 2.*



Position 3. *Position 4.*



Position 5.

Position 1: Delivery system is placed through the native valve.

Position 2: Deployment of the stabilization arches.

Position 3: Deployment of the upper crown and partial release position.

Position 4: Deployment of the lower anchoring crown.

Position 5: final release position.

Figure 9: ACURATE *neo*™ implantation procedure (ovine animal model).

Furthermore, the entire implantation procedure occurs on the beating heart or under rapid pacing with moderate occlusion of the native valve through the ACURATE *neo*™ TA Delivery System. Final release (*Fig. 9 / Pos. 4*) of the ACURATE *neo*™ is performed under rapid pacing to offer stability and aid in visualization during fluoroscopic guidance. Due to the self-expanding properties of the stent, it is expected to have a full expansion.

The implanting physician will perform the ACURATE *neo*™ implantation procedure using standard practice, meaning that rapid pacing, balloon aortic valvuloplasty (BAV) and other procedure steps will not be described in this protocol.

The size of the ACURATE *neo*™ to be implanted will be defined according to the various imaging examinations (echocardiography, CT Scan, angiography) performed prior to procedure per standard of care applicable at the investigation sites.

Size Recommendations:

Denomination	Measured Native Annulus Diameter (mm)
ACURATE *neo*™ S	21 ≤ native annulus Ø ≤ 23
ACURATE *neo*™ M	23 < native annulus Ø ≤ 25
ACURATE *neo*™ L	25 < native annulus Ø ≤ 27

It is possible that the highly calcified native aortic annulus could create the need for a post-dilatation balloon to assist with desired outcomes after the ACURATE *neo*™ implantation.

In the case of any peri-procedural complication, the implanting physician will decide on the best bail-out strategy for the patient (conversion to conventional AVR, valve-in-valve, etc.), if necessary.

Peri-Procedure to 24 Hours Post-Procedure

During the procedure subjects will be continuously monitored clinically, hemodynamically, and electrocardiographically. All adverse events will be recorded. After completion of the procedure, all subjects will be monitored via telemetry with special attention to hemodynamic conditions and cardiac rhythm. This monitoring will be continued for a minimum of 24 hours post-procedure and will include:

- Adverse Event collection
- DAPT: ASA 100mg/QD for life + prescribed Plavix for 6 months post-procedure
- CBC with differential (red and white cell counts)
- Creatinine (Cr) and lactate dehydrogenase (LDH)
- Cardiac Enzymes; troponin I or T and/or CK/CK-MB
- Coagulation Profile (PT, PTT or aPTT, INR)
- Transthoracic or transesophageal echocardiogram (TTE or TEE)
- 12-lead electrocardiogram (ECG)

Once stable condition is achieved and maintained the subject may be transferred to a regular cardiology unit. Adverse events and DAPT medications will be recorded before the transfer.

4.1.4 Scheduled Follow-Up Visits

Each follow-up visit will be calculated from day of the study procedure (Day 0). All subjects will have a scheduled in-hospital visit at discharge or 7 Days (+/- 2 Days), whichever occurs first, and return to the clinic at 30 Days (+/- 7 Days window), 6 Months (+/- 30 Days window) and 12 Months (+/- 45 Days window) for a full examination and echocardiography

4.1.5 Discharge or 7 Days

The following assessments and their corresponding CRF pages will be completed at Discharge or 7 Days (+/- 2 Days), whichever occurs first:

- NYHA Functional Classification
- NIH Stroke Scale, MMSE determination and mRS
- Adverse Event collection
- DAPT: ASA 100mg/QD for life + prescribed Plavix for 6 months post-procedure
- CBC with differential (red and white cell counts)
- Creatinine (Cr) and lactate dehydrogenase (LDH)
- Cardiac enzymes; troponin I or T and/or CK/CK-MB
- Coagulation profile (PT, PTT or aPTT, INR)
- Transthoracic or transesophageal echocardiogram (TTE or TEE)
- 12-lead electrocardiogram (ECG)

4.1.6 30 Days Follow-Up Visit

The following assessments and their corresponding CRF pages will be completed at the 30 Days follow-up visit (+/- 7 Days):

- NYHA Functional Classification
- NIH Stroke Scale, MMSE determination and mRS
- Adverse Event collection
- DAPT: ASA 100mg/QD for life + prescribed Plavix for 6 months post-procedure
- CBC with differential (red and white cell counts)
- Creatinine (Cr) and lactate dehydrogenase (LDH)
- Cardiac enzymes; troponin I or T and/or CK/CK-MB
- Coagulation profile (PT, PTT or aPTT, INR)
- Transthoracic or transesophageal echocardiogram (TTE or TEE)
- 12-lead electrocardiogram (ECG)

4.1.7 6 Months Follow-Up Visit

The following assessments and their corresponding CRF pages will be completed at the 6 Months follow-up visit (+/- 30 Days):

- NYHA Functional Classification
- NIH Stroke Scale, MMSE determination and mRS
- Adverse Event collection
- ASA 100mg/QD for life
- CBC with differential (red and white cell counts)
- Creatinine (Cr) and lactate dehydrogenase (LDH)
- Transthoracic or transesophageal echocardiogram (TTE or TEE)
- 12-lead electrocardiogram (ECG)

4.1.8 12 Months Follow-Up Visit

The following assessments and their corresponding CRF pages will be completed at the 12 Months follow-up visit (+/- 45 Days):

- NYHA Functional Classification
- NIH Stroke Scale, MMSE determination and mRS
- Adverse Event collection
- ASA 100mg/QD for life
- CBC with differential (red and white cell counts)
- Creatinine (Cr) and lactate dehydrogenase (LDH)
- Transthoracic or transesophageal echocardiogram (TTE or TEE)
- 12-lead electrocardiogram (ECG)

4.1.9 2 - 5 Years Telephone Check

Annually from 2 to 5 years post-procedure (+/-45 Days) the investigator, clinical research coordinator or designee will contact the subject or the subject's private physician by phone for adverse event and NYHA assessment and status of aspirin regimen. Corresponding CRF pages will be completed. As recommended by European guidelines for management of valvular heart disease (ESC/ESA- 2012) patients will be annually followed by their own Cardiologists.

4.1.10 Unscheduled Visits

An 'unscheduled' visit might be required during the course of the study for several reasons, e.g. adverse event, request of sponsor, investigator decision to follow subject more closely, unrelated medical appointment. The investigator is requested to attempt collection of the following information during each unscheduled visit if considered necessary:

- NYHA Functional Classification
- NIH Stroke Scale, MMSE determination and mRS
- Adverse event collection

- Record changes (addition/discontinuation) in DAPT since last recorded follow-up
- Transthoracic or transesophageal echocardiogram (TTE or TEE)
- 12-lead ECG

The subject's unscheduled visit assessment will be recorded and entered on the Follow-up CRF. Information pertaining to adverse events that have occurred, or are still occurring since the last visit, must be recorded on the Adverse Event CRF.

4.2 Medication Regimen

The physician will prescribe medication according to his/her own specific site protocol. In addition, it is recommended to prescribe dual antiplatelet medication (DAPT):

- Aspirin 100mg per day, for life
- Prescribed Plavix dose (e.g. 75 mg per day) for 6 months post-implant

Antiplatelet medications must be recorded on CRF pages for each patient. Enrolled subjects who undergo dental or other surgical procedures within six months after the ACURATE *neo*™ implantation should receive a routine prophylactic antibiotic regimen as is general practice after valve replacement in order to minimize the possibility of infection.

4.3 Histopathology Studies

In case of severe or fatal event, histopathology studies of explanted valves might be requested Explants will be appropriately prepared and preserved and sent to an independent histopathology laboratory for macroscopic and microscopic analysis. Gross pathological examination of the entire valve and the support structure (i.e. shape, if occurrence of intravascular trauma, tissue abrasion, uniformity of the frame, position the natural valve cusps) will be assessed.

Specific assessment of the ACURATE *neo*™ will be performed. The explanted study devices are to be assessed for cusp excursion and the presence of leaflet fenestrations, rigidity tears, hematomas, thrombi and calcified nodules, cell proliferation, tissue overgrowth, fibrous sheath and local inflammatory reaction. One half of each leaflet must be used for the quantitative determination of inorganic calcium and phosphate.

4.4 Study Discontinuation

Subjects may discontinue their participation in the study at any time and without prejudice of further treatment.

4.4.1 Criteria for Early Discontinuation

Subjects who withdraw from the study will be asked to follow-up with their doctor in a customary manner. If the subject decides not to continue with any further visits the investigator should complete the "Study Exit" CRF page before discontinuation. Early

discontinuation in this protocol is defined as not completing the final study visit on Day 360 ± 45 Days. A subject may exit from the study for the following reasons:

- Subject withdrew consent
- Request of primary care physician or investigator
- Subject is lost to follow-up
- Death

Documented attempts will be made to follow subjects who prematurely discontinue the study. Reasons for premature withdrawal from the study must be stated in the CRF and in the site source documentation.

4.4.2 Replacement of Withdrawn Subjects

Withdrawn subjects will not be replaced.

4.4.3 Sponsor's Termination of Study

The sponsor reserves the right to discontinue the study at any time for any reason. The sponsor may also discontinue the study at a site for poor performance or compliance. The investigator must implement the Sponsor's request to terminate the study in a time frame that fits with the subject's best interest. In any case, the EC must approve the study termination before it occurs and all included patients will be followed per plan.

4.4.4 Screen Failure

Subjects are assigned a unique identifier during the screening process. In the case of a subject not meeting inclusion/exclusion criteria or deciding prior to the study procedure not to participate in the study, the appropriate CRF should be completed documenting the reason for screening/enrolment failure. Patients may “screen out” of the study due to procedural pre-implant TEE showing native aortic annulus size restrictions or morphology not appropriate for the ACURATE *neo*™, as well as patient not meeting the echocardiographically determined inclusion criteria. In the case of screen failure during pre-implant phase of the procedure, another TA-AVI device, commercially available or investigational, can then be selected for treatment of said patients.

4.5 Recommendations Beyond Study Participation

Long-term patient management, beyond the participation in the present study, should be performed according to the current guidelines. [6] As pointed out by European Society of Cardiology (ESC), these patients require periodic clinical and selected laboratory examinations.

Clinical assessment should be performed yearly or as soon as possible if new cardiac symptoms occur. Transthoracic echocardiography (TTE) should be performed if any new symptoms occur after valve replacement or if complications are suspected. As recommended by the ESC Guidelines [6], yearly echocardiographic examination is recommended after the fifth year for patients with implanted bioprostheses.

Furthermore, study patients should be followed up regarding anti-thrombotic therapy, risk of valve thrombosis, risk of thromboembolism, hemolysis and central or paravalvular leak, bioprosthetic failure and heart failure.

5 INVESTIGATIONAL DEVICE MANAGEMENT

All investigational devices are provided to the clinical sites by Symetis.

5.1 Study Device Acquisition / Disposition

5.1.1 Packaging & Labeling

The ACURATE *neo*™ TA Transapical Delivery System will possess a label that states: *"Exclusively for Clinical Investigations*".

The ACURATE *neo*™ Aortic Bioprosthesis is already CE-approved for use with its ACURATE *neo*™ Transfemoral Delivery System. This same bioprosthesis will be implanted in Study 2015-01 using the investigational ACURATE *neo*™ TA Transapical Delivery System.

All labels will include a fixed information section (to include the product name, storage conditions, instructions etc.) and variable information section. Several identical "device identification" labels will be part of the package. The minimum will be to have one label attached to a worksheet: one part will be attached to the accountability log, if necessary, and one to the source document and one for the patient card. The variable information section will include the following variable data: batch number, serial number, expiration date and blank fields for subject number and initials and investigator name. The blank fields are to be completed by the study nurse.

5.1.2 Distribution & Shipment

Distribution and shipment of product is managed by Symetis according to study guidelines. Each shipment of device supplies for the study will contain a shipment form to assist in maintaining current and accurate inventory records. When a shipment is received, the investigator/coordinator will acknowledge receipt.

5.2 Device Storage

Devices must be kept in a secure, limited-access storage area. Storage of the ACURATE *neo*™ components require some special handling that will keep the system intact and in ready-to-operate condition once a patient is enrolled to the study. The device should be examined immediately upon arrival at the study site. If the device supplies appear to be damaged or have reached the expiration date, the sponsor should be contacted immediately and another product utilized for the implant procedure. Only authorized site personnel will have access to study devices.

5.3 Device Preparation for Implantation

Symetis personnel will attend all procedures to ensure proper device usage. Investigation site personnel will be thoroughly trained before any human implantations

can begin at the investigation site. Preparation of the device and its investigational delivery system are performed by Symetis personnel or by site personnel who have successfully completed the ACURATE *neo*™ and the ACURATE *neo*™ TA Delivery System Training Program.

5.4 Device Accountability

Symetis is responsible for managing the device supply and tracking and will follow study specific device accountability procedures for the investigational ACURATE *neo*™TA Transapical Delivery System. The accountability records will be maintained at all times. The identification number of the subject, the date used, lot number, expiry date of the study device implanted and the date and quantity of study devices returned will be recorded. All study devices not used during implantation will be returned to the sponsor or stored in an appropriately secure place onsite. Accountability of the received devices, as well as used and returned study devices, should be performed and recorded on the proper study device accountability record.

The ACURATE *neo*™ Aortic Bioprosthesis will be tracked using a clinical site's usual means of accounting for commercial product including the use of patient cards.

5.5 Device Return

The Principal Investigator (PI) will be notified in writing upon completion of patient recruitment. Any unused supplies will be returned to Symetis upon receipt of notice. Symetis will supply detailed return information to the PI. If an investigational device has been in contact with a subject, a Symetis representative will provide detailed information on how to return the product.

6 ASSESSMENT OF SAFETY

6.1 Definitions & Relationships

6.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or study subject administered a therapeutic product and which does not necessarily have a causal relationship with this treatment. An AE can be an unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the therapeutic investigational product, whether or not related to the therapeutic investigational product.

A new condition, or the worsening of a pre-existing condition, is considered an AE. Stable chronic conditions, such as arthritis that is present prior to study entry and does not worsen during the study are not considered as AE. An abnormal result of diagnostic procedures including abnormal laboratory findings is considered an AE if it:

- results in the subject's withdrawal from the study by the investigator;
- is associated with a serious adverse event;
- is associated with clinical signs or symptoms;
- is considered by the physician to be of clinical significance.

6.1.2 Serious Adverse Event / Serious Adverse Device Effect

Serious adverse event (SAE) is defined as an AE that:

- Led to death;
- Led to serious deterioration in the health of a subject that:
  - Resulted in a life-threatening illness or injury;
  - Resulted in a permanent impairment of a body structure or a body function;
  - Required inpatient hospitalization or prolongation of existing hospitalization;
  - Resulted in medical or surgical intervention to prevent permanent impairment to a body structure or a body function;
- Led to foetal distress, foetal death or a congenital abnormality or birth defect.

Hospitalization for elective treatment of a pre-study condition that did not worsen during the study and hospitalizations for treatment of non-adverse events (e.g., cosmetic surgery or diagnostic procedure) are not considered as Serious Adverse Events.

A serious adverse device effect (SADE) is a SAE attributed to the device.

Adverse events, serious adverse events and serious adverse device effects will be reported for the investigational ACURATE *neo* TA™ Transapical Delivery System as well as the ACURATE *neo*™ Aortic Bioprosthesis implanted in Study 2015-01.

6.1.3 Unanticipated Adverse Device Event

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

6.1.4 Severity Definition

Mild: AE which is easily tolerated;
Moderate: AE sufficiently discomforting to interfere with daily activity;
Severe: AE that prevents normal daily activities.

The investigator will document his opinion of the relationship of the AE to the investigational medical device using the criteria outlined below.

6.1.5 Relationship to Study Device and/or Study Procedure

Unrelated: The AE has no temporal relationship to the study device or study procedure, and/or there is evidence of alternative cause such as concurrent medication or illness;
Possibly related: A temporal relationship with study device or study procedure is not clear, alternative causes are also possible;
Probably related: A clear cut temporal relationship to the use of study device or study procedure and potential alternative etiology is not apparent;
Definitely related: A clear-cut temporal relationship to the use of study device or study procedure and no other possible cause.

6.1.6 Handling & Reporting of Adverse Events

In order to satisfy regulatory requirements, any serious (SAE) and unanticipated adverse events (UADE), whether deemed investigational device-related or not, must be reported to the Sponsor/ Designee as soon as possible after the investigator or coordinator has become aware of its occurrence. The AE CRF page completion and reporting must **not be delayed** even if not all of the information is available at the time of the initial contact. The AE CRF page should be submitted to the Sponsor (Symetis) **within 24 hours** of knowledge of the SAE/ UADE event.

SAE/SADE/UADE notification should be made immediately to Symetis at +41 21 694 0245. Additional follow-up information regarding an already reported SAE must be forwarded to Symetis within 24 hours of the information becoming available.

The procedures for notification of suspected serious unexpected / unanticipated adverse device reactions shall be carried out in accordance with the applicable sections of the Medical Device Directives (MDD) and ISO 14155:2011(E).

SAE/SADE/UADE must be reported to the Ethics Committee and Competent Authority according to local requirements.

The SAE notification procedure for German sites will follow the process describes on the memo called “Procedure SAE reporting to the German Competent Authorities (BfArM)) dated 14 April 2015.

Subjects who have had SAE/SADE should be followed clinically until all parameters (including laboratory) have either returned to normal or have stabilized or are otherwise explained.

Subjects will be carefully monitored during the study for possible adverse events. Any adverse events observed will be fully investigated by the Investigator. Appropriate treatment of the patient will be initiated but the study follow-up will continue. The Investigator will attempt to assess the involvement of the investigational device in the adverse event. All observations and clinical findings, including the nature and severity, will be documented on the appropriate case record forms.

In the event of subject death every effort should be made to obtain a copy of the autopsy report and/or death summary. Information on the cause of death and its relationship to the study device will be determined by the Principal Investigator and recorded on the appropriate CRF. Copies of an autopsy report, if available, and/or a death summary must be included with this CRF form.

The Data Safety Monitoring Board will review all AE/SAE throughout the first 12 months of study follow-up.

6.2 Study Device Failure/Malfunction

All device failures and malfunctions will be documented and reported in the Procedure CRF and if applicable, on the Adverse Event Form. In the case of a study device failure or malfunction, the study device, if retrievable, must be returned to Symetis for analysis.

6.2.1 Device Failure

A device has failed if it is used in accordance with the Instructions for Use (IFU), but does not perform according to the IFU and negatively impacts treatment.

6.2.2 Device Malfunction

A device malfunction is an unexpected change to the device that is contradictory to the IFU and may or may not affect performance.

6.2.3 Device Misuse

A misused device (one that is used by the Investigator in a manner that is contradictory to the IFU) will not be considered a malfunction.

6.3 Known & Anticipated Risks

Risks that may be associated with TAVI include those risks related to conventional surgical AVR, as well as those related to the implantation of the ACURATE *neo*™

Aortic Bioprosthesis with the ACURATE *neo*™ TA Transapical Delivery System. Those known or anticipated risks are listed below:

- Abnormal pressure gradient
- Access site injury or complications
- Additional valve within a valve (valve-in-valve)
- Air embolism
- Allergic dye reaction
- Aneurysm of the left ventricle
- Aortic dissection
- Arrhythmia
- Bleeding
- Cardiac arrest
- Cardiac tamponade
- Cardiovascular injury including cardiac perforation, aortic rupture or aneurysm
- Conduction defects which may require a permanent pacemaker
- Death
- Device embolization requiring intervention
- Device migration
- Device malposition (potentially causing coronary flow obstruction / occlusion or mitral valve impairment / damage)
- Emergency cardiac surgery
- Fever
- Heart failure
- Hematoma
- Hemolysis
- Hemorrhage
- Hypertension
- Hypotension
- Infection including endocarditis and access site inflammation
- Mitral valve injury
- Myocardial infarction
- Myocardial injury
- Nerve injury
- Non-structural valve dysfunction including implant distortion, improper deployment or sizing
- Paravalvular or intravalvular (central) leak
- Pericardial effusion
- Pleural effusion
- Primary hemolysis
- Renal failure / insufficiency
- Respiratory complications
- Septicemia
- Stroke or transient ischemic attack
- Structural valve deterioration including calcification, thickening, perforation, stenosis, or tearing of the valve leaflets

- Systemic peripheral ischemia
- Thrombosis / thromboembolism
- Valvular thrombosis
- Vascular complications requiring intervention including acute coronary occlusion
- Wound healing disorders

The risks associated with the use of the ACURATE *neo*™ and the ACURATE *neo*™ TA Transapical Delivery System are minimized by requiring that the balloon aortic valvuloplasty (BAV) and the valve implantation procedure are performed by physicians experienced in contemporary transcatheter or percutaneous treatment techniques and trained in the use of the study device.

6.4 External Study Resources

6.4.1 Screening Committee

The Sponsor will appoint a Screening Committee (SC). The role and composition of the SC will be described in the SC charter for this clinical Investigation.

6.4.2 Data Monitoring Committee (DMC)

6.4.2.1.1. Data Safety Monitoring Board (DSMB)

The Sponsor will appoint a Data Safety Monitoring Board (DSMB). Its role and composition will be described in the DSMB charter.
The DSMB will evaluate accumulating safety data to ensure the safety of patients and to identify and relevant clinical trend.

6.4.2.1.2. Clinical Event Committee (CEC)

The Sponsor will appoint a CEC who will be responsible for the adjudication of potential clinical endpoints (endpoints). Its role and composition will be described in the CEC charter.

6.4.3 Clinical Research organization

The Sponsor may transfer any or all of the duties and functions related to the clinical investigation, including monitoring, to an external organization (such as CRO or individual contractor), but the ultimate responsibility for the quality and integrity of the clinical investigation data shall reside with the sponsor. All requirements for applicable standards applying to a Sponsor shall also apply to the external organization as this organization assumes the clinical investigation related duties and function of the sponsor. The Sponsor shall specify in writing any clinical investigation related duties and function assume by the external organization, retaining any clinical investigation related duties and functions not specifically transferred to, and assume by, the external organization. The Sponsor shall be responsible for verifying the existence of an adherence to written procedures at the external organization.

6.4.4 Echocardiography Core Laboratory

All echocardiography-imaging assessments must be sent to a Core Laboratory for independent analysis. The Core Laboratory will analyze echocardiographic data

collected at screening, pre- and post-implant, at 7 days/ Discharge and 30 Days and at 6 and 12 Months follow-up visits. The Core Laboratory will analyze the data per the Core Lab Analysis Plan (CAP)

A separate echocardiography protocol will be provided to each participating clinical center.

7 DATA ANALYSIS & STATISTICS

The ACURATE *neo*™ Aortic Bioprosthesis received the CE mark in June 2014 for implantation using the ACURATE TF™ Transfemoral Delivery System through a transfemoral access. Since market authorization more than 250 procedures have been performed corroborating the safety and performance of the ACURATE *neo*™ Aortic Bioprosthesis. Furthermore, the ACURATE *neo*™ Aortic Bioprosthesis in combination with the ACURATE *neo*™ TA Transapical Delivery System was successfully used in the first in man study (2014-02) with no re-intervention or bail out procedures. Investigator's recommendations regarding the ACURATE *neo*™ TA Transapical Delivery System have been implemented on the final design of the Delivery System and implemented in the current clinical investigation.

Therefore, safety and performance assessment for CE-mark authorization, of the ACURATE *neo*™ Aortic Bioprosthesis in combination with the ACURATE *neo*™ Transapical Delivery System, will be based on the interim safety and performance analysis at 30-days. Main clinical results will be compared with ACURATE TA™ and ACURATE TF™ data on file.

The current clinical investigation is part of a global regulatory strategy. Clinical data from the current study will be also considered for regulatory purposes in Japan. Furthermore, in Japan a clinical investigation is in preparation to evaluate the ACURATE *neo*™ Aortic Bioprosthesis in combination with the ACURATE Transfemoral and Transapical Delivery systems. To avoid bias, the interim analysis of the current study will not be public until the 6-Months primary endpoint is available. Furthermore, the primary and secondary endpoint analysis will be performed after the last eligible patient has completed the 6 and 12 Months follow-up visit respectively.

This protocol follows a multicenter, open-label trial design. Data from all investigation sites will be combined and summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements and accordingly to the statistical analysis plan (SAP).

7.1 Sample Size Calculation

7.1.1 Sample Size Calculation for the primary Endpoint

The sample size defined in the current clinical investigation is part of the global regulatory strategy. The sample size of 60 patients was not defined on the basis of a statistical test and power requirement. Considering the existing mid and long term clinical data with the ACURATE *neo*™ Aortic Bioprosthesis and ACURATE *neo*™ Transapical Delivery System, patient number was defined in order to fulfill the following two characteristics:

1. It must adequately detect any safety signals should they arise
2. It must precisely estimate the various endpoints of the study.

For safety signals, such as MACCE and procedure success, we based our calculation on the risk of experiencing such an event from the ACURATE TA 2009-01 and ACURATE TA 2010-01 clinical investigations (clinical data used for CE-mark including 90 patients,TA90).. From those risks, we determined how many patients would be needed to observe at least one event with a given probability (> 95%). The resulting sample size would be adequate to assess the safety of the device in the sense that:

- It is big enough to detect events with a given high probability;
- The chosen sample size is not too small so that safety cannot be assessed and is inconclusive

For the precision of the point estimates, we based our approach on the precision of the confidence intervals (CI) around those estimates. An analysis of confidence interval precision is analogous to a traditional power analysis, with the half-width of the CI taking the place of effect size and width probability taking the place of power. The CI half-width is the margin of error associated with the confidence interval, the distance between the point estimate and an endpoint. The width probability is the probability of obtaining a confidence interval with at most a target half-width.

The probability of achieving the desired precision (that is, a small interval width) can be calculated either unconditionally or conditionally given that the true mean is captured by the interval. Here we used the conditional form, considering two of its advantages:

- The conditional probability is usually lower than the unconditional probability for the same sample size, meaning that the conditional form is generally conservative.
- The overall probability of achieving the desired precision *and* capturing the true mean is easily computed as the product of the half-width probability and the confidence level

From the ACURATE TA dataset (TA90), we know that the rates for the MACCE (primary endpoint), procedural failure (the inverse of procedural success) and all death at 30 days are respectively: 15.6%, 5.6% and 7.8%. With a sample size of 60, the probability of seeing at least one of the events is reported in the table below:

Endpoint	Probability
MACCE	97%
Procedural failure	>99%
All death	>99%

Therefore we have very high probabilities of identifying safety signals should they arise. For precision around those estimates we will be able to claim with 95% probability that the half width of the 90% CI for the above endpoints is as follows:

Endpoint	90% CI half width
MACCE	8.9%
Procedural failure	6.5%
All death	7.3%

So with 60 patients we will have a 95% chance of being able to correctly claim at the end of the study that:

- For MACCE, the study shows with 90% confidence that MACCE rate at 30 days of is X +/- 8.9%
- For procedural failure, the study shows with 90% confidence that event rate at 30 days of is X +/- 6.5%
- For all death, the study shows with 90% confidence that event rate at 30 days of is X +/- 7.3%

where the Xs are the percentages that we will observe at the end of the study. Those half-width CIs are reasonable and comparable with other valve studies of the same size.

Furthermore, as explained above, the overall probability of achieving the precision based on those half-widths and capturing the true event rate will be 95% x 90% = 85.5% which is quite high. Here CI are computed using the Wilson score interval method. This interval has good properties even for a small number of patients and/or an extreme probability.

This approach can also be used to evaluate the precision around the continuous endpoints that will be used to assess the performance of the ACURATE *neo*™ Aortic bioprothesis delivered using the ACURATE *neo*™ TA Delivery System. Those endpoints are: mean gradient, mean AVA and Peak jet velocity.

The ACURATE *neo*™ Aortic bioprothesis dataset (TF89) for CE-mark submission, reported the following results:

Endpoint	N	Mean	Standard deviation
Mean aortic gradient	79	8.02	2.92
Mean EOA	82	1.77	0.32

PVL		
	N	Percent
Grade 0	25	30.5%
Grade 1	53	64.6%
Grade 2	4	4.9%

For the precision of the confidence intervals around those endpoints we will be able to claim with 95% probability that the half widths of the 90% CI are as follows:

Endpoint	90% CI half width
Mean aortic gradient	0.73
Mean EOA	0.079

Those 90% CI half width values will produce CI that are in line with what is reported in the literature for comparable sized studies. As PVL is a categorical endpoint we model the probability of observing a moderate event (2+ Grade). The probability that the corresponding half width of the 90% CI is reported in the table below:

Endpoint	90% CI half width
PVL (Grades 0 - 1)	5.7%

Also, for PVL, the probability of observing at least one moderate event (Grade 2) is 95% with 60 patients.

All sample size calculation were made using the proc power procedure of SAS 9.3

7.1.2 Interim Analysis

The following data comparison will be performed for the interim analysis:

ACURATE *neo*™ TA Delivery System

Combined data from both pre-market studies of the ACURATE TA™, FIM Study 2009-01 and Pilot Study 2010-01 (TA 90 results) will be compared with results from the ACURATE *neo*™ TA studies. Safety and performance of the ACURATE *neo*™ TA Delivery System will be assessed comparing all cause mortality and the primary performance and 30-days.

Furthermore, MACCE at 30 days, performance endpoints of device success[4] and NYHA functional class improvement from baseline at 30 days will be compared.

ACURATE *neo*™ Aortic Bioprothesis

The ACURATE *neo*™ Aortic Bioprosthesis using the transfemoral access route proved to be safety and performance according to the intended use, and consequently received the CE-mark approval in June 2014. Therefore, in order to corroborate the safety and performance of the Aortic Bioprosthesis using the transapical access route, combined 30 days data addressing the Aortic Bioprosthesis' functionality (PVL grade,

[4] Device success defined as ACURATE *neo*™ implanted in intended location (no migration), no impingement of mitral valve, normal coronary blood flow, aortic insufficiency < Grade 3, mean aortic gradient < 20 mmHg, EOA ≥ 1.0 cm^2 and no further re-intervention performed on the implanted ACURATE *neo*™

AVA/EOA, peak velocity and mean gradient) from the pre-market studies with ACURATE TF™ (TF 89 results) will be compared with the ACURATE TA™ LP study results.

7.2 Population

A patient is considered enrolled in the study as soon as he/she has signed the EC-approved informed consent form, has met all inclusion criteria and did not meet any exclusion criteria and has been approved by the screening committee. The date of enrollment is recorded on the Patient Selection Form and is considered the start of study participation.

The intent-to-treat patient population (ITT) includes all patients enrolled in the study.

Per protocol patient population (PP) includes all patients enrolled in the study and the Delivery System has been placed in the body.

The implanted patient population (IPP) will include all patients enrolled in the study and an ACURATE *neo*™ has been implanted.

7.3 Baseline Characteristics

Patient characteristics assessed during the screening phase will be tabulated for visual comparison. For quantitative variables, the following descriptive statistics will be given: number (n), mean, Standard Deviation (SD), minimum, median and maximum values. For qualitative variables, the frequency and percentage of patients will be provided.

The following parameters will be described at baseline:

- Patient demographics
- Baseline disease characteristics
- Previous interventions or treatments
- Risk scores
- Neurologic assessment
- Functional assessment

7.4 Safety and Device Performance Analyses

The intent-to-treat patient population (ITT) includes all patients enrolled in the study.

The per protocol patient population (PP) includes all patients enrolled in the study and the Delivery System has been placed in the body.

The implanted patient population (IPP) will include all patients enrolled in the study and an ACURATE *neo*™ has been implanted

The device success at 7 days/ Discharge, 30 Days, 6 Months and at 12 months will be evaluated on the implanted patient population. The bioprosthesis performance measurements reported after implantation will also evaluated on the implanted patient population (IPP).

All analyses will be conducted according to the statistical analysis plan (SAP). Any crucial analysis not described in the statistical analysis plan will be specified and justified in the final clinical report.

7.5 Statistical Methods

Continuous variables will by summarized by the number of values (n), number of patients with missing data (missing), mean, standard deviation, median, ranges (minimum and maximum) and first and third quartile, 95% percent confidence interval will be calculated if appropriate.

Categorical variables will by summarized by the frequency and percentage. In general, the denominator for the percentage calculation will be based upon the number of non-missing values available, unless otherwise specified. The corresponding 95% confidence intervals will be calculated, if appropriate.

For time-to-event analysis, Kaplan-Meier survival curves as well as confidence intervals based on the log-log transformation will be reported.

For example, Kaplan-Meier estimates and curves will be done for the following endpoints:

- Device success at 30 Days
- Cardiovascular death at 30 Days
- All-cause death at 30 Days and 12 Months
- MACCE at 30 Days
- VARC2 at 30 Days

For the comparison of categorical variables, statistical differences will be assessed by a chi-square test or a Fisher's exact test as appropriate. For continuous variables comparison, the Student t-test or analysis of variance will be used where appropriate. For non-normal distributed data or where normalization is not possible, non-parametric test will be used (such as Mann-Withney), as appropriate.

All confidence intervals will be computed using the Wilson score interval method given the relative small size of this trial as well as the low expected even rate. All statistical analyses will be two-sided with an alpha level of 5%

7.6 Missing, Unused & Spurious Data

Attempts will be made to complete any missing data. In addition, the means and ranges of all variable distributions and outlying data or improbable combinations of variables will be examined before analysis is undertaken. Queries will be sent to investigators whenever inconsistent or missing data occurred.

8 DATA COLLECTION & REPORTING

8.1 General On-Site Methods/Procedures

Primary data collection will be monitored based on source-documented hospital chart reviews performed by Symetis personnel or its designee(s). Case report forms (CRF) will be completed and forwarded to the appropriate location in an expedited fashion. Each site will be visited regularly to ensure that the study is conducted in full compliance with all applicable regulations and the Clinical Investigation Plan.

A pre-study meeting will be held with each potential investigation site in order to inform the prospective investigator and staff concerning features of the investigational device, Clinical Investigation Plan, applicable regulations and requirements, and expectations of the study, including the number and time frame for subject enrolment, subject selection, informed consent, required clinical data and record keeping. The prospective investigation site will be evaluated to ensure that it has an adequate subject base and can provide sufficient staff and documentation support to conduct the study properly.

The Symetis study manager and site monitor will maintain personal contacts with the investigator and staff throughout the study by telephone, mail, and on-site visits. The monitor will compile and file an observation report at each visit. The study manager and monitor must ensure continued protocol compliance, adequate subject enrolment, accurate data reporting, and accounting of the ACURATE *neo*™ and ACURATE *neo*™ TA Delivery System.

Upon closure of the study at an investigation site, the study monitor will make a final onsite visit. The purpose of this visit is to collect all outstanding study documents, ensure that the investigator's files and case report forms are accurate and complete, review record retention requirements with the investigator, make a final accounting of all study supplies shipped to the investigator, provide for appropriate disposition of any remaining supplies, and ensure that all applicable requirements for the study are met. The observations and actions made at this visit will be documented in a final report for investigators and Symetis.

8.2 Method of Data Collection & Documentation

Symetis will provide the study center with the Clinical Investigation Plan, Case Report Forms, sample Informed Consent Form, and all other necessary study-related documentation. The study manager will oversee all aspects of data quality assurance (form collection, data auditing, and proper monitoring of the study center).

The study centers will adhere to all the requirements specified in this Clinical Investigation Plan. Subject assessments should be obtained for the following visits: screening and/or pre-procedure, procedure, discharge or 7 Days (whichever occurs

first), 30 Days, 6 Months and 1 year post-implantation. Survival status will be obtained at 2 – 5 years post-implantation via telephone check.

The Investigator should make every attempt to follow the subjects and document the information gathered during the follow-up visits on the CRF. The Investigator should encourage subjects to report any address or telephone number changes to site personnel. Subjects will also be informed of the importance of returning for scheduled follow-up visits. If a subject is lost to follow-up, the efforts undertaken to locate the subject should be documented.

8.3 Case Report Form (CRF)

Symetis will provide the study center a CRF for each individual subject. CRF are used to record study data and are an integral part of the study and subsequent reports. The CRF must be accurate and complete. All the data entered into the CRF **must** be supported by source documents (in the subject's medical record). No information should be entered into the CRF before it is first recorded in the subject's medical record. After completion, the Investigator must review and sign the CRF completed for each subject enrolled in the study.

Because of the potential for errors, inaccuracies, and illegibility in transcribing data into the CRF, originals or photocopies of all relevant procedural records and reports, post-procedural examinations, laboratory and other test results should be kept on file in each subject's medical file as permissible by each site's record keeping policy. CRF and copies of test results should be available at each monitoring visit for inspection by the study monitor. CRF must be kept current to reflect subject status at each phase during the course of the study.

8.4 Source Documentation Requirements

The Study Coordinator delegated by the Investigator will perform primary data collection drawn from source documentation (medical record) review. Data to be collected for study purposes must not be transcribed directly into the CRF before being recorded first in the patient medical record. The data must be recorded from original source documents and available for review by the study monitor.

8.5 Data Management

Data items from the CRF will be entered centrally into the study database. Discrepancies will be checked against the original source documentation and any required corrections will be made to the database. The data will then be fully validated, using study-specific range and consistency checks and database listings. Obvious error is corrected and a query will be sent to the clinical designee for confirmation of the correction by the investigator. Other errors or omissions will also be sent to the

clinical designee for resolution by the investigator. Resolved queries are signed by Investigator and corrected data entered into the database.

8.6 Data Quality Control & Quality Assurance Procedure

Data validation will be completed on a regular basis. Quality control audits of all key performance and safety data in the database will be made after the sites complete enrolment. The entire database will be re-validated to ensure that there are no outstanding data discrepancies, prior to database lock. Any changes to the database after that time will require joint written agreement between Symetis and the PI. Adverse events entered into the database will be reviewed and assigned the appropriate codes by qualified personnel.

8.7 Study Records Retention

It is the responsibility of the investigator to maintain a comprehensive and centralized filing system of all relevant study documentation. Investigators will be instructed to retain all study records required by Symetis and regulatory authorities in a secure and safe facility with limited access for one of the following time periods based on sponsor notification:

- A period of at least two years after discontinuation of clinical development of the investigational product as confirmed by Symetis;
- Or longer if required by local or international regulations.

The investigator will be instructed to consult with Symetis before disposal of any study records and to provide written notification to Symetis of any change in the location, disposition, or custody of the study files.

9 MONITORING

9.1 Description of Monitoring Methods

Symetis and/or their designee will oversee the progress of this clinical trial and ensure it is conducted, recorded, and reported in accordance with:

- The Clinical Investigation Plan, standard operating procedures, applicable country specific regulatory requirements and the International Conference for Harmonization Good Clinical Practice (ICH-GCP) regulations and guidelines;
- European Standard EN ISO 14155:2011: Clinical investigation of medical devices for human subjects - Good clinical practice.

Furthermore, the investigator must comply with the requirements of the Declaration of Helsinki or with the laws of the country - whichever will afford greater protection to the subject.

9.2 Monitoring Plan

A monitoring plan will be used to detail the roles and responsibilities of the study manager and the study monitor. All monitoring activities will be conducted according to the Clinical Investigation Plan, ICH GCP Guidelines, ISO 14155:2011(E), and all applicable regional regulations and any study specific processes developed by Symetis or its designees.

The study manager will ensure adherence to the Clinical Investigation Plan, oversee recruitment rates and adherence to follow-up schedules, as well as ensure timely data collection, review and quality.

The study monitor will ensure accurate data recording on the CRF and will perform monitoring visits on a regular basis and as required. The study monitor shall inform the Sponsor of any issues related to facilities, technical equipment or medical staff at the study centers. The Principal Investigator and/or designee shall permit and assist the study monitor in the verification of completed CRF against data in the source documents.

During the trial the study monitor will review all Patient Informed Consent Forms (PIC Forms) and the process for obtaining the PIC. The study monitor shall also be responsible for notifying such deficiencies, in writing, to the related site's Principal Investigator and convene with the study center personnel for appropriate re-training and timely corrective actions.

The study monitor shall submit written reports to the Sponsor, after each monitoring visit or contact with the Investigator or site.

9.3 Deviation from Clinical Investigation Plan

A study deviation is defined as an event where the Principal Investigator or site personnel did not conduct the study according to the Clinical Investigation Plan or the Clinical Investigator Agreement.

Principal Investigators are required to obtain prior approval from Symetis before initiating deviations from Clinical Investigation Plan, except where necessary to protect the life or physical well being of a subject in an emergency. Such approval shall be documented in writing and maintained in clinical study management and investigator files. When unforeseen circumstances occur that are beyond the Investigator's control, (e.g. subject did not attend scheduled follow-up visit, blood sample lost by laboratory, etc.) the event is still considered a deviation.

Deviations shall be reported to Symetis regardless of whether or not they are medically justifiable, pre-approved by Symetis, or taken to protect the subject in an emergency. Subject specific deviations will be reported on a CRF. Non-subject specific deviations (e.g. unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a physician who has not signed an investigator agreement, etc.) will be reported to Symetis in writing. Investigators will also adhere to procedures for reporting study deviations to the Ethics Committee in accordance with their specific reporting polices and procedures.

International Regulatory Body regulations require that Investigators maintain accurate, complete and current records, including documents showing the dates of and reasons for each deviation from the Clinical Investigation Plan.

For reporting purposes, Symetis classifies study deviations as major and minor:

Major deviation: Any deviation from subject inclusion and exclusion criteria, failure to obtain subject informed consent and deviations affecting subject safety.

Minor deviation: Any deviation from the Clinical Investigation Plan such as incomplete/inadequate subject testing procedures, non-compliance with medication regimens, follow-up visits performed outside of specified time windows, etc.

The site will receive a list of deviations on an annual basis as part of the Annual Progress Report and as part of the Final Report upon completion of the study.

10 QUALITY CONTROL & QUALITY ASSURANCE

10.1 Quality Assurance Program

This clinical trial may be audited according to the Symetis Quality Management System (QMS) program or a Symetis designee. The purpose of these audits is to determine whether or not the study is being conducted and monitored in compliance with the protocol as well as recognized GCP guidelines and regulations. These audits will also increase the likelihood that the study data and all other study documentation can withstand a subsequent inspection by any regulatory authority. Such audits, if necessary, will be pre-arranged with the site and conducted within a reasonable time frame.

10.2 Regulatory Inspections

The study may be inspected by regulatory agencies including the related authorities in Japan. These inspections may take place at any time during or after the study and are based on the national regulations, as well as ICH Guidelines.

11 RESPONSIBILITIES

11.1 Investigator Responsibilities

For the purposes of this study, there will be a Principal Investigator (PI) at each study center. The responsibilities of the PI(s) comply with the requirements set forth in:

- The Declaration of Helsinki by the World Medical Association *(October 2013)*;
- Local laws of the country including regulations of the European Union.

Additional responsibilities of the PI comprise:

- Submit the Clinical Investigation Plan (CIP) and the Patient Informed Consent (PIC) to the EC;
- Submit proposed amendments of the CIP and PIC to the EC and await written approval;
- Ensure the Clinical Study Agreement (CSA) is approved/executed by the site prior to enrolment initiation;
- Obtain **written informed consent** of the subjects;
- Enrol subjects, execute the study, and transcribe data from source documents to CRF;
- Conduct the study in accordance to the CIP;
- Submit annual progress reports, final reports, and Adverse Events reports to the EC and the Sponsor;
- Record the receipt, disposition, and return of the investigational devices;
- Ensure full access to source documents for the study monitor;
- Retain records for at least two years, or longer if requested by the sponsor, following completion of the study except country specific requirements.

11.2 Sponsor Responsibilities

Sponsor responsibilities that require PI cooperation and assistance:

- Assure EC written approval of the CIP and PIC is obtained by the investigator;
- Select and train investigators;
- Conduct the site initiation visit;
- Obtain CSA and Curriculum Vitae of investigator(s);
- Provide investigational devices and supplies;
- Investigate unanticipated, device related AE;
- Document protocol deviations and violations ;
- Conduct periodic monitoring visits;
- Verify the source documents for accuracy, completeness, and logical flow of the CRF, and carefully look at any AE to report;
- Review investigator's files for accuracy, and completeness;
- Conduct ongoing review of site for continued ability to conduct study;
- Assure PIC are obtained, assure EC review is current;
- Check for CIP compliance, document deviations and violations;
- Prepare reports of visits

12 ETHICAL & REGULATORY CONSIDERATIONS

12.1 Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki, or with the International Conference for Harmonization of Good Clinical Practice (ICH-GCP) regulations and guidelines, Singapore Regulations, including Health National Consul Resolution 196/96 and all its complimentary Resolutions whichever affords the greater protection to the subject.

12.2 Competent Authorities

The procedures laid out by the local regulatory authorities must be followed and documents must be submitted to all concerned authorities, and where needed, approved before a clinical study may commence.

12.3 Ethics Committee

Each participating site must justify for the review and approval of this protocol and the associated informed consent by an appropriate ethics review committee. Any amendments to the protocol or consent materials must also be approved before they are brought into use.

Prior to study initiation, the Investigator will submit the Clinical Investigation Plan (CIP) and the Patient Informed Consent (PIC) Form to his/her EC for review and approval. Insurance coverage has been obtained from Symetis to conduct this clinical trial in all countries and investigation sites. Insurance certificate is mandatory to receive EC review and approval.

A written statement by the EC indicating approval of the PIC and CIP must be submitted to the Sponsor prior to subject enrollment. Approvals for continuation of the trial must also be forwarded to Symetis. EC will receive annual and final reports on study progress and regular adverse event reports.

Ethics Committee responsibilities for this trial:

- Review and approve, modify or disapprove the CIP;
- Review and approve, modify or disapprove the PIC.
- Determination significant risk or non-significant risk of the investigational device.

12.4 Informed Consent Process

Informed consent is a process that is initiated prior to the patient's agreement to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the patients and their families. Consent forms describing in detail the study interventions/products,

study procedures and risks are given to the subject and written documentation of informed consent is required prior to starting intervention. Consent forms will be EC-approved in the native language of the country and the patient will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the patient and answer any questions that may arise. **The patient will sign the informed consent document prior to any new procedures being carried out specifically for the study.** The patient should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subject may withdraw consent at any time throughout the course of the trial.

A copy of the PIC will be given to the subjects for their records. The original signature PIC will be kept by the investigator and a copy will be placed in the patients' medical record. The subjects' rights and welfare are protected by emphasizing that the quality of their medical care is not adversely affected if they decline to participate in this study.

A patient will be considered a "subject" and ***eligible*** to be enrolled into the trial once the PIC is signed and dated. Only after screening has determined that all inclusion criteria are met, no exclusion criteria are met and the patient has signed the PIC, will the subject be considered ***enrolled*** in the study. The enrollment date is entered on the Patient Selection Form 2 to denote enrollment and start date of study.

12.5 Subject Confidentiality

All subject data will be identified with the unique patient identifier number. After obtaining subject's consent, the investigator will permit the study monitor, independent auditor or regulatory agency personnel to review that portion of the subject's medical record that is directly related to the study. This shall include all study relevant documentation including subject medical history to verify eligibility, laboratory test result reports, admission/discharge summaries for hospital admissions occurring while the subject is in the study, and autopsy reports for deaths occurring during the study (where available). All data will be kept confidential.

12.6 Clinical Trial Insurance

Symetis represents that it has an insurance program, insuring against the perils of bodily injury, and property damage. -

Symetis has arranged for Clinical Trial Insurance through policies written in accordance with the legal requirements of those countries in which the clinical investigations are planned. Evidence upon request of said Insurance will be supplied to each medical facility involved in the clinical investigation. A sample copy of the patient Informed Consent detailing the potential benefits and risks associated with the procedure is available upon written request. This consent clearly states the legal position for subjects participating in the clinical investigation. The patient Informed Consent will be provided to the subjects in his/her native language for signature prior to the first screening procedure.

13 PUBLICATION POLICY

Results of the investigation may be used in support of market approvals or expanded product claim. Results may also be published in peer- reviewed scientific journals, and/or presented at scientific symposia.

At various milestones in the investigation, including the conclusion, it is intended that multi- center papers will be published, in peer-reviewed scientific journals and scientific meetings. These publications/ presentations will be co-ordinated by Symetis via the Principal Investigator.

Publication of any study results related to investigational product or a comparison of investigational product with commercial product based on study results are subject to Sponsor review prior to article, manuscript or abstract submission or presentation. Sponsor retains the right to review and comment on manuscript/ presentation within sixty (60) days of receipt. If a multi-center publication is not issued after 1 year from the conclusion of the investigation (final database closure), single- center results may be published with review by Symetis within 60 days of submission. Exceptions to this rule require prior approval from Symetis.

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APPENDICES

A: Schedule of Procedures/Evaluations
B: NIH Stroke Scale (NIHSS) and Mini Mental State Exam (MMSE)
C: Logistic EuroSCORE
D: STS Risk Calculator
E: New York Heart Association (NYHA) Functional Classification

Appendix A: Schedule of Procedures/Evaluations

Assessments	Screening / Pre-procedure	Procedure to 24H	DC / 7D	30D	6M 180 - days	12M 360 days	2-5Y
Physical Assessment & Subject Evaluation							
Informed Consent	X						
Complete medical history & physical examination	X**						
Risk Scores: Logistic EuroSCORE I and II & STS Calculation	X**						
NYHA Functional Classification ****	X**		X	X	X	X	X
mRS ****, NIH Stroke Scale****, Mini-Mental State Exam	X**		X	X	X	X	
AE Query **(ECG & doctor's notes required for all VARC 2 endpoints)**		X	X	X	X	X	X
DAPT	X*	X	X	X			
ASA	X	X	X	X	X	X	X
Cardiac medications	X**						
Telephone check							X
Laboratory Measurements							
CBC with differential (RBC + WBC)	X*	X	X	X	X	X	
Cardiac Enzymes (Troponin I or T and/or CK/CK-MB)	X*	X	X	X			
Creatinine (Cr) and lactate dehydrogenase (LDH)	X*	X	X	X	X	X	
Coagulation Profile (PT, PTT,or aPTT, INR)	X*	X	X	X			
Non-Invasive Testing							
12-lead ECG (**Required for all VARC 2 endpoints in first year**)	X**	X	X	X	X	X	
TTE	X**	X***	X	X	X	X	
TEE	X***	X	X***	X***	X***	X***	
CT Scan of cardiac anatomy from LV to aortic outflow tract	X**						
Invasive Testing							
Angiography	X***	X					

**Must be performed no more than 24 hours prior to procedure but before implant*
***Must be performed no more than 30 days prior to procedure but before implant*
****Optional*
***** Must be evaluated by a physician*

Appendix B: NIH Stroke Scale (NIHS), Mini Mental State Exam (MMSE), modified Ranking Scale

N I H
STROKE
SCALE

Patient ID# _____
.....Site ID# _____

Date of Exam: _____/_____/_____ Time: _____:_____

Interval: □ Pre-procedure □ Prior to discharge

4. Facial Palsy: Ask – or use pantomime to encourage – the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barriers obscure the face, these should be removed to the extent possible.	**0= Normal** symmetrical movements. **1= Minor paralysis** (flattened nasolabial fold, asymmetry on smiling). **2= Partial paralysis** (total or near-total paralysis of lower face). **3= Complete paralysis** of one or both sides (absence of facial movement in the upper and lower face).	____
5. Motor Arm: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine). Drift is scored if the arm falls before 10 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice.	**0= No drift;** limb holds 90 (or 45) degrees for full 10 seconds. **1= Drift;** limb holds 90 (or 45) degrees, but drifts down before full 10 seconds; does not hit bed or other support. **2= Some effort against gravity;** limb cannot get to or maintain (if cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity. **3= No effort against gravity;** limb falls. **4= No movement.** **UN= Amputation** or joint fusion, explain: _____ **5a. Left Arm** **5b. Right Arm**	____
6. Motor Leg: The limb is placed in the appropriate position: hold the leg at 30 degrees (always tested supine). Drift is scored if the leg falls before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime, but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic leg. Only in the case of amputation or joint fusion at the hip, the examiner should record the store as untestable (UN), and clearly write the explanation for this choice.	**0= No drift;** leg holds 30-degree position for full 5 seconds. **1= Drift;** leg falls by the end of the 5-second period but does not hit bed. **2= Some effort against gravity;** leg falls to bed by 5 seconds, but has some effort against gravity. **3= No effort against gravity;** leg falls to bed immediately. **4= No movement.** **UN= Amputation** or joint fusion, explain: _____ **6a. Left Leg** **6b. Right Leg**	____
7. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, ensure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion, the examiner should record the score as untestable (UN), and clearly write the explanation for this choice. In case of blindness, test by having the patient touch nose from extended arm position.	**0= Absent**. **1= Present in one limb.** **2= Present in two limbs.** **UN= Amputation** or joint fusion, explain: _____	

		_____
8. Sensory: Sensation or grimace to pinprick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas (arms [not hands], legs, trunk, face) as needed to accurately check for hemisensory loss. A score of 2, "severe or total sensory loss," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will, therefore, probably score 1 or 0. The patient with brainstem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic, score 2. Patients in a come (item 1a=3) are automatically given a 2 on this item.	**0= Normal;** no sensory loss**.** **1= Mild-to-moderate sensory loss;** patient feels pinprick is less sharp or is dull on the affected side; or there is a loss of superficial pain with pinprick, but patient is aware of being touched. **2= Severe to total sensory loss;** patient is not aware of being touched in the face, arm, and leg.	_____
9. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. For this scale item, the patient is asked to describe what is happening in the attached picture, to name items on the attached naming sheet and to read from the attached list of sentences. Comprehension is judged from responses here, as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in a coma (item 1a=3) will automatically score 3 on this item. The examiner must choose a score for the patient with stupor or limited cooperation, but a score of 3 should be used only if the patient is mute and follows no one-step commands.	**0= No aphasia;** normal. **1= Mild-to-moderate aphasia;** some obvious loss of fluency or facility of comprehension, without significant limitation on ideas expressed or form of expression. Reduction of speech and/or comprehension, however, makes conversation about provided materials difficult or impossible. For example, in conversation about provided materials,examiner can identify picture or naming card content from patient's response. **2= Severe aphasia;** all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener. Range of information that can be exchanged is limited; listener carries burden of communication. Examiner cannot identify materials provided from patient response. **3= Mute, global aphasia;** no usable speech or auditory comprehension.	_____
10. Dysarthria: If patient is thought to be normal, an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barriers to producing speech, the examiner should record the score as untestable (UN), and clearly write an explanation for this choice. Do not tell the patient why he or she is being tested.	**0= Normal.** **1= Mild-to-moderate dysarthria;** patient slurs at least some words and, at worst, can be understood with some difficulty. **2= Severe dysarthria;** patient's speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. **UN= Intubated** or other physical barrier, explain: _____	_____
11. Extinction and inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.	**0= No abnormality.** **1= Visual, tactile, auditory, spatial, or personal inattention** or extinction to bilateral simultaneous stimulation in one of the sensory modalities. **2= Profound hemi-inattention or extinction to more than one modality;** does not recognize own hand or orients to only one side of space.	_____

The Mini Mental State Examination (MMSE) is the most commonly used test for complaints of memory problems or when a diagnosis of dementia is being considered. This guide is intended to provide information about the MMSE so that that you can be prepared for the test.

The MMSE is the test that the NHS recommends for deciding whether a drug treatment for Alzheimer's disease should be prescribed. NHS guidance recommends that you should score 12 points or more out of a maximum of 30 points to be considered for treatment with donepezil (Aricept), rivastigmine (Exelon) or galantamine (Reminyl).
The MMSE is a series of questions and tests, each of which scores points if answered correctly. If every answer is correct, a maximum score of 30 points is possible. People with Alzheimer's disease generally score 26 points or less.
Important: This is not a test for Alzheimer's disease. There are many other reasons why you might score less than 26 points.

Section 1: Orientation

The first 10 points are gained for giving the correct date and location. For example:

- What is the day of the week?
- What year was last year?
- What is the street name?
- What building are we in?

Section 2: Memory (part 1)

The first part of the memory test tests the ability to remember immediately three words. You will be given the names of three objects to remember – table, ball and pen, for example.
You will then be asked to repeat the three names, scoring 1 point for each object correctly recalled (3 points maximum).
If you can't remember all three objects, the person testing you will repeat the words. However, you only score points on the first attempt.
You should try to remember the three items as you will be asked to recall them later in the test.

Section 3: Attention and calculation

The next part of the MMSE tests the ability to concentrate on a tricky task. Two different tests are used, and the best of the two scores is included in the final score.
You will be asked to count backwards. For example, start at 50 and count backwards by 5. One point is given for each correct subtraction, with a maximum of 5 points.
You may also be asked to spell a word backwards such as 'lunch'. Again, the maximum score is 5.

Section 4: Memory (part 2)

You will now be asked to recall the three items from Section 2. The attention and calculation section may have been quite a stressful experience, so this can be tricky.
One point is given for each correctly recalled object. Sometimes the person doing the testing will drop hints!

Section 5: Language, writing and drawing

The final part of the test makes an assessment of spoken and written language, and the ability to write and copy.
The person being tested is shown two everyday items – a hammer and a crayon, for example – and asked to name them. You score 1 point for each correct answer. You will then be asked to say aloud a tongue-twister sentence such as 'Pass the peas please'.

Correctly repeating the sentence gains 1 point. The sentence is always the same, so is worth practicing once you have heard it the first time.
You will then be given a piece of paper, and asked to carry out a three-step process: 'Take this paper in your hand' (1 point); 'Fold it in half' (1 point); 'Place it on this chair' (1 point). One point is gained for each correctly completed step. The instruction is given only once, but as with the tongue-twister, the task is **always** the same.

A card is then shown with an instruction for a simple task – 'Clap your hands'. If you clap your hands you score 1 point.
The next stage of the test is to write a sentence on a piece of paper. The sentence needs to make sense.
One point is scored for an acceptable sentence, and this is again something that can be practised in advance. Examples of acceptable sentences include:

- 'It's a lovely day today.'
- 'My name is Roger.

Finally, your ability to copy a design of two intersecting shapes is assessed. One point is awarded for correctly copying it. All angles on both figures must be present, and the figures must have one overlapping angle.

This is the end of the test.
You should ask for your score and ideally have it written down for you to take away. If you feel that you haven't done the test very well, perhaps because of nervousness, or simply because you were having a bad day, you could ask for the test to be repeated on another day.

MODIFIED RANKIN SCALE (MRS)

Patient Name: _____

Rater Name: _____

Date: _____

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

TOTAL (0–6): _____

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Appendix C: EuroSCORE (www.euroscore.org)

EuroSCORE Risk Profile

Patient Name *Enter name here* **Date of Birth** **Patient number** *Enter number here*	**Date** *Enter Date here* **Surgeon** *Enter surgeon here*

Operation *Enter operation here*

Notes

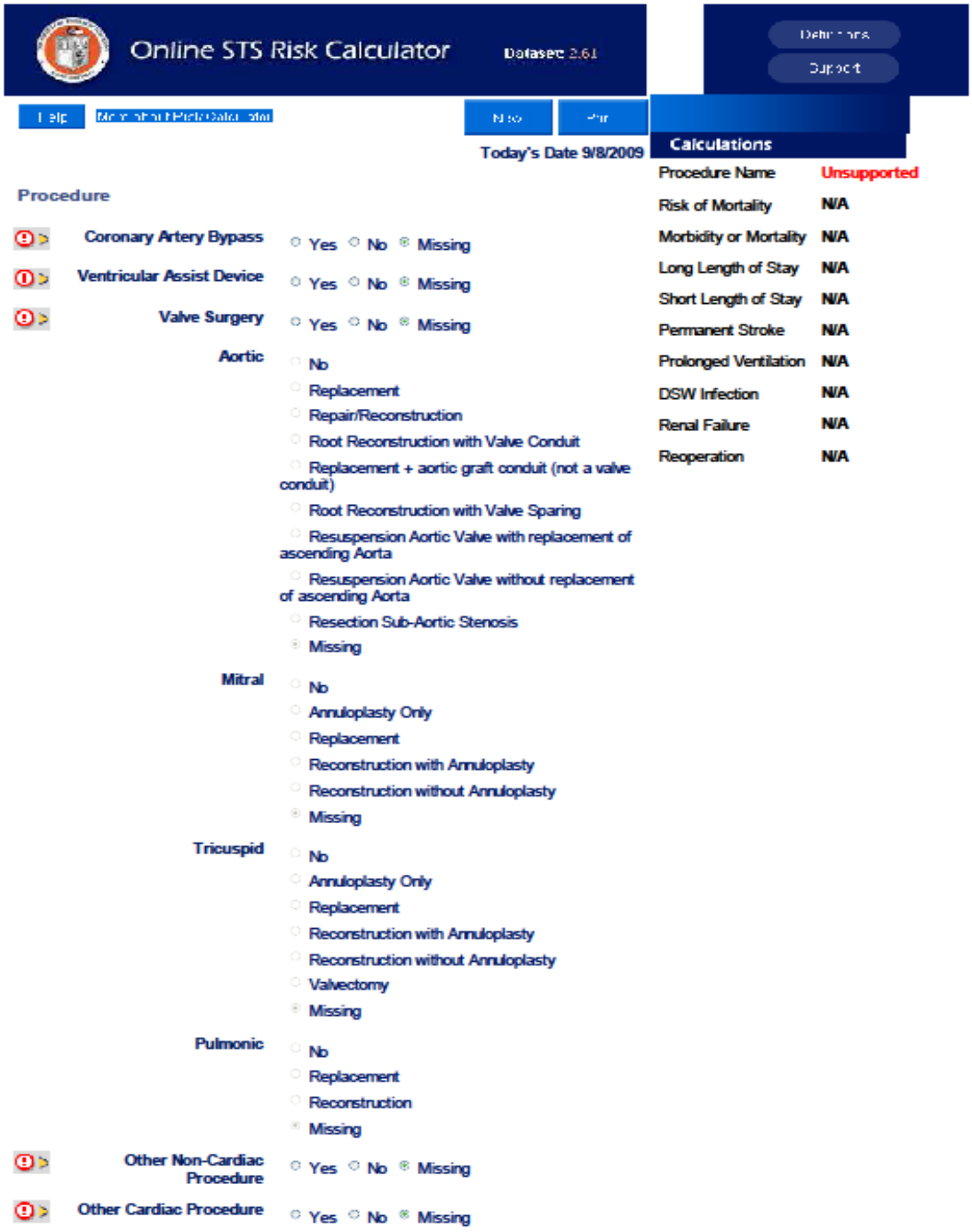
		Additive **EuroSCORE** Φ	***Logistic*** **EuroSCORE** βi Xi
Patient Factors			
Age			
Sex	☐ Female		
Chronic pulmonary disease	☐ Yes		
Extracardiac arteriopathy	☐ Yes		
Neurological dysfunction	☐ Yes		
Previous cardiac surgery	☐ Yes		
Serum creatinine >200 µmol/ L	☐ Yes		
Active endocarditis	☐ Yes		
Critical preoperative state	☐ Yes		
Cardiac Factors			
Unstable angina	☐ Yes		
LV dysfunction moderate or LVEF 30-50%	☐ Moderate		
Lv dysfunction poor or LVEF<30	☐ Poor		
Recent myocardial infarct	☐ Yes		
Pulmonary hypertension	☐ Yes		
Operation Factors			
Emergency	☐ Yes		
Other than isolated CABG	☐ Yes		
Surgery on thoracic aorta	☐ Yes		
Postinfarct septal rupture	☐ Yes		
EuroSCORE		ΣΦ	$e^{(-4.789594 + \Sigma\beta i\ Xi)} / 1 + e^{(-4.789594 + \Sigma\beta i\ Xi)}$
Downloaded from http://euroscore.org		**0**	

Beta coefficients for the Logistic regression model of EuroSCORE

Patient-related factors		***Beta***
Age	Continuous	0.0666354
Sex	female	0.3304052
Chronic pulmonary disease	longterm use of bronchodilators or steroids for lung disease	0.4931341
Extracardiac arteriopathy	any one or more of the following: claudication, carotid occlusion or >50% stenosis, previous or planned intervention on the abdominal aorta,limb arteries or carotids	0.6558917
Neurological dysfunction disease	severely affecting ambulation or day-to-day functioning	0.841626
Previous cardiac surgery	requiring opening of the pericardium	1.002625
Serum creatinine	>200m micromol/L preoperatively	0.6521653
Active endocarditis	patient still under antibiotic treatment for endocarditis at the time of surgery	1.101265
Critical preoperative state	any one or more of the following: ventricular tachycardia or fibrillation or aborted sudden death, preoperative cardiac massage, preoperative ventilation before arrival in the anaesthetic room,preoperative inotropic support, intraaortic balloon counterpulsation or preoperative acute renal failure (anuria or oliguria<10 ml/hour)	0.9058132
Cardiac-related factors		***Beta***
Unstable angina	rest angina requiring iv nitrates until arrival in the anaesthetic room	0.5677075
LV dysfunction	moderate or LVEF30-50%	0.4191643
	poor or LVEF <30	1.094443
Recent myocardial infarct	(<90 days)	0.5460218
Pulmonary hypertension	Systolic PA pressure>60 mmHg	0.7676924
Operation-related factors		***Beta***
Emergency	carried out on referral before the beginning of the next working day	0.7127953
Other than isolated CABG	major cardiac procedure other than or in addition to CABG	0.5420364
Surgery on thoracic aorta	for disorder of ascending, arch or descending aorta	1.159787
Postinfarct septal rupture		1.462009

Appendix D: STS Risk Calculator (http://209.220.160.181/STSWebRiskCalc261/de.aspx)

Online STS Risk Calculator **http://209.220.160.181/STSWebRiskCalc261/de.aspx**



Online STS Risk Calculator Dataset: 2.61

Today's Date 9/8/2009

Procedure

Coronary Artery Bypass	○ Yes ○ No ◉ Missing
Ventricular Assist Device	○ Yes ○ No ◉ Missing
Valve Surgery	○ Yes ○ No ◉ Missing
Aortic	○ No ○ Replacement ○ Repair/Reconstruction ○ Root Reconstruction with Valve Conduit ○ Replacement + aortic graft conduit (not a valve conduit) ○ Root Reconstruction with Valve Sparing ○ Resuspension Aortic Valve with replacement of ascending Aorta ○ Resuspension Aortic Valve without replacement of ascending Aorta ○ Resection Sub-Aortic Stenosis ◉ Missing
Mitral	○ No ○ Annuloplasty Only ○ Replacement ○ Reconstruction with Annuloplasty ○ Reconstruction without Annuloplasty ◉ Missing
Tricuspid	○ No ○ Annuloplasty Only ○ Replacement ○ Reconstruction with Annuloplasty ○ Reconstruction without Annuloplasty ○ Valvectomy ◉ Missing
Pulmonic	○ No ○ Replacement ○ Reconstruction ◉ Missing
Other Non-Cardiac Procedure	○ Yes ○ No ◉ Missing
Other Cardiac Procedure	○ Yes ○ No ◉ Missing

Calculations

Procedure Name	Unsupported
Risk of Mortality	N/A
Morbidity or Mortality	N/A
Long Length of Stay	N/A
Short Length of Stay	N/A
Permanent Stroke	N/A
Prolonged Ventilation	N/A
DSW Infection	N/A
Renal Failure	N/A
Reoperation	N/A

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Left Ventricular Aneurysm Repair	○ Yes ○ No ◉ Missing
Ventricular Septal Defect Repair	○ Yes ○ No ◉ Missing
Atrial Septal Defect Repair	○ Yes ○ No ◉ Missing
Batista	○ Yes ○ No ◉ Missing
Surgical Ventricular Restoration	○ Yes ○ No ◉ Missing
Congenital Defect Repair	○ Yes ○ No ◉ Missing
Transmyocard Laser Revasc	○ Yes ○ No ◉ Missing
Cardiac Trauma	○ Yes ○ No ◉ Missing
Cardiac Transplant	○ Yes ○ No ◉ Missing
Arrhythmia Correction Surgery	○ None ○ Permanent Pacemaker ○ Permanent Pacemaker with Cardiac Resynchronization Technique (CRT) ○ Automatic Implatend Cardioverter Defibrillator (AICD) ○ AICD with CRT ◉ Missing
Atrial Fibrillation Correction Surgery	○ None ○ Standard Surgical Maze Procedure ○ Other Surgical Ablative Procedure ○ Combination of Standard and Other Procedures ◉ Missing
Aortic Aneurysm	○ Yes ○ No ◉ Missing
Other	○ Yes ○ No ◉ Missing

Procedure Name **Unsupported**

Appendix E: New York Heart Association (NYHA) Functional Classification

***Class**:*

- ***I*=** No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea

- ***II*=** Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea

- ***III*=** Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea

- ***IV*=** Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased