The Medtronic CoreValve™ Evolut R™ FORWARD Study

Clinical Investigational Plan

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Sponsors		
Global Sponsor		Medtronic Plc., Coronary and Structural Heart Clinical 8200 Coral Sea St NE, MVS 66, Mounds View, MN 55112, United States
Local Sponsors	**Europe**	Medtronic Bakken Research Center BV Coronary and Structural Heart Disease Management Department Endepolsdomein 5, 6229 GW Maastricht, The Netherlands
	Australia	Medtronic Australasia Pty Ltd 97 Waterloo Road, North Ryde, NSW 2113, Australia
	Canada	Medtronic of Canada Ltd. 99 Hereford St., Brampton, ON, L6Y 0R3, Canada
	Latin America	Medtronic Latin America Plc 3750 NW 87th Avenue, Miami, Florida 33178, United States

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Change History record

CIP Change History		
Version	**Summary of Changes**	**Author**
1.0	Initial Release	Rijk de Jong

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SYNOPSIS

Title	Medtronic CoreValve™ Evolut R™ FORWARD Study
Purpose	The study objective is to document the clinical and device performance outcomes of the Evolut R system used in routine hospital practice in a large patient cohort for the treatment of symptomatic native aortic valve stenosis or a stenosed, insufficient, or combined surgical bioprosthetic valve failure necessitating valve replacement.
Design	Prospective, single arm, multi-center, observational, post market study. In Australia and Canada it is a prospective, single arm, multi-center pre-market study.
Product Name	Medtronic CoreValve™ Evolut R™ System
Objectives	Document safety and clinical performance in a large patient cohort in a routine hospital setting
Endpoints	Primary Endpoint: All-cause mortality at 30 days post implant Secondary Endpoints: VARC-2 safety and efficacy endpoints as well as hemodynamic performance metrics (incl. mean gradient, effective orifice area and prosthetic regurgitation)
Study Sites	Up to 60 centers worldwide. Geographies may include Europe, Australia, Middle East and Africa, Latin America and Canada.
Sample Size	Approximately 1000 implanted subjects, consented for follow-up through three years.
Subject Evaluation	For each subject, data will be collected preoperatively, intra-operatively, at hospital discharge, 30 days, 1, 2 and 3 years.
Inclusion Criteria	Patients must meet ALL of the following inclusion criteria: • Symptomatic native aortic valve stenosis or a stenosed, insufficient, or combined surgical bioprosthetic valve failure necessitating valve replacement • Acceptable candidate for **elective** treatment with the Evolut R System and in conformity with the local regulatory and medico economic context • Age ≥80 years **OR** considered to be at high or greater risk for surgical aortic valve replacement (AVR) where high risk is defined as: o Society of Thoracic Surgeons (STS) predicted risk of mortality ≥8% **OR** o Documented heart team agreement of risk for AVR due to frailty or comorbidities. • Geographically stable and willing to return to the implanting site for all follow-up visits • Of legal age to provide informed consent (patient Informed Consent or Data Release Form) in the country where they enroll in the trial • The patient has been informed of the nature of the study, is able and willing to provide consent without assistance from a legal representative and has consented to participate, and has authorized the collection and release of his/her medical information by signing a Patient Informed Consent or Data Release Form.

Exclusion Criteria		Patients are NOT eligible for study participation if they meet ANY of the following exclusion criteria: • Known hypersensitivity or contraindication to aspirin, heparin (HIT/HITTS) and bivalirudin, ticlopidine, clopidogrel, Nitinol (Titanium or Nickel), or sensitivity to contrast media, which cannot be adequately premedicated • Preexisting mechanical heart valve in aortic position • Ongoing sepsis, including active endocarditis • Anatomically not suitable for the Evolut R system • Estimated life expectancy of less than 1 year • Participating in another trial that may influence the outcome of this trial • Need for emergency surgery for any reason
Professional Services		Echo Core Laboratory, Clinical Events Committee, CRO for monitoring in Australia
Global Sponsor		Medtronic Plc., Coronary and Structural Heart Clinical 8200 Coral Sea St NE, MVS 66, Mounds View, MN 55112, United States
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Coordinating Principal Investigators		Prof. Eberhard Grube *Medizinische Klinik u. Poliklinik II* *Universitätsklinikum Bonn* *53105 Bonn, Germany* Prof. Stephan Windecker *Bern University Hospital* *Department of Invasive Cardiology* *3010 Bern, Switzerland*

1 GENERAL INFORMATION

1.1 Introduction

Transcatheter aortic valve implantation (TAVI) has become a routine treatment option at specialized heart centers treating patients with severe aortic stenosis who are at high risk for surgical aortic valve replacement (SAVR). Growing clinical evidence from observational and now randomized controlled studies demonstrates that TAVI provides good hemodynamic outcomes and is an effective and useful treatment for high and extreme risk patients with severe aortic stenosis.[1,2,3,4,5,6,7]

Currently, two different TAVI device systems have been widely used: the balloon expandable Edwards Sapien™ valve (Edwards Lifesciences, Irvine CA, USA), and the self-expanding Medtronic CoreValve System (Medtronic, Santa Ana, CA, USA). The 18 French (Fr) Medtronic CoreValve system (hereafter, "CoreValve") was CE Marked in 2007, and to date, more than 65,000 devices have been sold in more than 70 countries. There is extensive published experience demonstrating the CoreValve system is fulfilling its intended role with a favorable risk/benefit ratio,[8,9,10,11] and large clinical trials in the United States have further demonstrated its safety and effectiveness in patients at extreme[6] and high risk for SAVR.[7]

The CoreValve system is approved for implantation via the transfemoral, subclavian, and direct aortic approaches, and is commercially available in four valve sizes (23 mm, 26 mm, 29 mm, and 31 mm) to accommodate a wide range of patient anatomies. In June 2013, the CoreValve system was also CE approved for use in failed surgical bioprostheses, where the approved indication was expanded to include patients with stenotic or regurgitant surgical aortic bioprostheses.

While there have been significant improvements in TAVI outcomes due to better patient selection, increasing operator experience, and iterations in device technology, important issues remain. Clinical challenges where further advances would be desirable include the occurrence of major procedural complications,[12,13,14] stroke,[15,16,17] paravalvular leak,[18,19] vascular complications,[20,21] and need for new pacemaker insertion.[22,23,24,25]

To this end, Medtronic has developed modifications to the CoreValve frame and delivery catheter system to enable resheathing or full recapture of the device before it is released from the delivery system. These modifications are incorporated in the CoreValve Evolut R™ system (hereafter "Evolut R"). The ability to resheath or recapture the device allows the operator to reposition the bioprosthesis if the initial implant positioning is sub-optimal (too high or too low). This feature is desirable in that it facilitates accurate and precise final positioning and may mitigate risks associated with sub-optimal positioning such as paravalvular leak,[26,27] acute migration,[14] and AV-conduction disturbance related to implant depth.[22]

The 23 mm size Evolut R system was issued the CE mark on 12 August, 2014 on the basis of the established CoreValve clinical data and supportive data from the literature on competitive recapturable technology and represents the first commercial approval of the Evolut R recapture technology.

In October 2013, Medtronic initiated a 60 subject multi-center clinical study in Europe, Australia, and New Zealand to confirm that changes incorporated into the 26 and 29 mm size Evolut R systems have not adversely impacted the established safety and clinical performance of the Medtronic CoreValve System. Taken together, these data demonstrated the Evolut R system is safe, performs as intended, and that the benefits outweigh the risks for use in the intended patient population, resulting in CE marking on 30 January 2015.

1.2 Medtronic CoreValve™ Evolut R™ System

The Evolut R system (manufactured by Medtronic, Plc.) is a recapturable transcatheter aortic valve implantation system, which includes the Evolut R transcatheter aortic valve, the EnVeo™ R delivery catheter system, and the EnVeo™ R loading system.A detailed description of the system components is provided in sections 1.2.1 through 1.2.3.

Additional information on the description of each important component, ingredient, property and principle of operation of the device system/product, including any materials in contact with tissues or body fluids, details of any medicinal products, human and/or animal tissues or their derivatives or other biologically active substances, are on file at Medtronic and can be provided upon request. For Australia, this information can be found in the Investigator's Brochure.

1.2.1 CoreValve™ Evolut™ R Transcatheter Aortic Valve (TAV)

The Evolut R TAV (Figure 2, A) is currently available in three sizes (23 mm, 26 mm and 29 mm), covering an aortic annulus diameter of 18 to 26 mm (Table 1). The Evolut R TAV is comprised of three leaflets and a sealing skirt constructed from gluteraldehyde-fixated porcine pericardium, sewn to a compressible and self-expandable Nitinol support frame. Consistent with the approved CoreValve TAV, the Evolut R TAV is processed with the same anti-mineralization treatment of alpha-amino oleic acid (AOA), a compound derived from oleic acid, a naturally occurring long-chain fatty acid frame.

Table 1. Patient Anatomical Diameters

Bioprosthesis Model	**Bioprosthesis Size**	**Aortic Annulus Diameter**
EVOLUTR-23	23 mm	18 mm–20 mm
EVOLUTR-26	26 mm	20 mm–23 mm
EVOLUTR-29	29 mm	23 mm–26 mm

1.2.2 CoreValve™ EnVeo™ R Delivery Catheter System (DCS) with EnVeo™ R InLine Sheath

The EnVeo R delivery catheter system facilitates the placement of the TAV within the annulus of the aortic valve (Figure 2, B). The catheter assembly is flexible and compatible with a 0.889 mm (0.035-inch) guidewire. The distal (deployment) end of the system features an atraumatic, radiopaque catheter tip and a capsule that covers and maintains the bioprosthesis in a crimped position. The capsule includes a distal flare to enable full recapture of the bioprosthesis after partial deployment. A stability layer is fixed at the handle and extends down the outside of the catheter shaft. It provides a barrier between the

retractable catheter and the introducer sheath and vessel walls, thus enabling the catheter to retract freely.

The EnVeo R InLine Sheath is assembled over the stability layer, which functions as a hemostatic introducer sheath, which effectively reduces the access site size by approximately 4 Fr (the additional diameter of an external introducer sheath) to the capsule diameter (18 Fr), Figure 1. The EnVeo R delivery catheter system is also compatible with an external 18 Fr introducer.

Figure 1. *Illustration of the reduction of the access site size with the Enveo R InLine Sheath (Fr = French; OD = Outer Diameter)*

The catheter packaging contains an integrated loading bath and a removable tray with three rinsing bowls for loading and rinsing the bioprosthesis. The integrated loading bath features a mirror, which aids in accurate placement of the bioprosthesis frame paddles during loading. In addition, the device packaging is swiveled and secured to facilitate the bioprosthesis loading procedure.

1.2.3 CoreValve™ EnVeo R Loading System (LS)

The EnVeo R loading system facilitates manual loading of the TAV into the deployment sheath capsule of the delivery catheter system by gradually reducing the diameter of the bioprosthesis radially to an optimal diameter (Figure 2, C). The manual loading is performed during the procedure prior to implantation. The loading procedure is performed while immersing the loading system, the TAV, and the distal end of the delivery catheter system in cold sterile saline.

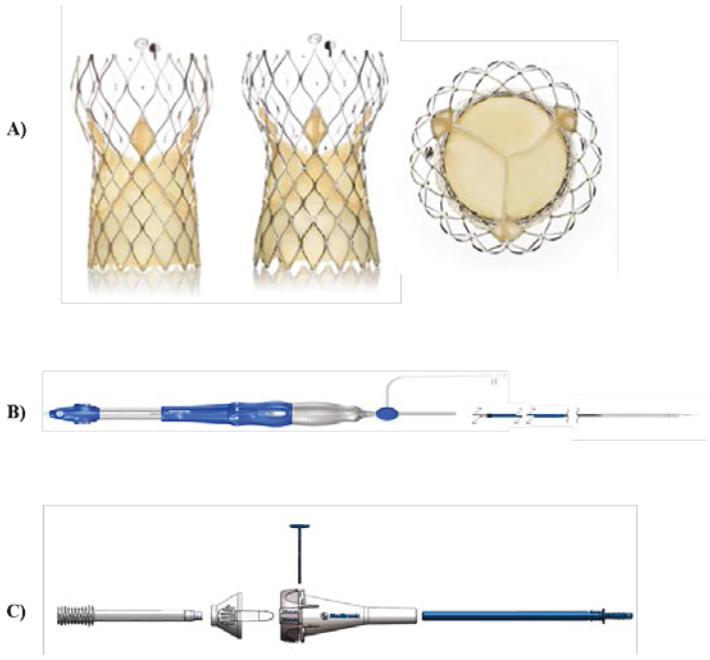


Figure 2 A) *Evolut R 26 mm and 29 mm TAVs (left) and representative top view (right),* ***B)*** *EnVeo R delivery catheter system with the EnVeo R InLine sheath,* ***C)*** *EnVeo R loading system*

For more detailed information on intended use of the device, indications and contraindications, as well as a complete list of warnings, precautions and potential adverse effects, please refer to the IFU (and/or IB for Australia) of device, which is provided with the product and available in the appropriate local language.

Any future CE-Mark approved CoreValve Evolut R models (including TAV, DCS and LS systems) may be used in all participating countries (excluding Australia and Canada) in the study as well.

1.2.4 Intended Use

The Evolut R System is intended for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, to be at high or extreme risk for open heart surgery. The Evolut R TAV treats aortic stenosis by displacing and functionally replacing the dysfunctional native valve with a bioprosthetic valve delivered on a catheter while the heart is still beating, thus avoiding the risks of cardiopulmonary bypass.[28,29,30,31] Its intended performance is to relieve aortic valve stenosis without inducing significant regurgitation, thereby restoring effective aortic valve function. A detailed description of the Evolut R System, including a complete list of indications and contraindications, is provided in the Instructions for Use and Investigator's Brochure (IB).

The intended purpose of the Evolut R System in this clinical study is in line with the intended purpose in the Instruction for Use and IB. The Evolut R system is an investigational device in Australia and Canada and is market approved in all other participating countries; labelling for all devices will be done in compliance with local regulatory requirements.

For necessary training and experience needed to use the Evolut R system – regardless whether the device is investigational or not at the site – refer to section 4.1.1.

2 STUDY PLAN

2.1 Study objectives

The study objective is to document the clinical and device performance outcomes of the Evolut R system used in routine hospital practice in a large patient cohort for the treatment of symptomatic native aortic valve stenosis or a stenosed, insufficient, or combined surgical bioprosthetic valve failure necessitating valve replacement.

2.2 Clinical endpoints

The endpoints used to evaluate the study objective are defined in this section.

2.2.1 Primary endpoint

1. All-cause mortality rate at 30 days post procedure

2.2.2 Secondary Efficacy Endpoints

2. Device success rate at 24 hours to 7 days[i], defined according to the Valve Academic Research Consortium-2 (VARC-2) guidelines as:[32]
   - Absence of procedural mortality, **AND**
   - Correct positioning of a single prosthetic heart valve into the proper anatomical location, **AND**
   - Intended performance of the prosthetic heart valve, defined as the absence of patient-prosthesis mismatch and mean gradient < 20 mmHg (or peak velocity < 3 m/sec), **AND** No moderate or severe prosthetic valve regurgitation.
3. Hemodynamic performance at 24 hours to 7 days (discharge) and 1 year post procedure, including the following hemodynamic metrics as measured by transthoracic echocardiography (TTE) and assessed by an independent core laboratory:
   - Mean prosthetic valve gradient
   - Effective orifice area
   - Degree of prosthetic valve regurgitation (transvalvular, paravalvular, and total)

2.2.3 Secondary Safety Endpoints

4. Early Safety composite endpoint at 30 days post procedure, defined according to the VARC-2 guidelines[32], defined as any of the following components:
   - All-cause mortality
   - All stroke (*disabling and non-disabling*)

[i] Time window for Echo assessment

- Life-threatening bleeding
- Acute kidney injury: stage 2 or 3 (*including renal replacement therapy*)
- Coronary artery obstruction requiring intervention
- Major vascular complication
- Valve-related dysfunction requiring repeat procedure (*BAV, TAVI, or SAVR*)

5. Event rates of the individual components of the VARC-2 composite Early Safety endpoint[32] at 30 days post procedure
6. Rate of new permanent pacemaker implant at 30 days post procedure

2.2.4 Rationale for Selection of Study Endpoints

The basis for the selection of these endpoints includes the following considerations:

- They are clinically relevant and address important safety and efficacy aspects of the Evolut R System.
- They are objectively defined and measurable in the majority of subjects.[ii]
- They are consistent with current recommendations for endpoints in TAVI clinical studies.[34]

2.3 Study population

The study population includes patients with symptomatic native aortic valve stenosis or a stenosed, insufficient, or combined surgical bioprosthetic valve failure necessitating valve replacement who are scheduled for an **elective** transcatheter aortic valve implantation. Patients who will undergo an emergency procedure should not be included in this study.

2.4 Study design

This is a prospective, single arm, multi-center, observational, post market study. In Australia and Canada it is a prospective, single arm, multi-center pre-market study.

Approximately 1000 subjects implanted with the Evolut R system will be included. Subjects will be followed at 1 month, 1, 2 and 3 years after the procedure. Based on clinical assessments during the course of the study, follow up may be extended to up to 5 years post procedure.

Enrollment parameters are included in the study to avoid introduction of bias to the trial results due to disproportionate enrollment. Enrollment shall not exceed 7.5% (75 patients) of the total implanted patients at any individual site. In addition, enrollment shall not exceed 40% (400 patients) of the total implanted patients at any individual country.

Enrollment will be competitive across sites. The per-site and per-country enrollment cap may be increased upon Sponsor approval. There is no set minimum number of patients to be enrolled per site; however there is an expected minimum enrollment of 15 subjects per site.

[ii] In some cases, transthoracic echocardiography can be technically difficult, and image quality may be sub-optimal for assessment of prosthetic regurgitation or hemodynamic performance variables.

At the time when the study-wide enrollment cap of 1000 implanted subjects has been reached, further enrollment into the study will cease regardless of whether individual sites have reached their per-site cap.

The study methods include the following measures to minimize potential sources of bias:

- An external, independent Clinical Events Committee (CEC) will review and adjudicate, at minimum, all deaths and safety endpoint related adverse events. Safety endpoint results will be based on CEC adjudications.
- All sites will follow a standardized protocol for acquisition of echocardiographic endpoint data.
- An Echo Core Lab will evaluate all echocardiograms. Echocardiographic study endpoint results will be based on Core Lab assessments.
- Study sites should follow their institutional procedures for maintenance of echocardiography and laboratory equipment used for assessing the study variables.
- Study monitors will verify patients' data and ensure compliance with the Clinical Investigational Plan and other study requirements.

2.5 Number of investigation sites and study duration

The study will be a multicenter, multinational study conducted at up to 60 investigational sites. These centers may be located in Europe, Middle East and Africa, Latin America, Australia and Canada. Other regions may be added depending on the regulatory status of the device. At the time this Clinical Investigation Plan was finalized not all participating investigation sites were identified. A list of participating investigation sites which includes the name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s). They will be submitted under a separate cover and will be available in the Investigator Site File.

It is anticipated that enrollment will take approximately 18 months. As each implanted subject is to be followed for three years, the estimated study duration is approximately 54 months, excluding the time required for preparing the final report. If each subject will be followed for 5 years, the estimated study duration is approximately 78 months.

2.6 Randomization and blinding

The study is a non-randomized trial and does not require blinding techniques.

2.7 Statistical Methods and Analysis

Any deviations from this section and/or the Statistical Analysis Plan will be described and justified in the Final Clinical Study Report, as appropriate.

2.7.1 Primary Hypothesis

The primary endpoint of the study is the all-cause mortality at 30 days post procedure, which will be compared to a performance goal of 10.0%. Therefore the study hypotheses are:

H_0: $\pi \geq 10.0\%$

H_A: $\pi < 10.0\%$

Where π denotes the binary rate of all-cause mortality rate at 30 days post procedure. This one-sided test will be carried out at the 0.05 significance level using the exact test.

2.7.2 Rationale for Choice of Hypothesis

The performance goal for all-cause mortality at 30 days was established through the following data sources:

1. Data from the CoreValve IDE clinical study
2. Review of the published literature on the Medtronic CoreValve System current through April 2013

Criteria for selection of the articles included the following:

- Study was published in peer reviewed journal
- Study was multi-center
- Results were representative of high risk population
- Results for all-cause mortality were reported by device type
- Study was not a first in man, feasibility, or confined to early Medtronic CoreValve experience

Of the literature reviewed, 4 articles were selected. Information on the historical data is presented in Table 2.

Table 2. *Information on control data sources for all-cause mortality at 30 days*

Author	Study Name	Number of CoreValve Patients	Age (years) Mean ± SD	Logistic Euroscore (%) Mean ± SD	STS Score (%) Mean ± SD	All-Cause Mortality at 30 days (%)
US CoreValve IDE study: Extreme Risk Cohort[1]		639	83 ± 8	23 ± 17	10 ± 6	9.1
US CoreValve IDE study: High Risk Cohort[1]		390	83 ± 7	18 ± 13	7 ± 3	3.3
Bosmans[33]	Belgian Registry	141	82 ± 6	25 ± 15	Not reported	11.0
Gilard[34]	FRANCE 2 Registry	1043	82 ± 7	21 ± 14	14 ± 11	9.4
Chieffo[35]	PRAGMATIC	453	81 ± 7	21 ± 13	8 ± 6	7.5
Moat[36]	UK TAVI Registry	452	81 ± 7	18 (11-28)	Not reported	5.8
Random effects meta-analytic rate						7.3 (95% CI 5.4 - 10.0)

1. Data include all access routes.

The random effect meta-analysis showed that the all-cause mortality rate at 30 days post procedure for

CoreValve was 7.3% with a 95% C.I. of 5.4% to 10.0%. We expect EVOLUT R TAV will have a similar rate as CoreValve, which is 7.3% at 30 days. And the all-cause mortality rate for EVOLUT R will not be higher than the upper bond of the 95% C.I. for CoreValve. Therefore the performance goal was set to 10.0%.

2.7.3 Sample Size Calculation and Methods

The following are assumptions for the sample size estimate:

One-sided alpha = 0.05

π_0 = 10.0%

π = 7.3%

Power = 90%

In the above expressions, π_0 and π denote the Performance Goal (null hypothesis proportion) and true proportion, respectively, for all-cause mortality rate at 30 days. Using an exact binomial test, Power Analysis and Sample Size (PASS) software calculates that a total of 934 evaluable subjects is required to attain 90% power in a one-sided test at the 0.05 level of significance. The final sample size is increased to 1000 evaluable subjects to account for 7% attrition rate.

2.7.4 Analysis of Clinical Data

Subjects who are taken to the procedure room for implantation will comprise the study population evaluated for the study objectives and associated endpoints.

The analysis sets are further defined as follows:

1. **Safety Set.** The safety set includes all subjects who are brought into the procedure room for implantation.
2. **Device Success/ Hemodynamic Performance Set.** The device success/ hemodynamic performance set includes all subjects who are implanted with the Evolut R TAV, defined as the Evolut R TAV is placed in the aortic annulus and completely released from the EnVeo R catheter delivery system.

The Final Report will be prepared when all patients have completed their follow-up evaluations or exited the study. All analyses will be described in a Statistical Analysis Plan (SAP) which will be completed prior to analysis. No interim analysis is planned.

Every effort will be undertaken to minimize missing data. A minimal amount of missing data is anticipated for the primary endpoint. However, if outcome data are missing, the primary analysis will be based on the complete case. And the Kaplan-Meier rate at 30 days and its standard error, as a secondary analysis, will be used in the calculation of the test statistic. To assess the potential impact of these missing data, a sensitivity analysis will be conducted which will include a complete case, a best case (assume missing subjects are alive), a worst-case (assume missing subjects have died), and a tipping point analysis.

Descriptive statistics will be provided for baseline demographic and clinical variables, as well as for the secondary endpoints. For categorical variables the numbers and percentages will be displayed. For

continuous variables the means, medians, standard deviations, and ranges will be presented. For time to event variables, Kaplan-Meier event rates and confidence intervals will be calculated.

No statistical techniques will be used to impute missing data for continuous or categorical outcomes. If a subject's data are missing for any reason, that subject will not be included in that portion of the analysis. The number of subjects included in each analysis will be reported so that the reader can assess the potential impact of missing data.

Additional (annual) reports providing only descriptive statistics will only be written upon request of the EC/IRB and/or Regulatory Authority, as applicable.

3 SUBJECT SELECTION

Subject selection criteria are based on the Instructions for Use of the Evolut R System.

3.1 Inclusion criteria

Patients must meet ALL of the following inclusion criteria:

- Symptomatic native aortic valve stenosis or a stenosed, insufficient, or combined surgical bioprosthetic valve failure necessitating valve replacement
- Acceptable candidate for **elective** treatment with the Evolut R System and in conformity with the local regulatory and medico economic context
- Age ≥80 years **OR** considered to be at high or greater risk for surgical aortic valve replacement (AVR) where high risk is defined as:
    - Society of Thoracic Surgeons (STS) predicted risk of mortality ≥8%
      OR
    - Documented heart team agreement of risk for AVR due to frailty or comorbidities.
- Geographically stable and willing to return to the implanting site for all follow-up visits
- Of legal age to provide informed consent (patient Informed Consent or Data Release Form) in the country where they enroll in the trial
- The patient has been informed of the nature of the study, is able and willing to provide consent without assistance from a legal representative and has consented to participate, and has authorized the collection and release of his/her medical information by signing a Patient Informed Consent or Data Release Form.

3.2 Exclusion criteria

Patients are NOT eligible for study participation if they meet ANY of the following exclusion criteria:

- Known hypersensitivity or contraindication to aspirin, heparin (HIT/HITTS) and bivalirudin, ticlopidine, clopidogrel, Nitinol (Titanium or Nickel), or sensitivity to contrast media, which cannot be adequately premedicated
- Preexisting mechanical heart valve in aortic position
- Ongoing sepsis, including active endocarditis
- Anatomically not suitable for the Evolut R system
- Estimated life expectancy of less than 1 year
- Participating in another trial that may influence the outcome of this trial
- Need for emergency surgery for any reason

4 STUDY PREPARATION PROCEDURES

4.1 Investigator/Investigation site selection

4.1.1 Investigator selection criteria

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical study as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical study.

An investigator may be included in the clinical study if compliant with the following requirements:

- Is appropriately qualified practitioner legally entitled to practice, and experienced in the diagnosis and treatment of patients requiring an aortic valve treatment with a TAVI;
- Prior to their first implant under this study protocol, each participating implanter must have performed - either as first or second implanter - at least 50 cumulative CoreValve implants, of which at least 10 were Evolut R implants;
- The Principal Investigator has demonstrated experience with conducting clinical (device) trials that comply with applicable regulatory standards;
- Principal Investigator, co-investigators, and study staff must be willing to provide their Curriculum Vitae and training evidence;

4.1.2 Investigation site selection criteria

An investigation site may be selected for participation in the clinical study if compliant with the following requirements:

- Site must have sufficient patient population to meet enrollment expectations
- Site must have the presence of an active multi-disciplinary heart team for patient evaluation (refer to section 4.5.2 for more information)
- Site must use Multi Slice Computed Tomography (MSCT) routinely for screening patients
- Site is willing to participate in follow-up of patients for 60 months;
- Site should have adequate staff that is accessible and has time to manage the study for 7 days per week, 24 hours per day;
- Site must be willing to sign and comply with the protocol-specific Clinical Trial Agreement;
- Site must be willing to comply with the Clinical Investigation Plan and data collection requirements, including Adverse Event reporting;
- Site must be willing to comply with all requirements of the relative regulatory agencies, Ethics Committees and Institutional Review Boards.
- Site must have an internet connection with sufficient speed of data transfer.

4.1.3 Clinical Investigation Agreement

A Clinical Investigation Agreement shall be in place, signed by the participating investigation site and/or principal investigator of each investigation site, as per the local legal requirements, and returned to Medtronic prior to the commencement of any clinical study activities. The investigator is indicating

approval of the Clinical Investigation Plan and subsequent amendments, by a fully executed agreement. Amendments to this Clinical Investigation Plan shall be agreed upon between Medtronic and investigator(s) and be recorded with a justification for the amendments.

4.1.4 Curriculum Vitae

An up to date signed and dated Curriculum Vitae from all key members of the investigation site team participating in this clinical study as listed on the Delegated task List shall be obtained, evidencing the required qualifications, including the year and where obtained, and including their current position at the investigation site. The signature on the CV must be dated within 3 years prior to the date of activation of the investigation site.

4.2 Ethics

4.2.1 EC/IRB approval

Prior to enrolling subjects in this clinical study, each investigation site's EC/IRB will be required to approve the current Clinical Investigation Plan, the Patient Informed Consent form or Patient Data Release Form, including any other written information to be provided to the subjects. EC/IRB approval of the clinical study must be received in the form of a letter and provided to Medtronic before commencement of the clinical study at an investigation site. The approval letter must contain enough information to identify the version or date of the documents approved. If this information is not contained in the approval letter, it must be retrievable from the corresponding submission letter. In addition, the approval letter needs to be accompanied by an EC/IRB roster or letter of compliance, to allow verification that the investigator, other investigation site personnel, and/or Medtronic personnel are not members of the EC/IRB. If they are members of the EC/IRB, written documentation is required stating that he/she did not participate in the approval process. If the EC/IRB imposes any additional requirements (e.g. safety reports, progress reports etc.), Medtronic will prepare the required documents and send them to the investigator for reporting to the EC/IRB. Investigators must inform Medtronic of any change in status of EC/IRB approval once the investigation site has started enrolment. If any action is taken by an EC/IRB with respect to the investigation, that information will be forwarded to Medtronic by the respective investigator.

4.2.2 Informed consent process

Patient Informed Consent

The investigator or authorized designee must obtain written informed consent before any clinical study related activity takes place.

Well in advance of the consent discussion, the patient should receive the EC/IRB approved Patient Informed Consent Form. During the consent discussion the investigator or his/her authorized designee must fully inform the patient of all aspects of the clinical study that are relevant to the patient's decision to participate in the clinical study. If a patient is illiterate, an impartial witness must be present during the entire informed consent discussion. All items addressed in the Patient Informed Consent Form must

be explained. The language used shall be as non-technical as possible and must be understandable to the patient and the impartial witness, where applicable.

The patient must have ample time and opportunity to read and understand the Patient Information and the Informed Consent Form, to inquire about details of the clinical study, and to decide whether or not to participate in the clinical study. All questions about the clinical study should be answered to the satisfaction of the patient.

Neither the investigator, nor the investigation site staff shall coerce or unduly influence a patient to participate or to continue to participate in the clinical study. The informed consent process shall not waive or appear to waive the patient's rights.

When the patient decides to participate in the clinical study, the Informed Consent Form must be signed and personally dated by the patient and investigator or authorized designee. If applicable, the witness shall also sign and personally date the consent form to attest that the information in the Patient Information and Informed Consent Form was accurately explained and clearly understood by the patient, and that informed consent was freely given.

After all persons have signed and dated the Informed Consent Form, the investigator must provide the patient with a copy of the Patient Information and the signed and dated Informed Consent Form.

The study data can only be submitted to Medtronic upon fully execution of the Patient Informed Consent Form.

Patient Data Release

The investigator must obtain written Data Release Consent prior to releasing personal information of the subject.

During the consent discussion the investigator or his/her designee must fully inform the subject of the study in a non-technical wording understandable for the subject. If a patient is illiterate, an impartial witness must be present during the entire informed consent discussion.

The subject must have ample time and opportunity to inquire about details of the study, and to decide whether or not to participate in the clinical study. All questions about the study should be answered to the satisfaction of the subject.

When the subject decides to participate in the clinical study, the written Data Release Consent form must be signed and personally dated by the subject and the investigator. If applicable, the witness shall also sign and personally date the Data Release Consent form to attest that the information in the Data Release Consent Form was accurately explained and clearly understood by the patient, and that informed consent was freely given.

After all persons have signed and dated the Data Release Consent Form the investigator must provide the subject with a copy of the signed and dated Data Release Consent form.

The study data can only be submitted to Medtronic upon fully execution of the Data Release Consent Form.

4.2.3 Revisions in Patient Informed Consent and Data Release Form

Medtronic will inform the investigators whenever information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The investigator or his/her authorized designee should inform the subject in a timely manner.

Medtronic will revise the written Patient Informed Consent and Data Release Forms whenever new information becomes available that may be relevant to the subject's confirmed participation in the clinical study. The revised information will be sent to the investigator for approval by the EC/IRB. After approval by the EC/IRB, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated.

4.2.4 Regulatory submission

In countries where submission to the regulatory authority is required per local law, no patients will be enrolled in the clinical study until the particular regulatory authority has approved the current Clinical Investigation Plan of the clinical study and other documents as required according to the local requirements.

If the regulatory authority imposes any additional requirements (e.g. safety reports, progress reports etc.), Medtronic will prepare the required documents and send them to the respective authority, either directly or through the investigational site.

Other documents that are referred to in this Clinical Investigation Plan are listed below and will be made available upon request:

- Patient Informed Consent Form / Patient Data Release Form
- Instructions for Use
- Investigator's Brochure
- Case Report Forms
- Monitoring Plan
- Data Management Plan
- Statistical Analysis Plan

4.3 Regulatory compliance

This clinical study will be conducted in compliance with the latest version of the Declaration of Helsinki (2013), the international standard ISO 14155: 2011 (except for full device accountability and Adverse Event reporting), laws and regulations of the countries in which the clinical study is conducted, including data protection laws, the Clinical Investigation Agreement and the Clinical Investigation Plan. Only in the countries where this is a pre-market study (Australia and Canada), full device accountability will be done.

All principles of the Declaration of Helsinki (2013) have been implemented in this clinical study by means of the informed consent process, EC/IRB approval, study training, clinical trial registration, preclinical testing, risk benefit assessment and publication policy. Pediatric, legally incompetent, or otherwise vulnerable patients are not eligible for the study. Further, the Evolut R system will not be used as an emergency treatment.

The sponsor will avoid improper influence on, or inducement of the subject, monitor, and investigator(s) or other parties participating in, or contributing to, the clinical study by implementing the informed consent process, Clinical Investigation Agreements and EC/IRB approval.

4.4 Training requirements

Prior to investigation site activation or subsequent involvement in clinical study activities, Medtronic or designated local CRO will provide clinical study training relevant and pertinent to the involvement of personnel conducting clinical study activities, including, investigator responsibilities, ISO 14155:2011, the CIP, PIC, use of data collection tools and applicable local regulations.

All study personnel should be trained in accordance to their responsibilities (as documented in the Delegated Task List) and no specific study activities should be performed before training is done.

Training may be conducted via site (initiation) visits, investigator meetings, and/or other media sessions.

4.5 Study Center Investigative Team Members

The following is a description of the key personnel who typically forms the investigative team at each study center.

4.5.1 Principal Investigator

Each center will have at least one Principal Investigator (PI), who is an interventional cardiologist or a cardiothoracic surgeon. The PI has overall responsibility for the conduct of the study at the center, including protecting the rights, safety, and welfare of the study subjects at their center, for the integrity of the study data generated by their center, and for ensuring the study is conducted in compliance with the CIP and their local regulatory and EC/IRB requirements.

4.5.2 Heart Team

A Heart Team will assess individual patient risks as well as the technical suitability of TAVI, including determinations regarding eligibility of the prospective subject for the study as detailed in section 5.1.

Typically the local Heart Team comprises of the following members:

1) A cardiothoracic surgeon
2) An interventional cardiologist
3) An echocardiographer

The PI or delegated Investigator(s) may serve as one of the members of the Heart Team. The PI or delegated Investigator(s) (as documented on the Delegated Task List) is/are responsible for documentation of the Heart Team assessment decision.

Heart Team members who – apart from their involvement in patient evaluation and assessment - do not perform any study specific activity do not need to be trained or delegated on the study.

4.5.3 Cardiologist / Echocardiographer

Each center typically has a designated cardiologist whose responsibility includes the assessment of echocardiograms. Please refer to Appendix B for recommended echocardiogram acquisition guidelines and images.

4.5.4 Other Trial Support Staff

The PI will ensure that the investigative site has the appropriate support staff to maintain the trial. Additional staff may include co-investigators, research coordinators, and other specialized health care professionals. The PI will document authorization of delegated tasks using the Delegation of Tasks Log provided by Medtronic.

4.6 Clinical study materials and clinical study-specific equipment

Medtronic will control the supply of the latest version of the Clinical Investigation Plan and all other materials required to conduct the clinical investigation.
Medtronic will provide the Investigator Site File and e-CRF access to the center upon receipt or completion of the following:

- A signed Clinical Investigation Agreement;
- A copy of the Ethics Committee approval letter, including a membership list or a statement that no Ethics Committee approval is necessary;
- The Ethics Committee and Medtronic approved Patient Informed Consent or Patient Data Release Form
- Regulatory Authority approval/notification, if applicable;
- Delegated Task List (DTL); the Principal Investigator can delegate tasks to the study staff. These tasks must be documented on the Delegated Task List and the study team must have been trained to perform these tasks as documented in the Study Training Form.
- Curriculum Vitae of the Principal Investigator and study staff signed and dated within 3 years prior to center activation date;
- Study team training documentation;

No study-specific equipment will be provided by the sponsor; all exams are performed with hospital equipment and used within standard of care. Maintenance and calibration of study-specific equipment is the responsibility of the investigation site and will be performed per hospital procedures.

4.7 CoreValve Evolut R system traceability

In countries where the Evolut R system is CE-marked and commercially available, the Evolut R system will be obtained by the sites according to standard hospital procedures for commercial products. Existing approved procedures for commercial product regarding distribution, shipment, storage, handling, and return of these devices will be followed. The devices should be used within the intended approved indication. Serial number of implanted Evolut R TAV and LOT number for the Evolut R DCS will be captured in the e-CRF. Additional device traceability is not applicable and a full device tracking as

required by ISO 14155 will not be performed due to the post-market nature of the study (use of the device within its intended labeling).

In countries where the Evolut R system is not approved for commercial use and is considered investigational, the Evolut R system should be stored as labeled and in a secure location. The method of storage should prevent the use of these investigational devices for other applications than mentioned in this CIP.

Medtronic will only allow shipment of investigational devices to the investigation site or investigator, after the Clinical Study Manager has declared the investigation site ready to start the clinical study. Medtronic registers the number of used investigational devices and will only ship additional investigational devices to the investigation site in case a substantial number of the previously shipped devices have been used and the CRFs have been received.

Centers are required to maintain investigational device records that contain the following information:

- Investigational device name
- Serial number
- Lot number (for delivery and loading systems only)
- Date of receipt of device
- Name of person receiving the device
- Name of person using the device
- Date of implant or use
- ID number of subject receiving or using the device
- Disposition (implanted, disposed of, or returned to Medtronic)

For Investigational devices that are returned to Medtronic or disposed of, centers are required to document the following information:

- The device serial numbers
- Lot numbers (for delivery systems only)
- The quantity and reason for the device being returned to Medtronic or disposed of
- Name of the person who returned or disposed of each device
- Date of shipment back to Medtronic

At the end of the trial enrollment period, all remaining investigational devices must be returned to Medtronic.

5 STUDY METHODS

5.1 Screening and Enrollment

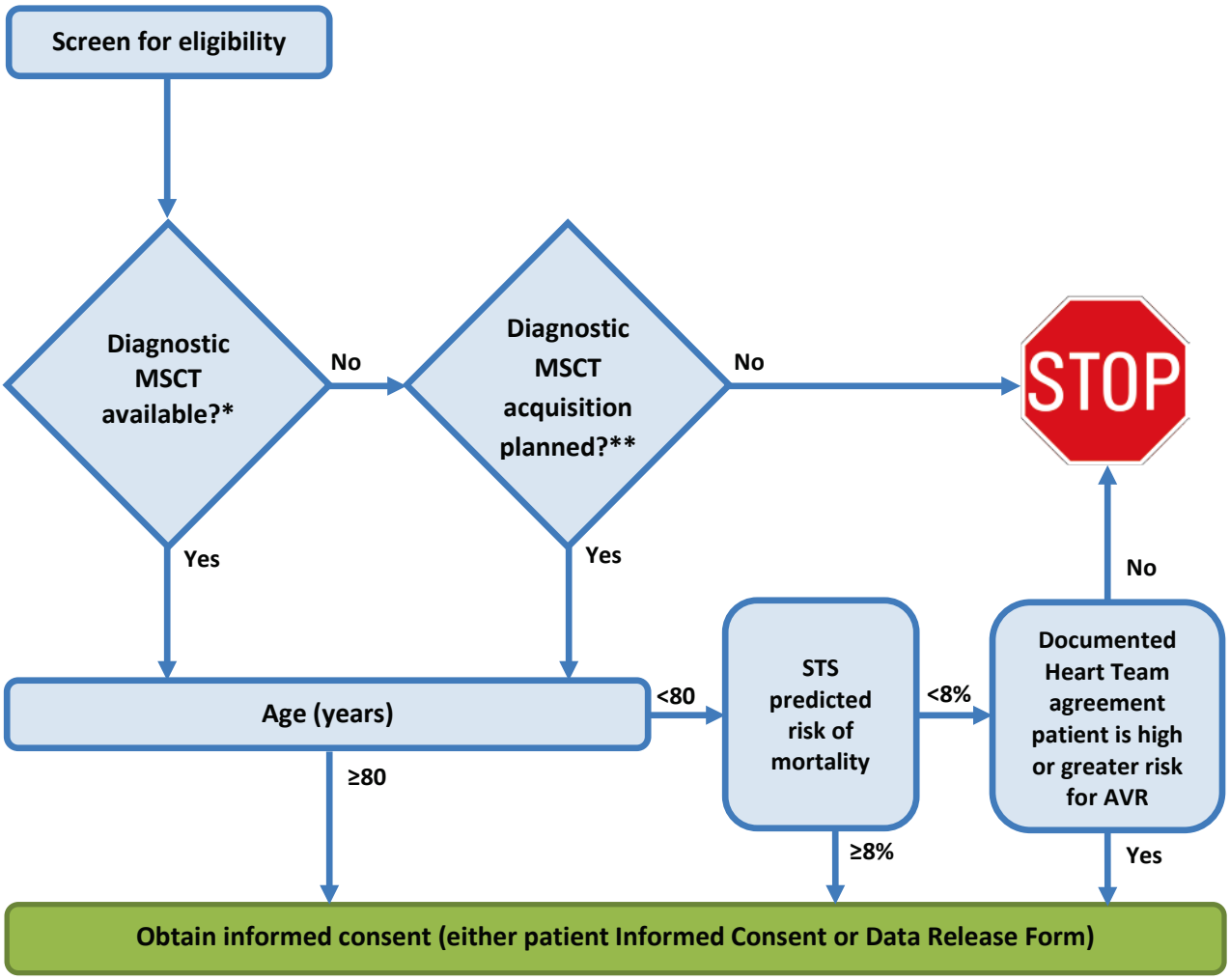
The process of patient screening and subject enrollment is as follows (Figure 3):

1. Patients identified by the study center to have aortic stenosis will be screened by the investigative team for the criteria described in Section 3 using available medical records, including relevant imaging studies that have been previously performed for diagnostic purposes.
    - A recent[iii] Multi-Slice Computed Tomography (MSCT) of the patient's peripheral vasculature and aortic annulus must be available to assess anatomic suitability for Evolut R TAV implantation[iv]. If no recent[iii] MSCT is available or is planned per standard care, the patient should **not** be considered for any further for participation in this study.
2. Evaluate risk profile of the patient based on age and STS score. Patients with age <80 years and a STS predicted risk of mortality of <8% must be evaluated by a heart team to confirm and document the patient is at high or greater risk for AVR due to frailty or comorbidities.
3. If, based on the review of available information, the patient is deemed to be a potential candidate for the Evolut R system and the study, all aspects of the study will be explained to the patient. The patient will then be invited to participate in the study.
4. If the patient agrees to participate, written informed consent (patient Informed Consent or Data Release Form) will be obtained. This will be considered the point of enrollment, and the subject will be assigned a Subject ID number. The site should document in the patient's medical record that the subject gave informed consent (patient Informed Consent or Data Release Form). Furthermore, the subject shall be provided with a copy of the signed Patient Informed Consent or Patient Data Release Form.

Centers will maintain a log of patients consented, procedure-attempted, and implanted, as well as the Subject ID numbers assigned to each subject.

[iii] MSCT should be within 365 days of index procedure

[iv] Recommended multi-slice computed tomography acquisition guidelines are provided in Appendix C



* MSCT should be within 365 days of index procedure

** If diagnostic MSCT acquisition is planned per standard care, refer to recommended MSCT acquisition guidelines provided in Appendix C.

Figure 3. *Flow diagram of the study entry process*

5.2 Procedures for Trial Conduct

An overview of all data collection requirements is given in Table 3. All exams are typical for TAVI and are considered standard of care exams in the participating hospitals.

5.2.1 Study Visit Requirements Matrix

The following table indicates the parameters expected to be routinely evaluated by investigational sites.

Table 3: Schedule of assessments

Data Collection Requirement	Assessment Intervals						
	Baseline[5]	Implant	Discharge	30 Days[5]	1 Year[5]	2 & 3 Years[5]	Study Exit
Heart Team Assessment[1]	X						
Informed Consent (either patient Informed Consent or Data Release Form)	X						
Demographics and Medical History	X						
Physical Examination	X		X	X	X	X	
NYHA Classification	X			X	X	X	
Risk scores (STS risk score, Log. EuroSCORE and EuroSCORE II)	X						
Katz ADL	X						
Relevant Medications	X		X	X	X	X	
MSCT	X[2]						
Transthoracic Echo (TTE)	X		X[3]		X		
12-lead ECG	X		X	X	X	X	
Operative Information		X					
Modified Rankin Score[4]	X		X	X	X	X	
Adverse Events/ Device Deficiency	X	X	X	X	X	X	
Vital Status							X

Notes

1. Heart Team assessment documentation required for enrolled subjects who are <80 years of age and have a STS predicted risk of mortality of <8%.
2. Pre-implant MSCT should be within 365 days of index procedure.
3. It is recommended to perform TTE for device success within 24 hours to 7 days post-procedure
4. Modified Rankin Score to be performed at 90 days following any stroke as well.
5. Patients are followed per standard of care, therefore there are no mandatory visit windows defined in this study, however the visit windows defined below are provided as recommendation and guidance.
   - Baseline Within 10 weeks prior to index procedure (except for TTE and MSCT)
   - 30 Days Between 30 and 60 days post procedure
   - 1 Year Between 365 and 425 days post procedure
   - 2 Years Between 730 and 790 days post procedure
   - 3 Years Between 1095 and 1155 days post procedure

5.2.2 Baseline Procedures

There are no mandatory visit windows defined in this study, however it is recommended that baseline assessments should occur within 10 weeks prior to the index procedure; except for MSCT[v].

- Heart Team assessment for enrolled subjects who are <80 years of age and have a STS predicted risk of mortality of <8%. The Heart Team's assessment must be documented on the Heart Team Assessment form.
- Informed Consent (patient Informed Consent or Data Release Form)
- Demographics and Medical History
- Physical Examination
- NYHA functional classification
- Risk Scores[vi], including
    - Logistic EuroSCORE
    - EuroSCORE II
    - Society of Thoracic Surgeons Score for predicted risk of mortality
- Katz ADL score
- Trans-Thoracic Echocardiogram (TTE)
    - Please refer to the Appendix B for recommended TTE acquisition guidelines and images.
- MSCT (peripheral vasculature and aortic annulus)
    - Please refer to Appendix C for recommended MSCT acquisition guidelines.
- 12-lead Electrocardiogram (ECG)
- Relevant medications
- Modified Rankin Score (mRS)
- Review of relevant adverse events and device deficiencies (see section 5.7 for requirements)

5.2.3 Implant Procedure

The implantation procedure is performed according to the standard procedures of the implanting physicians. Procedural aspects specific to the Evolut R System should be performed according to the Instructions for Use (and/or IB for Australia).

Per VARC 2, up to 72 hours continuous rhythm monitoring is recommended in order to maximize detection of arrhythmias.

The following implant data will be collected and recorded on the implant e-CRF:

- Operative information
- Serial number, valve size and disposition of implanted valve or opened valve packages
- Documentation of device failure or malfunction (as applicable)
- Review of relevant adverse events and device deficiencies (see section 5.7 for requirements)

[v] Pre-implant MSCT and TTE must be performed within 365 days of index procedure

[vi] Definitions of EuroSCORE, STS, and other co-morbidities are provided in Appendix D

Attempted procedure

An attempted procedure is one where the trial subject has entered the procedure room for implantation, but did not receive an Evolut R TAV for any reason.

If a procedure was attempted, and the Evolut R TAV is not implanted, the subject will be followed for safety reporting for 30 days post-attempted implant, and then exited from the trial. AE data should be collected on the AE e-CRF, and trial exit data on the Trial Exit e-CRF.

5.2.4 Discharge

Prior to hospital discharge, the following data will be collected.

- 12-lead ECG
- Modified Rankin Score (mRS)
- Physical Examination
- Trans-Thoracic Echocardiogram (for device success)
    - Per the VARC 2 definition for Device Success, the recommended time window for the TTE is 24 hours to 7 days Post Procedure;
    - Please refer to the Appendix B for recommended TTE acquisition guidelines and images.
- Relevant medication use.
- Review of relevant adverse events and device deficiencies (see section 5.7 for requirements)

5.2.5 Follow-up Visits

Patients are followed per standard of care. Information from visits performed at the implanting hospital should preferably be used for the follow-up visits. If the patient did not return to the implanting hospital, but was followed at a local hospital, this information can be used as an alternative. If no hospital visit occurred, a telephone follow-up visit can be performed.

5.2.6 30 days

There are no mandatory visit windows defined in this study; however it is recommended that the 30-day follow up visit should occur between 30 and 60 days post procedure.

- NYHA functional classification
- 12-lead ECG
- Physical Examination
- Relevant medication use.
- Modified Rankin Score (mRS)
- Review of relevant adverse events and device deficiencies (see section 5.7 for requirements)

5.2.7 One Year

There are no mandatory visit windows defined in this study; however it is recommended that the 1-year follow up visit should occur between 365 and 425 days post procedure.

- NYHA functional classification
- Trans-Thoracic Echocardiogram (TTE)
    - Please refer to the Appendix B for detailed instructions, guidelines and required images.
- 12-lead ECG

- Physical Examination
- Relevant medication use.
- Modified Rankin Score (mRS)
- Review of relevant adverse events and device deficiencies (see section 5.7 for requirements)

5.2.8 Two Years

There are no mandatory visit windows defined in this study; however it is recommended that the 2-year follow up visit should occur between 730 and 790 days post procedure.

- NYHA functional classification
- 12-lead ECG
- Physical Examination
- Relevant medication use.
- Modified Rankin Score (mRS)
- Review of relevant adverse events and device deficiencies (see section 5.7 for requirements)

5.2.9 Three Years

There are no mandatory visit windows defined in this study; however it is recommended that the 3-year follow up visit should occur between 1095 and 1155 days post procedure.

- NYHA functional classification
- 12-lead ECG
- Physical Examination
- Relevant medication use.
- Modified Rankin Score (mRS)
- Review of relevant adverse events and device deficiencies (see section 5.7 for requirements)

5.2.10 Four and Five Years

If, based on clinical assessments during the course of the study, follow up is extended to up to 5 years post procedure, the follow up visits are recommended to occur between 1460 and 1520 days for the 4-year follow up visit and between 1825 and 1885 days for the 5-year follow up visit.

- NYHA functional classification
- 12-lead ECG
- Physical Examination
- Relevant medication use.
- Modified Rankin Score (mRS)
- Review of relevant adverse events and device deficiencies (see section 5.7 for requirements)

5.2.11 Other Evaluations

- A mRS assessment should be performed at baseline, all scheduled visits and at 90 days after the onset of any stroke.

5.3 Trial Assessments

5.3.1 Relevant Medications

Use of the following medications will be collected at baseline and at each postoperative interval and recorded on the appropriate e-CRF:

- Anticoagulants
- Antiplatelets
- Aspirin (including Carbasalate calcium)

The Investigator's standard clinical practice will determine the appropriate anti-thrombotic medication use for each subject.

5.3.2 Risk Scores

The Logistic EuroSCORE, EuroSCORE II and Society of Thoracic Surgeons' (STS) risk models predict the risk of operative mortality after adult cardiac surgery on the basis of patient demographic and clinical variables.

The risk scores should be calculated at baseline for each subject using the online calculator:

- Logistic EuroSCORE: *http://euroscore.org/calcold.html*
- EuroSCORE II: *http://euroscore.org/calc.html*
- STS Risk Score: *http://riskcalc.sts.org/stswebriskcalc/#/*

The online calculator provides additional guidance and definitions for each of the parameters used to calculate the scores. The predicted risks of mortality should be recorded on the Baseline e-CRF. The Risk Scores should be printed from the online calculators and filed as source documentation for trial subjects.

5.3.3 Heart Team Assessment

Patients with age <80 years and a STS predicted risk of mortality of <8% must be evaluated by a heart team to confirm the patient is at high or greater risk for AVR due to frailty or comorbidities.

The Heart Team's assessment must be documented on the Heart Team Assessment form and signed by the PI or delegated Investigator(s) (as documented on the Delegated Task List) (see section 4.5.2).

5.3.4 Katz ADL

Katz Index of Independence in Activities of Daily Living: the Katz Index of Independence in Activities of Daily Living, in short, the Katz ADL, is a questionnaire to assess functional status as a measurement of the patient's ability to perform activities of daily living independently. The index ranks adequacy of performance in six functions. Patients are scored yes or no for independence in each of the six functions. A score of six indicates full function and 2 or less indicates severe functional impairment.

Detailed information about the Katz ADL including guidelines to perform them can be found in the Investigator Site File. The site will record frailty assessment data on the appropriate e-CRF.

5.3.5 Multi-slice Computed Tomography

All subjects enrolled in this study must have a routine cardiac Multi-slice Computed Tomography (MSCT) recording available at baseline for evaluation of the aortic valve anatomy, determination of aortic root dimensions for device sizing, and for evaluation of peripheral vessel dimensions and anatomy.

MSCT's are performed per standard care in all investigational sites (see section 4.1.2.). Please refer to Appendix C for recommended MSCT acquisition guidelines. If no recent[vii] MSCT image is available or planned per standard care, the patient should **not** be enrolled in this study (see section 5.1).

Data to be recorded from the MSCT recording on the appropriate e-CRF include the following:

- Aortic valve annulus perimeter
- Mean Sinus of Valsalva diameter
- Mean Sinus of Valsalva height
- Calcification of Aorta and LVOT
- Access vessel tortuosity and calcification

5.3.6 Echocardiography

Transthoracic echocardiography (TTE) exams, performed per standard care, are collected at the following intervals: baseline (pre-implant), 24 hours to 7 days (for device success) and 1 year.

These TTE exams will be sent to the Echo Core Lab for central assessment. Please refer to Appendix B for recommended TTE acquisition guidelines and images.

Sites should make every effort to utilize the same echo machine for all patients at the above mentioned intervals. Additionally, sites should perform regular maintenance and calibration of echo machines per local standards and ensure proper documentation is available for audit, as applicable.

5.3.7 12-Lead ECG

The standard 12-lead ECG will be utilized as a diagnostic and prognostic tool. All ECGs are analyzed utilizing both qualitative and quantitative methodology, to assess cardiac rhythm, noting any cardiac arrhythmias and indications for pacing. The site will record ECG data on the appropriate e-CRF.

5.3.8 NYHA Functional Classification

The New York Heart Association (NYHA) Functional Classification is a system for defining cardiac disease and related functional limitations into four broad categorizations as defined in Table 4.

[vii] Pre-implant MSCT must be performed within 365 days of index procedure

***Table 4**. New York Heart Association (NYHA) Functional Classification*

Classification	Description
Class I	Subject with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Subjects with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Subjects with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Subjects with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

NYHA classification will be assessed at baseline, 30 days, 1, 2 and 3 years, and the results recorded on the appropriate e-CRF.

5.3.9 Neurologic Assessment

The incidence of new clinically detectable neurological events or deficits, or any comparative change in indices of higher cognitive function following implantation of the Evolut R system in the treatment of patients with symptomatic severe aortic stenosis is an important clinical endpoint. Per the VARC-2 guidelines, it is recommended to complete mRS assessments at baseline, all scheduled visits and at 90 days after onset of any confirmed or suspected neurological event (see Table 3). The mRS will be used to classify non-disabling versus disabling stroke in accordance with the VARC-2 definitions. In addition, it is recommended to use neuroimaging to assess the ethiology of the stroke.

Confirmed or suspected strokes (disabling and non-disabling) meeting the VARC-2 criteria should be reported as Serious Adverse Events (SAEs) according to the requirement in section 5.7.

5.3.10 Vital Status

A vital status (alive or deceased) should be confirmed for trial subjects at trial exit and recorded on the appropriate e-CRF.

5.4 Subject Accountability

5.4.1 Missed Follow-up Visit

The Investigator should make every effort to contact the subject preferably within the visit window, to collect the subject's vital status as well as information related to potential adverse events, safety data, and hospitalizations.

As only standard of care data are being collected, subjects cannot miss study-specific visits. In case no standard of care visit has taken place in the pre-specified follow-up interval period, sites should conduct a telephone follow-up visit just prior to the closure of the visit window. Up to 3 attempts and any information received during a telephone follow-up should be filed as source documentation by the sites. If the subject cannot be reached by phone, the visit should be considered missed and, if applicable a protocol deviation must be completed, as outlined in section 5.8.

5.4.2 Lost To Follow-Up

The subject may only be considered lost to follow-up after all efforts to obtain compliance are exhausted. At a minimum, four attempts must be made to contact the subject and documented in the subject's trial records:

- 3 telephone attempts to the subject's last known phone number, and if unsuccessful,
- 1 certified letter from the PI to the subject's last known address

If the site is unable to reach the subject after the documented attempts, the site should make every attempt to verify the subject's vital status (alive or deceased).

5.4.3 Subject Withdrawal

All subjects will be encouraged to remain in the study through the last follow-up visit at three years and up to 5 years, if the study is extended based on clinical assessments during the course of the study. Subjects who discontinue participation prematurely will be included in the analysis of results (as appropriate) but they will not be replaced in the enrollment of total study subjects. If a study subject is discontinued from the study early, the reason for discontinuation should be documented in the subject file and a Study Exit e-CRF must be completed. If discontinuation is because of safety or lack of effectiveness, the patient shall be asked to be followed for collecting safety data outside the clinical study.

Once a subject has been enrolled in the study (i.e. written Informed Consent has been obtained) he/she may withdraw his/her consent to participate in the study at any time without prejudice. Participation in this study is entirely voluntary.

If a subject discontinues the study at any time, is withdrawn from the study early, or completes all follow-up visits they should continue to be followed-by the implanting center according to their standard clinical practice for transcatheter aortic valve patients.

5.4.4 Subject Disposition

The Investigation site will maintain a log of all subjects enrolled in the clinical study, assigning an identification code linked to their names, alternative subject identification or contact information.

There are several scenarios in which a subject may exit the trial. Table 5 below details how the data will be handled for each scenario.

Table5. Trial Exit Scenarios

Scenario	Follow-up Required	e-CRFs Required
Subject enrolled, but no implant attempted (i.e. not taken to the procedure room for implantation)	None	▪ Inclusion/Exclusion e-CRF ▪ Baseline e-CRF (as applicable) ▪ AE e-CRF (as applicable) ▪ Trial Exit e-CRF
Subject enrolled, implant attempted (i.e. taken to the procedure room), but the subject does not receive the Evolut R TAV	30 days post-attempted implant for safety only	▪ Inclusion/Exclusion e-CRF ▪ Baseline e-CRF (including TTE) ▪ Implant e-CRF ▪ Discharge e-CRF ▪ 30 Day e-CRF ▪ AE e-CRF (as applicable) ▪ Trial Exit e-CRF
Subject enrolled, implanted with Evolut R TAV, and has his/her valve explanted	Discharge following explant hospitalization or 30 days post implant (whichever comes later).	▪ All required e-CRFs through last visit completed ▪ Surgical Reintervention e-CRF ▪ AE e-CRF (as applicable) ▪ Trial Exit e-CRF
Subject enrolled, implanted with Evolut R TAV, and exits the trial early due to any of the following: ▪ Lost to Follow-up ▪ Death ▪ Withdrawal	Through point of death, withdrawal, or last visit completed	▪ All required e-CRFs through last visit completed ▪ AE e-CRF (as applicable) ▪ Trial Exit e-CRF
Subject enrolled, implanted and completes the trial requirements	Through 3 year follow-up	▪ All required e-CRFs ▪ AE e-CRF (as appropriate) ▪ Trial Exit e-CRF

5.5 Role of the sponsor's representatives

Representatives from Medtronic may provide technical support during the implant procedures to the implanting physicians and study center staff relative to the use of the Evolut R system. This activity will be performed under supervision of the Principal Investigator and will not bias the data integrity in any

way. The sponsor representatives providing technical support shall be listed on the Sponsor Technical Support List.

5.6 Source documents

Entered data must be traceable to source documents. Source documentation is defined as the first time the data appear and may include all clinical records, hospital records, procedural reports, autopsy reports, and any other material that contains original information used for study data collection or adverse event reporting.

The e-CRFs may not serve as source documents. Source documentation for data elements not routinely captured in medical records (e.g. echocardiography variables, Modified Rankin Score, risk score calculators) may vary from center to center: the site may use technical worksheets if identified as source documents. Worksheets need to be signed and dated by the Principal Investigator or a delegated Investigator.

Data reported on the e-CRFs should be traceable to source documents. Source documents must be available for review by Medtronic personnel and/or applicable regulatory agencies or EC/IRB and will be used for verification of the data reported on the e-CRFs and adjudication of AEs.

Where copies of the original source document as well as print outs of original electronic source documents are retained, these shall be signed and dated by a member of the investigation site team with a statement that it is a true reproduction of the original source document.

The Investigator must ensure the availability of source documents from which the information on the e-CRFs was derived. In addition, the medical records of study subjects should be marked or flagged in such a way to indicate their participation in the study. For Investigational sites in Sweden, the investigator should also provide a short explanation on the clinical study in the patient medical files.

5.7 Adverse events and Device Deficiencies

5.7.1 Definition/classification

For the purposes of the clinical report, Medtronic will classify each adverse event according to ISO 14155:2011 (Table 6).

Where the definition indicates “device”, it refers to <u>any</u> component of the Evolut R system used in the study.

Table 6. Adverse Event Definitions

Adverse Event (AE): ***(ISO14155:2011 3.2)***
Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device
NOTE 1: This definition includes events related to the investigational medical device or the comparator.

NOTE 2: This definition includes events related to the procedures involved.
NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse Device Effect (ADE): **(ISO14155:2011 3.1)**

Adverse event related to the use of an investigational medical device

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device

Serious Adverse Event (SAE): **(ISO 14155:2011 3.37)**

An adverse event that

a) led to death,
b) led to serious deterioration in the health of the subject, that either resulted in
    1. a life-threatening illness or injury, or
    2. a permanent impairment of a body structure or a body function, or
    3. in-patient or prolonged hospitalization, or
    4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Device Effect (SADE): **(ISO 14155:2011 3.36)**

Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.

Unanticipated Serious Adverse Device Effect (USADE): **(ISO 14155:2011 3.42)**

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report

NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

Device deficiency: **(ISO 14155:2011 3.15)**

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance

NOTE: Device deficiencies include malfunctions, use errors, and inadequate labelling.

An event is not considered an AE if it has been identified as a pre-existing condition, unless there is a change in nature, severity or degree of incidence of the event.

5.7.2 Recording and reporting of Adverse Events

Investigators are required to report all serious adverse events (SAE) and all VARC 2 Adverse Events (AE) regardless of seriousness observed in the study subjects from their point of enrollment until completion of follow-up. The list of VARC 2 Adverse Events is provided in table 7. The event definitions and event code list can be found in Appendix E and G, respectively.

***Table 7**. List of VARC 2 Adverse Events*

Event Type
All-cause Mortality
Myocardial Infarction
Stroke and TIA
Thrombo-embolic events (eg, stroke)
Bleeding
Vascular Access Site and Access-Related Complications
Acute Kidney Injury
New and/or worsened conduction disturbances
Repeat procedure (BAV, TAVI, or SAVR)
Hospitalizations for valve-related symptoms or worsening congestive heart failure
TAV iin TAV deployment
Conversion to open surgery
Unplanned use of cardiopulmonary bypass (CPB)
Coronary artery obstruction
Ventricular septal perforation
Mitral valve apparatus damage or dysfunction
Cardiac tamponade
Prosthetic valve endocarditis
Prosthetic valve thrombosis
Valve migration
Valve embolization
Ectopic valve deployment
Stent fracture

The VARC-2 document provides standardization of endpoint definitions for studies evaluating the use of TAVI. This study follows VARC-2 to allow for improved comparability and interpretability of study results. Due to the nature and regulatory strategy of this study, the scope of Adverse Event reporting in this study has been limited to reporting of all SAE's and all VARC 2 Adverse Events (AE) regardless of seriousness. This is a deviation from ISO14155:2011.

These Adverse Events, documented in the subject's medical record will be reported to Medtronic on an Adverse Event e-CRF as described in this section.

For all reportable AEs, investigators should assess and document the following information on the Adverse Event e-CRF:

- Date of onset or first observation
- Date site became aware of the event
- AE code number
- Description of the event
- Seriousness of the event
- Causal relationship of the event to the Evolut R™ TAV
- Causal relationship of the event to the Enveo R™ DCS
- Causal relationship of the event to the implant procedure
- Treatment required
- Outcome or status of the event

Refer to section 5.7.6 for emergency contact details for reporting events and device deficiencies, especially for immediate reporting.

5.7.3 Classification of Causal Relationships

For each reported AE, the causal relationship between the AE and the trial devices and implant procedure will be classified as related, not related or unknown. The causal relationships are defined in table 8.

The following definitions are intended as guidelines for classifying causal relationships between the event and the Evolut R valve, the EnVeo R catheter delivery system and the implant procedure

Table 8. *Adverse Event Causal Relationship Definitions*

Related to the Evolut R valve	The event is associated with the Evolut R valve by the chronology and physiology and was caused by the Evolut R valve.
Not related to the Evolut R valve	The event is not related to the Evolut R valve.
Unknown relation to the Evolut R valve	There is not enough evidence to confirm or deny the relation to the Evolut R valve.
Related to the EnVeo R delivery system	The event is associated with the EnVeo R delivery system by the chronology and physiology and was caused by the EnVeo R delivery system.
Not related to the EnVeo R delivery system	The event is not related to the EnVeo R delivery system.
Unknown relation to the EnVeo R delivery system	There is not enough evidence to confirm or deny the relation to the EnVeo R delivery system.
Related to the implant procedure[1]	The event is associated with the implant procedure by the chronology or physiology and was caused by the implant procedure.
Not related to the implant procedure[1]	The event is not related to the implant procedure.
Unknown relation to the implant procedure[1]	There is not enough evidence to confirm or deny relation to the implant procedure.

[1] Timeframe for assessing implant procedure relationships begin when subject is being prepared for the implant (or re-implant) procedure.

5.7.4 Recording and reporting of Device Deficiencies

Device deficiency information will be collected throughout the trial and reported to Medtronic. Device deficiencies that led to an AE are reported on the AE e-CRF only.

Device deficiencies that did not lead to an AE should be reported on a Device Deficiency e-CRF (one for each device deficiency).

Device deficiencies that did not lead to an adverse event but might have led to a SADE if a) a suitable action had not been taken, or b) an intervention had not been made, or c) circumstances had been less fortunate, should be reported to Medtronic immediately of the site's first learning of the event on a Device Deficiency e-CRF (see table 9).

Refer to section 5.7.6 for emergency contact details for reporting events and device deficiencies, especially for immediate reporting.

5.7.5 Adverse Event and Device Deficiency Reporting Requirement

Adverse events and device deficiencies that occur during and are recorded in this trial are required to be reported to Medtronic via the AE or device deficiency e-CRF, as per the timeframes listed in Table 9 (for countries where the device is investigational) and 10 (for countries where the device is commercially available) or per local requirements, whichever is more stringent.

***Table 9**. Investigator Reporting Requirements to Medtronic in countries where the device is investigational*

Event Type	Investigator Timeframe for Reporting to Medtronic
Canada	
Serious Adverse Event (SAE)	Immediately, but no later than 5 calendar days of the investigator's / site's first knowledge of the event
Adverse Device Effect (ADE) or Device Related Adverse Event	Immediately, but no later than 5 calendar days of the investigator's / site's first knowledge of the event
Serious Adverse Device Effect (SADE)	Immediately, but within **72 hours** of the investigator's / site's first knowledge of the event
Unanticipated Adverse Device Effect (UADE)	Immediately, but no later than 5 calendar days of the investigator's / site's first knowledge of the event
Unanticipated Serious Adverse Device Effect (USADE)	Immediately, but within **72 hours** of the investigator's / site's first knowledge of the event
Endpoint Adverse Event (AE)	No later than 15 calendar days of the investigator's / site's first knowledge of the event
Device Deficiency	Immediately, but within **72 hours** of the investigator's / site's first knowledge of the event
Device Deficiency that might have led to an SADE	Immediately, but within **72 hours** of the investigator's / site's first knowledge of the event
Australia	
Serious Adverse Event (SAE)	Immediately, but within 24 hours of the investigator's / site's first knowledge of the event

Adverse Device Effect (ADE) or Device Related Adverse Event	Immediately, but no later than 5 calendar days of the investigator's / site's first knowledge of the event
Serious Adverse Device Effect (SADE)	Immediately, but within 24 hours of the investigator's / site's first knowledge of the event
Unanticipated Adverse Device Effect (UADE)	Immediately, but no later than 5 calendar days of the investigator's / site's first knowledge of the event
Unanticipated Serious Adverse Device Effect (USADE)	Immediately, but within 24 hours of the investigator's / site's first knowledge of the event
Endpoint Adverse Event (AE)	No later than 15 calendar days of the investigator's / site's first knowledge of the event
Device Deficiency	No later than 15 calendar days of the investigator's / site's first knowledge of the event
Device Deficiency that might have led to an SADE	Immediately, but within 24 hours of the investigator's / site's first knowledge of the event

***Table 10**. Investigator Reporting Requirements to Medtronic in countries where the device is commercially available*

Event Type	Investigator Timeframe for Reporting to Medtronic
Serious Adverse Event (SAE)	Immediately, but no later than 5 calendar days of the investigator's / site's first knowledge of the event
Adverse Device Effect (ADE) or Device Related Adverse Event	Immediately, but no later than 5 calendar days of the investigator's / site's first knowledge of the event
Serious Adverse Device Effect (SADE)	Immediately, but no later than 5 calendar days of the investigator's / site's first knowledge of the event
Unanticipated Adverse Device Effect (UADE)	Immediately, but no later than 5 calendar days of the investigator's / site's first knowledge of the event
Unanticipated Serious Adverse Device Effect (USADE)	Immediately, but no later than 5 calendar days of the investigator's / site's first knowledge of the event
Endpoint Adverse Event (AE)	No later than 15 calendar days of the investigator's / site's first knowledge of the event
Device Deficiency	No later than 15 calendar days of the investigator's / site's first knowledge of the event
Device Deficiency that might have led to an SADE	Immediately, but no later than 5 calendar days of the investigator's / site's first knowledge of the event

In addition, Investigators are obligated to report adverse events in accordance with the requirements of their reviewing Ethics Board, Regulatory Authority and local regulations. Table 11 provides a list of reporting requirements for Australian sites.

***Table 11**: Investigator responsibility for adverse event reporting to HREC*

Report	Submit to	Description/Constraints
USADE	HREC	The investigator should comply with the applicable regulatory requirement(s) related to the reporting of USADE to the HREC. *(The Australian Clinical Trial Handbook section 4.11.1)*
USADEs	HREC	At least six-monthly, the investigator must provide to HREC responsible for trial; • listing of all USADEs, Australian and international a report which includes sponsor and investigator comment as to whether action is planned for the trial *(NHMRC Safety Monitoring Position Statement May 2009 section 2.3)*
Annual Safety Report/ updated IB/ approved PI	HREC	At least annually, the investigator must provide to HREC responsible for trial; • an updated Investigator Brochure, or • an EU Annual Safety Report (or similar format report), or • current, approved Product Information (PI), if appropriate (eg in a study for a product approved in Australia or where an Investigator Brochure is no longer maintained) • other reports consistent with section 5.5.5 of the *National Statement1* and *Good Clinical Practice (GCP)* as adopted by the *Therapeutic Goods Administration (TGA)* *(NHMRC Safety Monitoring Position Statement May 2009 section 2.4)*
Death	Sponsor of trial, HREC	For reported deaths, the investigator should supply the sponsor and the HREC with any additional requested information (e.g., autopsy reports and terminal medical reports). *(The Australian Clinical Trial Handbook section 4.11.3)*
Other information in a prompt manner	HREC	For each trial, the investigator must also provide: • information which materially impacts the continued ethical acceptability of the trial or • information that requires, or indicates the need for, a change to the protocol, including changed safety monitoring in the view of the investigator or sponsor (*NHMRC Safety Monitoring Position Statement May 2009 section 2.2)*

The Sponsor is obligated to report adverse events and device deficiencies that occur during this trial to the Regulatory Authorities and Ethics Board as per local requirements. The applicable timeframes are described in the Evolut R FORWARD Safety Plan.

A list of anticipated adverse events that are expected in nature can be found in the Instructions for Use of the Evolut R system (and/or IB for Australia).

5.7.6 Emergency Contact for Reporting Events and Device Deficiencies

Investigators should contact their responsible field monitor if they have any questions regarding reportable AE's and/or Device Deficiencies. Sponsor contact information (including name, title, address, and telephone number(s)) is subject to change and will be maintained in a document separate from the protocol and provided to sites.

For Adverse Events or Device Deficiencies that require immediate reporting (see table 9 and 10), initial reporting shall be done by completing the appropriate e-CRF. If the e-CRF is not available, the Adverse Event or Device Deficiency Form in the Investigator Site File must be completed and submitted to the rs.evolutr.emergency@medtronic.com email box and/or to the responsible field monitor (contact information is provided in a document separate from the protocol and provided to sites). In due time, the Adverse Event or Device Deficiency needs to be entered in the e-CRF as well.

5.7.7 Clinical Events Committee

A Clinical Events Committee (CEC) will provide independent medical review and adjudication of adverse event data. The CEC will adjudicate at least all deaths and safety endpoint events reported by the investigators. Further adverse events could be reviewed and adjudicated upon request of the Sponsor. The CEC will follow the recommendations of VARC-2[34] for classifying adverse events that relate to clinical safety endpoints

The CEC members will be free from bias towards the study and will be independent from both the study and investigators and Medtronic. The committee will consist of at least 3 independent experts (non-Medtronic employed physicians) with expertise relevant to the study. This may include experience in the areas of:

- Cardiac surgery
- Interventional cardiology
- Neurology
- Electrophysiology

A CEC charter will be developed and approved by Medtronic.

5.8 Study deviations and CIP changes

A study deviation is an event where the investigator or investigation site personnel did not conduct the clinical study according to the Clinical Investigation Plan or Clinical Investigation Agreement.

The investigator is not allowed to deviate from the above mentioned documents except with prior approval. All deviations shall be documented and explained, regardless the reason for the deviation.

Examples of protocol deviations include but are not limited to the following:

- Failure to obtain informed consent (either signed patient Informed Consent or Data Release Form) prior to participation
- Incorrect version of the Patient Informed Consent or Patient Data Release Form used
- Failure to obtain EC/IRB approval before the start of the study
- Implanted subject did not meet inclusion/exclusion criteria

- Follow-up visit not done
- Adverse events not reported in the required time frame as required by regulation or as specified in the CIP
- Source data permanently lost
- Enrollment of patients during lapse of EC/IRB approval

5.8.1 Request for approval of study deviations

The investigator shall obtain documented approval from Medtronic, before implementation, for any change in- or deviation from the Clinical Investigation Plan. In case of study deviations that can affect the subject's rights, safety and well-being or the scientific integrity of the clinical study, approval from the EC/IRB and regulatory authority (if applicable) must also be obtained before implementation. The investigator shall timely contact the Clinical Study Manager for review of the proposed change/deviation.

Prior approval is not always realistic in situations where unforeseen circumstances are beyond the investigator's control. However, also in these cases, the event is considered a deviation, and shall be reported.

In any emergency situation the investigator shall exercise his/her judgment to safeguard the subject's interest. Such deviations from the Clinical Investigation Plan do not require the prior approval of Medtronic. The investigator shall report the deviation as soon as possible to Medtronic and the reviewing EC/IRB, if applicable. Medtronic will inform the regulatory authorities, if required.

5.8.2 Reporting requirements for study deviations

Study deviations should be reported to Medtronic via the Study Deviation e-CRF (one e-CRF for each protocol deviation). Relevant information for each deviation will be documented on a deviation form completed by site personnel and reviewed by the Investigator.

Investigators should report the following deviations to Medtronic and their reviewing EC/IRB:

- Failure to obtain written informed consent (either patient Informed Consent or Data Release Form)
- Deviations to protect the life or physical well-being of a subject in an emergency

In addition, Investigators are required to adhere to local EC/IRB procedures for reporting deviations.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any corrective and/or preventive actions that may be warranted. Repetitive or serious investigator compliance issues may represent a need to initiate a corrective action plan, which may include suspension of enrollment or termination of the investigator's or site's participation in the study, in accordance with Medtronic SOPs.

Medtronic will provide investigation site-specific reports to the investigators on a periodic basis summarizing information on deviations that occurred at the investigation site.

5.8.3 Amendments to the Clinical Investigation Plan

The investigator will propose any appropriate modification(s) of the Clinical Investigation Plan or product use. Medtronic will review this proposal and decide whether the modification(s) will be implemented.

Medtronic will submit any significant amendment to the Clinical Investigation Plan, including a justification for this amendment, to the appropriate regulatory authorities, EC/IRB's and to the investigators. The investigator will only implement the amendment after approval of the EC/IRB, regulatory authority (if applicable) and sponsor. Furthermore investigators shall sign any approved amendment for agreement.

6 QUALITY CONTROL PROCEDURES

6.1 Procedures for database management

6.1.1 Data collection

This study will utilize an Oracle Clinical Remote Data Capture (RDC) system that is the property of Medtronic. Each enrolled subject will be assigned to a unique study ID number, which is pre-configured in Oracle Clinical. Records of the subject/subject ID relationship will be maintained by the study site. Individual subject medical information obtained as a result of this study will be considered confidential.

Required data will be recorded on electronic case report forms (e-CRFs) by authorized site personnel as indicated on the Delegation Task List (DTL), which can be found in the Investigator Site File. Study personnel delegated for e-CRF completion and/or approval per the DTL will be trained on the use of the RDC system and thereafter provided with a user name and password to access the system. The e-CRFs must be completed and/or updated to reflect the latest observations on the subjects participating in the study. The investigator (or approved sub-investigator) will electronically sign the appropriate pages of each e-CRF.

Data from the core lab will be entered into the Oracle Clinical RDC system by core lab personnel per their procedures established for the study. The core lab cardiologist will approve core lab e-CRFs.

The Oracle Clinical RDC system maintains an audit trail of entries, changes, and corrections in e-CRFs. If a person only authorized to complete e-CRFs makes changes to an already signed e-CRF, the investigator shall re-approve this e-CRF.

The investigator must ensure accuracy, completeness, legibility and timeliness of the data reported in the e-CRFs and in all other required reports. Data reported on the e-CRFs which are derived from source documents must be consistent with the source documents or the discrepancies need to be justified in a documented rationale, signed and dated by an Investigator and filed in the patient medical file.

6.1.2 Time windows for completion and submission of Case Report Forms

It is the intention to complete the e-CRF no later than 20 working days after the procedure or follow-up visit took place, except for e-CRFs documenting AEs or Device Deficiencies that require immediate reporting.

6.1.3 Data review and processing

Medtronic will be responsible for the processing and quality control of the data. Data review, database cleaning and issuing and resolving data queries will be done according to Medtronic internal SOPs and the Data Management Plan for this study. The study database will employ validation programs (e.g. range and logic checks) on entered data to identify possible data entry errors and to facilitate data validation.

6.2 Monitoring procedures

Monitoring visits will be conducted at the start, during and at the closure of the clinical study in accordance with Medtronic SOPs and the Monitoring Plan.

Periodic monitoring visits will be conducted at the start, during and at the closure of the clinical study. Monitoring visits will occur based on implant rate and volume, duration of the study, study compliance at each center, and any suspected inconsistency in data that require investigation. At a minimum, there will be one visit per year at each investigation site that has enrolled subjects.

Regulatory documents, Informed Consents or Data Release Forms, Investigator Site File and CRFs will be reviewed for each study center. Over time, 100% of the Informed Consent or Data Release forms will be reviewed for accurate completion. Moreover, CRF data related to the primary and secondary endpoints as well as study-specific adverse events will be verified against the patient's medical records.

Site personnel will complete e-CRFs following each subject visit. Study data submitted will be reviewed against patient charts and other sources containing original records of patient data. Source document verification will occur in accordance to the Monitoring Plan.

The progress of the study will be monitored by:

- On-site review, as deemed appropriate by Medtronic
- Telephone communications between the site personnel (e.g., investigator, study coordinator) and study monitors
- Review of e-CRFs and the associated clinical records
- Review of regulatory documents

Monitoring and monitoring oversight will be provided by Medtronic. Representatives of Medtronic (i.e. contractors and designees) may also act as study monitors.

6.2.1 Accessibility of investigation site staff and study materials

The principal investigator(s), his/her delegate(s) and the study coordinator(s) shall be accessible to Medtronic field personnel and the Clinical Study Manager. This accessibility is of particular importance for reviewing data in the Case Report Form (CRF). Direct access to patient medical files for source data verification will need to be granted and prepared prior to any monitoring visits.

6.2.2 Audits and investigation site inspections

In addition to regular monitoring visits, Medtronic may conduct audits at participating investigation sites. The purpose of an audit is to verify the adequate performance of the clinical study related activities. Independent of the employees involved in the clinical study. Regulatory bodies may also perform inspections at participating investigation sites. Any regulatory authority inspection announcements shall be forwarded immediately to the Clinical Study Manager.

The investigator and/or institution shall permit Medtronic and regulatory bodies direct access to source data and documents, taking into account any restrictions due to local law, to perform clinical study-related monitoring, audits, EC/IRB review, and regulatory inspections.

6.3 Study suspension or early termination

6.3.1 Early study suspension or termination

Medtronic or Regulatory Authority may decide to suspend or prematurely terminate the clinical study. If the clinical study is terminated prematurely or suspended, Medtronic shall promptly inform the investigators and regulatory authorities (if applicable) of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing EC/IRB and the study subjects.

6.3.2 Early investigation site suspension or termination

Medtronic, EC/IRB or Regulatory Authority may decide to suspend or prematurely terminate an investigation site. If an investigation site is suspended or prematurely terminated, Medtronic shall promptly inform the investigator(s) of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing EC/IRB and the study subjects.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definite outcomes, investigators must assess whether to continue, modify or immediately stop the clinical study in the respective investigation site and immediately inform the sponsor and EC/IRB, if applicable.

6.3.3 Subject follow-up in case of termination

In case of early termination, all subjects should be followed by their physicians per their standard hospital practice and no further patient data will be collected under this Clinical Investigation Plan.

6.4 Study close out

A study closeout visit can be performed either in person or by phone. Study closeout visits may be performed to ensure that study data are correctly entered on the e-CRFs and all patients are exited from the study. In addition, all open queries should be resolved and closed. During these visits, the monitors will also ensure that the Investigator Site File is up to date and complete and that any outstanding action items from previous visits have been resolved.

After study close-out, all patients will be followed accordingly to the hospitals standard of care practices.

Medtronic and/or its designees will notify the site in writing of the intention to close the study and if required will notify/report to EC/IRB and Regulatory Authority.

7 PUBLICATION POLICY

Medtronic is committed to the widespread dissemination of all primary and secondary endpoint results. Publications and presentations referring to the Medtronic CoreValve™ Evolut R™ FORWARD Study will be coordinated by a Publication Committee to allow the use of all available data. The Publication Committee will consist of the Steering Committee and Medtronic representatives.

Medtronic intends to publish the results of the study in a reputable peer reviewed scientific journal and present the data at major congresses.

Following analysis and presentation of the endpoint results, active participation of all participating investigators, CEC committee members, and core laboratory personnel will be solicited for data analysis and abstract and manuscript preparation. Submission of all abstracts and publications regarding the primary endpoint and secondary endpoints from the study requires approval by the Principal Investigators after review by the Publications Committee.

A separate publication plan will provide detailed information about the publication committee, authorship, publication proposals, and requests for data.

8 STUDY MANAGEMENT

8.1 Study staff

A list of sponsor personnel (including, study management, monitors and safety representatives) and their contact details will be maintained in the Investigator Site File and provided to the study centers.

8.2 Advisory committees

8.2.1 Principal Coordinating Investigators

Two Principal coordinating Investigators will take responsibility for the scientific validity of the clinical investigation plan, assessment of the study quality and conduct as well as for the scientific quality of the final study report. The Principal Coordinating Investigators are:

- Prof. Eberhard Grube
  MED. Klinik u. Poliklinik II
  Universitätsklinikum Bonn
  53105 Bonn, Germany

- Prof. Stephan Windecker
  Bern University Hospital
  Department of Invasive Cardiology
  3010 Bern, Switzerland

8.2.2 Steering Committee

The Steering Committee will take responsibility for the scientific validity of the clinical investigation plan, assessment of the study quality and conduct as well as for the scientific quality of the final study report. This committee will meet periodically to monitor patient enrollment, clinical site progress, and protocol compliance. A detailed description of their activities can be found in the Steering Committee charter.

8.2.3 Clinical Events Committee

A Clinical Event Committee (CEC) will be installed. See section 5.7.7 for more details.

8.2.4 Publication Committee

A Publication Committee will review and approve publication of ideas and facilitate submissions, including abstracts and manuscripts. The Publication Committee will be responsible for:

- Defining and refining the publication strategy
- Overseeing the development of manuscripts, abstracts, and presentations
- Identifying and appointing the manuscript/abstract first author(s)/writer(s)/presenters(s)
- Reviewing the publication

See section 7 for more details.

8.3 Records and reports

8.3.1 Investigator records

At a minimum, the following records must be kept by the investigator:

- Clinical Investigation Plan and, if applicable, any amendments
- Instructions for Use (and/or IB for Australia))
- EC notification, approval and correspondence, and EC voting list
- Medtronic and EC/IRB approved Patient Informed Consent or Patient Data Release Form
- Regulatory Authority approval or notification if applicable
- Fully signed Clinical Investigation Agreement and confidentiality agreement (if not included in the Clinical Investigation Agreement)
- Insurance certificates, where applicable
- Completed Delegated Task List and Curriculum Vitae of all investigation site personnel
- Training documentation of all investigation site personnel
- Relevant communications
- Subject screening log, enrollment log and/or subject identification log
- Signed, dated and fully executed Patient Informed Consent or Patient Data Release Form.
- Medical records of each enrolled subject, including, for example, progress notes of the physicians, the subject's hospital chart(s) and the nurses' notes
- All adverse event/device deficiency information
- Device accountability Records (for Australia and Canada only)
- Financial Disclosure Information, if requested by the local EC/IRB or regulatory authority

8.3.2 Investigator reporting responsibilities

Table 12. *Investigator reporting responsibilities*

Report	Submitted to	Description
Adverse Events	Sponsor, EC/IRB, and local regulatory authority, where applicable	Refer to section 5.7 for reporting requirements.
Withdrawal of EC/IRB approval	Sponsor	Investigator must inform Medtronic in case EC/IRB approval is withdrawn within 5 working days.
Final Clinical Study Report	EC/IRB	A copy of the Final Clinical Study Report will be provided to the EC/IRB.

Report	Submitted to	Description
Deviations from Investigational Plan		
Planned deviation	Sponsor, EC/IRB	Prior approval from Medtronic must always be obtained. If the deviation affects scientific soundness of the clinical study or the rights, safety, or welfare of the subject and is not an emergency, prior approval must be obtained from the reviewing EC/IRB if required.
Other Deviations	Sponsor	Deviations that are beyond the control of the investigator (such as subject who fails to return to follow-up visit) or deviations that do not affect the scientific soundness of the clinical study or the rights, safety, or welfare of the subject and are not an emergency, should be submitted as they are identified by the investigation site or Medtronic staff.

8.3.3 Sponsor records

At a minimum, the sponsor will keep the following records:

- All essential study documents and correspondence that pertains to the clinical study
- CIP and, if applicable, any amendments
- Instructions for Use (and/or IB for Australia)
- Curriculum Vitae of investigators and investigation site personnel
- Delegated Task Lists and training records of investigators and investigation site personnel
- EC/IRB approvals/notifications
- Signed Clinical Investigation Agreements and signed agreements with third parties
- Insurance certificates
- Medtronic and EC/IRC approved Patient Informed Consent or Patient Data Release Form
- Site selection reports, site initiation reports and monitoring visit letters and reports
- Adverse event and Device Deficiency reports
- Fully executed e-CRFs and corrections
- Regulatory Authority approval or notification if applicable
- Financial Disclosure Information, if requested by the local EC/IRB or regulatory authority
- Shipping records for investigational devices and clinical-investigation related documents and materials
- Sample of labeling attached to the investigational device

8.3.4 Sponsor reporting responsibilities

***Table 13**. Sponsor reporting responsibilities*

Report	Submit to	Description
Adverse Events	EC/IRB, Investigators, and regulatory authorities, where applicable	Medtronic will report adverse events as required and in compliance with local regulatory requirements, as applicable.
Withdrawal of EC/IRB approval	EC/IRB, Investigators, and regulatory authorities, where applicable	In case of withdrawal of EC/IRB approval Medtronic will suspend the clinical study as described below.
Premature termination or suspension of study	EC/IRB, Investigators, and regulatory authorities, where applicable	Medtronic will provide prompt written notification of termination or suspension and reason(s) to investigator and where required to EC/IRB and regulatory authorities.
Emergency Deviations from Investigational Plan	Regulatory authorities, where applicable	If required, Medtronic will inform regulatory authorities as soon as possible about any emergency deviations that affect scientific soundness of the clinical study or the rights, safety, or welfare of the subject.
Final Report	Investigators, and regulatory authorities, where applicable	Medtronic will provide all investigators with a copy of the Final Clinical Study Report of the clinical study. EC/IRBs and regulatory authorities will be informed when required.

8.3.5 Record retention and inspection

Medtronic records and reports will be stored at Medtronic during the course of the study. After the closure of the study, all records and reports will be archived by Medtronic permanently.

The investigator must be willing to give access to study monitors, auditors, MEC/IRB members and inspectors, and have appropriate facilities to retain relevant study documents.

The investigator must retain the Investigator Site File, patient data sources and e-CRFs for a minimum of two years after study closure or longer if required by local law and regulations.

The investigator and sponsor must take measures to prevent accidental or early destruction of the study related materials.

8.4 Miscellaneous

8.4.1 Insurance

The global sponsor Medtronic Plc., and the local sponsors: Medtronic Bakken Research Center BV, Medtronic of Canada Ltd. and Medtronic Australasia, maintain appropriate clinical study liability insurance coverage if required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage.

8.4.2 Study reimbursement and indemnification

Study reimbursement is outlined in the Clinical Study Agreement. Indemnification will be done according to local laws.

8.4.3 Subject confidentiality

All information and data sent to parties involved in study conduct concerning patients or their participation in this study will be considered confidential. Each enrolled subject will be assigned to a unique study ID number, which is pre-configured in Oracle Clinical. Records of the subject/study ID number relationship will be maintained by the study center. The study ID number is to be recorded on all study documents to link them to the subject's medical records at the site. To maintain confidentiality, the subjects' name or any other personal identifiers should not be recorded on any study document other than the Patient Informed Consent or Patient Data Release Form. In the event a subject's name is included for any reason, it will be blinded as applicable. In the event of inability to blind the identification (e.g., digital media), it will be handled in a confidential manner by the authorized personnel.

Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data.

9 RISKS AND BENEFITS

9.1 Anticipated Clinical Benefits

Participation in this clinical study will not result in any direct benefit to the patient. Trial subjects implanted with an Evolut R TAV receive the same medical treatment as if they were not participating in this post-market study. Participation contributes to expansion the knowledge base with respect to the use of the Evolut R system in a routine hospital setting.

9.2 Risks

There are possible risks and side effects connected to the Evolut R TAV implant but the risks are similar to those for an implant of the Evolut R TAV without participation in this study.

Risks and events will be continuously monitored, assessed and documented by the investigator. Refer to the Instructions for Use (and/or IB for Australia) for the list of anticipated adverse events which may be associated with the use of the Evolut R System.

9.3 Risk-to-benefit rationale

Appropriate risk management activities have been performed for the Evolut R System resulting in a positive risk-to-benefit rationale as confirmed by CE mark. Risks and potential benefits are similar for subjects being implanted as part of this study protocol compared to subjects implanted while not participating in this study.

10 APPENDICES

APPENDIX A. ABBREVIATIONS

APPENDIX B. RECOMMENDED ECHOCARDIOGRAPHY PROCEDURES

APPENDIX C. RECOMMENDED MSCT PROCEDURES

APPENDIX D. DEFINITIONS: RISK SCORES AND OTHER CO-MORBIDITIES

APPENDIX E. DEFINITIONS: SAFETY ENDPOINTS AND EFFICACY EVENTS

APPENDIX F. RESHEATH AND RECAPTURE DEFINITIONS

APPENDIX G. EVENT CODE LIST

The following information will be kept separate from the CIP and independently provided to the investigators. The sponsor will maintain updated lists.

- List of names and addresses of the investigation sites in which the clinical study will be conducted
- Initial list of names, addresses, and professional positions of clinical investigators, principal clinical investigators and coordinating clinical investigators
- List of names and addresses of other institutions involved in the clinical study
- Case Report Forms. CRFs shall be developed to capture the data for each enrolled subject as required by the CIP. The CRFs shall include information on the condition of each subject upon entering, and during the course of, the clinical study, exposure to the investigational device/product and any other therapies
- Instructions For Use
- Investigators Brochure

APPENDIX A. ABBREVIATIONS

Abbreviation	Term
2D	Two Dimensional
AE	Adverse Event
ADE	Adverse Device Effect
AF	Atrial Fibrillation
AR	Aortic Regurgitation
AS	Aortic Stenosis
AVR	Aortic Valve Replacement
BAV	Balloon Aortic Valvuloplasty
CE	European Conformity
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CLS	Compression Loading System
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed Tomography
CVA	Cerebrovascular Accident
DCS	Delivery Catheter System
ECG	Electrocardiogram
e-CRF	Electronic Case Report Form
EDC	Electronic Data Capture
EF	Ejection Fraction
EuroSCORE	European System for Cardiac Operative Risk Evaluation
Fr	French
GCP	Good Clinical Practice
HVD	Heart Valve Dysfunction
HR	Heart Rate
IB	Investigators Brochure
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IRB/EC	Institutional Review Board/Ethics Committee
IFU	Instructions for use
ITT	Intent-to-treat
LA	Left Atrial/Atrium
LBBB	Left Bundle Branch Block

Abbreviation	Term
LVEF	Left Ventricular Ejection Fraction
LVOT	Left Ventricular Outflow Tract
MACCE	Major Adverse Cardiovascular and Cerebrovascular Event
MCS	Medtronic CoreValve® System
MEC	Medical Ethics Committee
MI	Myocardial Infarction
mRS	Modified Rankin Score
NYHA	New York Heart Association
PAV	Percutaneous Aortic Valve
PCI	Percutaneous Coronary Intervention
TAVI	Transcatheter aortic valve implant
QoL	Quality of Life
RBBB	Right Bundle Branch Block
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAVR	Surgical Aortic Valve Replacement
SOP	Standard Operating Procedures
STS	Society of Thoracic Surgeons
TEE	Transesophageal Echocardiography
TIA	Transient Ischemic Attack
TTE	Transthoracic Echocardiography
U(S)ADE	Unanticipated (Serious) Adverse Device Effect

APPENDIX B. RECOMMENDED ECHOCARDIOGRAPHY PROCEDURES

B.1 Required Exams

Transthoracic echocardiography is required at the following intervals:

Interval	Time Window
Baseline (Pre-implant)	Within 10 weeks prior to index procedure
Device Success	Between 24 hours and 7 days post-procedure
1 year	Between 365 and 395 days post procedure

B.2 General Imaging and Recording Procedures

- A list of recommended images is provided in Section B.3, List of Recommended Images.
- The subject's ID number and exam interval should be annotated on the image.
- A simultaneous ECG with a clearly defined R-wave should be displayed on all clips.
- Digital cine clips should be a minimum of two cardiac cycles in length (preferably three cycles)
- Color Doppler images should be obtained at a minimum frame rate of 20 Hz through optimization of sector width and depth settings.
- Still frames of measured variables (e.g. LVOT diameter, velocities) should be captured. In addition, still frames of spectral Doppler tracings without the measurements should be captured to facilitate analysis by the Echo Core Lab. Still frames of spectral Doppler tracings should contain a minimum of 3 cardiac cycles for subjects in sinus rhythm, and a minimum of 5 cardiac cycles for subjects in atrial fibrillation (two sequential frames per variable may be necessary).
- Spectral Doppler waveforms should be recorded at a minimum sweep speed of 50 mm/sec.
- Echocardiograms should be recorded and archived on a DICOM digital format for transmission to the Echo Core Lab. Note: This may be done only after the subject has provided Informed Consent by signing the Patient Informed Consent or Data Release Form!
- Exams will be transmitted to the Echo Core Lab via compact disc (CD-R) or Web-based picture archiving and communication system. Details of the image transmission process for each site will be established during site initiation process.
- Exams sent to the Echo Core Lab should be DICOM files in a true or pure DICOM format.
- The following information should be documented on CD-R disks sent to the Echo Core Lab:
  - Study site ID number
  - Subject ID number
  - Exam date
  - Study interval

B.3 List of Recommended Images

Parasternal long-axis window

1. 2D gray scale standard view (LV in a sagittal section)
2. 2D color Doppler for mitral regurgitation (MR)
3. 2D color Doppler of aortic (or prosthetic) regurgitation (AR)
4. If AR is present, ZOOM & narrow sector with focus on vena contracta of regurgitant jet
5. 2D gray scale ZOOM for LV outflow tract diameter (LVOT)
6. Frozen image of measured LVOT diameter
7. 2D gray scale; ZOOM at an intercostal space higher for aortic root / aortic prosthesis

Parasternal short-axis window

8. 2D grayscale LV at mitral valve level
9. 2D grayscale LV at papillary muscle level
10. 2D grayscale-guided M-mode at LV minor axis (LV dimensions, avoid papillary muscles)
11. Frozen image of measured LV dimensions (without measurements)
12. Frozen image of LV m-mode with measurements
13. 2D grayscale LV at apical level
14. 2D grayscale aortic valve level (post TAVI the native annulus is usually identified by maximal calcification)
15. 2D grayscale-guided M-mode of left atrial & aortic dimensions
16. 2D color Doppler of AR: post-TAVI start scanning from highest position and record first visible AR jet, scan more downwards and look for additional jets – confirm origin of AR jets from PLAX
17. 2D grayscale ZOOM & focused on RV outflow tract (RVOT) – pulmonic valve should be visible
18. Frozen image of measured RVOT diameter
19. PW Doppler of RVOT velocity (within 0.5 -1 cm below the pulmonic valve) (frozen image without measurements)
20. Frozen image of RVOT velocity with measured VTI

Parasternal long-axis view (RV inflow)

21. 2D color Doppler of tricuspid regurgitation (TR)
22. If TR is present, CW Doppler of TR jet (frozen image without measurements)
23. Frozen image of TR jet velocity with measurements

Apical 4-Chamber window

24. 2D grayscale standard view
25. 2D color Doppler of MR
26. If MR is present, ZOOM & narrow sector, shift Nyquist 35-40 for PISA measurements
27. If MR is present, CW Doppler of MR jet (frozen image)
28. 2D color Doppler of TR
29. If TR is present, CW Doppler of TR jet (frozen image without measurement)
30. Frozen image of TR jet velocity with measurements
31. 2D grayscale focussed on LV with decreased depth
32. PW Doppler of transmitral flow at mitral valve tips (frozen image)
33. Tissue Doppler of the septal mitral annulus (frozen image)

34. Tissue Doppler of the lateral mitral annulus (frozen image)

Apical long–axis view

35. 2D grayscale standard view
36. 2D color Doppler of AR
37. If AR is present, ZOOM & narrow sector
38. If AR is present, CW Doppler of AR jet (frozen image without measurement)
39. Frozen image of CW Doppler of AR jet (with measurements)
40. CW Doppler of aortic/prosthetic valve (frozen image without measurement)
41. Frozen image of measured aortic/prosthetic valve velocity
42. PW Doppler LVOT (native aortic valve): within 0.5 – 1 cm below native aortic valve (frozen image without measurements
43. PW Doppler LVOT (post –implant) immediately proximal to inflow of stent (frozen image without measurements)
44. Frozen image: measured LVOT velocity

Apical 2-Chamber view

45. 2D grayscale standard view
46. 2D grayscale focused on LV with decreased depth

Sub-costal Position

47. 2D grayscale; long-axis view
48. 2D grayscale; short-axis view
49. 2D grayscale: IVC and hepatic vein
50. If TR moderate by color Doppler, PW Doppler of hepatic vein (frozen image)
51. IF AR moderate by color Doppler, PW Doppler from descending aorta (frozen image)

Supra-Sternal Position

52. CW Doppler of aortic valve velocity; non-imaging probe (frozen image without measurements)
53. Frozen image: measured aortic valve velocity

Right Parasternal Position

54. CW Doppler of aortic valve velocity; non-imaging probe (frozen image without measurements)
55. Frozen image: measured aortic valve velocity

Results Reporting

56. Screen prints of all results pages

B.4 Acquisition of Key Variables

B.4.1 LVOT Diameter

Pre-implant LVOT diameter is measured from the inner edge to inner edge of the septal endocardium, and the anterior mitral leaflet in mid-systole (Figure 4A and B).[37,38]

Following implantation of the Evolut R, LVOT diameter is measured from the parasternal long-axis view, immediately proximal to the inflow aspect of the stent, and in mid systole (Figure 4C and D).[37,38,39]

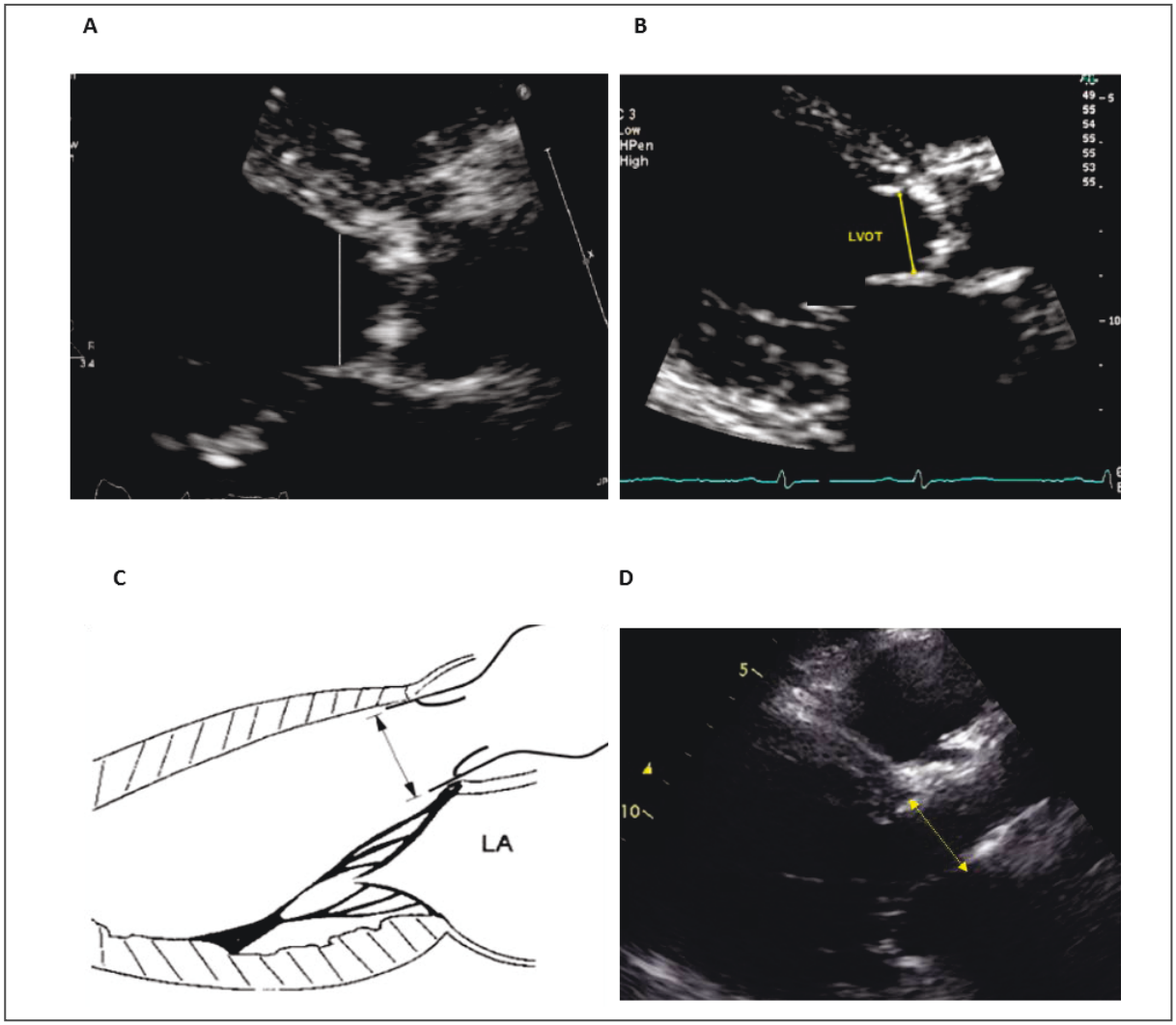


Figure 4*. (A) and (B) Examples of measurement of pre-implant LVOT diameter. LVOT diameter is measured from the white-black interface of the septal endocardium to the anterior mitral leaflet, parallel to the aortic valve plane, approximately 0.5 cm below the level of the aortic annulus, and in mid systole; (C) and (D) Post-implantation, LVOT diameter measurement is from outer edge to outer edge of the inflow aspect of the stent.*

B.4.2 LVOT Velocity

LVOT velocity is recorded with PW Doppler from the apical position, in either the apical long-axis view or in the anteriorly angulated four-chamber view (or "5-chamber view").

The PW sample volume should be positioned just proximal to the aortic valve, with care to avoid the zone of pre-valve acceleration (usually 0.5 to 1.0 cm proximal to the cusps, Figure 5A).[37] The recommended procedure is to initially place the sample volume within the aortic valve leaflets, and then gradually move it apically until a clear spectral waveform is observed with a well-defined peak and minimal spectral broadening (Figure 5B).[34]

Post implantation, the sample volume should be placed proximal to the inflow aspect of the stent.[40] Full-screen imaging of the Evolut R should be used to verify positioning of the sample volume below the stent before switching to spectral Doppler mode (Figure 5C and D).[40,41]

The LVOT VTI is measured by tracing the modal velocity (middle of the dense signal) for use in the continuity equation.[37]

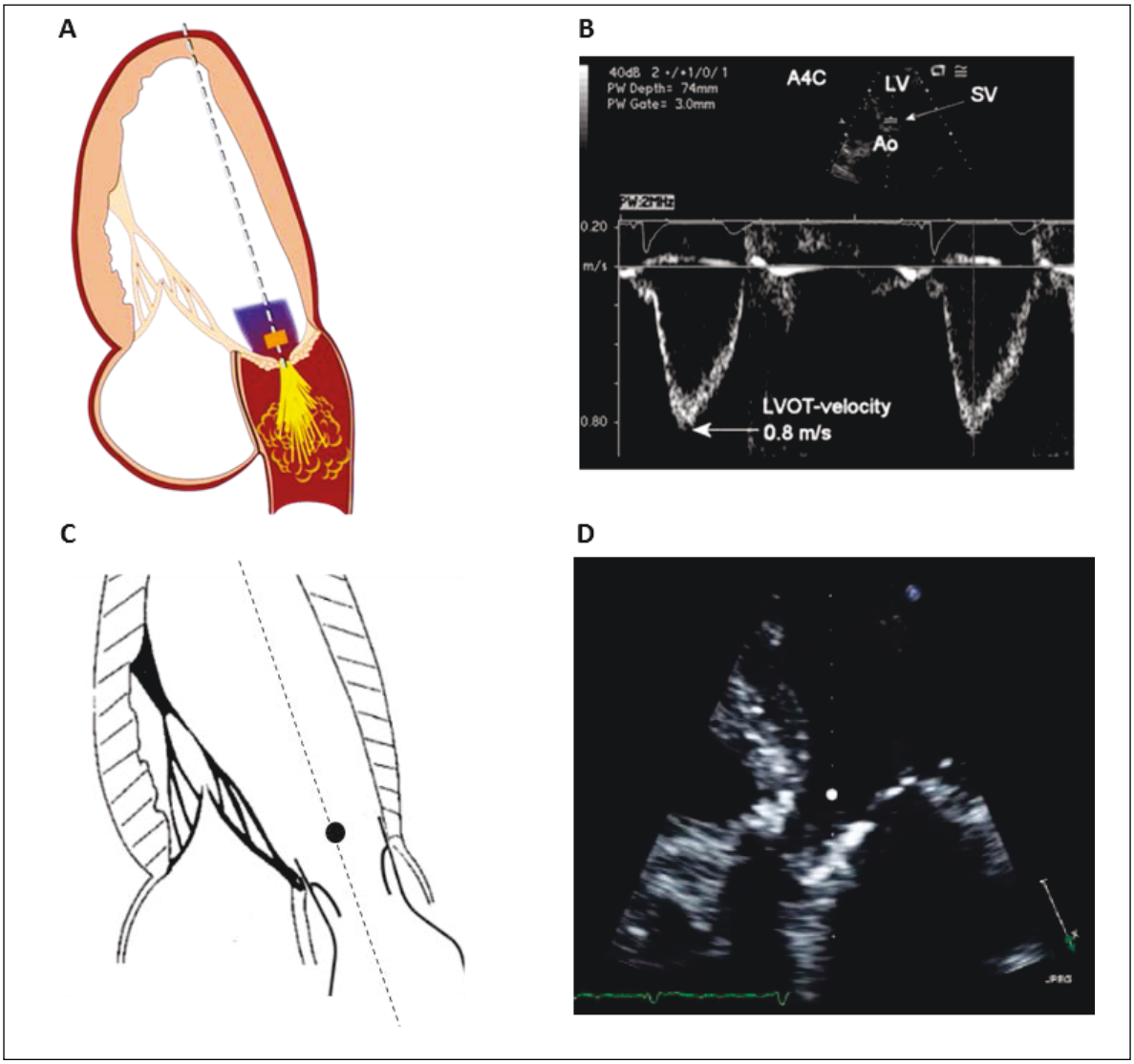


Figure 5. *(**A**) Sample volume placement just proximal to zone of pre-valve acceleration (illustration by Mayo Clinic, used with permission); (**B**) Optimal LVOT velocity signal showing a smooth spectral Doppler recording with a narrow velocity range at each time point; (**C**) Illustration showing correct sample volume placement just proximal to inflow of stent; (**D**) Full-screen imaging of stent to ensure positioning of sample volume below the stent.*

B.4.3 Aortic Valve Velocities

The aortic valve velocity should be interrogated with CW Doppler from a minimum of 2 transducer positions (apical and either a parasternal or suprasternal position). The position that provides the highest velocity is used for measurements. A smooth velocity curve with a clear outer edge and maximal velocity should be recorded. The maximal velocity is measured at the outer edge of the dark signal; fine linear signals at the peak should not be included in measurements. The outer edge of the dark "envelope" of the velocity curve is traced to provide both the VTI for the continuity equation and the mean gradient (Figure6).[37]

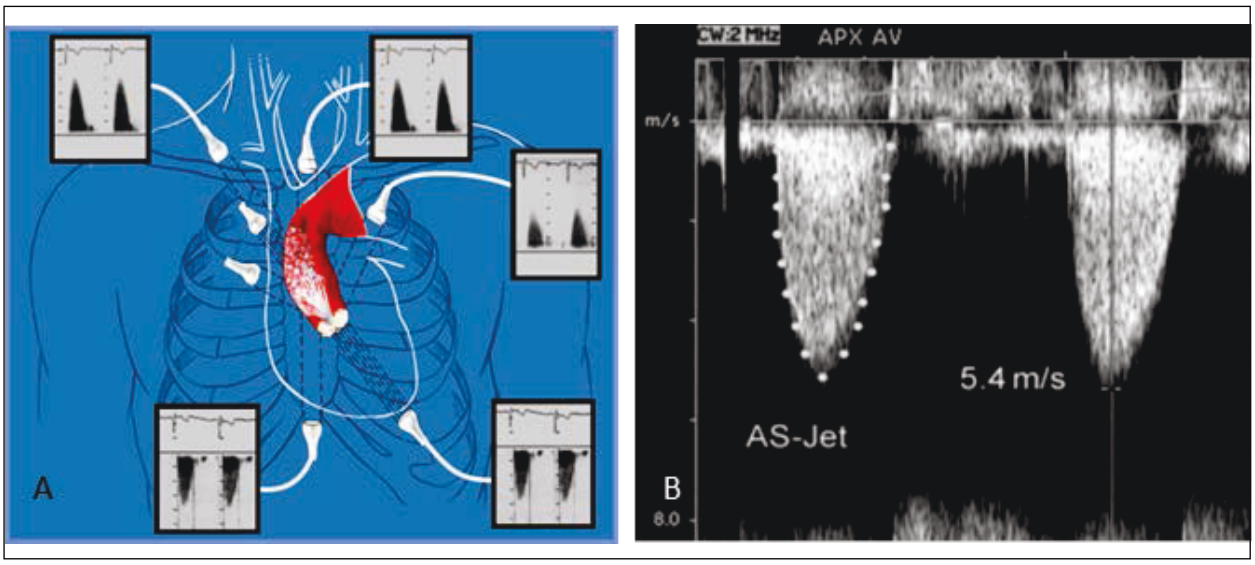


Figure 6. *(**A**) Aortic valve velocities interrogated from multiple transducer positions (illustration by Mayo Clinic, used with permission); (**B**) CW Doppler of severe aortic stenosis showing tracing of the velocity curve from mean gradient and VTI, and measurement of max velocity.*

B.4.4 Assessment of Prosthetic Aortic Regurgitation

An integrated exam approach using color flow, pulsed-wave (PW), and continuous-wave (CW) Doppler is used to assess the severity of transvalvular and paravalvular aortic regurgitation (AR). Color flow Doppler imaging should be performed from the parasternal long and short-axis views, and the apical long-axis and/or 5-chamber views. In the short axis view, color imaging should be performed just below the skirt and frame to assess paravalvular regurgitation, and at the coaptation point of the leaflets for transvalvular (central) regurgitation.[42]

If AR is seen by color Doppler, a CW Doppler recording of the regurgitant signal should be obtained for measurement of pressure half-time and assessment of jet density. If the degree of AR by color Doppler appears more than mild by visual estimate, the velocity in the proximal descending aorta should be recorded with PW Doppler. In addition, the right ventricular outflow tract diameter (RVOT) and RVOT velocity time integral (VTI) should be measured to allow derivation of regurgitant volume and fraction.

The degree of transvalvular, paravalvular, and total (transvalvular plus paravalvular) AR will be graded as none, trace, mild, moderate, and severe based on the synthesis of the Doppler parameters shown in Table 14.[36,37] The category of “trace” should be used in cases where regurgitation is barely detectable by color Doppler.[36] Regurgitant signals observed to originate within the stent will be considered transvalvular, and regurgitant signals observed to originate outside the stent will be considered paravalvular.

***Table 14**. Parameters for evaluation of the severity of aortic regurgitation*

Parameter	Mild	Moderate	Severe
Jet width in central jets (% LVOT diameter): color[1]	Narrow (≤25%)	Intermediate (26% - 64%)	Large (≥65%)
Jet density: CW Doppler	Incomplete or faint	Dense	Dense
Jet deceleration rate (PHT, ms): CW Doppler[2]	Slow (>500)	Variable (200 – 500)	Steep (<200)
LVOT flow vs pulmonary flow: PW Doppler	Slightly increased	Intermediate	Greatly increased
Diastolic flow reversal in descending aorta: PW	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic
Circumferential extent of prosthetic paravalvular regurgitation (%)	<10	10 – 19	≥20
Quantitative Parameters			
Regurgitant volume (ml/beat)	<30	30 – 59	≥60
Regurgitant fraction (%)	<30	30 – 49	≥50

PHT = pressure half-time

B.4.5 Assessment of Mitral Regurgitation

Color flow Doppler imaging of the left atrium should be performed from the parasternal long-axis view, and from the apical 4, 2, and long axis views.

Mitral regurgitant (MR) jets should be recorded with CW Doppler using a velocity scale that allows assessment of the density, shape, duration, and peak velocity of the MR jet. If the severity appears moderate or greater by visual assessment, pulmonary vein velocities should be recorded with PW Doppler to assess for the presence of systolic flow reversal. Grading of the severity of mitral regurgitation should be integrative using the parameters in Table 15.[43]

***Table 15**. Parameters for evaluation of the severity of mitral regurgitation*

Parameter	Mild	Moderate	Severe
Color flow jet area	Small, central jet (usually < 4 cm^2 or < 20% of LA area)	Variable	Large central jet (usually >10 cm^2 or > 40% of LA area), or variable wall-impinging jet swirling in the LA
Jet density (CW)	Incomplete or faint	Dense	Dense
Jet contour (CW)	Parabolic	Usually parabolic	Early peaking, triangular
Pulmonary vein flow	Systolic dominance	Systolic blunting	Systolic flow reversal

B.4.6 Assessment of Tricuspid Regurgitation

Color flow imaging of the right atrium should be performed from the apical 4-chamber view, the parasternal long-axis view of the RVOT, and the parasternal short-axis view at the level of the aortic valve.

Tricuspid regurgitant (TR) jets should be recorded with CW Doppler using a velocity scale that allows assessment of the density, shape, duration, and peak velocity of the TR jet. If the severity appears moderate or greater by visual assessment, hepatic vein velocities should be recorded with PW Doppler to assess for the presence of systolic flow reversal. Grading of the severity of tricuspid regurgitation should be integrative using the parameters in Table 16.[43]

***Table 16**. Parameters for evaluation of the severity of tricuspid regurgitation*

Parameter	Mild	Moderate	Severe
Jet area (cm^2)	< 5	5 – 10	> 10
VC width (cm)	Not defined	Not defined, but < 0.7	≥ 0.7
PISA Radius (cm)	≤ 0.5	0.6 – 0.9	> 0.9
Jet density & contour	Soft & parabolic	Dense, variable contour	Dense, triangular, with early peaking
Hepatic vein flow	Systolic dominance	Systolic blunting	Systolic flow reversal

B.4.7 Assessment of Left Ventricular Function and Left Atrial Size

Dimensions of the left ventricle and left atrium should be obtained by either 2-D linear measurements or using 2-D guided m-mode from either the parasternal long or short axis views (Figure 7). Left ventricular chamber dimensions, septal thickness, and posterior wall thickness are measured using the American Society of Echocardiography (ASE) measurement convention[44] (blood-tissue interface). In addition, standard 2-D views of the left ventricle should be obtained from parasternal and apical transducer positions for visual estimation and quantitative assessment of left ventricular ejection fraction using the modified Simpson's rule, and for assessment of regional wall motion.

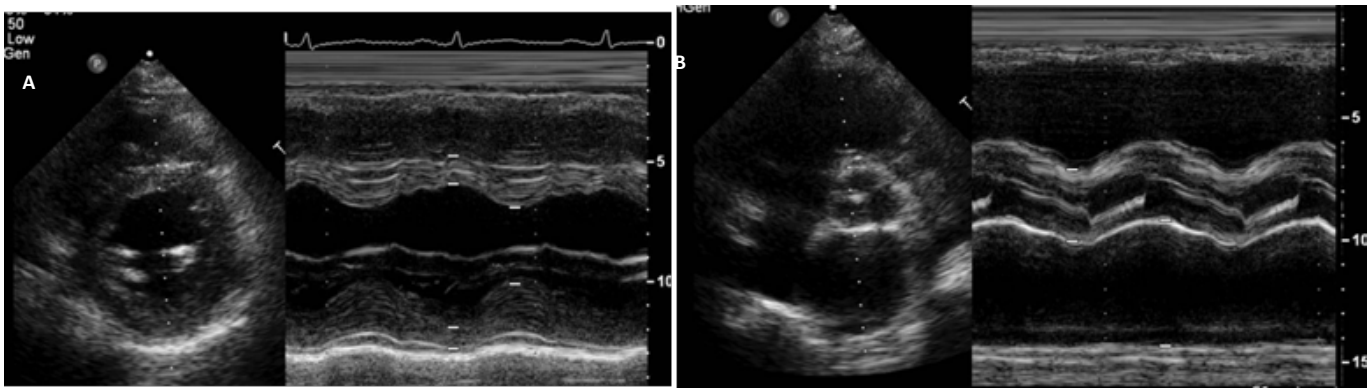


***Figure 7**. Measurements of the left ventricle (A) and left atrium (B) using 2-D guided m-mode*

B.4.8 Assessment of Left Ventricular Diastolic Function

A spectral Doppler recording of mitral inflow should be obtained with PW Doppler in the apical 4-chamber view, using a 1 to 3 mm sample volume placed between the mitral leaflet tips during diastole

Figure 8). The spectral gain and wall filter settings should be optimized to clearly display the onset and cessation of left ventricular inflow. The following variables should be measured:

- Mitral inflow "A" velocity
- Mitral inflow "E" velocity
- Mitral inflow E-wave deceleration time

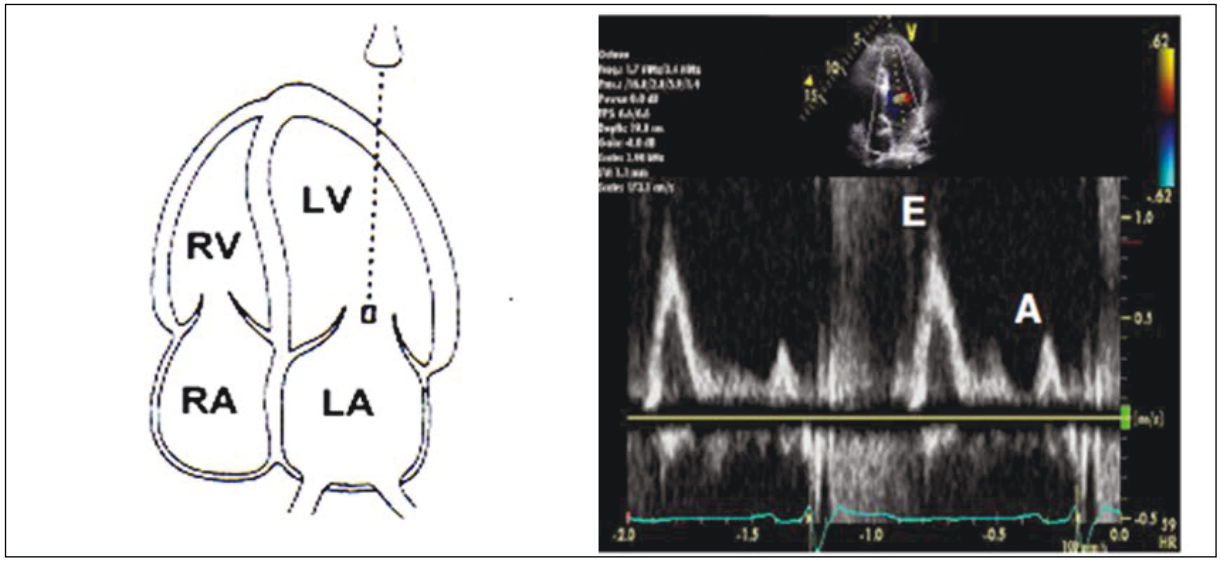


***Figure 8**. Positioning of the sample volume for recording of mitral inflow velocities.*

Mitral annular velocities should be obtained from the lateral and septal aspects of the mitral annulus using PW tissue Doppler (DTI) performed in the apical 4-chamber view. The sample volume should be positioned at or 1 cm within the septal and lateral insertion sites of the mitral leaflets and adjusted as necessary (usually 5 to 10 mm) to cover the longitudinal excursion of the mitral annulus in both systole and diastole. Minimal angulation (<20 degrees) should be present between the ultrasound beam and the plane of cardiac motion. The following variables should be measured:

- Mitral annular tissue Doppler systolic velocity (septal and lateral)
- Mitral annular tissue Doppler early diastolic velocity (septal and lateral)
- Mitral annular tissue Doppler late diastolic velocity (septal and lateral)

Diastolic function should be categorized as normal, mild dysfunction (impaired relaxation pattern), moderate dysfunction (pseudonormal filling), or severe dysfunction (restrictive filling) per the 2009 American Society of Echocardiography recommendations.[45]

B.5 Core Lab Analysis

Protocol-required echocardiograms will be sent to the Echo Core lab for assessment: the data generated by the Echo Core Lab will be the primary data used for analysis and reporting. Received echocardiograms will be logged in and analyzed by the Echo Core Lab according to their procedures determined for this study. Qualitative assessment of valvular regurgitation will be performed using the criteria described in Sections B.4.4 through B.4.6.

The Echo Core Lab will report the following variables:

- Heart rate
- Aortic annulus diameter (pre-implant only)
- Left ventricular outflow tract (LVOT) diameter in mid systole
- Max aortic/prosthetic valve velocity (V_2) by CW Doppler
- Aortic valve velocity time integral (VTI) by CW Doppler
- Mean gradient across aortic valve (MGV_2) by CW Doppler
- LVOT VTI by PW Doppler
- Right ventricular outflow tract (RVOT) diameter(post-implant; if aortic regurgitation > mild by visual estimate)
- RVOT VTI (post-implant; if aortic regurgitation > mild by visual estimate)
- Grade of aortic/prosthetic transvalvular regurgitation (post-implant only)
- Grade of aortic/prosthetic paravalvular regurgitation (post-implant only)
- Grade of prosthetic total (transvalvular plus paravalvular) regurgitation (post-implant only)
- Grade of mitral regurgitation
- Grade of tricuspid regurgitation
- Max tricuspid regurgitant (TR) jet velocity (if TR is present)
- Left ventricular internal dimension at end diastole
- Left ventricular internal dimension at end systole
- Interventricular septal thickness at end diastole
- Left ventricular posterior wall thickness at end diastole
- Left atrial diameter (anterior-posterior linear dimension) at systole
- Left ventricular ejection fraction by visual estimate
- Grade of diastolic dysfunction (if present)

In addition, the following variables will be derived by the central database from the appropriate measurements reported by the Echo Core Lab:

- Peak Pressure Gradient (Peak Δ P) Across the Aortic Valve in mmHg
  Peak Δ P = 4 x (V_2^2)
  Where: V_2 is the peak velocity across the prosthesis in m/sec
- Aortic Valve Area (AVA) in cm^2
  AVA = LVOT diameter in cm^2 x 0.785 x (VTI_{V1}/VTI_{V2})
  Where: VTI_{V1} is the velocity time integral of the left ventricular outflow tract in cm, and VTI_{V2} is the velocity time integral of the native aortic valve in cm

- Aortic Valve Area Index (AVAI) in cm^2/m^2
  AVAI = AVA/BSA
  Where: AVA is the native aortic valve area in cm^2, and BSA is the body surface area in m^2[viii]
- Effective Orifice Area (EOA) in cm^2
  EOA = LVOT diameter^2 x 0.785 x (VTI_{V1}/VTI_{V2})
  Where: VTI_{V1} is the velocity time integral of the left ventricular outflow tract in cm, and VTI_{V2} is the velocity time integral of the aortic prosthesis in cm
- Effective Orifice Area Index (EOAI) in cm^2/m^2
  EOAI = EOA/BSA
  Where: EOA is the effective orifice area in cm^2, and BSA is the body surface area in m^2
- LVOT/aortic valve velocity time integral ratio (Velocity Ratio)
  Velocity Ratio = VTIV1/VTIV2
  Where: VTIV1 is the velocity time integral of the left ventricular outflow tract in cm, and VTIV2 is the time velocity integral of the prosthetic aortic valve in cm
- Left Ventricular Mass (LVM) in grams
  LVM = 0.83 x [(LVIDD + LVPW + IVS)3 - (LVIDD)3] +0.6
  Where: LVIDD is the left ventricular internal dimension at end diastole in cm, LVPW is the left ventricular posterior wall thickness at end diastole in cm, and IVS is the interventricular wall thickness at end diastole in cm.
- Left Ventricular Mass Index (LVMI) in g/m^2 body surface area
  LVMI = LVM/BSA
  Where: LVM is left ventricular mass in g, and BSA is body surface area in m^2
- Fractional Shortening (FS) in %
  FS = [(LVIDD - LVIDS)/LVIDD] x 100
  Where: LVIDD is left ventricular internal dimension at end diastole in cm, and LVIDS is left ventricular internal dimension at end systole in cm
- Estimated Right Ventricular Systolic Pressure (RVSP) in mmHg
  RVSP = (4 x MVTR jet^2) + 10
  Where: MV TR jet is the max velocity of the tricuspid regurgitant jet, and 10 = the assumed mean right atrial pressure in mmHg
- Aortic Regurgitant Volume (RV) in ml/beat
  $RV = SV_{LVOT} – SV_{RVOT}$
  Where: SV_{LVOT} = LVOT diameter^2 x 0.785 x $LVOT_{VTI}$, and SV_{RVOT} = RVOT diameter^2 x 0.785 x $RVOT_{VTI}$
- Aortic Regurgitant Fraction (RF) in %
  $RF = RV/SV_{LVOT}$
- Body Surface Area (BSA) in m^2
  BSA = 0.007184 x (height in $cm^{0.725}$ x weight in $kg^{0.425}$)

[viii] BSA derived from height and weight reported on the site e-CRF

APPENDIX C. RECOMMENDED MSCT PROCEDURES

C.1 Introduction

Multi-slice Computed Tomography (Cardiac MSCT) is used to evaluate aortic valve anatomy, determine aortic root dimensions for device sizing, and to evaluate peripheral vessel dimensions and anatomy. The following sections are intended as recommended guidelines for acquiring the images for assessing anatomical suitability for implantation.

C.2 General Requirements

- Multi-detector CT scanner (64-slice minimum) with ECG-gating capability.
- ECG-gated contrast enhanced aortic root (slice thickness of ≤ 1.0 mm)
- Temporal resolution should be optimized to reduce motion artifact.
- Spatial resolution should be as high as possible (goal is smallest isotropic voxel size)

C.3 ECG-gated Contrast Enhanced Scan of Aortic Root

Retrospective ECG-gated scans are recommended, which allows for reconstruction in various phases of the cardiac cycle and optimal evaluation of anatomic dimensions and valve morphology. Recommended scan parameters are listed in Table 17.

Prospective ECG-gated sequential scans (step-and-shoot) and high-pitch spiral scans with ECG-gating (flash spiral) are also acceptable. The following parameters are important to the optimum scan:

- Detector collimation 0.4-0.625 mm.
- Slice thickness ≤ 1.0 mm.
- The recommended coverage area is from superior to the aortic arch to inferior to the cardiac apex. The minimum required coverage area is from 50 mm above the aortic annulus to 10 mm below the aortic annulus.
- The recommended slice overlap is 0.4 mm (will result in isotropic voxels with a 20 cm field of view).

C.4 Post-processing

- Retrospective ECG-gated scans
  - Verify heart rate ECG triggers are at consistent place in cardiac cycle, edit if necessary. Additional editing/removal of arrhythmias may be performed.
  - Reconstruct at multiple phases (10 increments of 10%), with ≤ 1.0 mm slice thickness. If the system has the capability, also reconstruct a “best systolic” and “best diastolic” phase.
- Prospective ECG-gated scans (including flash spiral)
  - Reconstruct with medium soft kernel and slice thickness ≤ 1.0 mm (slice overlap of 0.4 mm recommended)

Table 17. Recommended scan parameters

Parameter	Recommendation
IV injection with iodine contrast	80-100 (320mg/ml or higher), modify per patient as appropriate
Injection rate	4-6 mL/sec
Bolus tracking, delay	Delay time calculated using protocol for current scanner (bolus tracking or similar) with peak of contrast concentration in the ascending aorta during acquisition.
ECG-gating	Retrospective
Scan direction	Cranial-caudal
Scan coverage	From above the aortic arch to past the cardiac apex
Detector collimation	0.4 – 0.625 mm
Pitch	0.2–0.43 adapted to the heart rate
Dose modulation	Modulation and full current between 30 and 80% of the cardiac cycle
Slice thickness	0.8 mm
Slice overlap	0.4 mm
Reconstruction kernel	Medium Smooth
Post-processing	Retrospective ECG gating reconstruction algorithm that minimizes motion artifact. Reconstruct at multiple phases (10 minimum). Reconstructed slice thickness ≤ 0.8 mm.

C.5 Required Aortic Root Measurements

The following measurements of the aortic root are obtained for assessing anatomical suitability:

- Aortic valve annulus perimeter (measured at systole if retrospective gating is used)
- Mean sinus of Valsalva diameter (measured at diastole)
- Mean sinus of Valsalva heights (measured at diastole)

C.6 Reformatting of Images[46]

- Site image cross-hairs on aortic root in all windows where it is visible. Lock cross-hairs so they remain orthogonal for all steps.
- In the coronal window, rotate cross-hairs (horizontal line) counter-clockwise to align with virtual basal plane, (Figure 9, upper left panel).
- In the sagittal window, the horizontal line is rotated clockwise or counter-clockwise to align with virtual basal plane (Figure 9, lower left panel).
- On the newly defined double-oblique axial image, scroll up and down through the aortic root until the most caudal attachment points of the three native leaflets come into view (indicated by arrowheads in Figure 10). If one of the leaflets comes into view at a more cranial or caudal slice, adjust the coronal or sagittal cross-hairs until all three leaflets come into view on the same axial slice.

- For confirmation of the correct aortic annulus plane, scroll through the double oblique axial images starting in the mid sinus and ending at the level of the aortic annulus. The sinuses should appear to be relatively the same size at the level of the mid-sinus and the leaflets should all disappear equally at the level of the annulus.

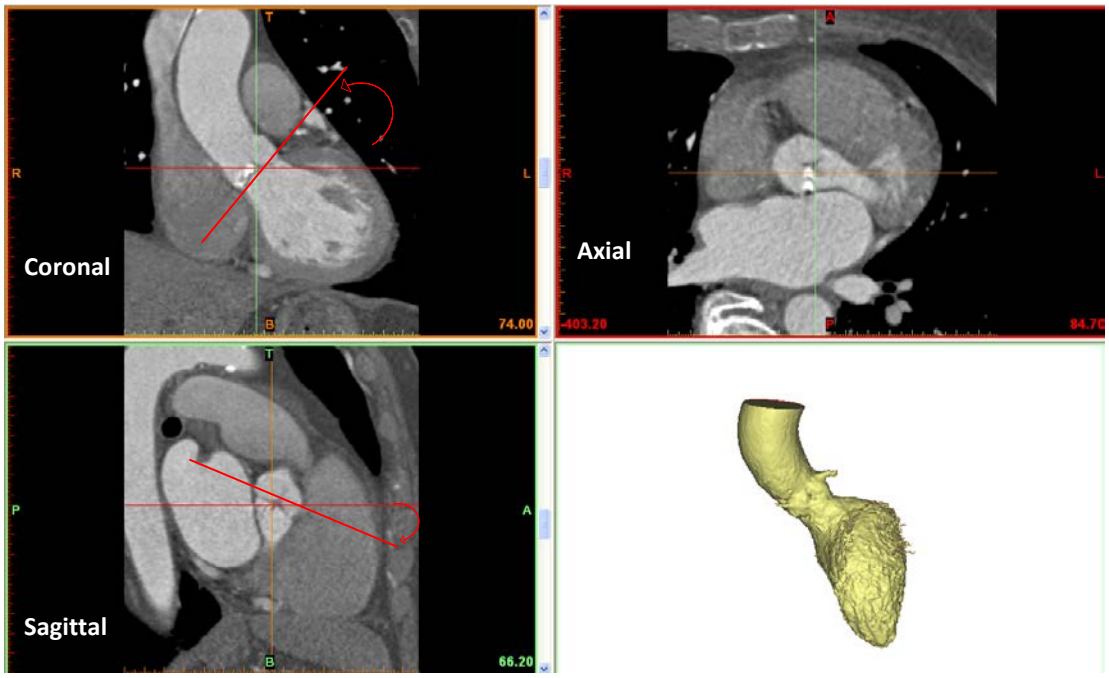


***Figure 9**. Example images in original orientation (axial, coronal, and sagittal). Red curved arrow and line indicate adjustment of coronal and sagittal planes to align with aortic basal annulus.*

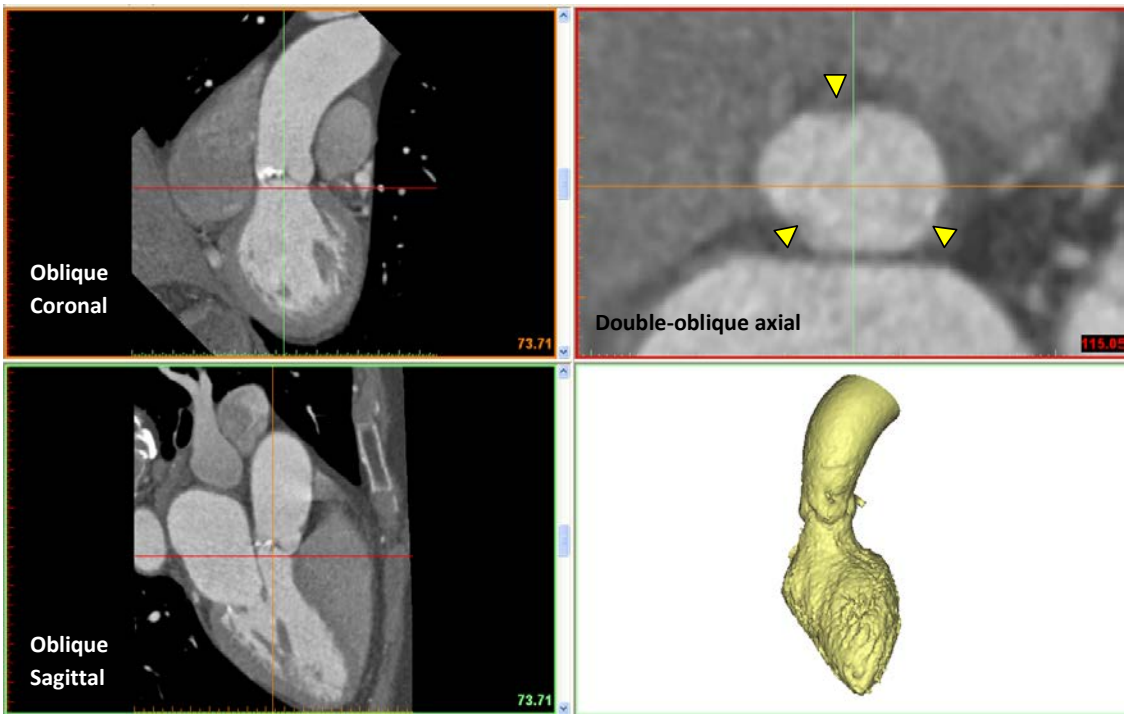


Figure 10. *Example images of reformatted oblique coronal (upper left), oblique sagittal (lower left), double oblique axial (upper right), and 3D reconstruction (lower right). Yellow arrowheads indicate most caudal attachment of three leaflets of the aortic valve).*

C.7 Aortic Annulus Measurements

- Choose the cleanest systolic images for the aortic annulus measurements, either automatically (e.g., best systolic) or by manually identifying. Measurement on a diastolic image is also acceptable.
- Aortic annulus measurements should be completed on the properly reformatted double-oblique axial image at aortic annulus level, as described in Section C.6, Reformatting of Images.
- Trace the perimeter of the basal annulus (Figure 11, left). Place cross-hairs at site of basal annulus, create major diameter through the site, create minor diameter defined as perpendicular to major and through site (Figure 11, right).

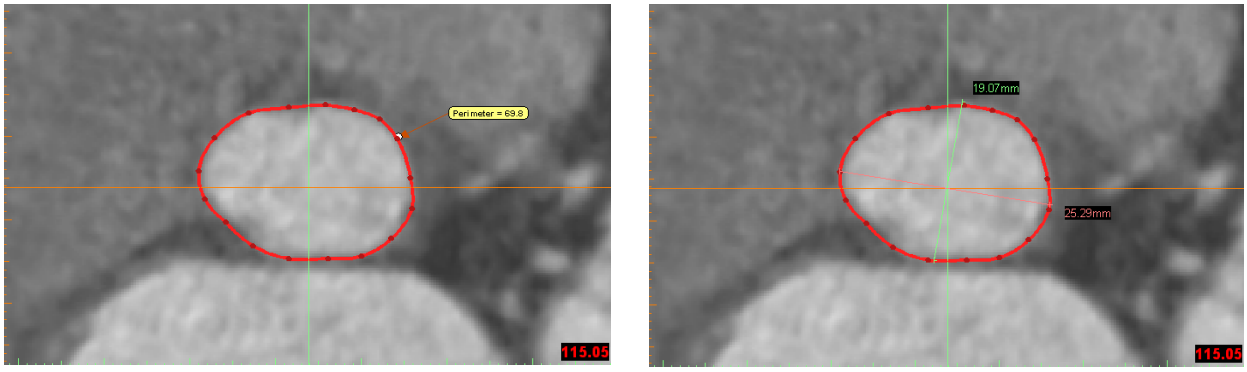


Figure 11*. Example of perimeter measurement (left) and major and minor diameter measurements (right).*

C.8 Sinus of Valsalva Measurements

Choose the best diastolic images for measurement of sinus of Valsalva diameters and heights from images using the same reformatting technique as described in Section C.6, Reformatting of Images.

C.8.1 Sinus of Valsalva Diameters

- Select the double oblique axial image where the widest portion of the three sinuses is visible.
- Measure a diameter from each commissure through the site of the root to the opposite sinus. Complete for all three sinuses (Figure 12).

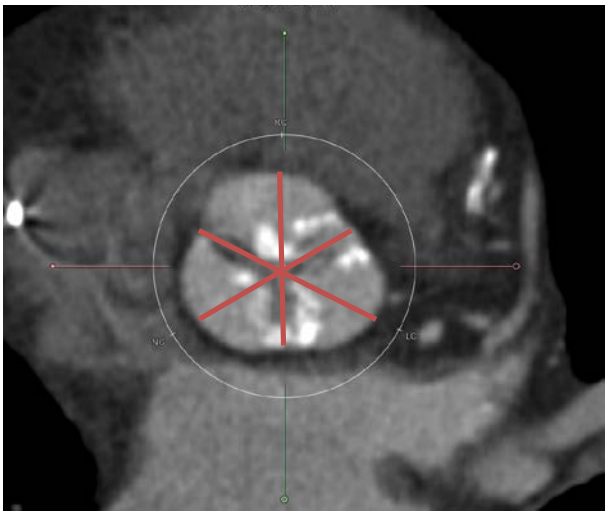


Figure 12. *Example of sinus of Valsalva diameters*

C.8.2 Sinus of Valsalva Heights

- The sinotubular junction is typically not co-planar with the aortic annulus. Therefore, a sinus of Valsalva height must be measured for each of the three sinuses. This height is defined as the distance between the aortic annular plane and the tallest point in the sinus.
- Choose the double oblique axial image so that it is located at the level of the aortic annulus. The reformatting line representing the double oblique axial image should now be visible in the oblique coronal and oblique sagittal images at the level of the aortic annulus.
- For the left coronary and non coronary heights, use the oblique coronal image. For the right coronary height, use the oblique sagittal image.
- To complete the measurement, scroll through the oblique coronal or sagittal image (depending on which sinus you are measuring) and locate the heights location of the sinotubular junction. On that image, measure the distance along the path of the aortic root from the aortic annular plane, marked by the reformatting line, to the sinotubular junction (Figure 13).

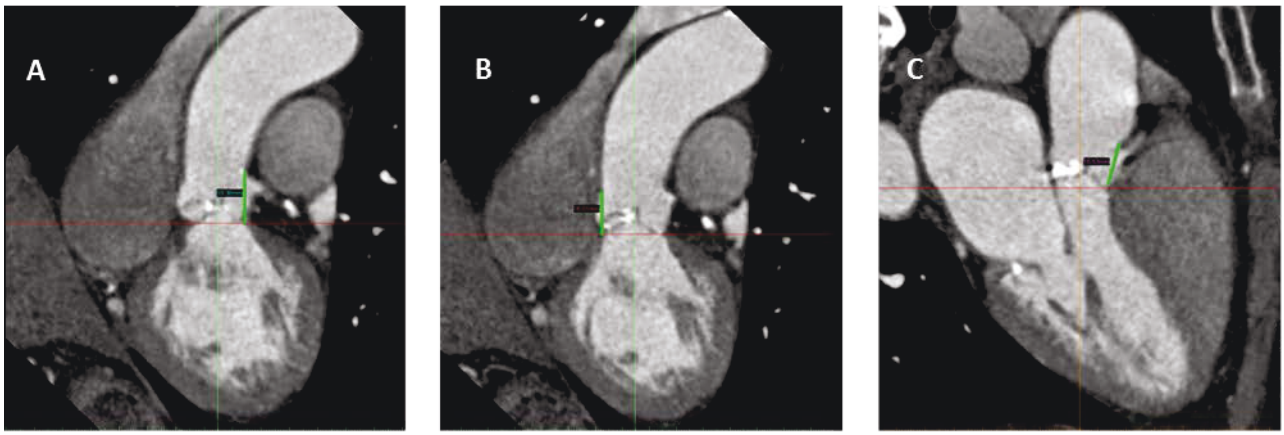


***Figure 13**. Examples of sinus of Valsalva heights; (**A**) left coronary; (**B**) non coronary; (**C**) right coronary*

C.9 Anatomic Suitability and Valve Size Selection

Device Size	Aortic Annulus		Sinus of Valsalva	
	Perimeter (mm)	Mean Diameter (mm)	Mean Diameter (mm)	Mean Height (mm)
23 mm	56.5 – 62.8	18 – 20	≥ 25	≥ 15
26 mm	62.8 – 72.3	20 – 23	≥ 27	≥ 15
29 mm	72.3 – 81.6	23 – 26	≥ 29	≥ 15

APPENDIX D. DEFINITIONS: RISK SCORES AND OTHER CO-MORBIDITIES

D.1 Risk Scores

The Logistic EuroSCORE, EuroSCORE II and Society of Thoracic Surgeons' (STS) risk scores should be calculated at baseline for each subject using the online calculator:

- Logistic EuroSCORE: *http://euroscore.org/calcold.html*
- EuroSCORE II: *http://euroscore.org/calc.html*
- STS Risk Score: *http://riskcalc.sts.org/stswebriskcalc/#/*

The online calculators provide additional guidance and definitions for each of the parameters used to calculate the scores. For the Logistic EuroSCORE and EuroSCORE II, the definitions for each of the parameters can be found as notes under the online calculator. The variable definitions for the STS risk score model can be accessed by clicking on the field names in the online calculator.

D.2 Other Factors Not Captured by Traditional Risk Score[32]

Co-morbidity	Definition/Criteria
Porcelain aorta or severely atherosclerotic aorta	Heavy circumferential calcification or severe atheromatous plaques of the entire ascending aorta extending to the arch such that aortic cross-clamping is not feasible.
Frailty	Slowness, weakness, exhaustion, wasting and malnutrition, poor endurance and inactivity, loss of independence Criteria: • 5 meter walking time • Grip strength • BMI <20 kg/m2 and/or weight loss 5 kg/yr • Serum albumin <3.5 g/dL • Cognitive impairment or dementia
Sever liver disease/cirrhosis	Any of the following: • Child-Pugh class C • MELD score ≥10 • Portal-caval, spleno-renal, or transjugular intrahepatic portal shunt • Biopsy proven cirrhosis with portal hypertension or hepatocellular dysfunction
Hostile chest	Any of the following or other reasons that make redo operation through sternotomy or right anterior thoracotomy prohibitively hazardous: • Abnormal chest wall anatomy due to severe kyphoscoliosis or other skeletal abnormalities (including thoracoplasty, Potts' disease) • Complications from prior surgery • Evidence of severe radiation damage (e.g. skin burns, bone destruction, muscle loss, lung fibrosis or esophageal stricture) • History of multiple recurrent pleural effusions causing internal adhesions
IMA or other critical conduit(s) crossing	A patent IMA graft that is adherent to the sternum such that injuring it during re-operation is likely. A patient may be considered extreme risk if any of the following

midline and/or adherent to posterior table of sternum	are present: • The conduit(s) are radiographically indistinguishable from the posterior table of the sternum. • The conduit(s) are radiographically distinguishable from the posterior table of the sternum but lie within 2-3 mm of the posterior table.
Severe pulmonary hypertension	Primary or secondary pulmonary hypertension with PA systolic pressures greater than 2/3 of systemic pressure
Severe right ventricular dysfunction	Criteria as defined by the guidelines (e.g. TAPSE <15mm, RV end-systolic area >20 cm2, etc)

APPENDIX E. DEFINITIONS: SAFETY ENDPOINTS AND EFFICACY EVENTS

Definitions of adverse events to be evaluated as clinical safety endpoints, other TAVI-related complications, and efficacy events are provided in Sections E.1, E.2, and E.3, respectively. Site investigators and the CEC will code events according to these definitions, using the associated code list provided in appendix G, Event Code List.

E.1 Safety Endpoint Definitions[32]

Mortality	
Cardiovascular mortality	Any of the following criteria: 1) Death due to proximate cardiac cause (eg, myocardial infarction, cardiac tamponade, worsening heart failure) 2) Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease 3) All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure 4) All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related adverse events 5) Sudden or unwitnessed death 6) Death of unknown cause
Non-cardiovascular mortality	Any death in which the primary cause of death is clearly related to another condition (eg, trauma, cancer, suicide).

Myocardial Infarction	
Periprocedural MI (≤72 h after the index procedure)	New ischemic symptoms (e.g, chest pain or shortness of breath), or new ischemic signs (e.g, ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q-waves in at least 2 contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality) AND Elevated cardiac biomarkers (preferable CK-MB) within 72 h after the index procedure, consisting of at least 1 sample post procedure with a peak value exceeding 15x as the upper reference limit for troponin or 5x for CK-MB. If cardiac biomarkers are increased at baseline (>99th percentile), a further increase in at least 50% post procedure is required AND the peak value must exceed the previously stated limit.
Spontaneous MI (>72 h after the index procedure)	Any of the following criteria: 1) Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least 1 value above the 99th percentile URL, together with the evidence of myocardial ischemia with at least 1 of the following: • Symptoms of ischemia • ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)] • New pathological Q-waves in at least 2 contiguous leads • Imaging evidence of a new loss of viable myocardium or new wall motion abnormality

	2) Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. 3) Pathological findings of an acute myocardial infarction

Stroke and TIA
Diagnostic criteria 1) Acute episode of a focal or global neurological deficit with at least 1 of the following: • change in the level of consciousness • hemiplegia, hemiparesis • numbness or sensory loss affecting 1 side of the body • dysphasia or aphasia • hemianopia • amaurosis fugax • other neurological signs or symptoms consistent with stroke **Stroke:** duration of a focal or global neurological deficit ≥24 h; OR <24 h if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death **TIA:** duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct 2) No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with the designated neurologist 3) Confirmation of the diagnosis by at least 1 of the following: • Neurologist or neurosurgical specialist • Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone
Stroke Definitions **Disabling stroke:** an mRS score of 2 or more at 90 days and an increase in at least 1 mRS category from an individual's pre-stroke baseline **Non-disabling stroke:** an mRS score of <2 at 90 days or one that does not result in an increase in at least 1 mRS category from an individual's pre-stroke baseline
Stroke Classifications **Ischemic:** an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue **Hemorrhagic:** an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage **Undetermined**: insufficient information to allow categorization as ischemic or hemorrhagic

Bleeding Complications	
Life-threatening or disabling bleeding	1) Fatal bleeding *(BARC type 5)* OR 2) Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome *(BARC type 3b and 3c)* OR 3) Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery *(BARC type 3b)* OR 4) Overt source of bleeding with drop in hemoglobin ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units* *(BARC type 3b)*
Major bleeding *(BARC type 3a)*	1) Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND 2) Does not meet criteria of life-threatening or disabling bleeding
Minor bleeding *(BARC type 2 or 3a, depending on the severity)*	Any bleeding worthy of clinical mention (eg, access site hematoma) that does not qualify as life-threatening, disabling, or major
*Given one unit of packed RBC typically will raise hemoglobin concentration by 1 g/dL, an estimated decrease in haemoglobin will be calculated; BARC: Bleeding Academic Research Consortium29; RBC: red blood cell	

Note: With respect to blood transfusions, it is critical to acknowledge that a bleeding complication has to be the result of overt bleeding and cannot be adjudicated based on blood transfusions alone.

Acute Kidney Injury (up to 7 days post procedure)	
Stage 1	1) Increase in serum creatinine to 150%-199% (1.5-1.99 x increase compared with baseline) OR increase of ≥0.3 mg/dL (≥26.4 mmol/L) OR 2) Urine output <0.5 mL/kg/h for >6 but <12 h
Stage 2	1) Increase in serum creatinine to 200%-299% (2.0%-2.99% increase compared with baseline) OR 2) Urine output <0.5 mL/kg/h for >12 but <24 h
Stage 3	1) Increase in serum creatinine to ≥300% (>3 x increase compared with baseline) OR serum creatinine of ≥4.0 mg/dL (≥354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) OR 2) Urine output <0.3 ml/kg/h for ≥24 h OR 3) Anuria for ≥12 h

Vascular Access Site and Access Related Complications	
Major vascular complication	1) Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudoaneurysm OR 2) Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) *leading to* death, life-threatening or major bleeding, visceral ischemia, or neurological impairment OR 3) Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR 4) The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia or neurological impairment OR 5) Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR 6) Surgery for access site-related nerve injury OR 7) Permanent access site-related nerve injury
Minor vascular complication	1) Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneuysms, hematomas, percutaneous closure device failure) *not leading to* death, life-threatening or major bleeding*, visceral ischemia, or neurological impairment OR 2) Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR 3) Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR 4) Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)
Percutaneous closure device failure	Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)

*Refer to VARC bleeding definitions

VALVE DYSFUNCTION REQUIRING REPEAT PROCEDURE
Any valve dysfunction that requires repeat procedure (e.g. balloon valvuloplasty, TAVI, or surgical AVR)

Note: Repeat procedures are reported on the appropriate e-CRF (Surgical Intervention or Catheter Reintervention)

E.2 Other TAVI Related Complications

Complication	Definition
Conversion to open surgery	Conversion to open sternotomy during the TAVI procedure secondary to any procedure-related complications
Unplanned use of cardiopulmonary bypass	Unplanned use of CPB for hemodynamic support at any time during the TAVI procedure
Coronary artery obstruction	Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary ostium, either by the Evolut R prosthesis itself, the native leaflets, calcifications, or dissection, occurring during or after the TAVI procedure.
Ventricular septal perforation	Angiographic or echocardiographic evidence of a new septal perforation during or after the TAVI procedure
Mitral valve apparatus damage or dysfunction	Angiographic or echocardiographic evidence of new damage (chordae, papillary muscle, or leaflet) to the mitral valve apparatus or dysfunction (e.g. restrictions due to the Evolut R) of the mitral valve during or after the TAVI procedure
Cardiac tamponade	Evidence of new pericardial effusion associated with hemodynamic instability and clearly related to the TAVI procedure
Prosthetic valve thrombosis	Any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment. **Valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve related should not be reported as valve thrombosis*.
Valve migration	After initial correct positioning, any observed movement (upward or downward) of the Evolut R within the aortic annulus from its initial position, with or without consequences.
Valve embolization	The Evolut R moves during or after deployment such that it loses contact within the aortic annulus
Ectopic valve deployment	Permanent deployment of the Evolut R in a location other than the aortic root
TAV in TAV deployment	Additional valve prosthesis is implanted within a previously implanted Evolut R because of sub-optimal device position and/or function, during or after the index procedure.
Hemolysis	Red cell destruction as evidenced by plasma free hemoglobin >50 mg/dl **Minor hemolysis:** No intervention required **Major hemolysis:** Requires intervention (e.g. iron supplements, transfusion, invasive intervention).
Frame fracture	Visual evidence on radiography or at explant of loss of contact between elements (cells) of the stent. **Minor frame fracture:** Does not require intervention, or is not associated with prosthetic valve dysfunction. **Major frame fracture:** Intervention required (e.g. reoperation, catheter re-intervention) or is associated with prosthetic valve dysfunction

PROSTHETIC VALVE ENDOCARDITIS

Any of the following:

1) Fulfillment of the following Duke criteria[47] for definite endocarditis:
   - Histologic and/or microbiologic evidence of infection at surgery or autopsy, or
   - 2 major criteria, or
   - 1 major criteria or 3 minor criteria, or
   - 5 minor criteria

   Major and minor criteria are as follows:

   Major Criteria:

   - Blood cultures positive for Infective Endocarditis (IE)
     - Typical microorganisms consistent with IE isolated from two separate blood cultures, as noted below
       - Viridans streptococci, *Streptococcus bovis*, *Staphylcoccus aureus*, or HACEK group
       - Community-acquired enterococci in the presence of a primary focus
     - Microorganisms consistent with IE isolated from persistently positive blood cultures defined as:
       - At least two positive cultures or blood samples obtained >12 hours apart, or
       - All of three, or a majority of four or more separate cultures of blood, the first and last sample obtained > one hour apart
     - Single blood culture positive for Coxiella burnetti or an antiphase I IG antibody titer >1:800
   - **Evidence of endocardial involvement**
     - Positive results of echocardiography for IE defined as:
       - Oscillating intracardiac mass on a valve or supporting structures in the path of regurgitant jets or on implanted material in the absence of an anatomic explantation, or
       - Abscess, or
       - New partial dehiscence of a valvular prosthesis
     - New valvular regurgitation (worsening or changing or pre-existing murmur not sufficient)

   Minor Criteria:

   - **Predisposition:** predisposing heart condition or intravenous drug use
   - **Fever:** temperature >38°C
   - **Vascular phenomena:** major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions
   - **Immunological phenomena:** glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor
   - **Microbiological evidence:** positive blood culture but does not meet a major criterion (as noted above) or serological evidence of active infection with organism consistent with infectious endocarditis.
   - **Echocardiographic findings:** consistent with IE but do not meet a major criterion as noted above

   If only 1 major and 1-2 minor criteria are fulfilled, or if only 3-4 minor criteria are fulfilled, the event will be coded as "possible endocarditis"

2) Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during a re-operation
3) Findings of abscess, pus, or vegetation involving the Evolut R at autopsy

E.3 Efficacy Event Definitions[32]

PROSTHETIC VALVE DYSFUNCTION	
Stenosis: mild	**For subjects with BSA ≥ 1.6 m^2:** Mean aortic gradient ≥ 20 and ≤40 mmHg, EOA ≥ 0.8 and ≤ 1.1 cm^2 AND/OR DVI ≥ 0.25 and ≤ 0.35 **For subjects with BSA < 1.6 m^2:** Mean aortic gradient ≥ 20 and ≤40 mmHg, EOA ≥ 0.6 cm^2 and ≤ 0.9 cm^2 AND/OR DVI ≥ 0.25 and ≤ 0.35
Stenosis: moderate/severe	**For subjects with BSA ≥ 1.6 m^2:** Mean aortic gradient > 40 mmHg, EOA < 0.8 cm^2 AND/OR DVI < 0.25 **For subjects with BSA < 1.6 m^2:** Mean aortic gradient > 40 mmHg, EOA < 0.6 cm^2 AND/OR DVI < 0.25
Paravalvular regurgitation: moderate	Moderate paravalvular regurgitation (per echo criteria in CIP)
Paravalvular regurgitation: severe	Severe paravalvular regurgitation (per echo criteria in CIP)
Transvalvular regurgitation: moderate	Moderate paravalvular regurgitation (per echo criteria in CIP
Transvalvular regurgitation: severe	Moderate or severe transvalvular regurgitation (per echo criteria in CIP)

Notes:

1. DVI = Doppler Velocity Index (LVOT VTI/valve VTI)
2. For subjects LVOT diameter > 2.5 cm, the DVI criteria for significant (moderate or severe) stenosis is 0.2
3. Reporting of prosthetic valve dysfunction will be based on core lab values (if available).
4. Prosthetic valve dysfunction events are not reported as adverse events, unless the dysfunction is accompanied with clinical sequelae at the time of event detection, and the clinical sequelae are chronologically and physiologically associated with the dysfunction. However, prosthetic dysfunctions that are associated with adverse events, and that meet the definition of a serious adverse event, should be reported as such.

APPENDIX F. RESHEATH AND RECAPTURE DEFINITIONS

The following definitions are applicable to the data elements on the Implant e-CRF that address the use of the resheath and recapture feature.

Resheath attempt	An attempt to intentionally resheath only a portion of the Evolut R TAV (including the frame) into the capsule of the delivery catheter (e.g. with the intent to reposition of the valve during deployment).
Recapture attempt	An attempt to intentionally fully resheath the entire Evolut R TAV (including the frame) into the capsule of the delivery catheter until there is no gap between capsule and the tip (e.g. with the intent to enable re-crossing of the aortic valve or retrieval of the system).
Point of no return	The point at which the capsule marker is aligned with the distal aspect of the spindle (Figure 14C).
Valve functionality	Functional valve performance is defined as the presence of stable systemic pressure (approximately > 80% of pre-implant mean arterial pressure).
Successful resheath attempt	Successful resheathing is defined as Evolut R TAV (including frame) was resheathed into the capsule of the delivery catheter to the desired amount intended, as verified by fluoroscopy.
Successful full recapture attempt	The entire Evolut R TAV (including the frame) is fully resheathed into the capsule of the delivery catheter until there is no gap between the capsule and the tip, as verified by fluoroscopy.

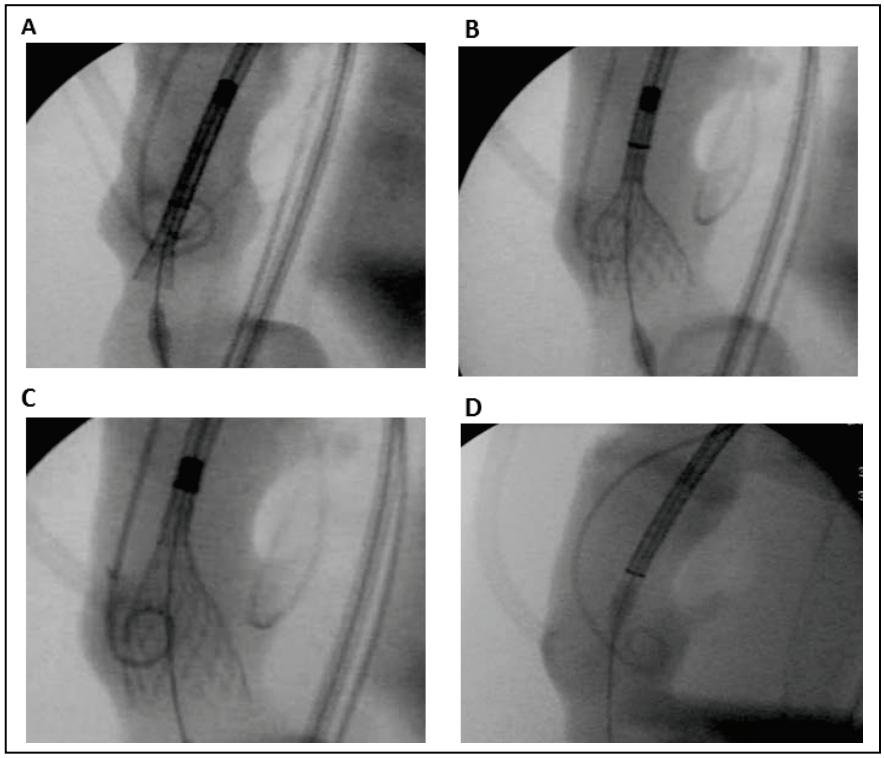


Figure 14. (A) Between 0 and 1/3 of the valve length outside of the capsule; (B) between 1/3 and 2/3 of the valve length outside of the capsule; (C) Point of no return: capsule marker in alignment with the spindle marker; (D) Full recapture: entire valve

APPENDIX G. EVENT CODE LIST

Myocardial Infarction

100 Peri-procedural myocardial infarction
101 Spontaneous myocardial infarction

Stroke and TIA

102 Disabling stroke: ischemic
103 Disabling stroke: hemorrhagic
104 Disabling stroke: undetermined origin
105 Non-disabling stroke: ischemic
106 Non-disabling stroke: hemorrhagic
107 Non-disabling stroke: undetermined origin
108 Transient ischemic attack

Bleeding Complications

110 Life threatening or disabling bleeding event
111 Major bleeding event
112 Minor bleeding event

Acute Kidney Injury

113 Acute kidney injury: stage 1
114 Acute kidney injury: stage 2
115 Acute kidney injury: stage 3

Vascular Access and Access Site Complications

Major

120 Major vascular complication: aortic dissection, aortic rupture, LV perforation, or new apical aneurysm/pseudoaneurysm
121 Major vascular complication: access site or access site-related vascular injury (dissection, stenosis, perforation, etc)
122 Major vascular complication: distal embolization from vascular source
123 Unplanned endovascular or surgical intervention
124 New ipsilateral lower extremity ischemia
125 Surgery for access site-related nerve injury
126 Permanent access site-related nerve injury
127 Other major vascular complication

Minor

130 Minor vascular complication: access site or access site-related vascular injury
131 Minor vascular complication: distal embolization from vascular source
132 Unplanned endovascular stenting or unplanned surgical intervention not meeting criteria for major complication
133 Vascular repair or need for vascular repair
134 Other minor vascular access site complication
140 Failure of closure device leading to alternative treatment

Other TAVI-Related Complications

150 Conversion to open surgery
151 Unplanned use of CPB
152 Coronary artery obstruction
153 Ventricular septal perforation
154 Mitral valve apparatus damage or dysfunction
155 Cardiac tamponade
156 Prosthetic valve thrombosis
157 Valve migration
158 Valve embolization
159 Ectopic valve deployment
160 TAV in TAV deployment
161 Major hemolysis
162 Minor hemolysis
163 Prosthetic valve endocarditis: definite
164 Prosthetic valve endocarditis: possible
165 Major frame fracture
166 Minor frame fracture
167 Other TAVI-related complication

Conduction Disturbances and Arrhythmias

170 Atrio-ventricular block, 1°
171 Atrio-ventricular block, 2°
172 Atria-ventricular block, 3°

173 LBBB

174 RBBB

175 Left anterior fascicular block

176 Left posterior fascicular block

180 Atrial fibrillation

181 Atrial flutter

182 Junctional rhythm (<100 bpm)

183 Junctional rhythm (≥100 bpm)

184 Sinus bradycardia (<50 bpm)

185 Supraventricular tachycardia

186 Ventricular fibrillation

187 Ventricular premature beats

188 Ventricular tachycardia

189 Other arrhythmia

Prosthetic Valve Dysfunction

190 Mild stenosis

191 Moderate/severe stenosis

192 Moderate paravalvular regurgitation

193 Severe paravalvular regurgitation

194 Moderate transvalvular regurgitation

195 Severe transvalvular regurgitation

Other Implantation/Catheterization Procedure-Related Adverse Events

200 Brachial plexus injury

201 Hypovolemia

202 Hypotension requiring intervention

203 Air embolism

204 Venous thrombosis, definite

205 Venous thrombosis, suspected

206 Metabolic acidosis

207 Catheter induced arrhythmia

208 Hemothorax

209 Radiation-induced erythema

210 Other implantation/catheterization

Other Cardiac Adverse Events

300 Cardiac arrest

301 Congestive heart failure

302 Cardiogenic shock

303 Valvular regurgitation, mitral

304 Valvular regurgitation, tricuspid

307 Syncope

308 Palpitations

309 Cyanosis

310 Chest pain

311 Pericardial effusion, hemorrhagic

312 Pericardial effusion, non-hemorrhagic

313 Intracardiac mass

399 Other cardiac event

Respiratory/Pulmonary Adverse Events

400 Respiratory arrest

401 Pneumothorax

402 Chronic pulmonary disease

403 Bronchospasm/asthma

404 Pleural effusion

405 Hemoptysis

406 Respiratory failure

407 Atelectasis

408 Hemothorax

409 Respiratory insufficiency

410 Apnea/hypoventilation

499 Other respiratory/pulmonary

Other Neurologic Adverse Events

500 Seizure(s)

502 Meningitis, infectious

504 Headaches

505 Dizziness

599 Other central nervous system

Gastrointestinal Adverse Events

600 Vomiting

601 Diarrhea

602 Protein losing enteropathy

603 Liver disease

604 Liver failure

699 Other gastrointestinal

Hematologic/Oncologic Adverse Events

700 Cancer/malignancy

701 Coagulopathy

702 Anemia (Hgb <10g or Hct <30%)

703 Thrombocytopenia

704 Transfusion reaction

799 Other hematologic/oncologic

Infection Adverse Events

801 Fever (≥ 39.0°C)

802 Sepsis, confirmed (positive blood culture)

803 Sepsis, suspected (by clinical findings)

804 Endocarditis, other than Evolut R

805 Urinary tract infection

806 Pneumonia

807 Gastroenteritis

808 Hepatitis

809 Upper respiratory tract infection

899 Other infection

Other Renal Adverse Events (Exclusive of AKI)

900 Renal insufficiency

902 Chronic renal failure

903 Proteinuria

904 Urinary retention

999 Other renal

Allergic Reactions

1000 Anaphylaxis

1001 Pruritus

1002 Rash

1003 Contrast reaction/allergy

1004 Medication reaction/allergy

1099 Other allergic reaction

Other

1200 Multi organ failure

1299 Other

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