# SMall Annuli Randomized To Evolut™ or SAPIEN™ Trial (SMART)

NCT04722250

StudyProtocol/Document Date: 15Dec2021

| Medtronic<br>**Clinical Investigation Plan** | |
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| **Clinical Investigation Plan/Trial Title** | SMall Annuli Randomized To Evolut™ or SAPIEN™ Trial (SMART Trial) |
| **Clinical Investigation Plan Identifier** | MDT20023EVR012 |
| **Trial Product Names** | 1. Medtronic Evolut™ PRO, Evolut™ PRO+ and Evolut™ FX* Transcatheter Aortic Valve (TAV) Systems<br>2. Edwards SAPIEN 3 and SAPIEN 3 Ultra Transcatheter Heart Valve (THV) Systems<br>*Note: The Evolut™ FX System is commercially available in the United States. The Evolut™ FX System may be used upon commercial availability in Canada. |
| **Sponsor/Local Sponsor** | Medtronic, Inc. (Global Sponsor)<br>Structural Heart and Aortic Clinical (formerly referred to as Coronary and Structural Heart Clinical)<br>8200 Coral Sea St NE, MVS 66<br>Mounds View, MN 55112, United States<br><br>Medtronic Canada ULC. (Local Sponsor)<br>99 Hereford St., Brampton,<br>ON, L6Y 0R3, Canada<br><br>Medtronic Bakken Research Center BV (Local Sponsor)<br>Endepolsdomein 5, 6229 GW Maastricht, The Netherlands |
| **Document Version Number/Date** | Version 4.0, 15-Dec-2021 |
| **Lead Principal Investigators (PIs)** | Dr. Howard Herrmann (Trial Principal Investigator (PI))<br>University of Pennsylvania<br>PCAM South Pavilion 11-107<br>3400 Civic Center Boulevard<br>Philadelphia, PA 19104, United States<br><br>Dr. Roxana Mehran (Trial Co-PI)<br>Mount Sinai School of Medicine<br>1190 Fifth Avenue - 1 South<br>New York, NY 10029, United States<br><br>Dr. Didier Tchétché (Trial Co-PI)<br>Clinique Pasteur<br>45 Avenue de Lombez<br>31076 Toulouse, France |

# 1. Investigator Agreement and Signature Page

| | |
|---|---|
| **Trial product Names** | 1. Medtronic Evolut™ PRO and Evolut™ PRO+, and Evolut™ FX* Transcatheter Aortic Valve (TAV) Systems<br>2. Edwards SAPIEN 3 and SAPIEN 3 Ultra Transcatheter Heart Valve (THV) Systems<br><br>*Note: The Evolut™ FX System is commercially available in the United States. The Evolut™ FX System may be used upon commercial availability in Canada. |
| **Sponsor** | Medtronic Inc., Structural Heart and Aortic Clinical (formerly referred to as Coronary and Structural Heart Clinical) |
| **Clinical Investigation Plan Identifier** | MDT20023EVR012 |
| **Version Number/Date** | Version 4.0, 15-Dec-2021 |

I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this trial as described. I will conduct this trial as outlined herein and will make a reasonable effort to complete the trial within the time designated.

I agree to comply with country, local, and internal institutional requirements included in section 15 of this protocol including the Declaration of Helsinki, the Clinical Investigation Plan, and Good Clinical Practice, as well as local laws, regulations, and standards. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic.

I will provide all trial personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the trial.

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| **Investigator's Signature:** | |
| **Investigator's Name:** | |
| **Institution:** | |
| **Date:** | |

# Table of Contents

# 2. Glossary

| Term | Definition |
|---|---|
| 6MWT | 6-minute walk test |
| ADE | Adverse device effect |
| AE | Adverse event |
| AR | Aortic regurgitation |
| AS | Aortic stenosis |
| ASADE | Anticipated serious adverse device effect |
| AT | As-treated |
| AVA | Aortic valve area |
| BAV | Balloon aortic valvuloplasty |
| BE | Balloon-expandable transcatheter aortic/heart valve (TAV/THV) |
| BVD | Bioprosthetic valve dysfunction |
| CEC | Clinical Event Committee |
| CHB | Complete heart block |
| CIP | Clinical Investigation Plan |
| CRO | Clinical Research Organization |
| CRF | Case report form |
| CFR | Code of Federal Regulations |
| CROs | Contract Research Organizations |
| CTA | Clinical Trial Agreement |
| CV | Curriculum Vitae |
| CW | Continuous-wave |
| DCS | Delivery catheter system |
| DD | Device deficiency |
| DSMB | Data Safety Monitoring Board |
| DTL | Delegated Task List |
| DVI | Doppler velocity index |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EMEA | Europe, Middle East and Africa |
| EOA | Effective orifice area |
| EOAI | Effective orifice area index |
| EQ | EuroQoL |
| EQ VAS | EQ Visual Analogue Scale |
| EQ-5D/EQ-5D-5L | EuroQol- 5 Dimension/EuroQol- 5 Dimension-5 Level |
| EU MDR | European Union Medical Device Regulation |

| Term | Definition |
|---|---|
| FD | Financial Disclosure |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HAVB | High degree atrioventricular block |
| HIPAA | Health Insurance Portability and Accountability Act |
| HF | Heart Failure |
| HSVD | Hemodynamic structural valve dysfunction |
| ICF | Informed Consent Form |
| ICH | International Conference of Harmonization |
| IE | Infective endocarditis |
| IFU | Instructions For Use |
| IRB | Institutional Review Board |
| IVCD | Intraventricular conduction delay |
| KCCQ | Kansas City Cardiomyopathy Questionnaire |
| LBBB | Left bundle branch block |
| LS | Loading system |
| LVOT | Left ventricular outflow tract |
| MDCG | Medical Device Coordination Group |
| MDCT | Multi-detector computed tomography |
| MGV | Mean gradient across aortic valve |
| MR | Mitral regurgitation |
| mRS | Modified Rankin Score |
| NSVD | Non-structural valve dysfunction |
| NYHA | New York Heart Association |
| PI | Principal investigator |
| PPI | Permanent pacemaker implantation |
| PPM | Prosthesis-patient mismatch |
| PVL | Peri-valvular leak |
| PVR | Paravalvular regurgitation |
| PW | Pulsed-wave |
| QoL | Quality of Life |
| RA | Regulatory authority |
| RBBB | Right bundle branch block |
| RDC | Remote data capture |
| REB | Research Ethics Board |
| RVSP | Right ventricular systolic pressure |
| SADE | Serious adverse device effect |
| SAE | Serious adverse event |
| SAV | Surgical aortic valve |
| SAVR | Surgical aortic valve replacement |
| SE | Self-expanding transcatheter aortic/heart valve (TAV/THV) |

| Term | Definition |
|---|---|
| SID | Subject identification |
| SoV | Sinus of Valsalva |
| STS-PROM | Society of Thoracic Surgeons-Predicted Risk or Mortality |
| SVD | Structural valve dysfunction |
| TAR | Total aortic regurgitation |
| TAV | Transcatheter aortic valve |
| TAVR | Transcatheter aortic valve replacement |
| TEE | Transesophageal echocardiology |
| THV | Transcatheter heart valve |
| TR | Tricuspid regurgitation/tricuspid regurgitant |
| TTE | Transthoracic echocardiogram |
| UAEs | Unavoidable adverse events |
| ULN | Upper limit of normal |
| URL | Upper reference limit |
| USADE | Unanticipated serious adverse device effect |
| VARC | Valve Academic Research Consortium |
| VTI | Velocity time integral |

# 3. Synopsis

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| **Title** | SMall Annuli Randomized To Evolut™ or SAPIEN™ Trial (SMART Trial) |
| **Product Names** | Medtronic Evolut™ PRO, Evolut™ PRO+, and Evolut™ FX* Transcatheter Aortic Valve (TAV) Systems<br><br>Edwards SAPIEN 3 and SAPIEN 3 Ultra Transcatheter Heart Valve (THV) Systems<br><br>Both products hereafter collectively referred to as transcatheter aortic valves 'TAV(s)'.<br><br>*Note: The Evolut™ FX System is commercially available in the United States. The Evolut™ FX System may be used upon commercial availability in Canada. |
| **Global Sponsor (funding source)** | Medtronic, Inc.<br>Structural Heart and Aortic Clinical (formerly referred to as Coronary and Structural Heart Clinical)<br>8200 Coral Sea St NE, MVS 66<br>Mounds View, MN 55112<br>United States<br>(800) 633-8766 |
| **Local Sponsors** | Medtronic Canada ULC.<br>99 Hereford St., Brampton,<br>ON, L6Y 0R3,<br>Canada<br><br>Medtronic Bakken Research Center BV<br>Endepolsdomein 5, 6229 GW Maastricht,<br>The Netherlands |
| **Indication under investigation** | Subjects with symptomatic heart disease due to severe native calcific aortic stenosis and a small annulus appropriate for transcatheter heart valve replacement therapy. |
| **Investigation Purpose** | The purpose of this trial is to generate clinical evidence on valve safety and performance of self-expanding (SE) versus balloon-expandable (BE) transcatheter aortic valve replacement (TAVR) in subjects with a small aortic annulus and symptomatic severe native aortic stenosis. |
| **Product Status** | Devices used in this trial must be commercially approved by the local regulatory agencies in the geography they are used. The devices will be used within the local commercially approved indication in the geographies in which each device is approved.<br><br>The Medtronic Evolut PRO System is a recapturable transcatheter aortic valve replacement (TAVR) system, which includes;<br>• Evolut PRO transcatheter aortic valve (TAV),<br>• EnVeo PRO delivery catheter system (DCS), and |

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| | • EnVeo PRO loading system (LS).<br>The Medtronic Evolut PRO+ System is a recapturable TAVR implantation system comprised of the following 3 components:<br>• Evolut PRO+ TAV<br>• Evolut PRO+ DCS<br>• Evolut PRO+ LS<br>The Evolut PRO and Evolut PRO+ Systems are CE marked and commercially available in Canada, participating countries in Europe, Middle East and Africa (EMEA) region, and the United States.<br><br>The Medtronic Evolut FX System is a recapturable TAVR implantation system comprised of the following 3 components:<br>• Evolut FX TAV<br>• Evolut FX DCS<br>• Evolut FX LS<br>The Evolut FX System is commercially available in the United States. The Evolut FX System may be used upon commercial availability in Canada.<br><br>The Edwards SAPIEN 3 and SAPIEN 3 Ultra Transcatheter Heart Valve (THV) Systems are comprised of the following components:<br>• SAPIEN 3 and SAPIEN 3 Ultra Transcatheter Heart Valve<br>• Commander Delivery System<br>• eSheath Introducer Set<br>• Crimper and Qualcrimp Crimping Accessory<br>The Edwards SAPIEN 3 and SAPIEN 3 Ultra THV Systems are CE marked and commercially available in Canada, participating countries in the EMEA region, and the United States. |
| **Trial Design** | Prospective, multi-center, international, randomized controlled, post-market trial. |
| **Randomization** | Subjects will be randomized on a 1:1 basis to receive transcatheter aortic valve replacement (TAVR) with either a Medtronic SE or an Edwards BE TAV. Randomization will be stratified by site and sex. |
| **Primary Endpoints** | The trial will have two powered primary endpoints comparing the Medtronic SE TAVs and Edwards BE TAVs to:<br>1. A clinical outcome composite endpoint of mortality, disabling stroke or heart failure rehospitalization at 12 months<br>2. A valve function composite endpoint of bioprosthetic valve dysfunction (BVD) at 12 months including any of the following:<br>▪ Hemodynamic Structural Valve Dysfunction (HSVD): hemodynamic mean gradient ≥ 20mmHg |

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| | ▪ Non-structural Valve Dysfunction (NSVD): severe prosthesis-patient mismatch (PPM), ≥ moderate aortic regurgitation (AR)<br>▪ Thrombosis<br>▪ Endocarditis<br>▪ Aortic valve re-intervention |
| **Powered Secondary Endpoints** | The powered secondary endpoints comparing the SE and BE TAVR are:<br>1. BVD in female subjects at 12 months<br>2. HSVD at 12 months<br>3. Hemodynamic mean gradient as continuous variable at 12 months<br>4. Effective orifice area (EOA) as continuous variable at 12 months<br>5. Moderate or severe prothesis-patient mismatch (PPM) at 30 days |
| **Non-powered Secondary Endpoints** | The non-powered secondary endpoints comparing the SE and BE TAVR are listed below:<br>1. Device success at 30 days<br>2. Incidence of an early safety composite at 30 days defined as:<br>▪ All-cause mortality<br>▪ All stroke (disabling and non-disabling)<br>▪ Life-threatening bleeding<br>▪ Acute kidney injury—Stage 2 or 3 (including renal replacement therapy)<br>▪ Coronary artery obstruction requiring intervention<br>▪ Major vascular complication<br>▪ Valve-related dysfunction requiring repeat procedure (balloon aortic valvuloplasty [BAV], TAVR, or Surgical aortic valve replacement [SAVR])<br>3. Hospital readmission for any cause at 30 days<br>4. Incidence of clinical efficacy (after 30 days) at 12 months and annually to 5 years defined as a composite of:<br>▪ All-cause mortality<br>▪ All stroke (disabling and non-disabling)<br>▪ Requiring hospitalizations for valve-related symptoms or worsening congestive heart failure<br>▪ NYHA class III or IV<br>▪ Valve-related dysfunction (mean aortic valve gradient ≥20 mmHg, EOA ≤0.9-1.1 $cm^2$ and/or Doppler Velocity Index (DVI) <0.35m/s, AND/OR moderate or severe prosthetic valve regurgitation)<br>5. Components of the primary clinical endpoint at 12 months and annually to 5 years:<br>▪ Mortality<br>▪ Disabling stroke<br>▪ Heart failure rehospitalization<br>6. New pacemaker implantation rate at 30 days, 12 months and annually to 5 years |

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| | 7. Aortic valve re-intervention at 30 days, 12 months and annually to 5 years<br>8. 6-minute walk test (6MWT) at 30 days, 12 months and annually to 5 years<br>9. Quality of Life (QoL) (Kansas City Cardiomyopathy Questionnaire [KCCQ], EuroQol- 5 Dimension [EQ-5D]) at 30 days, 12 months and annually to 5 years<br>10. BVD (HSVD, NSVD, thrombosis, endocarditis, and aortic valve re-intervention) at 2 to 5 years annually<br>11. Echocardiographic measurements (i.e. EOA, mean gradient, PVL, LV mass regression, and DVI (severe <0.25, moderate 0.25-0.5, mild >0.5)) at discharge, 30 days, 12 months and annually to 5 years<br>12. Mean gradient ≥ 20 mmHg based on stress echocardiogram at 12 months at select sites |
| **Sample Size** | Approximately 700 treated subjects at approximately 90 sites in Canada, EMEA and the United States. |
| **Inclusion/Exclusion Criteria** | **Inclusion Criteria**<br>Subjects must meet ALL of the following inclusion criteria:<br>I1. Symptomatic subjects with predicted risk of operative mortality < 15% at 30-days per multidisciplinary local heart team assessment<br>I2. Severe aortic stenosis, defined as: Aortic valve area ≤1.0 $cm^2$ (or aortic valve area index of ≤0.6 $cm^2/m^2$), OR mean gradient ≥40 mmHg, OR maximal aortic valve velocity ≥4.0 m/sec by transthoracic echocardiography at rest<br>I3. Aortic valve annulus area ≤ 430 $mm^2$ based on Multi- detector computed tomography (MDCT)<br>I4. Subject's anatomy is appropriate for both Medtronic TAV and Edwards TAV Systems used within the conduct of the trial<br>I5. Subject's anatomy is suitable for TAVR via transfemoral vessel access<br>I6. Commercial indication for transcatheter aortic valve replacement (TAVR), in conformity with both local regulations and Instructions for Use (IFU)<br>I7. Subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits<br><br>**Exclusion Criteria**<br>Subjects are NOT eligible for trial participation if they meet ANY of the following exclusion criteria:<br>E1. Estimated life expectancy of less than 2 years<br>E2. Multivessel coronary artery disease with a Syntax score >32 and/or unprotected left main coronary artery (Syntax score calculation is not required for patients with history of previous revascularization if repeat revascularization is not planned).<br>E3. Participating in another trial that may influence the outcome of this trial<br>E4. Need for an emergent procedure for any reason<br>E5. Contraindicated for treatment with the Medtronic and Edwards TAV Systems in accordance with the Instructions for Use |

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| | E6. Other medical, social, or psychological conditions that in the opinion of the Investigator precludes the subject from appropriate consent or adherence to the protocol required follow-up exams<br>E7. Pregnant, nursing or planning to be pregnant<br>E8. Subject is less than legal age of consent, legally incompetent, unable to provide his/her own informed consent, or otherwise vulnerable<br>E9. Subject has an active COVID-19 infection or relevant history of COVID-19. *Note: An active COVID-19 infection is defined as a positive Polymerase Chain Reaction (PCR) result. Relevant history of COVID-19 is defined as availability of a positive COVID-19 test with sequela or hospitalization for treatment of COVID-19 that was less than 3 months prior to enrollment. Subjects with a positive COVID-19 test who were asymptomatic or had mild symptoms should be excluded only if the positive test was less than 3 months prior to enrollment.*<br>E10. Previous aortic valve replacement |
| **Trial Procedures and Assessments** | All randomized and treated subjects will undergo a 5-year follow-up period. For each subject, data will be collected at pre- and post-procedure, at discharge, at 30 days and once a year until the 5-year follow-up is completed.<br>Main collected data will be:<br>• Baseline subject demographics, medical history, anatomical eligibility, MDCT, and Society of Thoracic Surgeons-Predicted Risk or Mortality (STS-PROM) score at Screening<br>• Procedural/discharge evaluations<br>• Clinical assessment at Screening, Baseline, Discharge, 30-day, 12-month, 2-year, 3-year, 4-year and 5-year follow-up visits<br>• Transthoracic echo at Screening, Discharge, 30-day, 12-month, 2-year, 3-year, 4-year and 5-year follow-up visits<br>• 12-lead ECG at Pre- and post-procedure, Discharge, 30-day and 12- month follow-up visits<br>• NYHA at Screening, Baseline, Discharge, 30-day, 12-month, 2-year, 3-year, 4-year and 5-year follow-up visits<br>• Quality of Life assessments at Baseline, 30-day, 12-month, 2- year, 3-year, 4-year and 5-year follow-up visits<br>• 6-minute walk test at Baseline, 30-day, 12-month, 2-year, 3-year, 4-year and 5-year follow-up visits |
| **Safety Assessments** | • Collection of all serious adverse events (SAEs), non-serious endpoint-related adverse events (AEs), adverse device effects (ADEs) and device deficiencies (DDs) through 5 years from enrollment until end of trial<br>• Modified Rankin Score (mRS) assessment at baseline and at 30 and 90 days after onset of any confirmed or suspected neurological event |

# 4. Introduction

## 4.1 Background

Transcatheter aortic valve replacement (TAVR) has been shown to be a safe and effective treatment for patients with severe aortic stenosis (AS) who are at extreme, high, intermediate or low surgical risk[1-8]. Since TAVR devices became commercially available in the global market, two valve types have been widely used: self-expanding (SE) and balloon-expandable (BE). Both types of valves have different designs in expansion mode, leaflet characteristics and stent frames, which translate into different rates of procedural complications, and differences in hemodynamic function and long-term performance.

In recent years, reports from randomized trials, registry data, meta-data analysis, propensity score matched or unmatched analysis, or single-center experience have been published to provide device performance comparison of SE vs BE valves. In the CHOICE trial, a total of 241 high-risk patients were randomized to receive a self-expanding CoreValve or a balloon-expandable SAPIEN XT, and the trial concluded that clinical outcomes at 1 year including death, all stroke, repeat hospitalization were not statistically different between the two devices despite the higher device success rate with the BE valve that was attributed to lower frequency of residual more-than-mild aortic regurgitation[9-10]. The SOLVE-TAVI trial randomized 447 high to intermediate risk patients to an Evolut R or SAPIEN 3 device and concluded the SE and BE devices were equivalent for the primary efficacy endpoint[11]. A propensity-matched comparison from the FRANCE-TAVI Registry compared the outcomes of SAPIEN XT/ SAPIEN 3 and CoreValve in a large nationwide registry and suggested the use of the SE devices was associated with a higher risk of paravalvular regurgitation (PVR) [12]. However, reports from single centers identified similar short-term outcomes between third-generation SE and BE devices and rare clinically significant paravalvular leak[13-14]. A meta-data analysis conducted by Osman, et al, showed similar outcomes were seen following transcatheter aortic valve replacement with BE (SAPIEN, SAPIEN XT, and SAPIEN 3) and SE (CoreValve, Evolut-R, and Evolut PRO) devices with the exception of a higher rate of pacemaker implantation and PVL in SE valve group[15].

Though these published data are based on various generations of devices, and are primarily comprised of earlier generations of the SE technology, there appears to be consistent evidence suggesting superior hemodynamic performance of SE compared with BE, with lower aortic valve mean gradient and/or large aortic valve area[9-12,13-14,16]. The difference of hemodynamic performance could be attributed to the valve design differences with the supra-annular leaflet function in SE as opposed to an intra-annular level in BE. Initial hemodynamic performance of prosthetic aortic valves has been reported to be prognostic of intermediate and longer term clinical outcomes including hemodynamic or structural deterioration[17-18], heart failure hospitalization[19], and mortality[19-21]. This is likely to be particularly true for patients with a small aortic annulus who are predisposed to having PPM when implanted with an intra-annular prosthesis[22]. PPM primarily affects patients with impaired preoperative left ventricular function and results in decreased survival, lower freedom from heart failure, and incomplete left ventricular mass regression[23]. The SE device appears to provide better performance compared to BE in

patients with small aortic valve annuli, resulting in low rates of PPM and at least comparable rates of PVR based on insights from the CHOICE Trial and the CHOICE-Extend Registry [24]. OCEAN-TAVI (Optimized CathEter vAlvular iNtervention) registry reported Evolut R seems to be superior to SAPIEN 3 in hemodynamic performance for patients with small annuli and body surface area up to 1 year after TAVR, and had significantly lower moderate PPM at 1 year in the extremely small annulus cohort (aortic annulus ≤ 21mm)[25]. Better hemodynamic profile of SE has also been reported for bicuspid patients via BEAT (self-expanding versus balloon-expandable valve for the treatment of bicuspid aortic valve stenosis) registry[26].

With indications of TAVR being approved for all surgical risk levels, and more TAVR devices becoming commercially available, it is critically important to generate comparative evidence for patients and physicians to consider and allow individualized selection of the TAVR device. Both SE and BE valve platforms have evolved over the last several years. For example, the iterations of the Edwards BE valve were made to address paravalvular leak major vascular complications[27] and the Medtronic SE valve iterations included repositionability, an outer pericardial wrap to enhance annular sealing to promote a decrease in paravalvular leak[28], and improved implantation methods with cusp overlap[29-30] and commissural alignment[31]. The SMall Annuli Randomized To Evolut or SAPIEN (SMART) Trial will provide a direct comparison of safety, efficacy, hemodynamics and long-term valve performance between SE and BE valves for patients with a small aortic annulus.

## 4.2 Purpose

Medtronic, Inc. is sponsoring the SMART Trial, a prospective, multi-center, international, randomized controlled, post-market trial. The purpose of this trial is to generate clinical evidence on valve safety and performance of SE versus BE TAVR in subjects with a small aortic annulus and symptomatic severe native aortic stenosis.

# 5. Objectives and Endpoints

## 5.1 Objectives

### 5.1.1 Primary Objectives

The primary objectives of the trial are to demonstrate clinical non-inferiority and hemodynamic superiority of the Evolut PRO/PRO+/FX System when compared to subjects treated with the SAPIEN 3/3 Ultra System at 12 months post-procedure.

### 5.1.2 Secondary Objectives

The secondary objective of the trial is to generate long-term valve function data for both SE and BE TAVR through 5 years of follow-up.

## 5.2 Endpoints

The endpoints in this section will be used to evaluate the primary and secondary trial objectives.

### 5.2.1 Primary Endpoints

The trial will have two powered primary endpoints comparing the Medtronic SE TAVs and Edwards BE TAVs to:

1. A clinical outcome composite endpoint of mortality, disabling stroke or heart failure rehospitalization at 12 months
2. A valve function composite endpoint of BVD at 12 months including any of the following:
    - HSVD: hemodynamic mean gradient ≥ 20mmHg
    - NSVD: severe PPM, ≥ moderate AR
    - Thrombosis
    - Endocarditis
    - Aortic valve re-intervention

### 5.2.2 Powered Secondary Endpoints

The powered secondary endpoints for the trial comparing the SE and BE TAVR are:

1. BVD in female subjects at 12 months
2. HSVD at 12 months
3. Hemodynamic mean gradient as continuous variable at 12 months
4. Effective orifice area (EOA) as continuous variable at 12 months
5. Moderate or severe prothesis-patient mismatch (PPM) at 30 days

### 5.2.3 Non-powered Secondary Endpoints

The non-powered secondary endpoints comparing the SE and BE TAVR are listed below:

1. Device success at 30 days
2. Incidence of an early safety composite at 30 days defined as:
    - All-cause mortality
    - All stroke (disabling and non-disabling)
    - 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, TAVR, or SAVR)

3. Hospital readmission for any cause at 30 days
4. Incidence of clinical efficacy (after 30 days) at 12 months and annually to 5 years defined as a composite of:
   - All-cause mortality
   - All stroke (disabling and non-disabling)
   - Requiring hospitalizations for valve-related symptoms or worsening congestive heart failure
   - NYHA class III or IV
   - Valve-related dysfunction (mean aortic valve gradient ≥20 mmHg, EOA ≤0.9-1.1 cm2 and/or DVI<0.35m/s, AND/OR moderate or severe prosthetic valve regurgitation)
5. Components of the primary clinical endpoint at 12 months and annually to 5 years:
   - Mortality
   - Disabling stroke
   - Heart failure rehospitalization
6. New pacemaker implantation rate at 30 days, 12 months and annually to 5 years
7. Aortic valve re-intervention at 30 days, 12 months and annually to 5 years
8. 6MWT at 30 days, 12 months and annually to 5 years
9. QoL (KCCQ, EQ-5D) at 30 days, 12 months and annually to 5 years
10. BVD (HSVD, NSVD, thrombosis, endocarditis, and aortic valve re-intervention) at 2 to 5 years annually
11. Echocardiographic measurements (i.e. EOA, mean gradient, PVL, LV mass regression, and DVI (severe <0.25, moderate 0.25-0.5, mild >0.5)) at discharge, 30 days, 12 months and annually to 5 years
12. Mean gradient ≥ 20 mmHg based on stress echocardiogram at 12 months at select sites

# 6. Trial Design

This trial is designed as a prospective, multi-center, international, randomized controlled, post-market trial to generate clinical evidence on valve safety and performance of self-expanding (SE) versus balloon-expandable (BE) transcatheter aortic valve replacement (TAVR) in subjects with a small aortic annulus and symptomatic severe native aortic stenosis.

Approximately 700 as-treated subjects will be recruited at approximately 90 sites located in Canada, EMEA and the United States. The trial may be expanded to include additional geographies based on enrollment rates, identification of qualified sites and local device indication approval.

Subjects will be randomized on a 1:1 basis to receive either a Medtronic SE or an Edwards BE TAV, and randomization will be stratified by site and sex (**Figure 4**).

To ensure a widespread distribution of data and minimize trial site bias in trial results, enrollments shall not exceed 20% (approximately 140 subjects) of total as-treated subjects at any individual site. Enrollment is competitive; therefore, there is no set minimum number of subjects to be enrolled per site and sites reaching 20% should seek approval from sponsor to continue enrollment.

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

- All sponsors and external trial personnel will be trained on the Clinical Investigation Plan (CIP) and related trial materials.
- Subjects will be screened to confirm eligibility with pre-defined inclusion and exclusion criteria prior to enrollment and randomization.
- An external, independent Clinical Events Committee (CEC) will review and adjudicate, at minimum, all deaths and 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 independent core laboratory will evaluate all echocardiograms. Echocardiographic trial endpoint results will be based on Core Lab assessments.

## 6.1 Duration

The enrollment period is estimated to be approximately 20 months and subjects will be followed for up to five years post TAVR procedure; therefore, the expected trial duration is approximately 6-7 years. The duration of individual subject participation will vary based on timing of trial site activation and their enrollment; however, at a minimum, participation of an individual subject will be 5 years.

## 6.2 Rationale

Published reports from various studies have suggested similar clinical outcomes between SE and BE valves, but superior hemodynamic performance has been observed for SE valves with outcomes demonstrating lower aortic valve mean gradient and/or large aortic valve area[9-12,13-14,16], especially for subjects with a small annulus[24]. Initial hemodynamic performance of prosthetic aortic valves has been reported to be prognostic of intermediate and longer term (i.e., 5-year) clinical outcomes including hemodynamic or structural deterioration[17-18], heart failure hospitalization[19], and mortality[19-21]. These published evidences were generated either based on previous generation valves some of which are no longer commercially available or from non-randomized studies with various limitations and potential biases. With several iterations over the last several years for both SE and BE valves, it is appropriate to conduct a randomized head-to-head trial to compare valve safety and performance of the most current commercially available SE and BE devices on the market for symptomatic severe AS subjects with small annuli, who represent 40% of the TAVR market.

The SMART Trial is designed to meet this purpose and will evaluate clinical outcome non-inferiority and hemodynamic superiority of the Evolut PRO/PRO+/FX System when compared to the SAPIEN 3/3 Ultra System at 12 months post-procedure. In addition, the trial will follow subjects for up to 5 years to

evaluate and compare long-term valve function between SE and BE. Due to its focus on small annulus patients, the SMART Trial will likely enroll predominantly women (~80%), which will provide important clinical insights into a currently underrepresented patient population in TAVR literature.

Trial endpoints were selected with the following considerations:

- Clinically relevant and address important safety and performance aspects of the SE and BE devices
- Objectively defined and measurable in the majority of subjects
- Consistent with current recommendations for endpoints in TAVR clinical studies and Valve Academic Research Consortium (VARC)

## 6.3 Trial Oversight

The trial will have an Executive Committee that consists of the Trial Principal Investigator (PI) and Co-PIs. The Executive Committee will provide clinical expertise to develop the clinical trial design and oversight of trial execution.

The trial will also have a Steering Committee that includes the Co-PIs and chaired by the Trial PI. The Steering Committee will advise on the scientific content of the trial and provides input for trial execution. The Steering Committee will support the execution of the SMART Trial and provide guidance, feedback and direction to the trial. Steering Committee members may be trial site investigators. As membership may change, the current list of the Steering Committee members can be made available upon request.

The trial will utilize a Case Planning Committee as part of the subject Confirmation of Qualification process. The Case Planning Committee will be utilized when final confirmation of qualification is required for a subject to be approved into the trial. As membership may change, the current list of Case Planning Committee members can be made available upon request.

The trial will have a Training and Education Committee (TEC) that will provide external procedural oversight for the safe use of TAVR during the SMART Trial. As membership may change, the current list of TEC members can be made available upon request.

## 6.4 Trial Organization

### 6.4.1 Participating Sites

This trial may be conducted at approximately 90 sites with around 65% sites in the United States and Canada, and 35% in EMEA. Investigative sites will meet the following criteria:

- The site will have extensive facility experience with TAVR. Operator 1 and Operator 2 must individually meet the minimum of ≥ 20 TAVR procedures in the prior year, or ≥ 40 TAVR procedures in the prior two years.
- The site will have the presence or capacity of establishing an investigative team consisting of the following roles:
    - Minimum of 2 TAVR implanters with expertise in transcatheter aortic valve replacement as noted above

- Electrophysiologist
- Echocardiographer
- Trial coordinator

The investigative team will include the Principal Investigator (PI) and qualified physicians who are responsible for medical decisions respective to their area of medical expertise. As the list of participating sites and investigative team may change, the current list of sites and contact information is maintained separately from this CIP and can be made available upon request.

### 6.4.2 Site Principal Investigator

Each site will have a PI who is either an interventional cardiologist or cardiothoracic surgeon. The PI will have overall responsibility for the conduct of the trial at the site, including protecting the rights, safety, and welfare of the trial subjects at their site, the integrity of the trial data generated by their site, and for ensuring the trial is conducted in compliance with the Clinical Investigation Plan and Institutional Review board, Research Ethics Board, or Ethics Committee (IRB/REB/EC) requirements.

### 6.4.3 Heart Team

Each site will utilize a local Heart Team to assess eligibility of the prospective subject for the trial according to the site's standard process and payer requirements.

At a minimum, the local Heart Team should include the TAVR implanter. The site PI may also serve as a member of the Heart Team.

### 6.4.4 Publication Committee

A Publication Committee will provide direction and support in the development of clinical publications. The Publication Committee will include the Executive Committee (Trial PI and Co-PIs), members from the Steering Committee, and the head of the Echocardiography Core Laboratory. The Publication Committee will be responsible to:

- Define the publication plan
- Review, approve, and prioritize publication proposals
- Provide input on the scientific merit and clinical relevance of ancillary publications
- Identify the manuscript/abstract first author(s)/writer(s)/presenter(s)
- Review publications prior to submission

Section 16.8 provides additional information on publications.

# 7. Product Description

## 7.1 Description of Devices

All products used in this trial will be market released in the geographies they are used.

### 7.1.1.1 Medtronic Evolut PRO System

The Medtronic Evolut™ PRO System is a recapturable transcatheter aortic valve replacement (TAVR) system comprised of the following three components (**Table 1**):

1. Medtronic Evolut PRO TAV
2. Medtronic EnVeo PRO DCS with EnVeo inline sheath
3. Medtronic EnVeo PRO LS

The system components for the Evolut PRO System are shown in **Figure 1**. Refer to the Evolut PRO Instructions for Use for product information.

**Table 1: Evolut™ PRO System Components**

| Component | US Model Number | Canadian Model Number | European Model Number | Size (mm) | Aortic Annulus Diameter (mm) |
|---|---|---|---|---|---|
| Medtronic Evolut PRO TAV | EVOLUTPRO-23-US | EVOLUTPRO-23 | EVOLUTPRO-23 | 23 | 18 – 20 |
| | EVOLUTPRO-26-US | EVOLUTPRO-26 | EVOLUTPRO-26 | 26 | 20 – 23 |
| | EVOLUTPRO-29-US | EVOLUTPRO-29 | EVOLUTPRO-29 | 29 | 23 – 26 |
| EnVeo PRO DCS with EnVeo inline sheath (20 Fr/16eFr) | ENVPRO-16-US | ENVPRO-16 | ENVPRO-16 | Used with 23,26, and 29 mm TAVs | Not applicable |
| EnVeo PRO LS | L-ENVPRO-1623US | L-ENVPRO-1623 | L-ENVPRO-1623 | Used with 23 mm TAV | Not applicable |
| | L-ENVPRO-16-US | L-ENVPRO-16 | L-ENVPRO-16 | Used with 26 and 29 mm TAVs | Not applicable |

Note: Model numbers are subject to change. Refer to the current model number per the respective country/geography.

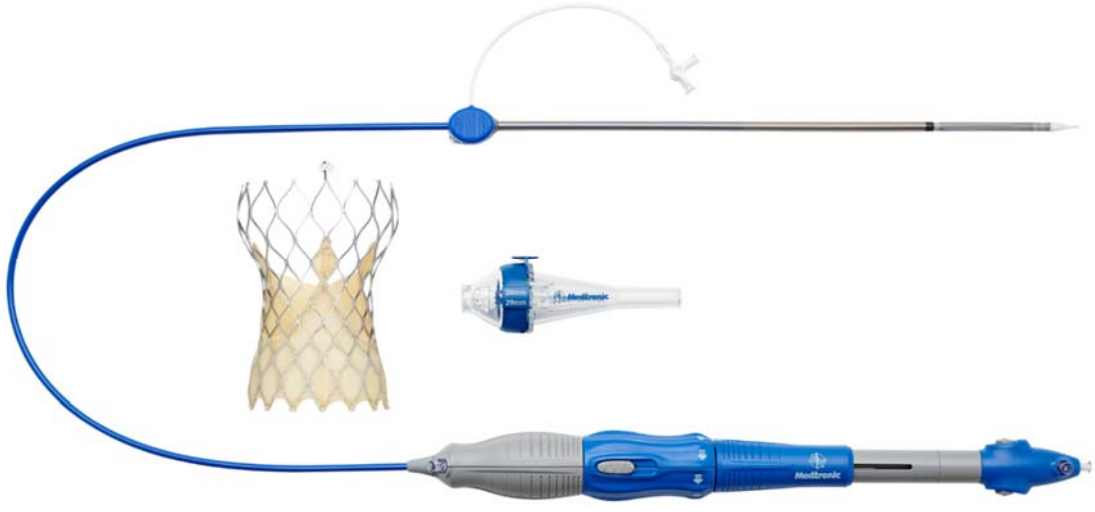

**Figure 1. Medtronic Evolut PRO System**

### 7.1.1.2 Medtronic Evolut PRO+ System

The Medtronic Evolut™ PRO+ System is a recapturable transcatheter aortic valve replacement (TAVR) system comprised of the following three components (**Table 2**):

1. Medtronic Evolut PRO+ TAV
2. Medtronic Evolut PRO+ DCS
3. Medtronic Evolut PRO+ LS

The system components for the Evolut PRO+ System are shown in **Figure 2** and refer to the Evolut PRO Instructions for Use for product information.

**Table 2: Evolut™ PRO+ System Components**

| Component | US Model Number | Canadian Model Number | European Model Number | Size (mm) | Aortic Annulus Diameter (mm) |
|---|---|---|---|---|---|
| Medtronic Evolut PRO+ TAV | EVPROPLUS-23US | EVPROPLUS-23 | EVPROPLUS-23 | 23 | 18 – 20 |
| | EVPROPLUS-26US | EVPROPLUS-26 | EVPROPLUS-26 | 26 | 20 – 23 |
| | EVPROPLUS-29US | EVPROPLUS-29 | EVPROPLUS-29 | 29 | 23 – 26 |
| Medtronic Evolut PRO+ DCS | D-EVPROP2329US | D-EVPROP23-29 | D-EVPROP23-29 | Used with 23, 26, and 29 mm TAVs | Not applicable |
| Medtronic Evolut PRO+ LS | L-EVPROP2329US | L-EVPROP23-29 | L-EVPROP23-29 | Used with 23,26, and 29 mm TAVs | Not applicable |

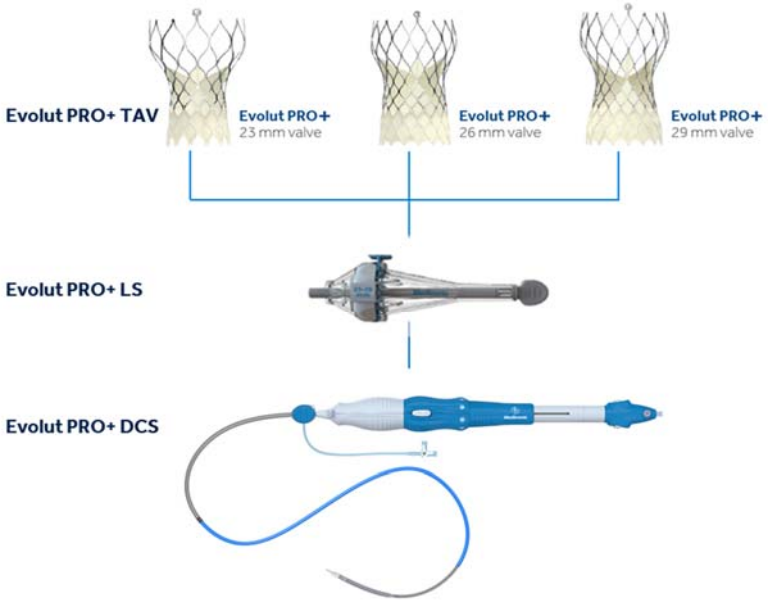


**Figure 2. Medtronic Evolut PRO+ System**

### 7.1.1.3 Medtronic Evolut FX System

The Medtronic Evolut FX System is a recapturable TAVR implantation system comprised of the following 3 components (**Table 3**):

1. Medtronic Evolut FX TAV
2. Medtronic Evolut FX DCS
3. Medtronic Evolut FX LS

The system components for the Evolut FX System are shown in **Figure 3** and refer to the Evolut Instructions for Use for product information.

**Table 3. Evolut™ FX System Components**

| Component | US Model Number | Size (mm) | Aortic Annulus Diameter (range in mm) |
|---|---|---|---|
| Medtronic Evolut FX TAV | EVOLUTFX-23 | 23 | 18 – 20 |
| | EVOLUTFX-26 | 26 | 20 – 23 |
| | EVOLUTFX-29 | 29 | 23 – 26 |
| Evolut FX DCS (18 Fr/14eFr) | D-EVOLUTFX-2329 | Used with 23, 26, and 29 mm TAVs | Not applicable |
| Evolut FX LS | L-EVOLUTFX-2329 | Used with 23, 26, and 29 mm TAVs | Not applicable |

Note: Model numbers are subject to change. Refer to the current model number per the respective country/geography. The Evolut FX System is commercially available in the United States. The Evolut FX System may be used upon commercial availability in Canada.

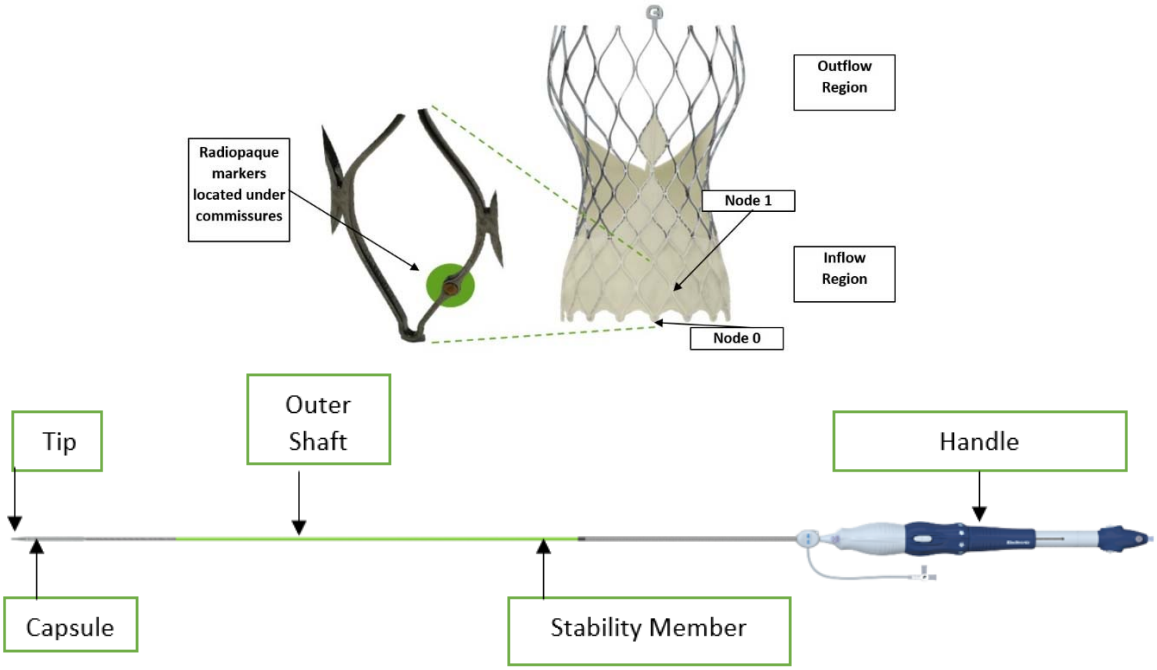


**Figure 3. Medtronic Evolut FX System**

#### 7.1.1.4 Edwards SAPIEN 3 and SAPIEN 3 Ultra Transcatheter Heart Valve (THV) Systems

Refer to the SAPIEN 3 and SAPIEN 3 Ultra Instructions for Use for product information.

## 7.2 Manufacturer

The legal manufacturer and design site of the Evolut PRO, Evolut PRO+, and Evolut FX systems is as follows:

Medtronic CoreValve LLC
1851 E Deere Avenue
Santa Ana, CA 92705
USA

Refer to the SAPIEN 3 and SAPIEN 3 Ultra Instructions for Use for manufacturer information.

## 7.3 Intended Population

The trial population includes subjects with symptomatic heart disease due to severe native calcific aortic stenosis and a small annulus appropriate for transcatheter heart valve replacement therapy. Subjects who will undergo an emergent procedure cannot be included in this trial.

## 7.4 Equipment

Trial sites should follow their institutional procedures for maintenance and calibration of echocardiography and ECG equipment used for assessing the trial variables. Documentation must be available for evaluation upon request.

## 7.5 Product Use

Evolut PRO, Evolut PRO+, Evolut FX, SAPIEN 3, and SAPIEN 3 Ultra will be used within the local commercially approved indication, in the geographies in which each device is approved, with exception to any exclusion criteria in this protocol, and obtained by the trial sites according to standard hospital procedures for commercial products and per the product Instructions for Use.

Each subject is anticipated to be implanted with at least 1 TAV and approximately 700 TAVs (approximately 350 Evolut PRO/PRO+/FX and 350 SAPIEN 3/3 Ultra) to be used in the trial. It is possible for more than 1 TAV to be used in the procedure to account for TAVs attempted but not implanted or implant errors for this patient population. All valve sizes of Evolut PRO/PRO+/FX and SAPIEN 3/3 Ultra commercial product, especially valve sizes and components suitable for subjects with small annulus, should be available at all sites.

## 7.6 Product Training Requirements

Medtronic will provide product-specific training on the cusp overlap implant technique for the Evolut PRO/PRO+/FX System. Local existing approved procedures for both the Evolut PRO/PRO+/FX and SAPIEN 3/3 Ultra commercial product regarding training, labelling, distribution, shipment, storage, and handling will be followed per the respective product Instructions for Use. In the event of a device malfunction or explant, refer to section 7.8.

## 7.7 Product Storage

It is the responsibility of the investigator to correctly handle and store market released product. Refer to the respective product Instructions for Use for handling and storage requirements.

## 7.8 Product Return for Device Malfunction or Explant

In the event of a device malfunction of the Medtronic TAV device or its components prior to implant or if explant is performed due to reintervention, the TAV and/or affected components should be returned to Medtronic. Subjects with explanted devices due to reintervention should be followed through the duration of the study. In the event of a subject's death, it is recommended that the implanted system will be explanted and returned to the manufacturer for analysis whenever possible per local process.

Additional details surrounding the device return process are contained within the Medtronic explant kit that will be provided upon notification of a device malfunction or explant.

Refer to the SAPIEN 3 and SAPIEN 3 Ultra Instructions for Use for explant return information for these devices.

## 7.9 Product Accountability

**Product delivery**

Commercially available product supply will be managed in a manner consistent with other market-released products. Sites will follow their institutional standard practice for device ordering and replenishment of commercial product for use in this trial.

**Product receipt and tracking**

All products used in this trial will be market released in the geographies they are used. Device Traceability may be required per local laws and regulations. If there are additional local requirements related to the Evolut PRO/ PRO+/FX or SAPIEN 3/ 3 Ultra Systems beyond what is collected by Medtronic on the Electronic Case Report Form (eCRF), this is the Investigator's responsibility and should be recorded according to local/national requirements, but will not be collected by Medtronic (e.g., national registration card number, identification code linked to names and contact information).

Device lot and serial numbers, as applicable, will be collected in the Device Identification eCRF. As this is a post-market trial, Product Accountability Logs will not be utilized. 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 trial.

# 8. Trial Site Requirements

## 8.1 Investigator/Investigation Site Selection

All investigators managing the subject's aortic stenosis must be qualified practitioners and experienced in the diagnosis and treatment of subjects with aortic stenosis. All implanting physicians must be experienced and/or trained in the handling of Evolut PRO, Evolut PRO+, Evolut FX, SAPIEN 3, and/or SAPIEN 3 Ultra devices.

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

The principal investigator shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation.
- Be experienced in the field of application and training in the use of Medtronic Evolut PRO, Evolut PRO+, and/or Evolut FX System and the Edwards SAPIEN 3 and/or SAPIEN 3 Ultra Systems.
- Be able to demonstrate that the proposed investigational trial site:
  - Has the required number of eligible subjects needed within the recruitment period
  - Has one or more qualified investigators, a qualified investigational trial site team and adequate facilities for the foreseen duration of the clinical investigation

Trial site personnel training will be completed and documented prior to participation in this trial.

## 8.2 Trial Site Activation

During the activation process (prior to subject enrollment), Medtronic will train trial site personnel on the clinical investigation plan, informed consent, and on data collection and reporting tools. If new members join the trial site team, they will receive training on the applicable trial requirements relevant to their role before contributing to the trial.

Prior to performing trial related activities, all regulatory requirements shall be fulfilled, including, but not limited to the following:

- EC/IRB/REB approval (and voting list, as required by local law) of the current version of the CIP and ICF.
- Regulatory Authority (RA) approval or notification (as required per local law)
- Fully executed Clinical Trial Agreement (CTA): Medtronic contracts with participating institutions/investigators through a CTA that defines the scope and responsibilities and associated compensation related to carrying out the obligations under a clinical trial sponsored by Medtronic.
- Investigator Agreement or Statement (if required by the geography)
- Curriculum Vitae (CV) of investigators and key members of the investigation trial site team (as required).
- Documentation of delegated tasks
- Documentation of trial training
- Additional requirements imposed by local regulations, the EC and RA shall be followed, if appropriate.

In addition, all participating trial site staff must be trained on the current version of the CIP as well as on the applicable trial requirements depending on their role and must be delegated by the site principal investigator to perform trial related activities.

Medtronic will provide each trial site with documentation of trial site/investigator readiness; this letter must be received prior to performing trial related activities.

## 8.3 Role of the Sponsor Representatives

In addition to performing monitoring and auditing activities, sponsor representatives may provide support at the trial site as required for the trial under supervision of the Principal Investigator, including:

- Provide trial training relevant and pertinent to the involvement of personnel conducting trial activities and investigator responsibilities
- Technical support by the manufacturer's representative at the time of procedure will be under the supervision of a trial investigator.
- No data entry shall be performed by Medtronic personnel or their representatives at trial sites.

# 9. Selection of Subjects

## 9.1 Trial Population

The trial population includes subjects with symptomatic heart disease due to severe native calcific aortic stenosis and a small annulus appropriate for transcatheter heart valve replacement therapy in accordance with Instructions for Use and local regulations.

## 9.2 Subject Enrollment

This trial will involve approximately 700 subjects in Canada, EMEA and the United States based on the number of subjects with as-treated TAVR procedure among all active sites. To ensure a widespread distribution of data and to minimize bias in the trial results, no site will implant more than 20% (approximately 140 subjects) of total as-treated subjects at any individual site without prior approval from Medtronic. Subjects who exit from the trial after enrollment will not be replaced.

## 9.3 Inclusion Criteria

Prospective subjects must meet ALL of the following inclusion criteria to be eligible for participation:

I1. Symptomatic subjects with predicted risk of operative mortality < 15% at 30-days per multidisciplinary local heart team assessment

I2. Severe aortic stenosis, defined as: Aortic valve area ≤1.0 $cm^2$ (or aortic valve area index of ≤0.6 $cm^2/m^2$), OR mean gradient ≥40 mmHg, OR maximal aortic valve velocity ≥4.0 m/sec by transthoracic echocardiography at rest

I3. Aortic valve annulus area ≤ 430 $mm^2$ based on MDCT

I4. Subject's anatomy is appropriate for both Medtronic and Edwards TAV Systems used within the conduct of the trial

I5. Subject’s anatomy is suitable for TAVR via transfemoral vessel access

I6. Commercial indication for transcatheter aortic valve replacement (TAVR), in conformity with both local regulations and Instructions for Use (IFU)

I7. Subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits

## 9.4 Exclusion Criteria

Subjects are NOT eligible for trial participation if they meet ANY of the following exclusion criteria:

E1. Estimated life expectancy of less than 2 years

E2. Multivessel coronary artery disease with a Syntax score >32 and/or unprotected left main coronary artery (Syntax score calculation is not required for subjects with history of previous revascularization if repeat revascularization is not planned)

E3. Participating in another trial that may influence the outcome of this trial

E4. Need for an emergent procedure for any reason

E5. Contraindicated for treatment with the Medtronic and Edwards TAV Systems in accordance with the Instructions for Use

E6. Other medical, social, or psychological conditions that in the opinion of the Investigator precludes the subject from appropriate consent or adherence to the protocol required follow-up exams

E7. Pregnant, nursing or planning to be pregnant.

E8. Subject is less than legal age of consent, legally incompetent, unable to provide his/her own informed consent, or otherwise vulnerable.*

** Notes:*

- Vulnerable subjects include individuals whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate[32]. EXAMPLE Individuals with lack of or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects include, for example, members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the sponsor, members of the armed forces, and persons kept in detention.
- If treated in France, any subject who is a "personne vulnerable" per French legislation, including protected adults and prisoners

E9. Subject has an active COVID-19 infection or relevant history of COVID-19. *Note: An active COVID-19 infection is defined as a positive Polymerase Chain Reaction (PCR) result. Relevant history of COVID-19 is defined as availability of a positive COVID-19 test with sequela or hospitalization for treatment of COVID-19 that was less than 3 months prior to enrollment. Subjects with a positive COVID-19 test who were asymptomatic or had mild symptoms should be excluded only if the positive test was less than 3 months prior to enrollment.*

E10. Previous aortic valve replacement

# 10. Trial Procedures

## 10.1 Schedule of Events

Follow-up protocol required evaluations should be performed at the trial site, however remote visits via phone contact are permitted, if an in-person clinic visit is not feasible. Every effort should be made to obtain the follow-up transthoracic echocardiogram (TTE), when required, following a phone contact. The protocol required evaluations for each trial interval are listed as follows and summarized in **Table 4**.

In general, the examinations and procedures in this trial are standard of care. At certain sites, some examinations and procedures during identified follow-up such as TTE image acquisition, Quality of Life Questionnaires (EQ-5D and KCCQ), Modified Rankin Score, 6-Minute Walk Test, 12-Lead ECG and Stress

Echocardiogram (at select sites) are not standard-of-care. All local and national regulations will be adhered to with regard to EC/IRB/REB and regulatory authority submissions, as applicable.

### 10.1.1 Screening Procedures, Enrollment and Randomization

The screening and enrollment flowchart for randomization is presented in **Figure 4**. Patients identified by or presented to the trial site with aortic stenosis will be screened by the site team for the inclusion and exclusion criteria described in 9.3 and 9.4, using available medical records, including relevant imaging studies previously performed for diagnostic purposes. If the patient is deemed a potential candidate for the trial, all aspects of the trial will be explained to the patient. The patient will then be invited to participate in the SMART Trial. If the patient agrees to participate, electronic (only applicable to US/Canada per IRB/REB approval) or written informed consent will be obtained. This will be considered the point of enrollment. If the local Heart Team considers the subject suitable for implantation, the subject's clinical information will be submitted to Medtronic via completion of the Screening Visit eCRFs and image transfer. Each subject will undergo a Confirmation of Qualification process (i.e., screening process) to review the subject's anatomical characteristics and verify eligibility criteria.

The following assessments must be completed within 12 weeks prior to submission for Confirmation of Qualification, unless otherwise indicated:

- Clinical assessment and medical history
    - Physical examination including height, weight, systolic and diastolic blood pressure, and body surface area.
    - NYHA classification
- Heart Team eligibility assessment
- STS-PROM Score
- Syntax Score to confirm exclusion criterion not met
    - Note that a diagnostic coronary angiogram to determine Syntax score will not be required if the subject has no history of coronary artery disease or prior coronary intervention
- MDCT angiogram, with contrast – *within 365 days prior to submission*
- Transthoracic Echocardiogram (TTE)

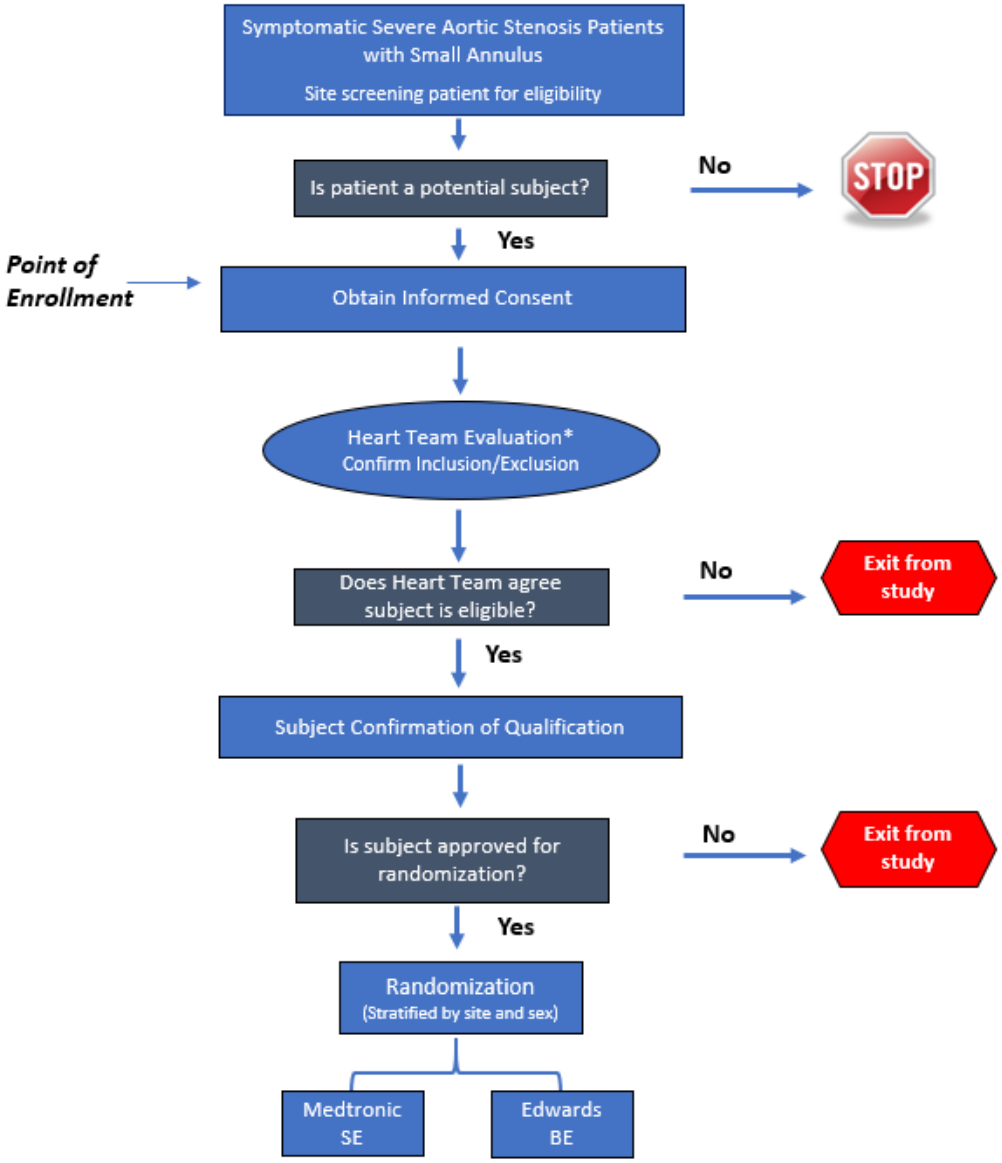


**Figure 4. Screening, Enrollment and Randomization Flowchart**

*Note: Timing of local Heart Team decision can differ from this flowchart but should always occur before a subject is submitted for Confirmation of Qualification

Subjects should give informed consent before undergoing any protocol-required testing. However, if any of the protocol-required baseline/screening evaluations (e.g., echocardiography and MDCT) have been performed for clinical diagnostic purposes prior to consenting, they can be used as the protocol-required exams, provided they were obtained within the protocol-required time windows and contain the necessary information.

All sites will be required to maintain the Subject Identification & Enrollment Log to record the subjects screened for the trial meeting general inclusion criteria who have signed the approved Informed

Consent document. Further, neither the Medtronic SE TAV nor the Edwards BE TAV will be used as an emergency treatment.

The SMART Trial will include a Confirmation of Qualification process conducted by Medtronic Clinical Analysts and an independent Case Planning Committee to review the anatomical suitability of potential subjects identified by the site for both Medtronic Evolut PRO/PRO+/FX TAV and Edwards SAPIEN 3/3 Ultra TAV. Subjects with questionable anatomical suitability due to exclusion criteria for the trial, warnings, precautions, or contraindications in the Instructions for Use, or risk factors for TAVR implantation per product training will be reviewed and discussed between the site and the independent Case Planning Committee. Questionable anatomical suitability includes valve area out of range, small sinus of Valsalva (SoV), small femoral, low coronary height, severe left ventricular outflow tract (LVOT) calcification, narrow sinotubular junction (STJ), horizontal aorta, and challenging bicuspid morphology. Depending on whether a subject's anatomical suitability meet entry criteria for the trial, a recommendation to proceed with randomization or reevaluate/exit the subject will be provided to the site.

The Confirmation of Qualification process and Case Planning Committee will ensure appropriate and consistent subject selection across all sites. Prior to the onset of the trial, a charter will be developed which outlines roles and responsibilities as well as describe the screening process.

Subjects confirmed eligible for implantation via the Confirmation of Qualification process will be randomized in a 1:1 basis electronically from an Interactive Response Technology (IRT) system to receive transcatheter aortic valve replacement (TAVR) with either a Medtronic SE or an Edwards BE TAV. Randomization will be stratified by site and sex.

Trial randomization will not be blinded to the subject and site investigative team. Once randomization is complete and a treatment arm is assigned, crossover is not permitted. In the event a crossover occurs, a protocol deviation will be reported and the subject should continue to be followed through the duration of the trial. Distribution of the subjects within the trial groups will be controlled at the implanting sites by means of a central randomization system. Implantation should occur within 30 days post randomization. If the TAVR procedure will occur after 30 days, prior approval of Medtronic is not required, however a protocol deviation must be completed.

### 10.1.2 Baseline

The following assessments must be completed within 14 days prior to TAVR index:

- Clinical assessment including physical examination
- Laboratory tests - glomerular filtration rate (GFR), hemoglobin, international normalized ratio (INR) for subjects on warfarin, and serum creatinine
- Use of relevant medications including anticoagulants and antiplatelets
- NYHA classification
- Modified Rankin Score (mRS)
- 6 Minute Walk Test (refer to Appendix Section 18.1)
- Quality of Life Questionnaires: EQ-5D and KCCQ
- Adverse Event Review

- Syntax score and TTE, to confirm eligibility criteria, if not determined at the Screening Visit (per Section 10.1.1) or prior to submission for Confirmation of Qualification

### 10.1.3 Implant Procedure (TAVR)

The implant visit must occur within 30 days after subject randomization. If the TAVR procedure will occur after 30 days, prior approval of Medtronic is not required, however a protocol deviation must be completed. The following information is required to be collected at the implant visit:

- 12-Lead ECG
  - within 48 hours prior to procedure
  - within 2 hours after the TAVR procedure. Refer to Appendix Section 18.2 Conduction Disturbance Management for subjects with pre-existing conduction abnormalities and new conduction disturbance
- Procedural angiogram
- Adverse Event Review

Subject eligibility criteria should be reviewed to confirm inclusion criteria still met and the subject does not meet any of the exclusion criteria prior to the TAVR procedure. Subjects must be treated via percutaneous transfemoral access only. Procedural aspects specific to the Medtronic SE TAV or Edwards BE TAV system should be performed according to the respective Instructions for Use. Concomitant procedures including percutaneous Coronary Intervention (PCI) are not permitted to be completed during the index procedure.

The Medtronic valve deployment should be performed in every case in accordance to the cusp overlap technique via procedural angiogram, unless patient related factors prevent using this procedural technique.

All procedural angiograms will be reviewed by an internal Procedural Oversight Committee of Medtronic physicians using the procedural checklist for both Medtronic SE TAV or Edwards BE TAV system. Procedures (refer to Appendix VI: Procedural Checklists). Those procedures for which there are questions or concerns about the implantation methods will be referred to the Training and Education Committee (TEC) for review.

#### 10.1.3.1 Procedural data

The implantation procedure is performed according to the standard procedures of the implanting physicians and according to the respective product Instructions for Use. The variables collected during the TAVR implantation procedure include:

- Name of the primary and secondary operator
- Anesthesia type
- Delivery catheter access site
- Use of the Evolut PRO/PRO+/FX or SAPIEN 3/3 Ultra platform delivery catheter/sheath OR use of separate introducer sheath size and type

- Pre-deployment BAV (yes/no)
- Use of pacing during deployment (yes/no)
- Size of TAV implanted
- Implant depth percentage ratio (only applicable for SAPIEN 3 and SAPIEN 3 Ultra)
- Balloon Inflation volume (only applicable for SAPIEN 3 and SAPIEN 3 Ultra)
- Was cusp overlap technique applied in the valve deployment (yes/no/not applicable)
- Procedural Angiographic views in RAO/LAO and Cranial/Caudal with associated degrees during initial positioning and final deployment
- Assessment of implant depth (NCS and LCS view) in RAO/LAO and Cranial/Caudal with associated degree.
- Post-implant dilation (yes/no)
- Post-implant pressures at final result (LV systolic and end-diastolic, aortic systolic and diastolic)
- Implantation of TAV within the desired location (yes/no)
- Post-implant degree of prosthetic regurgitation by angiography (none, 1+, 2+, 3+, 4+) by (Sellers criteria)[34]
- Post-implant degree of prosthetic paravalvular regurgitation by Transesophageal echocardiology (TEE), if performed
- Post-implant degree of prosthetic transvalvular regurgitation by TEE, if performed
- More than one TAV implanted (yes/no)
- Patency of coronary arteries post-implant (yes/no)
- Estimated contrast volume used
- Information on use of resheath/recapture feature, if applicable
- Occurrence of adverse events
- If TAV implantation not attempted, reason why
- Use of cerebral embolic protection

### 10.1.4 Prior to Discharge

- Physical examination including weight and systolic and diastolic blood pressure
- Use of relevant medications including anticoagulants and antiplatelets
- NYHA Classification
- 12-lead ECG (refer to Appendix Section 18.2 Conduction Disturbance Management for discharge 12-lead ECG requirements for subject with conduction abnormalities)
- TTE- must be done from 24 hours to 7 days post TAVR (or prior to Discharge, whichever comes first)
- Adverse event review

### 10.1.5 Follow-Up Evaluations

All treated subjects will undergo follow-up evaluations at the following time points post procedure. See section 10.3 for appropriate visit windows.

**30 days (between 30 – 45 days post procedure)**

- Clinical Assessment including physical examination
- Use of relevant medications including anticoagulants and antiplatelets
- NYHA Classification
- TTE
- 6-minute Walk Test (refer to Appendix Section 18.1)
- Quality of Life Questionnaires- EQ-5D and KCCQ
- 12-Lead ECG
- Adverse Event Review

**12 Months (Day 365 + 30 days)**

- Clinical Assessment including physical examination
- Use of relevant medications including anticoagulants and antiplatelets
- NYHA Classification
- TTE
- 6-minute Walk Test (refer to Appendix Section 18.1)
- Quality of Life Questionnaires- EQ-5D and KCCQ
- 12-Lead ECG
- Adverse Event Review
- Stress echocardiogram- (conducted at select sites. A CIP addendum detailing the assessment will be provided separately)

**2 Years (Implant anniversary date and ± 30 days)**

- Clinical Assessment including physical examination
- Use of relevant medications including anticoagulants and antiplatelets
- NYHA Classification
- TTE
- 6-Minute Walk test (refer to Appendix Section 18.1)
- Quality of Life Questionnaires- EQ-5D and KCCQ
- Adverse Event Review

**Annual 3-5 years (Implant anniversary date and ± 60 days)**

- Clinical Assessment including physical examination
- Use of relevant medications including anticoagulants and antiplatelets

- NYHA Classification
- TTE
- 6-Minute Walk test (refer to Appendix Section 18.1)
- Quality of Life Questionnaires- EQ-5D and KCCQ
- Adverse Event Review

**Other Evaluations**

- In addition to an assessment at baseline, a Modified Rankin Score assessment should be conducted at 30 and 90 days after onset of any confirmed or suspected neurological event.
- In addition to laboratory tests at baseline, laboratory test results relevant for event adjudication (i.e., hemoglobin to adjudicate bleeding events) should be collected

### 10.1.6 Unscheduled Follow-up Visits

If a subject returns to the trial site or is contacted via telephone between their scheduled follow-up visits for an event potentially related to a trial endpoint, the visit or telephone call will be treated as an unscheduled follow-up. Assessments completed at this unscheduled visit to collect data outside the scheduled follow-up window or evaluate an event potentially related to a trial endpoint should be entered in the eCRFs.

## 10.2 Data Collection

Data collection requirements are summarized in **Table 4** below.

**Table 4: Data collection and trial procedure requirements at subject visits**

| **Visit/Assessments** *(for all subjects unless noted otherwise)* | **Screening** | **Baseline** | **TAVR Procedure** | **Discharge** | **30 Days** | **12 Months** | **2 Years** | **Annually 3-5 Years** |
|---|---|---|---|---|---|---|---|---|
| Timeframe/Window | Within 12 weeks of submission for Confirmation of Qualification, unless noted otherwise | Within 14 days of TAVR Procedure | Day 0; within 30 days post-randomization | Between 24 hours and 7 days post - procedure (or prior to discharge, whichever comes first) | Between 30- and 45-days post implant | Day 365 + 30 days | Implant anniversary date and ± 30 days | Implant anniversary date and ± 60 days |
| Informed Consent (and Health Insurance Portability and Accountability Act (HIPAA) Authorization in the US) | X | | | | | | | |
| Demographics, Medical History and Comorbidities | X | | | | | | | |
| Inclusion and Exclusion Criteria | X | | X[1] | | | | | |
| STS-PROM Score | X | | | | | | | |
| Heart Team Assessment | X | | | | | | | |
| MDCT Angiogram, with contrast | X[2] | | | | | | | |
| Adverse Event Review[3] | X | X | X | X | X | X | X | X |
| Clinical Assessment (including Physical Examination) | X | X | | X | X | X | X | X |
| NYHA Classification | X | X | | X | X | X | X | X |

| Visit/Assessments *(for all subjects unless noted otherwise)* | Screening | Baseline | TAVR Procedure | Discharge | 30 Days | 12 Months | 2 Years | Annually 3-5 Years |
|---|---|---|---|---|---|---|---|---|
| Timeframe/Window | Within 12 weeks of submission for Confirmation of Qualification, unless noted otherwise | Within 14 days of TAVR Procedure | Day 0; within 30 days post-randomization | Between 24 hours and 7 days post - procedure (or prior to discharge, whichever comes first) | Between 30- and 45-days post implant | Day 365 + 30 days | Implant anniversary date and ± 30 days | Implant anniversary date and ± 60 days |
| Transthoracic Echocardiogram (TTE) | X | | | X | X | X | X | X |
| Laboratory tests | | X | | | | | | |
| Medications (i.e., anticoagulants and antiplatelets) | | X | | X | X | X | X | X |
| Modified Rankin Score[4] | | X | | | | | | |
| 6 Minute Walk Test | | X | | | X | X | X | X |
| Quality of Life Questionnaires[5] | | X | | | X | X | X | X |
| Procedural Angiogram | | | X | | | | | |
| 12-Lead ECG[6] | | | X[7] | X | X | X | | |
| Stress echocardiogram (conducted at select sites) | | | | | | X | | |

[1] Subject eligibility criteria reviewed prior to the TAVR procedure

[2] Pre-implant MDCT must be within 365 days prior to submission for Confirmation of Qualification

[3] SAEs, non-serious endpoint-related AEs, ADEs and DDs

[4] In addition to an assessment at baseline, a Modified Rankin Score assessment should be conducted at 30 and 90 days after onset of any confirmed or suspected neurological event

[5] Quality of Life Questionnaires include EQ-5D and KCCQ.

[6] Refer to CIP Appendix Conduction Disturbance Management for discharge 12-lead ECG requirements

[7] ECGs are required within 48 hours pre-procedure and then again within 2 hours post-procedure

### 10.2.1 Core Labs and Contract Research Organizations (CROs)

Transthoracic echocardiography (TTE) and explants will be sent to core labs for central assessment. Further details of the echocardiography methods are provided in Appendix Section 18.3.

A listing of current contact information for the Core Laboratories and CROs will be maintained separately from this CIP and provided to the sites.

## 10.3 Scheduled Follow-up Visit Windows

Should a subject miss a visit or the visit fall outside the pre-specified window, a trial deviation must be reported, and the original follow-up schedule maintained for subsequent visits.

Data analysis include the follow-up visits, regardless of whether the visit occurs within the window. Therefore, a late visit is preferred over a missed visit but must be accompanied by a deviation report. Follow-up visit windows are listed below and are based on days post implant procedure.

**Table 5: Follow-up Visit Windows**

| Trial Follow-up Visit | Window (Calculated days post-implant) Day 0 = day of TAVR Procedure | | |
|---|---|---|---|
| | Window Start (days post-implant) | Target (days post-implant) | Window End (days post-implant) |
| 30 Days | 30 days | 30 days | 45 days |
| 12 Months | 365 days | 365 days | 395 days |
| 2 Years | 700 days | 730 days | 760 days |
| 3 Years | 1035 days | 1095 days | 1155 days |
| 4 Years | 1400 days | 1460 days | 1520 days |
| 5 Years | 1765 days | 1825 days | 1885 days |

## 10.4 Subject Consent

Prior to enrolling in the trial, subjects should be fully informed of the details of trial participation as required by applicable regulations, the site's EC/IRB/REB and the Declaration of Helsinki. Informed Consent must be obtained from each subject prior to conducting any protocol-induced activities beyond standard of care, by using the Informed Consent Form (ICF) approved by that site's EC/IRB/REB and by Medtronic, Inc. All ICFs, including Authorization/Data Protection or other consenting forms required per local requirements and/or short form consents, must be approved by Medtronic, Inc. and the site's EC/IRB/REB prior to use. The ICF must be signed and dated by the subject and by the person obtaining the consent. Any additional persons required by the site's EC/IRB/REB to sign the ICFs must also comply.

Prior to the subject signing the ICF, the investigator or authorized designee will fully explain to the subject the nature of the research, trial procedures, anticipated benefits, and potential risks of participation in the trial. The investigator or delegate will allow adequate time for the subject to read and review the consent form and to ask questions. Signing the ICF serves to document the written/electronic and verbal

information that the investigator or authorized delegate provides to the subject, the subject's understanding of the information, and his/her agreement to participate. The investigator must document in the subject's medical records that the subject was consented and the date on which the consent was obtained. The original signed consent form will be retained in the subject's trial records and a copy of the ICF physically or electronically signed (only applicable to US/Canada per IRB approval) and dated by all parties will be provided to the subject. In some countries, patients must specifically opt-in for data use for other purposes than the study objectives. In those countries, patients will have the option to indicate that in the consent (e.g. via a checkbox or via a separate signature).

Subjects should give electronic (only applicable to US/Canada per IRB approval) or written consent before undergoing any protocol-required testing. However, if any of protocol-required baseline/screening evaluations (e.g. echocardiography and MDCT) have been performed for clinical diagnostic purposes prior to consenting, they can be used as the protocol-required exams, provided they were obtained within the protocol-required time windows and contain the necessary information.

Medtronic will provide each site with the trial specific informed consent separately from this CIP.

### 10.4.1 Revisions in Subject Information and Informed Consent Form

Medtronic will inform the investigators whenever information becomes available that may be relevant to the subject's continued participation in the trial. The revised information will be sent to the investigator for approval by the EC/IRB/REB (if required). After approval by the EC/IRB/REB, a copy of this information must be provided to the participating subjects, and the informed consent process as described above may need to be repeated if required by the site EC/IRB/REB. If re-consent is required per the site EC/IRB/REB's policies and procedures, the investigator or his/her designee should inform the subject in a timely manner (i.e., next available follow-up visit or contact).

## 10.5 Healthcare Utilization

Healthcare Utilization information will be collected throughout this trial in the eCRFs. Healthcare Utilization to be collected includes the reason for and type healthcare encounter, duration and location on terminal healthcare encounter.

Additionally, throughout this trial, UB-04 summary bills and/or itemized hospital bills may be collected at select clinical sites in the US. Prior to the collection of billing information, subjects will be asked to provide the information and permission to obtain such billing records for the length of their follow-up period. All related data will be kept in a secure and confidential database.

## 10.6 Quality of Life Questionnaires

The Quality of Life Questionnaires will be provided under a separate cover.

### 10.6.1 EQ-5D Questionnaire

The EQ-5D will be collected at baseline, 30 days and annually out to 5 years post-procedure.

The EQ-5D is a standardized measure of health status developed by the EuroQol Group. The EQ-5D consists of two pages; the EQ-5D descriptive system and the EQ Visual Analogue scale (EQ VAS).

The EQ-5D descriptive system comprises five dimensions and each dimension has five levels of severity, also referred to as the EQ-5D- five level scale, EQ-5D-5L, utilized in this trial. The subject is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the five dimensions. The EQ VAS records the subject's self-rated health on a 20 cm vertical, visual analogue scale. The subject simply marks an X on the scale to indicate how his/her health is TODAY and then writes the number they marked on the scale in the box below.

A validated telephone interview version will be used at 30-day follow-up visit and annually out to 5 years post-procedure, when subjects are unable to visit the trial site.

All original EQ-5D questionnaires are kept as source data and the total score will be recorded on the appropriate eCRF.

### 10.6.2 Kansas City Cardiomyopathy Questionnaire

The KCCQ will be collected at baseline, 30 days and annually out to 5 years post-procedure.

The KCCQ is a validated 23 item questionnaire which allows subjects to respond directly to questions designed to quantify physical limitations, symptoms, self-effectiveness, QoL, and social limitation. Scores for individual components are combined in an overall summary score with values ranging from 0-100, with higher values indicating fewer symptoms and better quality of life.

## 10.7 Assessment of Efficacy

The following methods will be used for assessing, recording, and analyzing efficacy. Refer to Section 10.1 for timing of these assessments.

- STS-PROM score
- Local heart team assessment
- MDCT Angiogram with contrast
- TTE
- 12-Lead ECG
- EQ-5D and KCCQ quality of life questionnaires

## 10.8 Assessment of Safety

Serious adverse events (SAEs), device deficiencies (DD), and non-serious endpoint-related adverse events will be collected from the time of enrollment until the end of the trial or until trial exit, whichever comes first. A Modified Rankin Score (mRS) assessment should be conducted at baseline and at 30 and 90 days after onset of any confirmed or suspected neurological event. See Section 12 for further information on the collection of AEs and safety information.

Safety assessments performed during this trial will be based on the relatedness to the TAVR implant procedure and the following devices:

- Commercial Trial Devices:
  - Medtronic Evolut™ PRO System and system components
    - Medtronic Evolut™ PRO Transcatheter Aortic Valve
    - Medtronic EnVeo™ PRO Delivery Catheter System with EnVeo™ inline sheath
    - Medtronic EnVeo™ PRO Loading System
  - Medtronic Evolut™ PRO+ System and system components

- Medtronic Evolut™ PRO+ Transcatheter Aortic Valve
- Medtronic Evolut™ PRO+ Delivery Catheter System
- Medtronic Evolut™ PRO+ Loading System

- Medtronic Evolut™ FX System and system components
  - Medtronic Evolut™ FX Transcatheter Aortic Valve
  - Medtronic Evolut™ FX Delivery Catheter System
  - Medtronic Evolut™ FX Loading System
- Edwards SAPIEN 3 and SAPIEN 3 Ultra Transcatheter Heart Valve Systems and system components
  - SAPIEN 3 and SAPIEN 3 Ultra Transcatheter Heart Valve
  - Commander Delivery System

## 10.9 Recording Data

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 trial data collection or adverse event reporting. Identified discrepancies between source documents and the eCRFs will be resolved through the on-line query resolution process per the Data Management Plan.

The eCRFs may not serve as source documents. Source documentation for data elements not routinely captured in medical records (e.g., echocardiography variables, MDCT variables, cath and surgical procedural data variables, local heart team assessment, Modified Rankin Score) may vary from center to center: the site may use technical worksheets if identified as source documents.

Source documents must be retained by the investigational site as required by local law (at least for a period of two years after trial conclusion) and made available for monitoring or auditing by the sponsor's representative or representatives of the competent authorities (CA) and other applicable regulatory agencies or EC/IRB/REB.

The Investigator must ensure the availability of source documents from which the information on the eCRFs was derived. Where printouts of electronic medical records, are provided as source documents, or where copies of source documents are retained as source documents, those should be certified. Certification must contain (1) the signature of the individual making the copy, (2) the date the copy was made and (3) a statement attesting to the accuracy and completeness of the copy. Either wet-ink or 21 CFR Part 11-compliant electronic signature is acceptable.

### 10.9.1 Data Entry

Trial sites staff will assign a unique ID number to each subject. Records of the subject/subject ID relationship will be maintained by the trial site staff. Individual subject medical information obtained as a result of this trial will be considered confidential.

This trial will utilize an Oracle Clinical Remote Data Capture (RDC) system that is the property of Medtronic. Required data will be recorded on electronic case report forms (eCRFs) by authorized site personnel as

indicated on the Delegated Task List (DTL). Trial personnel delegated for eCRF completion and/or approval per the DTL will be trained on the use of the RDC system and thereafter provided with a username and password to access the system. The eCRFs must be completed and/or updated to reflect the latest observations on the subjects participating in the trial. The investigator (or approved sub-investigator) will electronically sign the appropriate pages of each eCRF.

Data from the core lab will be entered into the Oracle Clinical RDC system by core lab personnel per their procedures established for the trial. The core lab physician will approve core lab eCRFs.

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

All trial-related documents must be retained until notification by Medtronic that retention is no longer required. Medtronic will inform the investigator/institution when these documents are no longer required to be retained.

No trial document or image should be destroyed without prior written agreement between Medtronic and the investigator. Should the investigator wish to assign the trial records to another party or move them to another location, advance written notice must be given to Medtronic.

#### 10.9.1.1 Time window for completion and submission of Case Report Forms

As a best practice, sites should complete the eCRFs no later than 5 working days following procedure and 10 working days after a follow-up visit or deviation took place, except for eCRFs documenting adverse events or device deficiencies that require immediate reporting (refer to **Table 6** for the reporting requirements).

## 10.10 Deviation Handling

A trial deviation is defined as an event within a trial that did not occur according to the CIP or CTA. Protocol deviations will be reported via an eCRF regardless of whether medically justifiable, pre-approved by Medtronic, or taken to protect the subject in an emergency.

A Protocol Deviation eCRF is to be completed for each trial protocol deviation, including, but not limited to the following:

- Failure to obtain informed consent prior to participation
- Incorrect version of the informed consent form used
- Failure to obtain EC/IRB/REB approval before the start of the trial
- Implanted subject did not meet inclusion/exclusion criteria
- Required assessment not done
- Subject did not attend follow-up visit or follow-up visit occurred outside the visit window
- Adverse events and device deficiencies not reported in the required time frame as required by regulation
- Source data permanently lost

- Enrollment of subjects during lapse of EC/IRB/REB approval
- Enrollment limits exceeded.

Investigators should obtain prior approval from Medtronic before initiating any change or deviation from the CIP, except when necessary to protect the life or physical well-being of a subject in an emergency situation. Such approval shall be documented in writing and maintained in the Investigator Site File and Sponsor Trial Master File. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the investigator's control (e.g. subject did not attend scheduled follow-up visit).

Trial deviations should be reported to Medtronic via the Protocol Deviation eCRF (one eCRF for each protocol deviation). As a best practice, sites should complete the Protocol Deviation eCRF no later than 10 working days after the deviation occurred. In addition, Investigators are required to adhere to local EC/IRB/REB 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 or enrollment or termination of the investigator's or site's participation in the trial.

## 10.11 Subject Exit, Withdrawal or Discontinuation

Subjects who discontinue participation prematurely will be included in the analysis of results (as appropriate) and will not be replaced in the enrollment of trial subjects. If a subject is discontinued from the trial early, the reason for discontinuation should be documented in the subject file and a trial Exit eCRF must be completed. If discontinuation is because of safety concerns or lack of effectiveness, the subject shall be asked to be followed for collection of ongoing safety data outside the clinical investigation.

The trial site will make every effort to have all subjects complete the follow up visit schedule. A subject will not be considered lost to follow-up unless all efforts to obtain compliance are unsuccessful.

At a minimum, the effort to obtain follow-up information must include 3 attempts to make contact via telephone and if contact via phone is not successful, a traceable letter from the investigator should be sent to the subject's last known address. Should both telephone and mail efforts to contact the subject be unsuccessful, the subject's primary physician should be contacted if the subject agrees in the ICF that their primary physician may be informed of their participation in the trial. Subjects will then be deemed lost to follow up. All contact efforts to obtain follow-up must be documented in both the subject's medical records and on the trial eCRFs. In the event a subject is lost to follow up, the monitor shall check the appropriateness of the center's attempts to contact both the subject and their primary physician (or other contact as appropriate).

When subjects are lost to follow-up the investigator will make efforts to confirm the vital status of the subject, as described in the ICF.

Site(s) in Switzerland:

1) When subjects can no longer be contacted, information about mortality and other SAE should not get lost. Adequate procedures need to be implemented in order to retrieve and promptly analyse the data. If trial subjects can no longer be found, the CIP should foresee that the trial site quickly clarifies their current address and state of health with an appropriate contact person (e.g. the subject's general practitioner).
2) Monitoring provisions: In case trial subjects can no longer be found, the monitor shall check the appropriateness of the centre's attempts to contact both the subject and his contact person.

If a subject discontinues the trial at any time, is withdrawn from the trial early, or completes all protocol required follow-up they should continue to be followed by the implanting site according to the routine clinical practice for aortic valve subjects. If, for any reason, this is not possible for a particular subject, or if a subject needs to change their follow-up site at any time point after conclusion of the trial, investigators should refer subjects to a local site with appropriate training and experience in managing subjects with implanted aortic valves.

# 11. Risks and Benefits

## 11.1 Potential Risks

There are possible risks and side effects connected to the Evolut PRO, Evolut PRO+, Evolut FX, SAPIEN 3, and/or SAPIEN 3 Ultra TAV implant, but the risks are the same as those for an implant of the TAVs without participation in this trial. Standard risks associated with the Evolut PRO, Evolut PRO+, Evolut FX, SAPIEN 3, and SAPIEN 3 Ultra Systems in the trial are provided in the Instructions for Use.

Risks and events will be continuously monitored, assessed and documented by the investigator. Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of a product, from the business analysis phase through development, market release, and post-market surveillance.

The devices will be used within the local commercially approved indication in the geographies in which each device is approved. There are no incremental risks introduced to the subject as a result of participation in this trial with the exception of subjects participating in the stress echocardiogram at select sites, which will be outlined in the ICF and applicable addendum CIP. These documents will be provided under a separate cover.

## 11.2 Risk Minimization

The following measures will be implemented to minimize risks to the trial subjects:

- Implanting physicians will have considerable experience with TAVR
- Trial sites will have significant experience with TAVR
- Subjects will undergo thorough imaging assessment during their pre-implant workup
- Subjects will be rigorously followed over the course of the trial
- An independent data safety monitoring board (DSMB) will review adverse events and safety results in order to advise Medtronic regarding trial conduct, should safety concerns be identified

## 11.3 Potential Benefits

Participation in this clinical trial may not result in any direct benefit to the subject. Trial subjects implanted with an Evolut PRO, Evolut PRO+, Evolut FX, SAPIEN 3, and/or SAPIEN 3 Ultra TAV receive the same medical treatment as if they were not participating in this post-market trial and implanted with one of these devices. Participation contributes to expansion of the knowledge base with respect to the use of the Evolut PRO, Evolut PRO+, Evolut FX, SAPIEN 3, and/or SAPIEN 3 Ultra TAV systems in a routine hospital setting.

## 11.4 Risk-Benefit Rationale

TAVR is now established as having an acceptable safety profile and is considered an effective treatment option for subjects with symptomatic severe native aortic stenosis who are at low to extreme risk for surgical aortic valve replacement. The Medtronic CoreValve™ system, the Evolut R system, the Evolut PRO system, and the Evolut PRO+ system (referred jointly as Medtronic TAVR) have been in widespread use since the first generation received CE Mark in 2007, and there is now extensive published experience demonstrating the Medtronic TAVR system is fulfilling its intended role with a favorable risk/benefit ratio.[35-38] Rigorous clinical trials have established its safety and effectiveness, with improved mortality and quality of life compared with medical therapy in extreme, high, intermediate and low risk subjects. [1-4]

Evolut FX has been demonstrated to be equivalent to the Evolut PRO+ system. Therefore, the results of the Low Risk, Low Risk Bicuspid, SURTAVI, and Medtronic CoreValve Evolut PRO US Clinical Trials are applicable to the Evolut FX system.

Appropriate risk management activities have been performed for the Evolut PRO, Evolut PRO+, Evolut FX, SAPIEN 3, and/or SAPIEN 3 Ultra system resulting in a positive risk-to-benefit rationale given the products have received local regulatory body approval. Other than a subset of subjects that will undergo a stress echocardiogram at select sites, the risks and potential benefits are identical for subjects implanted as part of this trial when compared to the commercial setting.

# 12. Adverse Events and Device Deficiencies

## 12.1 Adverse Events

Given that this is a post-market trial, all serious adverse events (SAEs) and non-serious endpoint-related adverse events (AE) (listed and defined in Appendix Section 18.5) and adverse device effects (ADEs) will be collected throughout the trial duration, starting at the time of signing the ICF. AE and ADE definitions of reportable events for this trial are provided in **Table 6**. Guidelines for classifying AE relatedness (listed and defined in Appendix Section 18.5).

Reporting of these events to Medtronic will occur on an AE Form. Each event must be reported separately. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened.

In all geographies, unavoidable adverse events (UAEs), listed in **Table 7**, need not be reported unless the adverse event worsens or is present outside the stated timeframe post-implant.

For AEs that require immediate reporting (**Table 8**), initial reporting may be done by phone, fax, or on the CRF completing as much information as possible. The AE CRF must be submitted to Medtronic as soon as possible.

Any medication/intervention associated with the treatment of an AE must be reported.

## 12.2 Device Deficiency

The device deficiency (DD) definition is provided in **Table 6**. DD information will be collected throughout the trial and reported to Medtronic. Note that DD that result in an AE to the subject should be captured as an AE only.

DD that did not lead to an AE but could have led to a SADE (i.e., if suitable action had not been taken, if intervention had not occurred, or if the circumstances had been less fortunate) require immediate reporting (see **Table 8**).

## 12.3 Processing Updates and Resolution

For any changes in status of a previously reported AE or DD (i.e. change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE or DD form. All AEs must be followed until the AE has been resolved, is unresolved with no further actions planned, the subject dies or exits the trial, or until trial closure, whichever occurs first.

In the event that a subject is exited from the trial prior to the 5-year follow-up, all efforts should be made to continue following the subject until all unresolved system or procedure related AEs, as classified by the investigator, are resolved or unresolved with no further actions planned.

At the time of trial exit, all collected adverse events that are unresolved must be reviewed and an update to the original AE must be reported.

## 12.4 Definitions/Classifications

All SAEs, non-serious endpoint-related AEs and ADEs (listed and defined in Appendix Section 18.5) and DDs will be collected throughout the trial duration, starting at the time of signing the ICF.

The definitions to be applied for the purposes of AE and DD reporting are provided in **Table 6**.

Where the definition indicates ‘device’, it refers to any device used in the trial. This might be the trial devices, or any market released component of the system, and includes but is not restricted to: Evolut PRO, Evolut PRO+, Evolut FX, SAPIEN 3, and SAPIEN 3 Ultra TAV Systems.

For the list of anticipated adverse events and anticipated adverse product effects associated with the use of the Evolut PRO, Evolut PRO+, Evolut FX, SAPIEN 3, and SAPIEN 3 Ultra TAV Systems refer to the respective product Instructions for Use.

**Table 6: Adverse Event Definitions for Reporting Requirements**

| Event Classification/Type | Definition |
|---|---|
| **General** | |
| Adverse Event (AE)<br>(ISO 14155:2020 section 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 and whether anticipated or unanticipated.<br>NOTE: This definition includes events related to the investigational medical device or the comparator.<br>NOTE: This definition includes events related to the procedures involved.<br>NOTE: for users or other persons, this definition is restricted to events related to investigational medical devices or comparators. |
| Adverse Device Effect (ADE)<br>(ISO 14155:2020, 3.1) | AE related to the use of an investigational medical device.<br>NOTE 1: This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.<br>NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device.<br>NOTE 3: this includes 'comparator' if the comparator is a medical device. (ISO 14155:2020, 3.1) |
| Device Deficiency (DD)<br>(ISO 14155:2020, 3.19) | Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.<br>NOTE 1: DD include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling.<br>NOTE2: This definition includes device deficiencies related to the investigational medical device or the comparator. |
| **Seriousness** | |
| Serious Adverse Event (SAE)<br>(ISO14155:2020 3.45) | AE that led to any of the following<br>a) death,<br>b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:<br>1) a life-threatening illness or injury, or<br>2) a permanent impairment of a body structure or a body function, including chronic disease, or<br>3) in-patient or prolonged hospitalization, or<br>4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,<br>c) fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment[39]<br>Note 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE |

| Event Classification/Type | Definition |
|---|---|
| Serious Adverse Device Effect (SADE)<br>(ISO 14155:2020, 3.44) | Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. |
| Unanticipated Serious Adverse Device Effect (USADE)<br>(ISO 14155:2020, 3.51) | (Serious adverse) device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment<br>NOTE 1: Anticipated Serious Adverse Device Effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment. |
| **Other** | |
| Unavoidable Adverse Event (UAE) | An AE inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the Investigator's opinion.<br>Refer to Section **Table 7** for a list of UAEs. |

Notes:

- The interpretation of Seriousness will exclude certain interventions considered standard of care during hospitalization (e.g. IV hydration, certain medications delivered intravenously due to available intravenous access or NPO (nothing by mouth) status, and the delivery of electrolytes to maintain electrolyte balance or to address mild electrolyte depletion). Any nonoral medication or fluid delivery used to treat an acute physical decompensation/deterioration episode or to otherwise resuscitate a subject will be considered serious by definition in that it prevents a permanent impairment of a body structure or to prevent life-threatening illness or injury
- Hospitalization requires admission for at least 24 hours (including an emergency department stay), or as measured by a change in calendar date.
- Ballooning as needed during the implant procedure is standard practice and should not be considered a reintervention.

### 12.4.1 Unavoidable Adverse Events

Unavoidable events are conditions which do not fulfill the definition of an Adverse Event, meaning those medical occurrences, clinical signs (including toward abnormal laboratory findings), diseases or injuries that are not untoward in nature; specifically, those resulting from the intended injury such as the index TAVR procedure. The events listed in **Table 7** are expected for subjects undergoing TAVR, and do not need to be reported as an AE, unless they worsen during the timeframe or occur outside of the stated timeframe, or are otherwise considered to be an SAE according to the treating investigator, or SAEs that are suspected or confirmed to be device-related.

**Table 7: Unavoidable Adverse Events Associated with the Index Procedure**

| Event | Timeframe (hours) from the Index Procedure |
|---|---|
| Short transient episode of arrhythmia (including ventricular fibrillation) during index procedure | 0 |
| Confusion, anxiety and/or disorientation (other than TIA/stroke) starting within 48 hours with or without medical intervention | 120 (5 days) |
| Temporary change in mental status (other than TIA/stroke) not requiring additional medical interventions or new medical assessments (e.g. CT) | 72 |
| Dizziness and/or lightheadedness with or without treatment | 24 |
| Headache with or without treatment | 72 |
| Sleep problems or insomnia with or without treatment | 120 (5 days) |
| Mild dyspnea or cough with or without treatment | 72 |
| Oxygen supply after extubation / "forced breathing therapy" | 48 |
| Diarrhea with or without treatment | 48 |
| Obstipation / Constipation with or without treatment | 72 |
| Anesthesia-related nausea and/or vomiting with or without treatment | 24 |
| Low-grade fever (<101.3°F or <38.5°C) without confirmed infection | 48 |
| Low body temperature | 6 |
| Pain (e.g. back, shoulder) related to laying on the procedure table with or without treatment | 72 |
| Incisional pain (pain at access site) with or without standard treatment and subject not returning to clinic to have additional treatment | No time limit |
| Pain in throat and/or trachea due to intubation | 72 |
| Mild to moderate bruising or ecchymosis | 168 (7 days) |
| Atelectasis / Pleural Effusion not requiring punctuation | 168 (7 days) |
| Edema resulting in weight increase up to 4 kg / 9lbs from baseline | 168 (7 days) |

## 12.5 Reporting of Adverse Events and Device Deficiencies

Investigators are required to report All SAEs, non-serious endpoint-related AEs, ADEs (listed and defined in Appendix Section 18.5) and DDs observed in the trial subjects from the point of enrollment until completion of follow-up.

The VARC- document provides standardization of endpoint definitions for studies evaluating the use of TAVR. This trial follows VARC to allow for improved comparability and interpretability of trial results. In addition, Investigators are obligated to report adverse events in accordance with the requirements and timeframes per their reviewing EC/IRB/REB and local regulations, if applicable.

The Sponsor is obligated to report adverse events and device deficiencies that occur during this trial to the EC/IRB/REB as per local requirements.

In EU/EEA safety reporting by the sponsor to National Competent Authorities will follow European Union Medical Device Regulation (EU MDR) requirements per MDCG 2020-10. In addition, it is the responsibility of the investigator and sponsor to abide by AE reporting requirements stipulated by local law and the study site's EC.

For Switzerland sites: Confirm that the documentation and reporting obligation is carried out in accordance with Art. 32-34 ClinO-MD.

**Table 8: Adverse Event and Device Deficiency Reporting Requirements**

| **Investigator shall submit to:** | |
|---|---|
| Medtronic | **All geographies:**<br>**SAEs:** Report to the sponsor, without unjustified delay, all serious adverse events.<br>**Non-serious endpoint-related AEs/ADEs:** Submit in a timely manner after the investigator first learns of the effect.<br>**SADEs and USADEs:** Immediately after the investigator learns of the event or of new information in relation to an already reported event.<br>**DDs with SAE potential:** Submit or report as required per local reporting requirements.<br>**All other Device Deficiencies:** Submit in a timely manner after the investigator first learns of the deficiency. |
| RA | **All geographies:** Submit to RA per local reporting requirement. |
| EC/IRB/REB | **All geographies:** Submit to EC/IRB/REB per local reporting requirement. |
| **Sponsor shall submit to:** | |
| RA | **All geographies:** Submit to RA per local reporting requirement. |
| EC/IRB/REB | **All geographies:** Submit to EC/IRB/REB per local reporting requirement. |

## 12.6 Emergency contact Details for Reporting AEs and Device Deficiencies

Investigators should contact their Medtronic site manager if they have any questions regarding reportable AEs. A listing of current contact information, including the Sponsor's medical expert, will be maintained separately from this CIP and provided to the sites.

## 12.7 Subject Death

All subject deaths must be reported by the investigator to Medtronic on an AE form (AE with outcome of death) as soon as possible after the investigator first learns of the death. In case of death, there should be one AE with the outcome of death.

In the event of a subject's death, it is recommended that the implanted system be explanted and returned to the manufacturer for analysis whenever possible per local process. Local laws and procedures must be followed where applicable. If any Evolut PRO/PRO+/FX system component is returned to Medtronic, internal return product reporting systems may be used to gather additional information about the returned device/component.

A copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic clinical trial team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records, if available should be sent to the Medtronic clinical trial team. If an autopsy is conducted per standard practice, a copy of the autopsy report should also be sent to the Medtronic clinical trial team if available and allowed by state/local law. When the death occurs at a remote trial site, it is the investigative trial site's responsibility to attempt retrieval of information about the death. Additionally, device disposition information should be updated.

In summary, the following information will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Relatedness to system and/or procedure
- Device disposition information
- Death summary/hospital records (if available and allowed by state/local law)
- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and allowed by state/local law)

## 12.8 Product Complaint Reporting

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device to the device manufacturer, regardless of whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. The reporting of Medtronic product complaints by the clinical team must be done according to the local Standard Operating Procedures. Medtronic will notify the Regulatory Authorities (e.g. Competent Authority) as applicable for the following incidents for the Medtronic devices immediately upon learning of them and is not limited to SAEs and DDs only:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a subject, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.

- Any serious deterioration in the state of health, including those that:
  - Led to death
  - Let to serious deterioration in the health of the subject, that either resulted in:
    - A life-threatening illness or injury, or
    - A permanent impairment of a body structure or permanent damage to a body structure, or
    - In-patient or prolonged hospitalization, or
    - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
  - Led to fetal distress, fetal death or a congenital abnormality or birth defect

# 13. Data Review Committees

## 13.1 Clinical Events Committee Review

At regular intervals, an independent CEC will conduct a medical review of clinical safety and efficacy endpoints for subjects participating in the trial as outlined in the CEC Charter.

The CEC will consist of a minimum of three (3) non-Medtronic employed physicians that are not participating investigators for the trial, including a CEC chairperson. At least three CEC members must adjudicate, at a minimum, all deaths and serious AEs related to any component of the system under investigation.

If the CEC disagrees with the investigator's classification of the event, the rationale will be provided to the investigator. If the investigator agrees with the CEC's adjudication, the Case Report Form (CRF) documenting the AE will be updated accordingly.

If the investigator does not agree with the CEC's adjudication classification, both determinations will be provided within the final report; however, the CEC's adjudication will be used for data analysis. The disagreement will also be included in reporting to EC/IRB/REBs and regulatory authorities, if required.

## 13.2 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will assess trial data and provide recommendations to Medtronic regarding trial conduct, should they identify any issues that may affect the safety of the trial subjects. DSMB members will be free from bias towards the trial and will be independent from both the trial and investigators and Medtronic.

The DSMB will consist of a minimum of 3 members that include the following specialties:

- Interventional cardiologist(s) or cardiac surgeon(s) with expertise in the management of aortic stenosis and aortic valve replacement
- A statistician

A DSMB charter will be established that describes the Committee roles, responsibilities, and processes. The DSMB will meet (via teleconference or in person) prior to the first subject enrollment to establish procedures for safety data review, chairman appointment, and guidelines for trial recommendations. The DSMB will meet on a periodic basis to perform a comprehensive data review, including at a minimum, all SAEs and deaths, and will meet more frequently when needed. Safety-related endpoints may also be reviewed at these meetings. DSMB meetings may consist of both open and closed sessions.

Following each meeting, the DSMB will report to Medtronic in writing and may recommend changes in the conduct of the trial. The DSMB recommendations may include recommendations on trial status such as continuing the trial without modifications, continuing the trial with modifications, stopping or suspending enrollment, or recommendations regarding trial conduct including recommendations around enrollment or protocol deviations.

In the case of USADEs, if Medtronic and the DSMB determine that the event presents an unreasonable risk to the participating subjects, Medtronic must terminate the clinical trial within 5 working days after making that determination and no later than 15 working days after Medtronic first receives notice of the effect. All clinical sites will be notified of this action.

The DSMB may call additional meetings if, at any time, there is concern about any aspect of the trial. All data presented at the meetings will be considered confidential.

## 13.3 Case Planning Committee

The SMART Trial will include a Confirmation of Qualification process conducted by Medtronic Clinical Analysts and an independent Case Planning Committee to review the anatomical suitability of potential subjects identified by the site for both Medtronic Evolut PRO/PRO+/FX TAV and Edwards SAPIEN 3/3 Ultra TAV. Depending on whether a subject's anatomical suitability meet entry criteria for the trial, a recommendation to proceed with randomization or reevaluate/exit the subject will be provided to the site.

The Confirmation of Qualification process and Case Planning Committee will ensure appropriate and consistent subject selection across all sites. Prior to the onset of the trial, a charter will be developed which outlines roles and responsibilities as well as describe the screening process.

# 14. Statistical Design and Methods

This is a prospective, multi-center, international, randomized controlled, post-market trial. Approximately 700 subjects with a small aortic annulus and severe native aortic stenosis will be randomized and treated to TAVR treatment with either Evolut PRO/PRO+/FX System or SAPIEN 3/3 Ultra System.

## 14.1 General Aspects of Analysis

Descriptive statistics of continuous outcomes will be presented by treatment arm and include count, mean, median, standard deviation, minimum and maximum. For categorical outcomes, the number and percentage of subjects in each category will be presented by treatment arm. All statistical analyses will be

performed using SAS for Windows (version 9.4 or higher) or other widely accepted statistical or graphical software. Subject data listings and tabular and graphical presentations of results will be provided. Unless otherwise specified, a two-sided 0.05 level of significance will be used to declare treatment arms significantly different. Additional details on the analysis will be provided in the Statistical Analysis Plan (SAP) for this trial. Deviation(s) from the SAP including the deviation description and justification will be documented.

## 14.2 Interim Analysis

No interim analyses are planned for this trial.

## 14.3 Analysis Sets

### 14.3.1 Screening Population

All subjects with a small aortic annulus and severe native aortic stenosis who provide an informed consent will be considered screened and enrolled and all available data will be entered into the Electronic Data Capture (EDC) system. Data from subjects who were consented but screen failed and exited prior to the TAVR procedure will not be analyzed and published.

### 14.3.2 Randomized Population

If the subject signs informed consent, meets all inclusion and none of the exclusion criteria, and the Heart Team determines the subject is suitable for randomization in the trial, then the subject will undergo a Confirmation for Qualification. If the subject is approved, the subject will be randomized and added to the randomized population. Within the randomized population the following analysis sets are distinguished:

The intention to treat (ITT) set: Subjects are reported according to the randomized assignment, either BE or SE TAV, regardless of what, if any, therapy was actually received.

The as treated (AT) set: The AT set consists of all ITT subjects with an attempted implant procedure, defined as when the subject is brought into the procedure room and any of the following have occurred: anesthesia administered, vascular line placed, TEE placed or any monitoring line placed. Subjects will be analyzed according to their first attempted procedure (BE or SE TAV).

The implanted set: The Implanted set consists of all the AT subjects who are actually implanted with either TAV.

The primary analysis for the non-ECHO related objectives will use the AT analysis set. The primary analysis for the ECHO related objectives (such as BVD) will use the implanted analysis set.

## 14.4 Primary Objectives

This trial has two primary objectives comparing the Medtronic SE TAV and Edwards BE TAV.

### 14.4.1 Primary Objective #1 (Safety)

The primary safety endpoint in this trial is the composite of all-cause mortality, disabling stroke or heart failure rehospitalization at 12 months post-procedure. The primary safety endpoint will be evaluated using the absolute difference of the Medtronic SE TAV rate and the Edwards BE TAV rate for the composite of all-cause mortality, disabling stroke or heart failure rehospitalization during a fixed follow-up time of 12 months post-procedure. The hypothesis test is designed to show non-inferiority of Medtronic SE TAV to the Edwards BE TAV. The primary analysis of the primary safety endpoint will be performed using the AT analysis set.

#### 14.4.1.1 Hypothesis

Hypothesis: The Medtronic SE TAV is non-inferior to Edwards BE TAV in the composite event rate of all-cause mortality, disabling stroke or heart failure rehospitalization at 12 months post-procedure with an absolute non-inferiority margin of 8.0%:

$H_o$: $\pi_{MDT} \geq \pi_{EW} + \delta$

$H_A$: $\pi_{MDT} < \pi_{EW} + \delta$

In the above expression $\pi_{MDT}$ and $\pi_{EW}$ denote the composite event rates of all-cause mortality, disabling stroke or heart failure rehospitalization at 12 months post-procedure for Medtronic SE TAV and Edwards BE TAV and $\delta$ denotes the non-inferiority margin (8%).

Assuming the true event rates for both arms in the SMART trial is 16.0%, with a one-sided type I error of 0.05, an evaluable sample size of 260 subjects in each arm would yield about 80% power and 360 subjects in each arm would yield 90% power. Accounting for attrition, a total sample size of 700 subjects treated which will provide greater than 85% power for the non-inferiority endpoint.

The assumption for the anticipated composite event rate of all-cause mortality, disabling stroke or heart failure rehospitalization at 12 months post-procedure was based on the literature. It is expected that the trial will enroll predominately women (approximately 80% of the population) due to the recruitment of subjects with small annulus. In prior studies, rates for the composite endpoint by surgical risk were approximately 8%, 20%, and 28% for the low, intermediate, and high surgical risk populations, respectively[4, 5, 8, 39-40]. It is anticipated that the recruited native population would be of 20%, 60% and 20% at low, intermediate, and high surgical risk respectively. Therefore, the estimate rate for the composite endpoint would be around 20%. Given improvement in TAVR technology and operator experience from prior randomized trials, the observed composite endpoint event rate in the present trial is expected to be lower and the anticipated event rate in each arm was therefore assumed to be 16%.

**Table 9: TAVR Safety Data from Literature**

| Literature | Surgical Risk | Valve Type | N | Composite Safety Event Rate at 12 Months |
|---|---|---|---|---|
| Popma JJ, Deeb GM, Yakubov SJ | Low | SE | 725 | 2.9%[1] |
| Mack MJ, Leon MB, Thourani VH, et al. | Low | BE | 496 | 8.5% |

| Literature | Surgical Risk | Valve Type | N | Composite Safety Event Rate at 12 Months |
|---|---|---|---|---|
| Leon MB, Smith CR, Mack MJ, et al. | Intermediate | BE | 994 | 27.1%[2] |
| Szerlip M, Gualano S, Holper E, et al. | Intermediate[3] | BE | 1661 | 22.4% (Female); 20.9% (Male) |
| Skelding KA, Yakubov SJ, Kleiman NS, et al. | High | SE | 183 | 14.9%[4] |

[1]All-cause mortality or disabling stroke.
[2]All-cause mortality, any stroke, or rehospitalization.
[3]Included 583 subjects at high surgical risk.
[4]All-cause mortality or major stroke. In the same cohort, the rate of rehospitalization was 16.3 % at 12 months.[i]

### 14.4.2 Primary Objective #2 (Efficacy)

The primary efficacy endpoint in this trial is the valve function composite endpoint of BVD at 12 months post-procedure including any of the following:

- HSVD: hemodynamic mean gradient ≥ 20mmHg
- NSVD: severe PPM, or ≥ moderate total aortic regurgitation (TAR)
- Thrombosis
- Endocarditis
- Aortic valve re-intervention

The primary analysis of the primary efficacy endpoint will use the implanted analysis set.

#### 14.4.2.1 Hypothesis

Hypothesis: The Medtronic SE TAV is superior to Edwards BE TAV in BVD at 12 months post-procedure:

$H_o$: $\pi_{MDT} \geq \pi_{EW}$

$H_A$: $\pi_{MDT} < \pi_{EW}$

In the above expression $\pi_{MDT}$ and $\pi_{EW}$ denote the BVD rates at 12 months post-procedure for Medtronic SE TAV and Edwards BE TAV.

Assuming the true event rates are 14.0% and 36.0% for Medtronic SE TAV System and Edwards BE TAV respectively, and with a one-sided type I error of 0.025, an evaluable sample size of 60 subjects in each arm would be required to have 80% power. The total sample size of 700 as-treated subjects will provide sufficient power for the endpoint.

## 14.5 Powered Secondary Objectives

This trial has five powered secondary objectives comparing the Medtronic SE TAV and Edwards BE TAV.

[i] Data on file at Medtronic

### 14.5.1 Powered Secondary Objective #1: BVD in Female Population

The first powered secondary endpoint in this trial is the BVD rate at 12 months post-procedure in the female population. The endpoint will be analyzed using the implanted analysis set.

#### 14.5.1.1 Hypothesis

##### 14.5.1.1.1 Female Population

Hypothesis: The Medtronic SE TAV is superior to Edwards BE TAV in BVD at 12 months post-procedure in the female population:

$H_o$: $\pi_{MDT} \geq \pi_{EW}$

$H_A$: $\pi_{MDT} < \pi_{EW}$

In the above expression $\pi_{MDT}$ and $\pi_{EW}$ denote the BVD rates at 12 months post-procedure for Medtronic SE TAV and Edwards BE TAV in the female population.

It is expected that approximately 80% of the trial population will be female. Assuming the true event rates are 14.0% and 36.0% for Medtronic SE TAV and Edwards BE TAV respectively, and with a one-sided type I error of 0.025, an evaluable sample size of 60 subjects in each arm would be required to have 80% power. With a total sample size of 700 as-treated subjects of which approximately 80% are expected to be female, the endpoint will have adequate power within the female population.

### 14.5.2 Powered Secondary Objective #2: HSVD

The second powered secondary endpoint in this trial is the HSVD rate at 12 months post-procedure. The endpoint will be analyzed using the implanted analysis set.

#### 14.5.2.1 Hypothesis

Hypothesis: The Medtronic SE TAV is superior to Edwards BE TAV in HSVD at 12 months post-procedure:

$H_o$: $\pi_{MDT} \geq \pi_{EW}$

$H_A$: $\pi_{MDT} < \pi_{EW}$

In the above expression $\pi_{MDT}$ and $\pi_{EW}$ denote the SVD rates at 12 months post-procedure for Medtronic SE TAV and Edwards BE TAV.

Assuming the true event rates are 4.0% and 19.0% for Medtronic SE TAV and Edwards BE TAV respectively, and with a one-sided type I error of 0.025, an evaluable sample size of 70 subjects in each arm would be required to have 80% power. The total sample size of 700 subjects will provide sufficient power for the endpoint.

### 14.5.3 Powered Secondary Objective #3: Hemodynamic Mean Gradient

The third powered secondary endpoint in this trial is the hemodynamic mean gradient as continuous variable at 12 months post-procedure. The endpoint will be analyzed using the implanted analysis set.

#### 14.5.3.1 Hypothesis

Hypothesis: The Medtronic SE TAV is superior to Edwards BE TAV in hemodynamic mean gradient at 12 months post-procedure:

$H_o$: $MGV_{MDT} \geq MGV_{EW}$

$H_A$: $MGV_{MDT} < MGV_{EW}$

In the above expression $MGV_{MDT}$ and $MGV_{EW}$ denote the hemodynamic mean gradient (MGV) as continuous variable at 12 months post-procedure for Medtronic SE TAV and Edwards BE TAV.

Assuming the true MGVs are 9.0±3.3 mmHg and 13.7±5.6 mmHg for Medtronic SE TAV[4] and Edwards BE TAV[8] respectively, and with a one-sided type I error of 0.025, an evaluable sample size of 20 subjects in each arm would be required to have 80% power. The total sample size of 700 subjects will provide sufficient power for the endpoint.

### 14.5.4 Powered Secondary Objective #4: Effective Orifice Area

The fourth powered secondary endpoint in this trial is effective orifice area (EOA) as continuous variable at 12 months post-procedure. The endpoint will be analyzed using the implanted set.

#### 14.5.4.1 Hypothesis

Hypothesis: The Medtronic SE TAV is superior to Edwards BE TAV in EOA at 12 months post-procedure:

$H_o$: $EOA_{MDT} \leq EOA_{EW}$

$H_A$: $EOA_{MDT} > EOA_{EW}$

In the above expression $EOA_{MDT}$ and $EOA_{EW}$ denote the effective orifice area (EOA) as continuous variable at 12 months post-procedure for Medtronic SE TAV and Edwards BE TAV, respectively.

Assuming the true EOA is 2.27 ± 0.65 $cm^2$ and 1.72 ± 0.37 $cm^2$ for Medtronic SE TAV[4] and Edwards BE TAV[8] respectively, and with a one-sided type I error of 0.025, an evaluable sample size of 16 subjects in each arm would be required to have 80% power. The total sample size of 700 subjects will provide sufficient power for the endpoint.

### 14.5.5 Powered Secondary Objective #5: Moderate or Severe Prosthesis-Patient Mismatch

The fifth powered secondary endpoint in this trial is the rate of moderate or severe prosthesis-patient mismatch (PPM) at 30 days post-procedure. The endpoint will be analyzed using the implanted analysis set.

#### 14.5.5.1 Hypothesis

Hypothesis: The Medtronic SE TAV is superior to Edwards BE TAV in moderate or severe PPM at 30 days post-procedure:

$H_o$: $\pi_{MDT} \geq \pi_{EW}$

$H_A$: $\pi_{MDT} < \pi_{EW}$

In the above expression $\pi_{MDT}$ and $\pi_{EW}$ denote the rate of moderate or severe PPM at 30 days post-procedure for Medtronic SE TAV and Edwards BE TAV.

Assuming the true event rates are 11.0% and 34.0% for Medtronic SE TAV and Edwards BE TAV respectively, and with a one-sided type I error of 0.025, an evaluable sample size of 51 subjects in each arm would be required to have 80% power. The total sample size of 700 subjects will provide sufficient power for the endpoint.

## 14.6 Non-Powered Secondary Objectives

The non-powered secondary endpoints comparing the SE and BE TAVR are listed below:

1. Device success at 30 days
2. Incidence of an early safety composite at 30 days defined as:
    - All-cause mortality
    - All stroke (disabling and non-disabling)
    - 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, TAVR, or SAVR)
3. Hospital readmission for any cause at 30 days
4. Incidence of clinical efficacy (after 30 days) at 12 months and annually to 5 years defined as a composite of:
    - All-cause mortality
    - All stroke (disabling and non-disabling)
    - Requiring hospitalizations for valve-related symptoms or worsening congestive heart failure
    - NYHA class III or IV
    - Valve-related dysfunction (mean aortic valve gradient ≥20 mmHg, EOA ≤0.9-1.1 $cm^2$ and/or DVI<0.35m/s, AND/OR moderate or severe prosthetic valve regurgitation)
5. Components of the primary clinical endpoint at 12 months and annually to 5 years:
    - Mortality
    - Disabling stroke
    - Heart failure rehospitalization
6. New pacemaker implantation rate at 30 days, 12 months and annually to 5 years
7. Aortic valve re-intervention at 30 days, 12 months and annually to 5 years
8. 6MWT at 30 days, 12 months and annually to 5 years
9. QoL (KCCQ, EQ-5D) at 30 days, 12 months and annually to 5 years
10. BVD (HSVD, NSVD, thrombosis, endocarditis, and aortic valve re-intervention) at 2 to 5 years annually

11. Echocardiographic measurements (i.e. EOA, mean gradient, PVL, LV mass regression, and DVI (severe <0.25, moderate 0.25-0.5, mild >0.5)) at discharge, 30 days, 12 months and annually to 5 years
12. Mean gradient ≥ 20 mmHg based on stress echocardiogram at 12 months at select sites

Device success, Safety, clinical efficacy, quality of life, and 6-minute walk test endpoints will be analyzed using the AT analysis set. Echo-related endpoints will be analyzed using the implanted analysis set.

## 14.7 Description of Baseline Variables

Baseline demographic and clinical variables will be summarized descriptively for each of the treatment groups for the ITT, AT, and implanted sets. Continuous variables will be compared between treatment groups using a two-sample t-test or the non-parametric Wilcoxon rank-sum test. Categorical variables will be compared between treatment groups using a Chi-square test or Fisher's exact test, as appropriate. Ordinal variables will be compared using Cochran-Mantel-Haenszel test with row mean scores.

## 14.8 Missing Data

Every effort will be undertaken to minimize missing data. In time-to-event outcomes, dropouts will be censored at the time of discontinuation, consistent with the Kaplan-Meier approach. Unless otherwise specified, no statistical techniques will be used to impute missing data. The number of subjects included in each analysis will be reported so that the reader can assess the potential impact of missing data. Further details will be provided in the statistical analysis plan.

# 15. Ethics

## 15.1 Statements of Compliance

The trial will be conducted in accordance with the Declaration of Helsinki (DoH), the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) E6 (R2) guidelines, the trial protocol, the Sponsor's standard operating procedures and/or guidelines, and in accordance with federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the trial is being conducted. These include but are not limited to:

- In the United States, the trial will be conducted in compliance with 21 CFR Parts 50, 56 and 803
- In the EU/EEA region the trial will be conducted in compliance with EU MDR and applicable data protection law.

All trial sites in all geographies will follow and comply with:

- Principles of DoH including the informed consent process, EC/IRB/REB review and approval, training, clinical trial registration, risk assessment, publication policy, etc.
- 21 CFR Part 11 (Electronic Records, Electronic Signatures)
- The Clinical Trial Agreement
- The procedures described within this CIP

- Providing accurate financial disclosure information, if required by Medtronic
- Local EC/IRB/REB and regulatory requirements

In addition to the requirements outlined above, any additional requirements imposed by the EC/IRB/REB or regulatory authority shall be followed, if appropriate. Any action is taken by an EC/IRB/REB with respect to the investigation, that information will be forwarded to the Sponsor.

This trial will be publicly registered prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act (FDAAA) and on http://clinicaltrials.gov (PL 110-85, Section 810(a)).

## 15.2 EC/IRB/REB Approval

The trial will be conducted in accordance with the requirements of local Ethics Committee (EC), Institutional Review Board (IRB) and Research Ethics Board (REBs). Trial activities will not commence prior to receipt of documentation of EC/IRB/REB approval (and regulatory agency approval, as appropriate) by the site and Medtronic. The Investigator and trial staff must comply with the requirements of their EC/IRB/REB, including any additional requirements imposed by the EC/IRB/REB after initial approval.

Prior to enrolling subjects in this clinical trial, each investigational site's EC/IRB/REB will be required to approve the current clinical investigation plan, the informed consent form or any other written information to be provided to the subjects. Trial sites in the United States must also utilize IRB approved Health Insurance Portability and Accountability Act (HIPAA) Authorization.

EC/IRB/REB approval of the clinical trial must be received in the form of a letter and provided to Medtronic before commencement of the trial at an investigation site. The approval must contain enough information to identify the version or date of the documents approved. If this information is not contained in the approval, it must be retrievable from the corresponding submission documentation. In addition, the approval needs to be accompanied by an EC/IRB/REB roster to allow verification that the investigator, other investigational site personnel, and/or Medtronic personnel are not members of the EC/IRB/REB. If a roster is not available, Medtronic will verify if the investigator or other investigational site personnel are members of the EC/IRB/REB. If they are members of the EC/IRB/REB, documentation is required stating that he/she did not participate in the approval process.

Any additional requirements imposed by the EC/IRB/REB or regulatory authority (if applicable) shall be followed. Investigators must inform Medtronic of any change in status of EC/IRB/REB approval once the investigational site has started enrollment. If any action is taken by an EC/IRB/REB with respect to the investigation, that information will be forwarded to Medtronic by the respective investigator.

# 16. Trial Administration

## 16.1 Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this trial. Trained Medtronic personnel or delegates appointed by Medtronic may perform trial monitoring on site or remotely in order to ensure

that the trial is conducted in accordance with the CIP, the CTA, and the applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed direct access to the subjects' case histories (clinic and hospital records whether paper or electronic, and other source data/documentation) upon request as per the ICF, Research Authorization (where applicable) and CTA. The principal investigator should also be available during monitoring visits.

Participating sites will be monitored to ensure compliance with the trial protocol, adherence to applicable regulations, and accuracy of trial data. Monitoring visits will be conducted primarily to ensure the safety and well-being of the subjects is preserved. Sites should provide appropriate access to the source data. Site personnel will complete eCRFs following each subject visit. Trial data submitted will be reviewed against subject charts and other source containing original records of subject data. Source document verification will occur via a risk-based approach as outlined in the Monitoring Plan.

The progress of the trial will be monitored by:

- On-site or remote review, as deemed appropriate by Medtronic or as allowed by local and national regulations
- Telephone communications between the site personnel (e.g. investigator, trial coordinator) and trial monitors
- On-site or remote review of eCRFs and the associated clinical records
- On-site or remote review of regulatory documents

Upon trial completion, Site Closeout Visits will be conducted as outlined in the Monitoring Plan.

Monitoring and monitoring oversight will be provided by Medtronic (8200 Coral Sea St NE, Mounds View, MN 55112). Representatives of Medtronic (i.e. contractors and designees) may also act as trial monitors.

Prior to the first activation a monitoring plan will be established outlining the above activities, as well as trial materials to be supplied to sites, the process for corrective and preventive actions and Investigator disqualification procedures.

## 16.2 Data Management

Data will be collected using an electronic data management system for studies. CRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to trial sites for resolution. Trial management reports may be generated to monitor data quality and trial progress. At the end of the trial, the data will be frozen and will be retained by Medtronic in accordance with applicable regulations.

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 trial. The trial database will be developed and validated per the Data Management Plan for this trial and will employ validation programs (e.g. range and logic checks) on entered data to identify possible data entry errors and to facilitate data validation. The trial database will maintain an audit trail of all changes made to the eCRFs.

All records and other information about subjects participating in this trial will be treated as confidential. Data will be transferred and processed by Medtronic or a third party designated by Medtronic in a key coded form, unless it's impossible to pseudonymize for instance, where the subject's name cannot be removed from the data carrier, such as imaging. Efforts will be made to pseudonymize records and imaging.

Procedures in the CIP require source documentation. Source documentation will be maintained at the trial site. Source documents, which may include worksheets and subject medical records must be created and maintained by the investigational trial site team.

## 16.3 Direct Access to Source Data/Documents

The Principal Investigator must be willing to give access to source data (whether paper or electronic) to Medtronic field personnel, trial monitors, auditors, EC/IRB/REB members and inspectors, and the clinical trial manager and have appropriate facilities to retain relevant trial documents. This accessibility is of particular importance for reviewing data in the eCRF.

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 trial-related monitoring, audits, EC/IRB/REB review, and regulatory inspections.

As soon as the Investigator is notified of a planned inspection by the authorities, he/she will inform Medtronic and authorized Medtronic to participate in this inspection.

## 16.4 Confidentiality

All information and data sent to parties involved in trial conduct concerning subjects or their participation in this trial will be considered confidential. Trial sites staff will assign a unique subject ID number (SID) to each subject. Records of the subject/SID relationship will be maintained by the trial site staff. The SID is to be recorded on all trial 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 trial document other than the Informed Consent Form. In the event a subject's name is included for any reason, it will be masked as applicable. In the event of inability to mask 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 trial. 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.

The Sponsor's representatives, EC/IRB/REB members, European or other international public regulatory authorities may have access to subject confidential information for monitoring, audits, and regulatory inspections.

## 16.5 Liability and Insurance Information

Medtronic maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a Clinical Trial Insurance statement/certificate will be provided to the EC/IRB/REB.

### 16.5.1 Insurance (Canada)

Medtronic of Canada Ltd. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate general liability insurance coverage as required under applicable laws and

regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a General Liability insurance statement/certificate will be provided to the EC.

### 16.5.2 Insurance (Europe, Middle East, Africa)

Medtronic Bakken Research Center B.V. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the EC.

## 16.6 CIP Amendments

Medtronic will submit any significant revisions or amendments to the CIP, including a justification for revisions or amendments, to the appropriate regulatory authorities, EC/IRBs/REBs and to the investigators. The investigator will only implement the revisions or amendments after approval of the EC/IRB/REB, regulatory authority (if applicable) and sponsor. Furthermore, investigators shall sign any approved amendment for agreement.

## 16.7 Record Retention

The investigator must retain the Investigator Site File, subject source documents and eCRFs for a minimum of two years after trial closure or longer if required by local law and regulations. Medtronic will inform the investigator/trial site when these documents are no longer required to be retained.

No trial document or image will be destroyed without prior written agreement between Medtronic and the investigator. The investigator should take measures to prevent accidental or premature destruction of documents. Should the investigator wish to assign the trial records to another party or move them to another location, advance written notice must be given to Medtronic.

Medtronic records and reports will be stored at Medtronic during the course of the trial. After the closure of the trial, all records and reports will be archived according to Medtronic corporate policy and record retention schedule or as required by local laws.

### 16.7.1 Investigator Records

The investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the trial binder provided to the investigator) or Subject Binder. CRFs must be maintained and signed electronically within the electronic data capture system during the trial. The following records are subject to inspection and must be retained for a minimum of two years after trial closure or longer if required by local law and regulations.

- All critical correspondence between the EC/IRB/REB, sponsor, monitor, RA and the investigator that pertains to the investigation, including required reports
- Subject's case history records, including:
    - Signed and dated ICF (In U.S. and Canada, signed by subject at a minimum. In EMEA signed by subject and investigator).

  - Observations of AEs, ADEs and DDs
  - Medical history
  - Implant and follow-up data
  - Documentation of the dates and rationale for any deviation from the protocol
- Randomization documentation
- FD (if requested by Medtronic)
- Subject screening log & ID log
- Normal value(s)/range(s) for clinical laboratory test
- Lab certificates
- All approved versions of the CIP and ICF
- Signed and dated CTA
- CV of site investigators and key members of trial site investigative team
- Documentation of delegated tasks
- EC/IRB/REB approval documentation. Written information that the investigator or other trial staff, when member of the EC/IRB/REB, did not participate in the approval process
- RA notification, correspondence and approval, where required per local law
- Trial training records for trial site staff
- Insurance certificates, if applicable (EMEA)
- Any other records that local regulatory agencies require to be maintained
- Final Trial Report

### 16.7.2 Sponsor Records

Medtronic shall maintain the following accurate, complete, and current records:

- All critical correspondence which pertains to the investigation
- Signed Investigator Trial Agreements, FD (if requested by Medtronic), CV of site investigators and key members of trial site investigative team, delegated task list
- All approved IC templates, and other information provided to the subjects and advertisements, including translations
- Randomization records
- Copies of all EC/IRB/REB approval letters and relevant EC/IRB/REB correspondence and EC/IRB/REB voting list/roster/letter of assurance
- Names of the institutions in which the trial will be conducted
- RA correspondence, notification and approval as required by national legislation
- Insurance certificates, if applicable (EMEA)
- Names/contact addresses of monitors

- Monitoring visit reports
- Statistical analyses and underlying supporting data
- Final report of the trial
- The CIP and trial related reports, and revisions
- Trial training records for trial site personnel and Medtronic personnel involved in the trial
- Any other records that local regulatory agencies require to be maintained

Medtronic records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in stored in secured file cabinets at Medtronic during the course of this trial.

After closure of the trial Medtronic will archive records and reports indefinitely.

## 16.8 Reporting Requirements

### 16.8.1 Investigator Reports

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects (reported per the country-specific collection requirements), device deficiencies, deaths, and any deviations from the CIP. If any action is taken by an EC/IRB/REB with respect to this trial, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Safety data investigator reporting requirements are listed in Section 12.5. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in **Table 10**.

**Table 10: Investigator reports applicable for all geographies per Medtronic requirements**

| Report | Submit to | Description/Constraints |
|---|---|---|
| Withdrawal of EC/IRB/REB approval | Sponsor and Relevant Authorities | Report if required by local law. |
| Progress Report | Sponsor and EC/IRB/REB | Provide if required by local law or EC/IRB/REB. |
| Trial Deviations | Sponsor and EC/IRB/REB | Provide if required by local law or EC/IRB/REB.<br>Any deviation from the CIP shall be recorded together with an explanation for the deviation. Deviations shall be reported to the sponsor who is responsible for analyzing them and assessing their significance. |
| Failure to obtain IC | Sponsor and EC/IRB/REB | IC shall be obtained in writing and documented before a subject is enrolled into the clinical investigation. |
| Final Report | EC/IRB/REB and relevant authorities | Provide if required by local law or EC/IRB/REB. |

### 16.8.2 Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in **Table 11**. In addition to the reports listed below, Medtronic shall, upon request of the reviewing EC/IRB/REB and RA, provide accurate, complete and current information about any aspect of the investigation. Safety data Medtronic reporting requirements are listed in Section 12.5.

**Table 11: Sponsor reports**

| Report | Submit to | Description/Constraints |
|---|---|---|
| Premature termination or suspension of clinical trial | EC/IRB/REB, Investigators, and regulatory authorities, where applicable | Medtronic will provide prompt notification of termination or suspension and reason(s) to investigator and where required to EC/IRB/REB and RAs. |
| Withdrawal of EC/IRB/REB approval | Investigators, Head of Institution, EC/IRB/REB and relevant authorities | Investigators, EC/IRBs/REB will be notified only if required by local laws or by the EC/IRB/REB. |
| Withdrawal of CA approval | Investigators, Head of Institution, EC/IRB/REB, and relevant authorities | Investigators, EC/IRBs/REB will be notified only if required by local laws or by the EC/IRB/REB. |

| Report | Submit to | Description/Constraints |
|---|---|---|
| Progress Reports | EC/IRB/REB and Ras | This will be submitted to the EC/IRB/REB only if required by the EC/IRB/REB. |
| Trial deviation | Investigators | Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the CRFs and the final report of the clinical investigation. Trial site specific trial deviations will be submitted to investigators periodically. |
| Final report | Investigators, EC/IRB/REB and relevant authorities if required | Investigators, EC/IRBs/REB will be notified only if required by local laws or by the EC/IRB/REB. |

## 16.9 Publication and Use of Information

Medtronic is committed to the widespread dissemination of all primary and secondary endpoint results. A separate Publication Plan will provide detailed information about the publication committee, authorship, publication proposals, and requests for data. At the conclusion of the trial, a multisite abstract reporting the primary results will be prepared by the Principal Investigators (in collaboration with others including but not limited to the echo core lab physicians and the CEC). A multisite publication will similarly be prepared for publication in a reputable scientific journal. The publication of the principal results from any single site experience within the trial is not allowed until after both the preparation and publication of the multisite results, and then only with written permission from Medtronic and the Trial Publication Committee.

Following analysis and presentation of the endpoint results, active participation of all participating investigators, CEC 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 trial requires approval by the principal investigators after review by the publications committee. Refer to Section 6.4.4 for details related to the Publication Committee.

## 16.10 Suspension or Early Termination

### 16.10.1 Planned Trial Closure

Trial closure is a process initiated by distribution of a trial closure letter. Trial closure is defined as closure of a trial that occurs when Medtronic and/or regulatory requirements have been satisfied per the CIP and/or by a decision by Medtronic or RA, whichever occurs first. The trial closure process is complete upon distribution of the Final Report or after final payments, whichever occurs last. Ongoing EC/IRB/REB oversight is required until the overall trial closure process is complete. Medtronic will provide additional information regarding trial exit procedures.

### 16.10.2 Early Trial Suspension or Termination

If the clinical trial 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/REB and the trial subjects. Medtronic will, as soon as possible, provide a written statement to the investigators to enable prompt notification of the EC/IRB/REB. If trial enrollment is terminated early, follow-up visits will continue for all implanted subjects.

Possible reasons for early trial termination include:

- Unanticipated Serious Adverse Device Effect (USADE) presents an unreasonable risk to patients
- Recommendation from DSMB (e.g. significant safety concerns, statistical futility)

### 16.10.3 Early Investigational Site Suspension or Termination

Medtronic may decide to suspend or prematurely terminate an investigation site (e.g. in case of expiring approval of the reviewing EC/IRB/REB, non-compliance to the CIP, or lack of enrollment). 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/REB and the trial subjects.

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# 18. Appendices

## 18.1 Appendix I: Six Minute Walk Test (6MWT) Procedures

The 6MWT test is administered per the site's standard procedure, although the following recommendations are intended to standard the test across sites and minimize sources of variability[41, 42].

**Technical Aspects.** The 6MWT should be performed indoors, along a long, flat, straight, enclosed corridor with a hard surface that is seldom traveled. The walking course should be 30 meters in length, and the course marked every 3 meters. Turnaround points should be marked (e.g. with an orange traffic cone). A starting line, which marks the beginning and end of each 60-meter lap, should be marked on the floor using brightly colored tape. A stopwatch and means to record the number of laps should be in place (e.g. lap counter or worksheet).

**Patient Preparation.** Subjects should wear comfortable clothing and appropriate walking shoes; and should not have exercised vigorously within 2 hours of beginning the test. A light meal is acceptable before early morning or early afternoon tests. Patients should use their usual walking aids during the test (cane, walker, etc.

**Test Procedures**

1. Repeat testing should be performed about the same time of day to minimize intraday variability.
2. A "warm-up" period before the test should not be performed.
3. The subject should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts.
4. Set the timer to 6 minutes and lap counter to zero (if used).
5. Instruct the patient as follows:

   *"The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting but resume walking as soon as you are able. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.*
6. Position the patient at the starting line. As soon as the subject starts to walk, start the timer. Do not walk with the subject.

   Use an even tone of voice when using standard phrases of encouragement. For example, after each minute tell the subject *"You are doing well and have X minutes to go".* Do not use other words of encouragement (or body language to speed up).

   If the subject stops walking during the test and needs to rest, do not stop the timer. The subject should be told to rest, "*but continue walking whenever you feel able.*" If the patient stops before the 6

minutes are up and refuses to continue (or you decide that they should not continue), bring a chair over for the patient to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

When the timer is 15 seconds from completion, tell the subject *"In a moment I'm going to tell you to stop. When I do, just stop right where you are, and I will come to you."* When the timer rings, mark the spot where they stopped walking.

7. Record the number of laps from the counter (or tick marks on the worksheet).
8. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record on the worksheet.

## 18.2 Appendix II: Conduction Disturbance Management

The following section is intended to provide consistency in the management of subject's conduction disturbance(s) peri and post the TAVR index procedure and developed based on the American College of Cardiology Foundation conduction disturbance management guidelines.[43] All subjects are required to have 12-lead ECG within 2 hours following the TAVR procedure and at discharge.

Temporary pacing should be performed in the event of AV block that persists after the procedure. Continue telemetry and daily ECG for at least 1 day for subjects with HAVB/CHB based on the 2 hours post-op ECG. Only implant pacemaker for subjects with persistent or recurrent HAVB/CHB.

Procedural pacing wire can be removed at the end of procedure with continuous telemetry for post procedural monitoring based on the following guidance in the absence of high degree AV block.

- Continue telemetry and daily ECG for at least 1 day for subjects with pre-existing Right Bundle Branch Block (RBBB), Left Bundle Branch Block (LBBB), Intraventricular Conduction Delay (IVCD) with QRS ≥ 120 ms or 1st degree atrioventricular block pre-procedure.
- For subjects with QRS>150ms or PR>240ms before discharge, consider options of 1) EPS to guide the decision about permanent pacemaker implantation (PPI); 2) continuous ECG monitoring; 3) PPI before discharge.
- Continue telemetry and daily ECG for at least 1 day for subjects with new onset LBBB based on the 2 hours post-op ECG.
- Discharge with continuous ECG monitoring for subjects with unresolved LBBB but QRS<=150ms and PR<=240ms. For subjects with unresolved LBBB with QRS>150ms or PR>240ms, consider options of 1) EPS to guide the decision about PPI; 2) continuous ECG monitoring; 3) PPI before discharge.

**Conduction Disturbances Definitions:**

| **Conduction Disturbances (infra nodal block)** | |
|---|---|
| **Right Bundle Branch Block (RBBB)** | 1) QRS duration ≥120 ms<br>2) rsr', rsR', rSR', or rarely a qR in leads V1 or V2. The R' or r' deflection is usually wider than the initial R wave<br>3) In a minority of subjects, a wide and often notched R wave pattern may be seen in lead V1 and/or V2<br>4) S wave of greater duration than R wave or >40 ms in leads I and V6<br>5) Normal R peak time in leads V5 and V6 but peak R wave >50 ms in lead V1 |
| **Left Bundle Branch Block (LBBB)** | 1) QRS duration ≥120 ms<br>2) Broad notched or slurred R wave in leads I, aVL, V5, and V6 and an occasional RS pattern in V5 and V6 attributed to displaced transition of QRS complex<br>3) Absent Q waves in leads I, V5, and V6, but in the lead aVL, a narrow Q wave may be present in the absence of myocardial pathology |

| Conduction Disturbances (infra nodal block) | |
|---|---|
| | 4) R peak time >60 ms in leads V5 and V6 but normal in leads V1, V2, and V3, when small initial R waves can be discerned in the precordial leads 5) ST and T waves usually opposite in direction to predominant QRS voltage |
| **Non-specific intraventricular conduction delay (IVCD) with QRS interval ≥120 ms** | QRS interval duration ≥120ms where morphology criteria for RBBB or LBBB are not present |

| Atrioventricular Block | |
|---|---|
| **First-degree atrioventricular block** | P waves associated with 1:1 atrioventricular conduction and a PR interval >200 ms |
| **Mobitz I** | Mobitz I heart block is characterized by progressive prolongation of the PR interval on consecutive beats followed by a blocked P wave (i.e., a 'dropped' QRS complex) |
| **High-degree atrioventricular block (HAVB)** | HAVB is defined as any of the following:<br>Second degree AV block type 2 (Mobitz II) in the presence of a QRS ≥120 ms<br>2:1 AV block in the presence of a QRS ≥120 ms<br>≥2 consecutive P waves at a constant physiologic rate that do not conduct to the ventricles<br>Transient third-degree AV block<br>In the setting of AF, a prolonged pause (> 3 seconds) or a fixed slow (<50 bpm) ventricular response rate |
| **Third-degree atrioventricular block (Complete heart block [CHB])** | P waves with a constant rate with dissociated ventricular rhythm (no association between P waves and R waves) or fixed slow ventricular rhythm in the presence of atrial fibrillation |

# 18.3 Appendix III: Echocardiography Procedure

## 18.3.1 General Procedures

- Protocol-driven exams should be performed by designated individuals delegated by the site PI
- 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 for assessment of prosthetic regurgitation 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., Left Ventricular Outflow Tract (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 and tissue 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.
- Exams will be transmitted to the Echo Core Lab via Web-based picture archiving and communication system. Details of the image transmission process for each site will be established during site initiation process.
- In the event, exams are sent to the Echo Core Lab via CD-R, the images should be DICOM files in a true or pure DICOM format. The following information should be documented on any CD-R disks sent to the Echo Core Lab:
  - Trial site ID number
  - Subject ID number
  - Exam date
  - Trial interval

## 18.3.2 Data Requirements

Sites should obtain the appropriate images and Doppler recordings in order for the Echo Core Lab to assess and report the variables listed below. Procedures for acquiring key variables are described in Section 18.3.3, Acquisition of Key Variables.

- Height (cm) and Weight (kg)
- Heart rate
- Left ventricular outflow tract diameter in mid systole
- Max aortic/prosthetic valve velocity ($V_2$) by CW Doppler
- Aortic or prosthetic valve velocity time integral (VTI) by CW Doppler
- Mean gradient across aortic or prosthetic valve by CW Doppler

- LVOT VTI by PW Doppler
- Grade of native aortic regurgitation (pre-TAVR baseline only)
- Grade of aortic/prosthetic transvalvular regurgitation (post-implant only)
- Grade of aortic/prosthetic paravalvular regurgitation (post-implant only)
- Grade of total prosthetic regurgitation (post-implant only)
- Grade of mitral regurgitation
- Grade of tricuspid regurgitation
- Max tricuspid regurgitant 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 on the site eCRF.

- Body surface area[44]
- Doppler Velocity Index

## 18.3.3 Acquisition of Key Variables

### 18.3.3.1 LVOT Diameter

The LVOT diameter is measured in the parasternal long-axis view, with the optimal imaging plane through the long axis of the aorta (anterior and posterior walls of the aortic root parallel with the maximal aortic diameter).[45]

LVOT diameter is measured in mid-systole at the level of the aortic annulus at the base of the aortic valve cusps, with a line drown from where the anterior aortic cusp meets the ventricular septum to where the posterior aortic cusp meets the anterior mitral leaflet perpendicular to the anterior aortic wall (**Figure 5**, A and B).[(46-51)] Post-implant, LVOT diameter is measured in the parasternal long-axis view in mid-systole, from the outer edge to outer edge of the inflow aspect of the stent (**Figure 5**, C and D). [(52,53)]

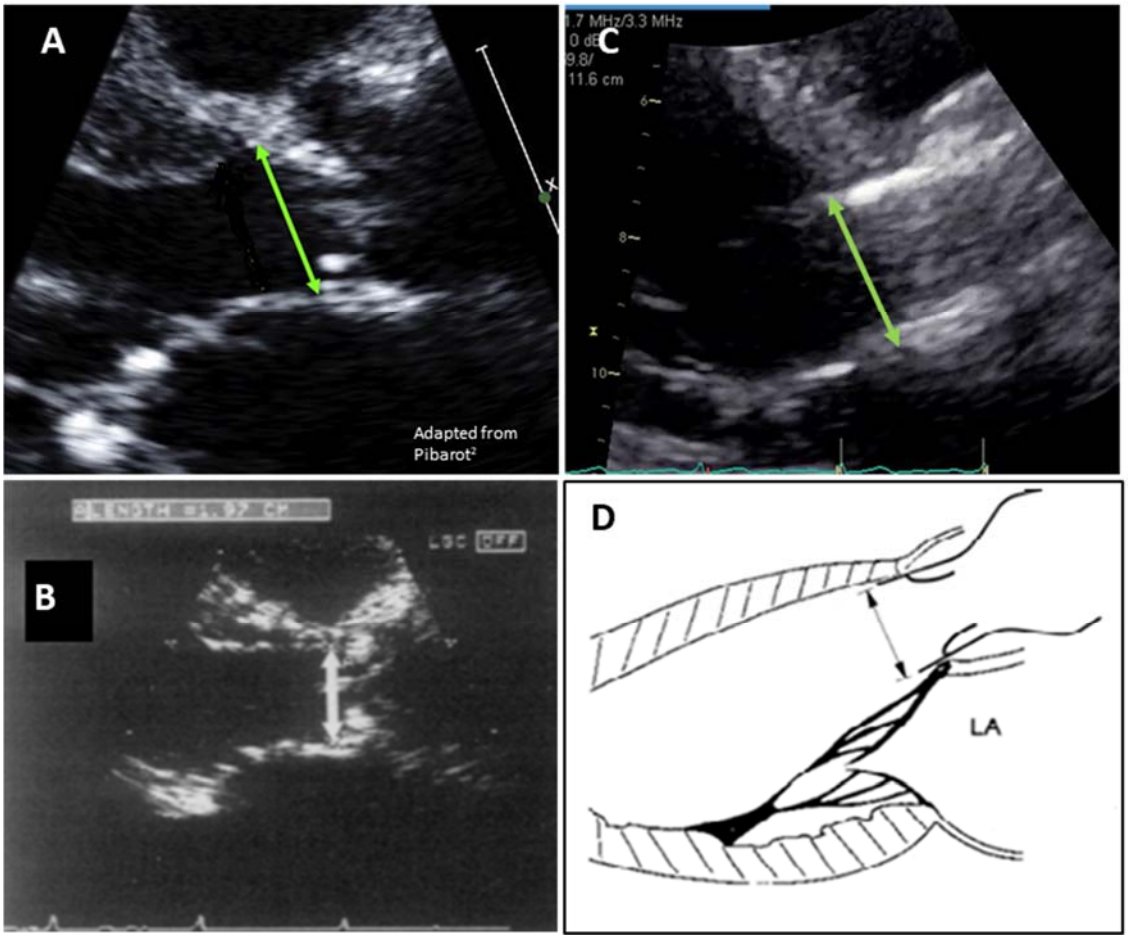



**Figure 5. (A)** and **(B)** Examples of measurement of pre-implant LVOT diameter. LVOT diameter is measured at the level of the aortic annulus, with a line drawn from where the anterior aortic cusp meets the ventricular septum to where the posterior aortic cusp meets the anterior mitral leaflet perpendicular to the anterior aortic wall; **(C)** and **(D)** Post TAV implantation, LVOT diameter measurement is from outer edge to outer edge of the inflow aspect of the stent.

### 18.3.3.2 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"). For pre-implant exams, 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 6**).[54,55] 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. Post TAV implantation, the sample volume should be placed proximal to the inflow aspect of the stent.[56] Full-screen imaging of the TAV should be used to verify positioning of the sample volume below the stent before switching to spectral Doppler mode (**Figure 6** C and D).[56,57] The LVOT VTI is measured by tracing the modal velocity (middle of the dense signal) for use in the continuity equation. [55]

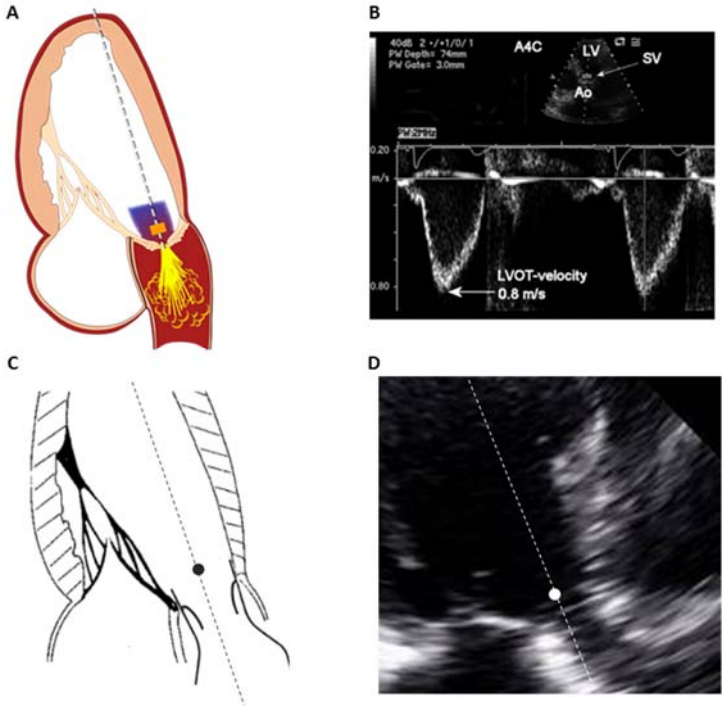



**Figure 6. (A)** Sample volume placement just proximal to zone of pre-valve acceleration (illustration by Mayo Clinic, used with permission) **(B)** Optimal LVOT velocity signal showing a smooth spectral Doppler recording with a narrow velocity range at each time point **(C)** Illustration showing correct sample volume placement just proximal to inflow of TAV stent **(D)** Full-screen imaging of stent to ensure positioning of sample volume below the TAV stent.

### 18.3.3.3 Aortic Valve Velocities

To avoid underestimation of the aortic valve gradient (native or prosthetic), the aortic valve velocity should be interrogated with CW Doppler from the apical, suprasternal notch, right supraclavicular, and right parasternal windows.[58] 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 (**Figure 7**).[55]

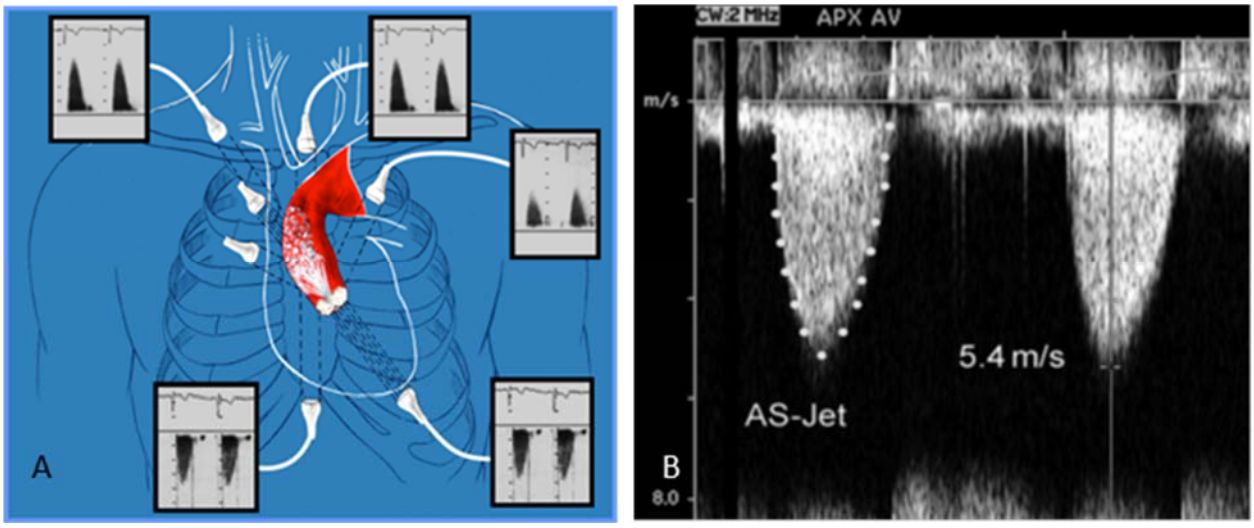



**Figure 7. (A)** Aortic valve velocities interrogated from multiple transducer positions *(illustration by Mayo Clinic, used with permission)* **(B)** CW Doppler of severe aortic stenosis showing tracing of the velocity curve from mean gradient and VTI, and measurement of max velocity.

### 18.3.3.4 Left-Ventricle and Left Atrium: Volumes, Ejection Fraction, and Dimensions

**Left Ventricle**. Standard 2-D views of the left ventricle should be obtained from parasternal and apical transducer positions for quantitative assessment of left ventricular volumes and ejection fraction, and visual assessment of regional wall motion.

Specifically, for LV volumes and ejection fraction, two orthogonal views (apical four-chamber and apical two-chamber) should be recording at equal depth settings for quantification using the modified Simpson's rule (biplane method of disks, (**Figure 8**, A). Image acquisition should aim to maximize LV areas, while avoiding foreshortening of the LV. Acquiring LV views at reduced depth to focus on the LV cavity can reduce likelihood of foreshortening and minimize errors in endocardial border tracings.59 Use of contrast agents to improve endocardial delineation when segments are poorly visualized is per discretion of the trial echocardiographer and institutional procedures. LV volumes should be traced at the actual endocardial border (between the compacted and non-compacted myocardium rather than at the blood-tissue interface). Trabeculations and papillary muscles should be included as part of the LV cavity, not part of the LV wall.[51] At the mitral valve level, the contour is closed by connecting the two opposite sections of the

mitral ring with a straight line. LV length is defined as the distance between the middle of this line and the most distant point of the LV contour.[57] M-mode recordings of the LV should also be obtained. Dimensions of the left ventricle should be obtained by either 2-D linear measurements or 2-D guided m-mode in the parasternal long-axis view, perpendicular to the LV long axis, and measured at the level of the mitral valve leaflet tips **(Figure 8**, B and C).

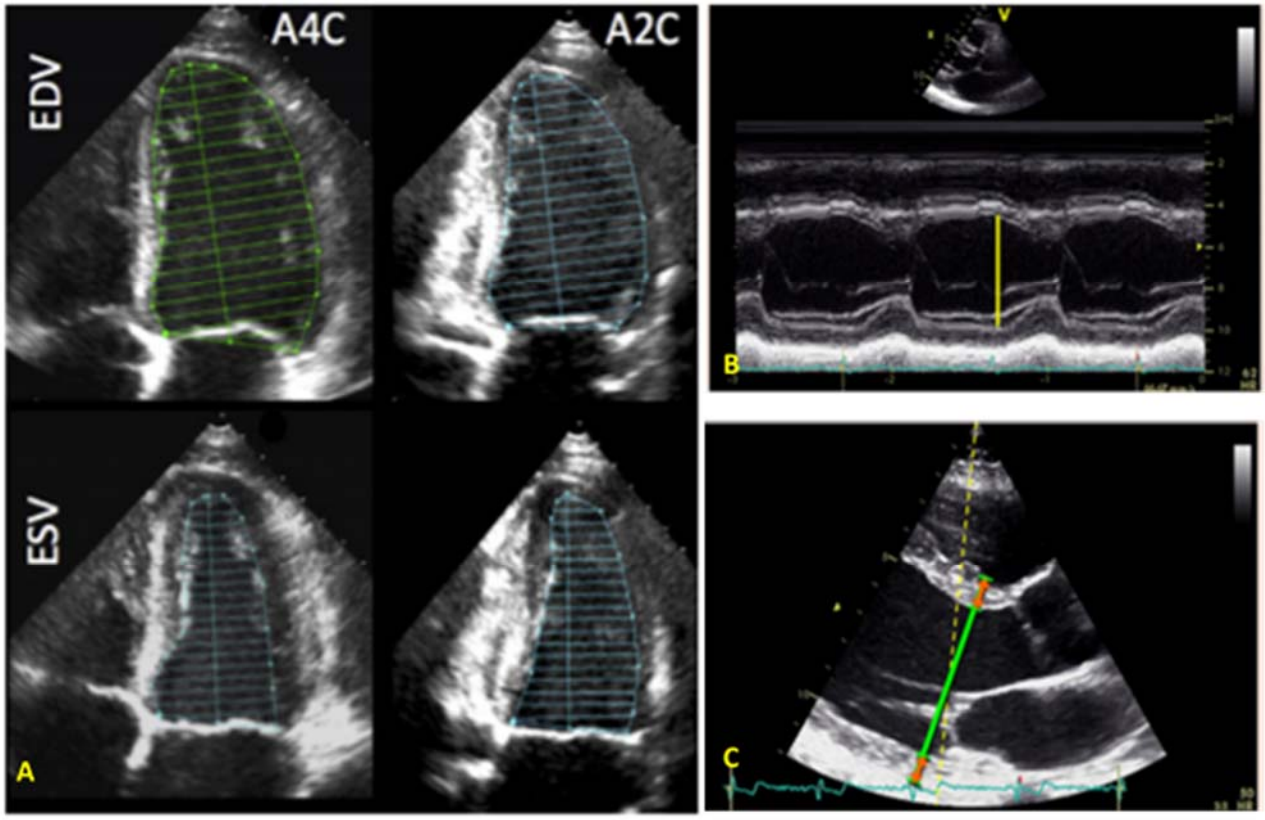



**Figure 8. (A)** Still frames of two orthogonal planes at end systole and diastole to calculate LV volumes and ejection fraction by modified Simpson; **(B)** measurement of LV end-diastolic diameter by 2-D guided m-mode; **(C)** Measurement of LV linear dimensions by 2-D, electronic calipers should be positioned on the interface between myocardial wall and cavity and the interface between wall and pericardium (orange arrow). [Journal of the American Society of Echocardiography 2015 281-39.e14DOI: (10.1016/j.echo.2014.10.003) Copyright © 2015 American Society of Echocardiography]

**Left Atrium.** Two-dimensional images should be obtained from the apical four-chamber and apical two-chamber views to enable quantification of left atrial volume by the bi-plane Simpson's method. The views should be adjusted to optimize left atrial size. Image optimization should include avoiding foreshortening and optimizing focus depth and gain.

Left atrial measurements are taken at ventricular end systole, with the left atrium at its maximal size just prior to mitral valve opening. The chamber area is traced at the blood tissue interface, starting at the

lateral mitral annulus and finishing at the medial annulus. The length of the left atrium is measured parallel to the long axis of the left atrium (**Figure 9** A). The left atrial appendage, pulmonary vein orifices, and any atrial septal aneurysm should be excluded from the area measurement. 59

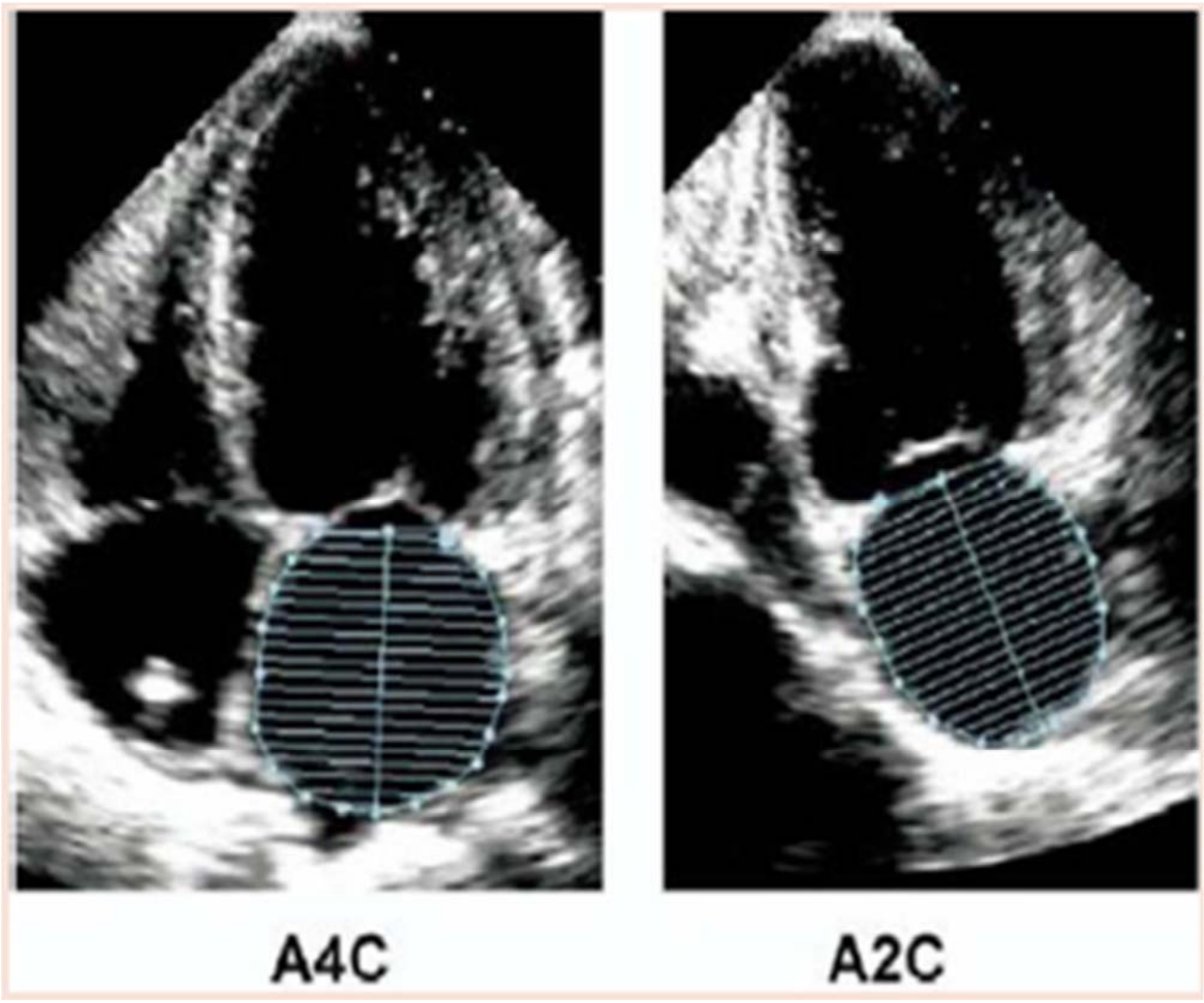



**Figure 9.** Still frame of apical 4 and 2 chamber views demonstrating bi-plane Simpson's method for quantification of LA volume. [Journal of the American Society of Echocardiography 2015 281-39.e14DOI: (10.1016/j.echo.2014.10.003) Copyright © 2015 American Society of Echocardiography]

### 18.3.3.5 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 2 mm sample volume placed between the mitral leaflet tips (**Figure 10**, A). The following variables should be measured:

- Mitral inflow "A" velocity

- Mitral inflow "E" velocity
- Mitral inflow E-wave deceleration time (MdT)

Mitral annular velocities should be recorded from the lateral and medial (septal) aspects of the mitral annulus using tissue Doppler imaging (TDI) in the apical 4-chamber view (**Figure 10**, C). 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 early diastolic velocity (e'); medial and lateral
- Mitral annular tissue Doppler late diastolic velocity (a'); septal and lateral

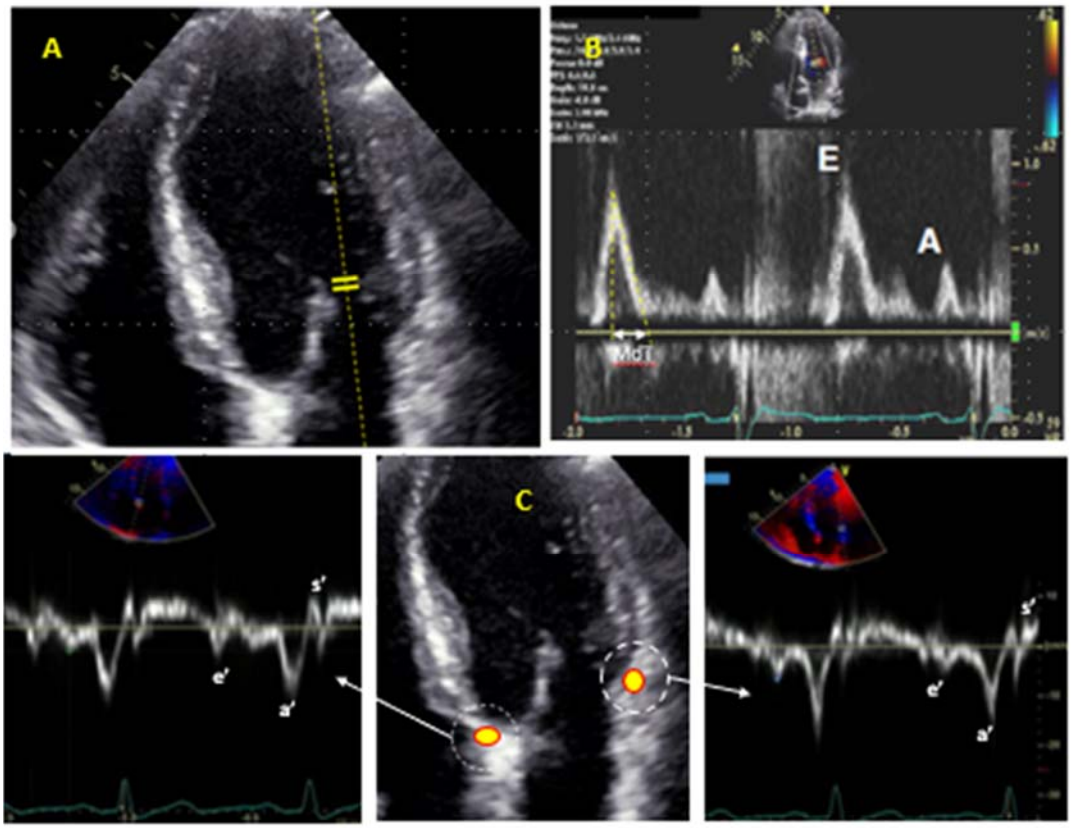



**Figure 10. (A)** Apical 4 chamber with sample volume placement between mitral leaflet tips during diastole; **(B)** Doppler gains and wall filters optimized to clearly show onset and cessation of mitral inflow; **(C)** A 2 to 5 mm sample volume should be positioned at or 1 cm within the septal and lateral insertion sites of the mitral leaflets and adjusted as necessary to cover the longitudinal excursion of the mitral annulus in both systole and diastole.

### 18.3.3.6 Prosthetic Aortic Regurgitation

An integrated exam approach using color flow, PW, and CW Doppler is used to assess the severity of transvalvular and paravalvular AR. Color flow Doppler imaging should be performed from the parasternal long and short-axis views, and the apical 5-chamber and apical 3-chamber views (**Figure 11**). The entire valve should be scanned, from the aortic to the ventricular end of the TAV to identify the number, location,

and direction of regurgitant jets, which can be multiple and eccentric. In the short axis view, color imaging should be performed at multiple levels (sweeping from level of the leaflets to below the skirt and frame to assess paravalvular regurgitation), and at the coaptation point of the leaflets for transvalvular (central) regurgitation (**Figure 12**).[60]

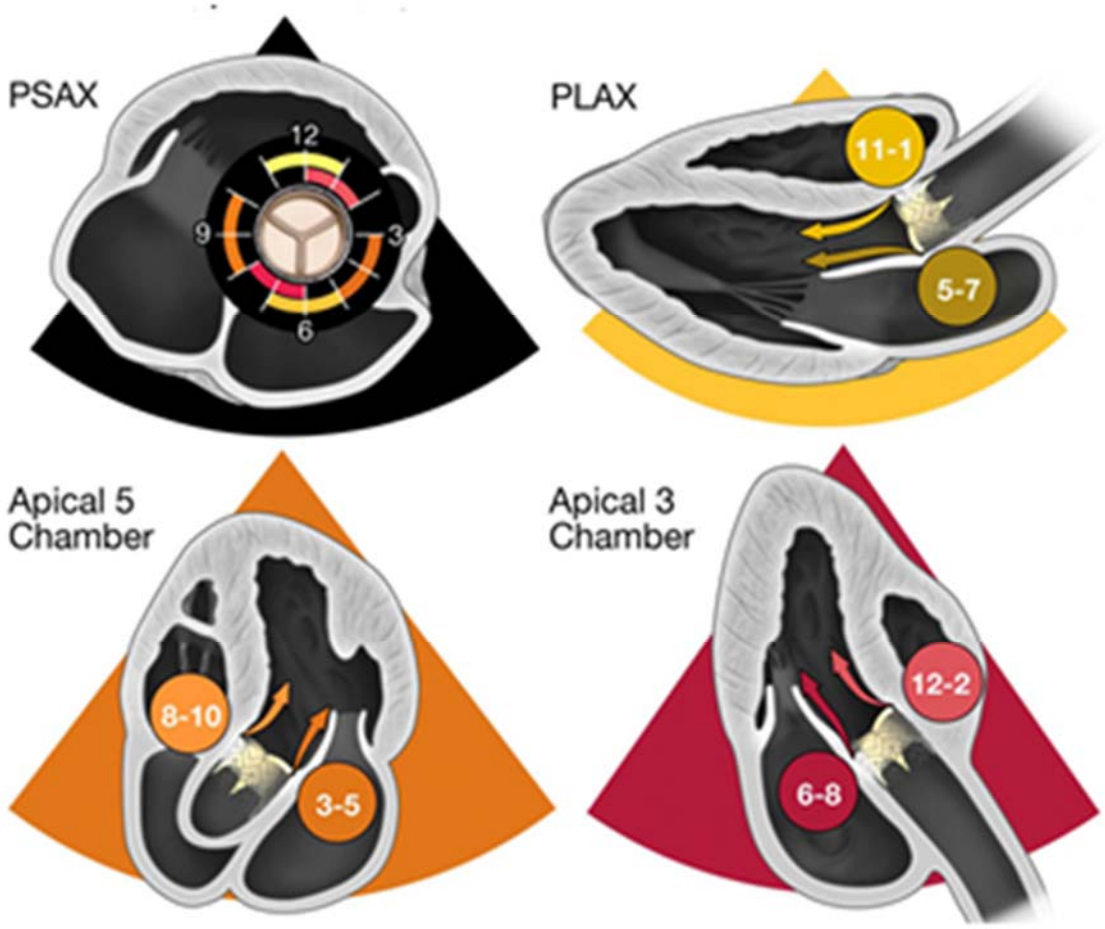



**Figure 11.** Standard views showing detection of paravalvular regurgitation. Color coding delineates the regions around the valve that can be visualized from the parasternal and apical views. With ultrasound plane rotation, tilting upwards or sideways, a more complete interrogation of the valve can be accomplished. Apical views are important in that some jets may not be detected in the parasternal views because of shadowing from the prosthesis. [Journal of the American Society of Echocardiography 2019 32431-475DOI: (10.1016/j.echo.2019.01.003, Copyright © 2019 American Society of Echocardiography]

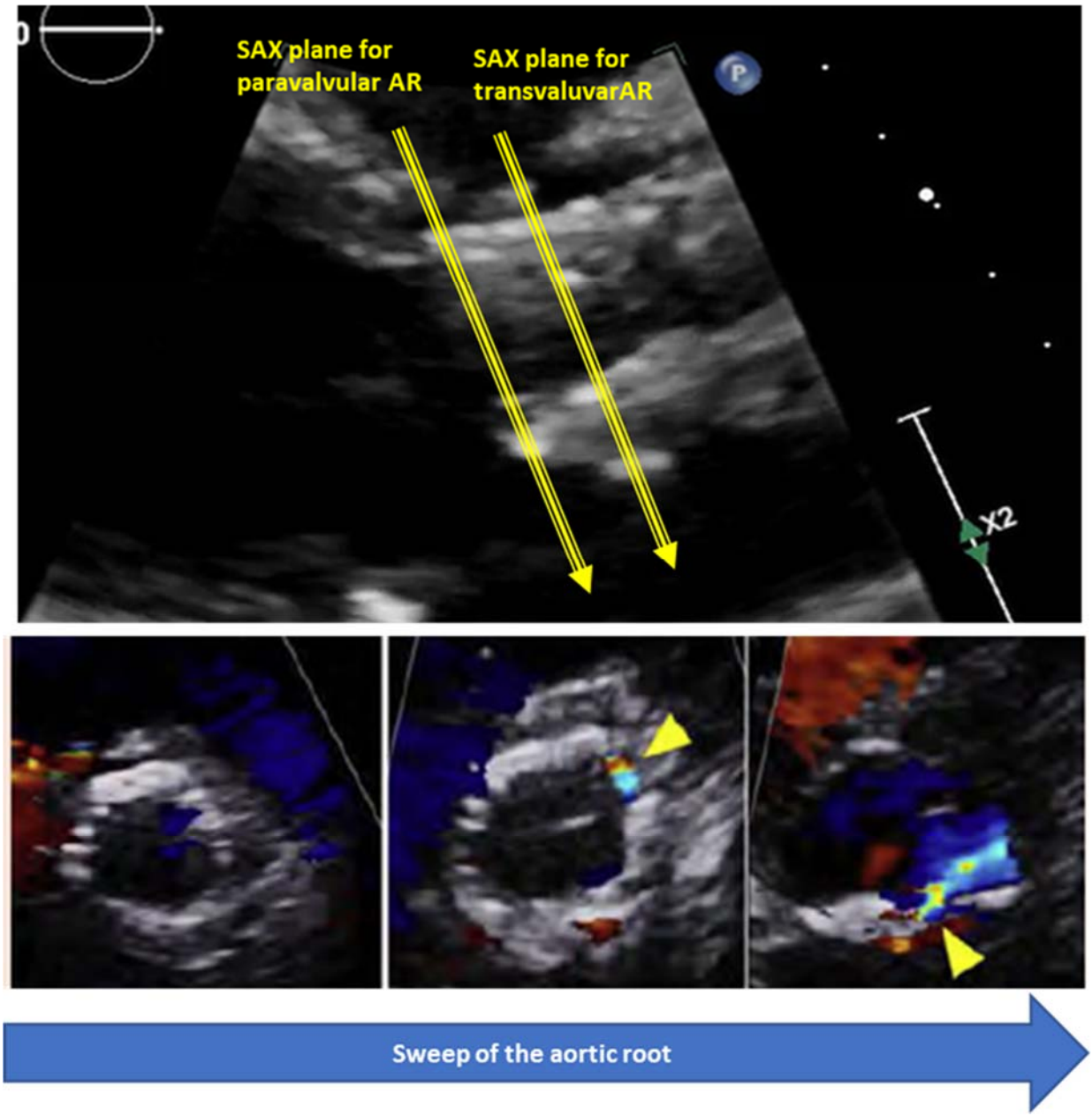



**Figure 12.** Imaging planes for detection for paravalvular and transvalvular regurgitation. Thorough imaging of the entire valve is needed to identify the origin and vena contracta of regurgitant jets, which may be multiple and not be all at the same level. A sweep of the aortic root from the parasternal SAX view is recommended. [Journal of the American Society of Echocardiography2019 32431-475DOI: (10.1016/j.echo.2019.01.003, Copyright © 2019 American Society of Echocardiography]

If prosthetic AR is seen by color Doppler, a CW spectral Doppler recording of the regurgitant signal should be obtained for measurement of pressure half-time and assessment of jet density (**Figure 13**, A). In addition, a PW spectral Doppler recording from the proximal descending or abdominal aorta should be recorded to assess the degree of flow reversal (**Figure 13**, B).

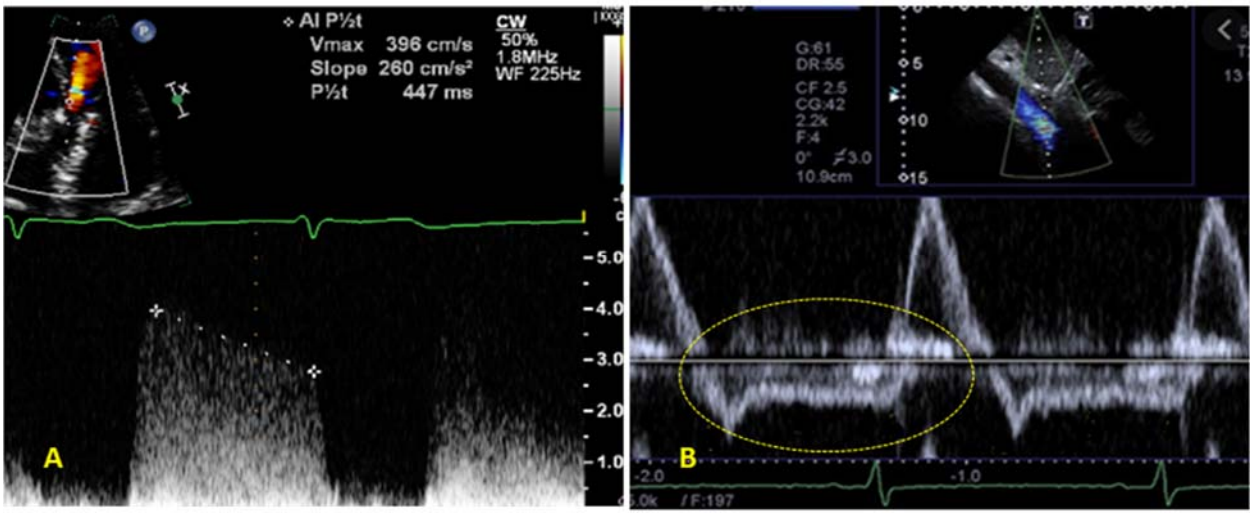



**Figure 13. (A)** CW Doppler spectral recording of AR regurgitant signal and measurement of pressure half-time; **(B)** PW Doppler spectral recording from abdominal aorta showing flow reversal.

**Grading of Prosthetic Regurgitation.** The degree of transvalvular, paravalvular, and total (transvalvular plus paravalvular) AR should be graded as none, mild, moderate, or severe based on overall comprehensive evaluation the echocardiographic findings in **Table 12**, **Figure 14**.60 The category of "trace" can be used if regurgitation is barely detectable laminar flow. The following caveats are noted in the ASE 2019 Guidelines for the evaluation of valvular regurgitation after percutaneous valve replacement.

1. Central AR jets will occur at the level of leaflet coaptation whereas PVR will be seen at the proximal (ventricular) edge of the valve. The jet must enter the LV to be considered true regurgitation, thus imaging just below the edge of the stent will confirm the presence of true PVR; however, the vena contracta of the jet should be measured at its narrowest region.
2. Color flow around the TAV within the sinuses of Valsalva but above the annular valve skirt should not be mistaken for PVR. Flow in the sinuses has low velocity and does not connect with the LVOT in diastole. Scanning through the long axis of the valve is useful in distinguishing color flow in the sinuses from PVR.
3. Small jets of regurgitation are typically isolated to open stent cells and not at the "nodes" of the stent frame. It is important not to include the stented frame in the measurement of circumferential extent of the regurgitation but to integrate only the regurgitant jets when determining the circumferential extent.

**Table 12. Evaluation of severity of prosthetic aortic regurgitation post TAVR**

| | Mild | Moderate | Severe |
|---|---|---|---|
| **Structural Parameters** | | | |
| Position of prosthesis | Usually normal | Variable | Frequently abnormal |
| Stent and leaflet morphology | Usually normal | Variable | Frequently abnormal |
| **Doppler Parameters** | | | |
| Proximal flow convergence (CD) | Absent | May be present | Often present |
| AR velocity waveform density (CWD) | Soft | Dense | Dense |
| Diastolic flow reversal in proximal aorta | Brief, early diastolic | May be holodiastolic | Holodiastolic (end-diastolic velocity ≥ 20 cm/sec) |
| Diastolic flow reversal in abdominal aorta | Absent | Absent | Present |
| Vena contracta width (cm) (CD) | < 0.3 | 0.3 – 0.6 | > 0.6 |
| Vena contracta area ($cm^2$) * (2D, CD) | < 0.10 | 0.10 – 0.29 | ≥ 0.30 |
| Circumferential extent of PVR (%)[ŁŁ] | <10 | 10-29 | ≥ 30 |
| Jet deceleration rate (PHT, ms)[#] (CWD) | Variable<br>Usually > 500 | Variable | Steep |
| Regurgitant volume (mL) | <30 | 30-59 | >60 |
| Regurgitant fraction (%) | <30 | 30-49 | ≥50 |
| EROA ($cm^2$)[##] | <0.10 | 0.10 – 0.29 | ≥0.30 |

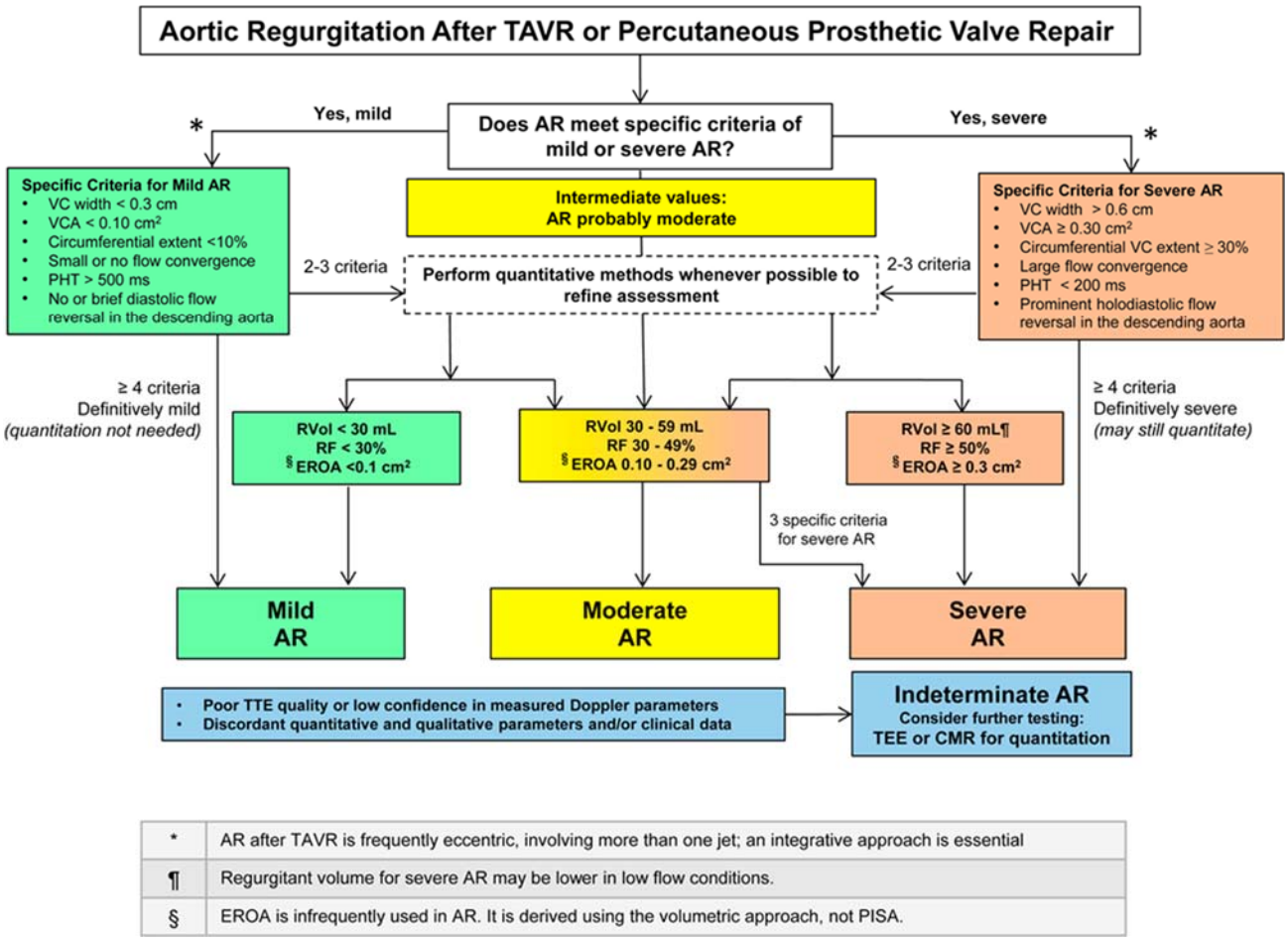
CD, Color Doppler; CWD, continuous wave Doppler; PVR, paravalvular regurgitation; PHT, pressure half-time

*Vena contracta area is measured by planimetry of the vena contracta of the jet(s) on the 2-D color Doppler images in the short-axis view

[Ł]Circumferential extent of PVR best not to be used alone, but in combination with vena contracta width or area

[#]Influenced by LV and aortic compliance

[##]ERO is infrequently used in A




| | |
|---|---|
| * | AR after TAVR is frequently eccentric, involving more than one jet; an integrative approach is essential |
| ¶ | Regurgitant volume for severe AR may be lower in low flow conditions. |
| § | EROA is infrequently used in AR. It is derived using the volumetric approach, not PISA. |

**Figure 14.** Suggested algorithm to guide integration of multiple parameters of AR severity after TAVR. Good-quality echocardiography imaging and complete data acquistion are assumed. [Journal of the American Society of Echocardiography2019 32431-475DOI: (10.1016/j.echo.2019.01.003, Copyright © 2019 American Society of Echocardiography]

### 18.3.3.7 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. A spectral Doppler recording of mitral inflow should be recorded to assess the early filling velocity (E) and the A wave inflow pattern. If image quality is technically adequate, quantitative assessment of the mitral regurgitant orifice area using PISA, or derivation of regurgitant volume and regurgitant fraction (stroke volume method) can be performed. Grading of the severity of mitral regurgitation should be integrative using the parameters in **Table 13**.[61]

**Table 13**: **Parameters for grading the severity of mitral regurgitation**

| Parameter | Mild | Moderate | Severe |
|---|---|---|---|
| **Structural** | | | |
| MV Morphology | None or mild leaflet abnormality (e.g., mild thickening, calcifications or prolapse, mild tenting | Moderate leaflet abnormality or moderate tenting | Severe valve lesions (primary: flail leaflet, ruptured papillary muscle, severe retraction, large perforation; secondary: severe tenting, poor leaflet coaptation |
| LA and LV Size† | Usually normal | Normal or mildly dilated | Dilated‡ |
| **Qualitative Doppler** | | | |
| Color flow jet area§ | Small, central, narrow, often | Variable | Large central jet (>50% of LA) or eccentric wall-impinging jet of variable size |
| Flow convergence‖ | Not visible, transient or small | Intermediate in size and duration | Large throughout systole |
| CWD jet | Faint/partial/parabolic | Dense but partial or parabolic | Holosystolic/dense/triangular |
| **Semi-quantitative** | | | |
| Vena contracta width (cm) | <0.3 | Intermediate | ≥0.7 (>0.8 for biplane) |
| Pulmonary vein flow | Systolic dominance (may be blunted in LV dysfunction or AF) | Normal or systolic blunting | Minimal to no systolic flow systolic flow reversal |
| Mitral inflow | A-wave dominant | Variable | E-wave dominant (>1.2 m/sec) |
| **Quantitative** | | | |
| EROA, 2D PISA ($cm^2$) | <0.20 | 0.20-0.39 | ≥0.40 (may be lower in secondary MR with elliptical ROA) |
| RVol (mL) | < 30 | 30-44 | ≥ 60 |
| RF (%) | < 30 | 30-49 | ≥ 50 |

EROA, Effective regurgitant orifice area; RVol, Regurgitant volume; RF, Regurgitant fraction; PISA, Proximal isovelocity surface area
Bolded qualitative and semiquantitative signs are considered specific for their MR grade.
†This pertains mostly to patients with primary MR.
‡LV and LA can be within the ''normal'' range for patients with acute severe MR or with chronic severe MR who have small body size, particularly women, or with small LV size preceding the occurrence of MR.

§With Nyquist limit 50-70 cm/sec.
K Small flow convergence is usually <0.3 cm, and large is ⩾ 1 cm at a Nyquist limit of 30-40 cm/sec.

### 18.3.3.8 Tricuspid Regurgitation and Estimated RVSP

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 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 and tricuspid inflow pattern, respectively. If image quality is technically adequate, quantitative assessment of the regurgitant orifice area using PISA, or derivation of regurgitant volume (stroke volume method) can be performed. Grading of the severity of tricuspid regurgitation should be integrative using the parameters in **Table 14**.[61]

**Table 14**: **Parameters for evaluation of the severity of tricuspid regurgitation**

| Parameter | Mild | Moderate | Severe |
|---|---|---|---|
| **Structural** | | | |
| TV Morphology | **Normal** or mildly abnormal leaflets | Moderately abnormal leaflets | **Severe valve lesions** (e.g., flail leaflet, severe retraction, large perforation |
| RV and RA Size† | Usually normal | Normal or mildly dilated | Usually dilated‡ |
| **Qualitative Doppler** | | | |
| Color flow jet area | Small, narrow, central | Moderate central | **Large central jet** or eccentric wall-impinging jet of variable size |
| Flow convergence | Not visible, transient or small | Intermediate in size and duration | **Large throughout systole** |
| CWD jet | **Faint/partial**/parabolic | Dense, parabolic or triangular | Dense, often triangular |
| **Semi-quantitative** | | | |
| Color flow jet area ($cm^2$)† | Not defined | Not defined | > 10 |
| Vena contracta width (cm) | <0.3 | 0.3-0.69 | ≥ 0.7 |
| PISA radius (cm) ‡ | ≤0.5 | 0.6-0.9 | > 0.9 |
| Hepatic vein flow§ | Systolic dominance | Systolic blunting | **Systolic flow reversal** |
| Tricuspid inflow§ | **A-wave dominant** | Variable | E-wave >1.0 m/sec |
| **Quantitative** | | | |
| EROA, 2D PISA ($cm^2$) | <0.20 | 0.20-0.39 | ≥ 0.40 |
| RVol (mL) | <30 | 30-44 | ≥ 45 |

RA, Right atrium; RV, Right ventricle; EROA, Effective regurgitant orifice area; RVol, Regurgitant volume; PISA, Proximal isovelocity surface area
Bolded signs are considered specific for their TR grade.
*RV and RA size can be within the ''normal'' range in patients with acute severe TR
†With Nyquist limit >50-70 cm/sec.
‡With baseline Nyquist limit shift of 28 cm/sec.
§Signs are nonspecific and are influenced by many other factors (RV diastolic function, atrial fibrillation, RA pressure).

### 18.3.4 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 trial.

The variables evaluated by the Echo Core Lab include:

- Heart rate
- Left ventricular outflow tract (LVOT) diameter in mid systole
- Max aortic/prosthetic valve velocity ($V_2$) by CW Doppler
- Aortic valve velocity time integral by CW Doppler
- Mean gradient across aortic valve by CW Doppler
- LVOT VTI by PW Doppler
- Grade of native aortic regurgitation (pre-TAVR baseline only)
- 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 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
- Left ventricular ejection fraction (LVEF) by modified-Simpson's rule
- 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 $\Delta$ P) Across the Aortic Valve in mmHg
  Peak $\Delta$ 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 $m^2$

- 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 $m^2$

- Doppler Velocity Index (DVI)
  DVI= $VTI_{V1}/VTI_{V2}$
  Where: $VTI_{V1}$ is the velocity time integral of the left ventricular outflow tract in cm, and $VTI_{V2}$ is the 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 $m^2$

- Estimated Right Ventricular Systolic Pressure 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

- Body Surface Area* (BSA) in $m^2$
  BSA = 0.007184 x (height in cm$^{0.725}$ x weight in kg$^{0.425}$)

* BSA derived from height and weight reported on the site eCRF

## 18.4 Appendix IV: MDCT Procedures: Pre-TAVR Planning

MDCT is required to confirm anatomical suitability for transfemoral TAVR with the Evolut PRO/PRO+/FX and SAPIEN 3/3 Ultra Systems. MDCT is used to evaluate aortic valve anatomy, determine aortic root dimensions for device sizing, and to evaluate peripheral vessel dimensions and anatomy. The MDCT exam should be performed at the trial center, but exams performed for diagnostic purposes outside the trial center and prior to consent can be used, provided they are within 365 days prior to submission for Confirmation of Qualification and contain the protocol-required data.

**Technical Aspects.** Technical aspects of the exam are per the site's standard routine for clinical TAVR cases; however, the following are recommended parameters:

- Detector collimation 0.4-0.625 mm.
- Slice thickness ≤ 1.0 mm.
- Coverage area from superior to the aortic arch to inferior to the cardiac apex.
- Slice overlap of 0.4 mm (will result in isotropic voxels with a 20 cm field of view)

**Required Variables.** The following variables should be captured to confirm anatomical suitability for implantation and TAV size selection (**Figure 15**).

- Annulus area (measured at systole and diastole)
- Annulus perimeter (measured at systole if retrospective gating is used)
- Sinus of Valsalva (SoV) diameters (measured at diastole)
    - Right coronary sinus diameter
    - Left coronary sinus diameter
    - Non coronary sinus diameter
    - Mean sinus diameter (mean of the three coronary sinus diameters)
- SoV heights (measured at diastole)
    - Right coronary SoV height
    - Left coronary SoV height
    - Non coronary SoV height
    - Mean SoV height (mean of the three SoV heights)
- Mean diameter of left iliofemoral artery
- Mean diameter of right iliofemoral artery

These variables should be documented in the MDCT report for the subject's medical record or on an alternative source document to be maintained in the subject's trial files (e.g. a report from dedicated off-line cardiac image analysis system such as 3mensio, Vital Images, etc.).

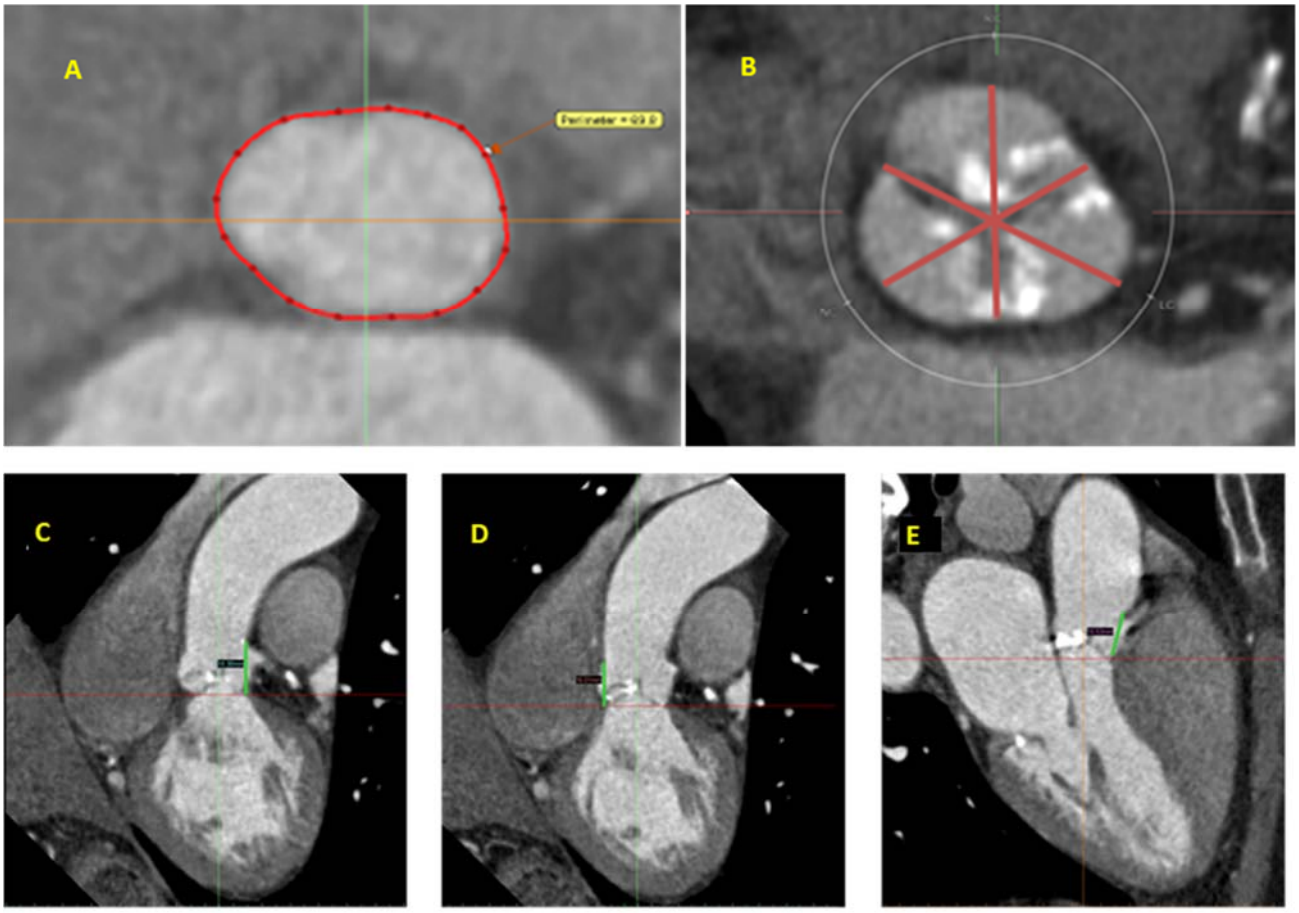



**Figure 15. (A)** Annular perimeter measured from a reformatted double-oblique axial image at aortic annulus level. Measurement is recommended at systole if retrospective gating was used, although measurement at diastole is also acceptable; **(B)** SoV diameter is measured at diastole from the double oblique axial image where the widest portion of the three sinuses is visible. A diameter from each commissure is measured through the site of the root to the opposite sinus. The mean of the three SoV diameters is reported on the eCRF; **(C, D, & E)** Measurement of the left, non, and right coronary SoV heights, respectively. SoV heights measured at diastole from double oblique axial image located 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. SoV height is measured from the aortic annular plane to the sinotubular junction.

### 18.4.1 Anatomic Suitability and Valve Size Selection

Evolut PRO, Evolut PRO+, and Evolut FX valve size selection is specified below:

| 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 – 81.7 | 23 – 26 | ≥ 29 | ≥ 15 |

SAPIEN 3 and SAPIEN 3 Ultra valve size selection is specified below:

| Device size | Native Valve Annulus Size | | Native Valve Annulus Size (mm) |
|---|---|---|---|
| | Area ($mm^2$) | Area Derived Diameter (mm) | |
| 20 mm | 273 - 345 | 18.6 - 21 | 16 – 19 |
| 23 mm | 338 - 430 | 20.7 - 23.4 | 18 - 22 |
| 26 mm | 430 – 546* | 23.4 – 26.4 | 21-25 |

*Note: Although in some cases 26mm can be selected as an appropriate valve, the SMART Trial only enrolls subjects with an aortic valve annulus area ≤ 430 $mm^2$ based on MDCT

# 18.5 Appendix V: Endpoint Definitions

## 18.5.1 Safety and Efficacy Definitions

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

| **Myocardial Infarction**[62] | |
|---|---|
| **Type 1**<br>(Spontaneous MI)<br>(>48 h after the index procedure) | • Detection of a rise and/or fall of cardiac troponin (cTn) values with at least one value above the 99th percentile URL with at least one of the following:<br>○ Symptoms of acute ischaemia<br>○ New ischaemic ECG changes (new ST-segment or T-wave changes or new LBBB)<br>○ New pathologic Q-waves in ≥ 2 contiguous leads<br>○ Imaging evidence of a new loss of viable myocardium or new wall motion abnormality in a pattern consistent with an ischaemic aetiology<br>○ Identification of a coronary thrombus by angiography or autopsy<br>• Post-mortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large circumscribed area of necrosis with or without intramyocardial haemorrhage, meets the type 1 MI criteria regardless of cTn values |
| **Type 2**<br>(Imbalance between myocardial oxygen supply and demand) | • Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile upper reference limit (URL), and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following:<br>○ Symptoms of ischaemia |

| Myocardial Infarction[62] | |
|---|---|
| | ○ ECG changes indicative of new ischaemia (new ST-segment or T-wave changes or new LBBB)<br>○ New pathologic Q-waves in ≥2 contiguous leads<br>○ Imaging evidence of a new loss of viable myocardium or new wall motion abnormality |
| **Type 3**<br>(MI associated with sudden cardiac death) | Patients who suffer cardiac death, with symptoms suggestive of myocardial ischaemia accompanied by presumed new ischaemic ECG changes or ventricular fibrillation but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination. |
| **Type 4A**<br>(Criteria for PCI-related MI ≤48 h after the index procedure) | • **In patients with normal baseline creatine kinase-MB (CK-MB):** The peak CK-MB measured within 48 h of the procedure ≥10x the local laboratory upper limit of normal (ULN) or CK-MB ≥5x ULN with one or more of the following:<br>○ New pathologic Q-waves in ≥2 contiguous leads<br>○ New persistent LBBB‡<br>○ Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch<br>○ Substantial new loss of viable myocardium on imaging related to the procedure<br>• In the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the procedure rises to ≥70x the local laboratory ULN or ≥35x ULN with one or more of the following:<br>○ New pathologic Q-waves in ≥2 contiguous leads<br>○ New persistent LBBB‡<br>○ Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch<br>○ Substantial new loss of viable myocardium on imaging related to the procedure<br>• **In patients with elevated baseline CK-MB (or cTn)**: The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level plus new ECG changes as described. |
| **Type 4B**<br>(Stent thrombosis) | • Stent thrombosis as documented by angiography or autopsy using the same criteria utilized for type 1 MI.<br>○ Acute: 0 to 24 h<br>• Subacute: >24 h to 30 days<br>• Late: >30 days to 1 year<br>• Very late: >1 year after stent implantation |

| Myocardial Infarction[62] | |
|---|---|
| **Type 4C** (Coronary stent restenosis) | Focal or diffuse restenosis, or a complex lesion associated with a rise and/or fall of cTn values above the 99th percentile URL applying, the same criteria utilized for type 1 MI |
| **Type 5** Periprocedural (post-SAVR, TAVR or CABG) MI (⩽48 h after the index procedure) | • **In patients with normal baseline CK-MB**: The peak CK-MB measured within 48 h of the procedure ≥ 10x the local laboratory ULN or CK-MB ≥ 5x ULN with one or more of the following:<br>○ New pathologic Q-waves in ≥ 2 contiguous leads<br>• New persistent LBBB‡<br>• Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch<br>• Substantial new loss of viable myocardium on imaging related to the procedure<br>• In the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the procedure rises to ≥ 70x the local laboratory ULN or ≥ 35x ULN with one or more of the following:<br>○ New pathologic Q-waves in ≥ 2 contiguous leads<br>• New persistent LBBB‡<br>• Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch<br>• Substantial new loss of viable myocardium on imaging related to the procedure<br>• ***In patients with elevated baseline CK-MB (or cTn)****:* The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level plus new ECG changes as described. |

Note: The use of high-sensitivity (hs)-troponins is recommended for diagnosis of spontaneous MI, but has not been studied for assessment of periprocedural MI. Standard troponin assays are therefore recommended for evaluation of periprocedural MI. Periprocedural biomarker elevation >ULN not meeting the criteria for MI should be categorized as 'myocardial injury not meeting MI criteria'.

‡LBBB criteria to be used with caution after TAVR or SAVR given the relatively high rate of new LBBB after these procedures.

| Stroke and TIA | |
|---|---|
| **Diagnostic Criteria** | 1) Acute episode of a focal or global neurological deficit with at least 1 of the following:<br>• change in the level of consciousness<br>• hemiplegia, hemiparesis<br>• numbness or sensory loss affecting 1 side of the body<br>• dysphasia or aphasia<br>• hemianopia |

| Stroke and TIA | |
|---|---|
| | • amaurosis fugax<br>• other neurological signs or symptoms consistent with stroke<br>**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<br>**TIA:** duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct<br>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<br>3) Confirmation of the diagnosis by at least 1 of the following:<br>• Neurologist or neurosurgical specialist<br>• 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<br>• **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 Classification** | • **Ischemic:** an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue<br>• **Hemorrhagic:** an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage<br>• **Undetermined**: insufficient information to allow categorization as ischemic or hemorrhagic |

| Rehospitalization |
|---|
| **Rehospitalization is defined as follows:** Any admission after the index hospitalization or study enrollment to an inpatient unit or hospital ward for at least 24 hrs (including an emergency department stay), or as measured by a change in calendar date. Hospitalizations planned for pre-existing conditions are excluded unless there is worsening of the baseline condition. |

| Cardiovascular Hospitalizations | |
|---|---|
| Includes hospitalizations for heart failure, stroke or TIA, conduction disturbances and arrhythmias, vascular or access-site related complications, cardiac structural complications, myocardial infarction, unstable angina, cardiogenic shock, or other cardiovascular hospitalizations. | |
| **Heart Failure Hospitalization (or rehospitalization)** [63] | **Definition:**<br>1. Admission to the hospital with a primary diagnosis of Heart Failure (HF)<br>2. Documented new or worsening symptoms due to HF on presentation, including at least one of the following: dyspnoea (dyspnoea with exertion, dyspnea at rest, orthopnoea, paroxysmal nocturnal dyspnoea); decreased exercise tolerance; fatigue; or other symptoms of worsened end-organ perfusion or volume overload<br>3. Objective evidence of new or worsening HF, consisting of at least two physical examination findings or one physical examination finding and one laboratory or invasively measured criterion, including:<br>a. Physical examination findings considered to be due to HF include new or worsened: peripheral oedema; increasing abdominal distention or ascites (in the absence of primary hepatic disease); pulmonary rales/crackles/crepitations; increased jugular venous pressure and/or hepatojugular reflux; S3 gallop; clinically significant or rapid weight gain thought to be related to fluid retention.<br>b. Lab evidence of new or worsening HF, if obtained within 24 hr or presentation, including: increased B-type natriuretic peptide (BNP)/N-terminal pro B-type natriuretic peptide (NT-proBNP) concentrations consistent with decompensation of HF (in patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline); radiological, ultrasonographic, or implantable monitor evidence of pulmonary congestion; non-invasive or implantable diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure, or low cardiac output.<br>c. Invasive evidence of new or worsening HF including right heart catheterization showing elevated pulmonary capillary wedge pressure (pulmonary artery occlusion pressure), elevated central venous pressure, depressed cardiac index, or left heart catheterization showing elevated LVEDP consistent with decompensation of HF.<br>4. The patient receives at least one of the following treatments specifically for HF: |

| Cardiovascular Hospitalizations | |
|---|---|
| | a. Significant augmentation in oral diuretic therapy (at least a doubling of loop diuretic dose, initiation of maintenance loop diuretic therapy, initiation of combination diuretic therapy).<br>b. Initiation of intravenous diuretic (even a single dose)<br>c. Initiation of an intravenous vasoactive agent (catecholamine, phosphodiesterase-3 inhibitor, other vasopressor, vasodilator).<br>d. Mechanical or surgical intervention, including mechanical circulatory support (IABP, temporary or durable VAD, including both percutaneous and surgically placed devices, ECMO, or total artificial heart).<br>e. Mechanical fluid removal (ultrafiltration, haemofiltration, haemodialysis).<br>However, in cases where documentation of the above criteria may not be obtained, the following definition of a HF hospitalization may be used: If agreed by consensus of a clinical events committee, events of symptomatic HF that include at least one worsening symptom, as well as either one physical examination finding or one laboratory finding or invasively measured criterion, in addition to at least one intravenous or mechanical treatment specific for HF, may be considered HF hospitalizations, with or without supporting documentation.<br>An independent Clinical Events Committee (CEC) will review all available source documentation for all hospitalizations to determine if they are aortic valve disease or worsening heart failure (as described below) related hospitalizations. The CEC adjudication will be used for final analysis. |
| **Stroke or TIA** | Refer to the **Stroke and TIA** definition in this Appendix |
| **Conduction disturbance or arrhythmia** | Hospitalization for new or worsening of any of the following conduction disturbances or arrhythmia:<br>• First-degree atrioventricular (AV) block<br>• Second-degree AV block (Mobitz I or Mobitz II)<br>• Third-degree AV block<br>• Incomplete right bundle branch block<br>• Right bundle branch block<br>• Intraventricular conduction delay<br>• Left bundle branch block<br>• Left anterior or posterior fascicular block<br>• Atrial fibrillation<br>Atrial fibrillation (or flutter), defined as any arrhythmia within hospitalization that has the ECG characteristics of atrial fibrillation (or flutter) and lasts sufficiently long to be recorded on a 12-lead ECG or at least 30 seconds on a rhythm strip. |
| **Vascular or access-site** | Refer to the **Vascular Access Site and Access Related Complications** definition in this Appendix |

| Cardiovascular Hospitalizations | |
|---|---|
| **related complications** | |
| **Cardiac structural complications** | Hospitalization for new or worsening cardiac structural complications, defined as follows:<br>**Major Cardiac Structural Complication (one of the following):**<br>1) Cardiac structure perforation, injury, or compromise resulting in death, VARC type ≥2 bleeding, hemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention.<br>2) New pericardial effusion resulting in death, VARC type ≥ 2 bleeding, hemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention.<br>3) Coronary obstruction resulting in death, hemodynamic compromise, myocardial infarction, or unplanned surgical or percutaneous intervention. Coronary obstruction may be acute (during the procedure) or delayed (after completion of the procedure).<br>4) Coronary artery access difficulties for needed coronary angiography or intervention, resulting in death, hemodynamic compromise, myocardial infarction, coronary or aortic root injury, compromise in aortic valve prosthesis integrity, unplanned surgical or percutaneous intervention, or the inability to perform the intended procedure.<br>**Minor Cardiac Structural Complication (one of the following):**<br>1) Cardiac structure perforation, injury, or compromise not resulting in death, VARC type ≥2 bleeding, hemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention.<br>2) New pericardial effusion not resulting in death, VARC type ≥ 2 bleeding, hemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention.<br>3) Coronary obstruction not resulting in death, hemodynamic compromise, myocardial infarction, or unplanned surgical or percutaneous intervention. Coronary obstruction may be acute (during the procedure) or delayed (after completion of the procedure).<br>4) Coronary artery access difficulties for needed coronary angiography or intervention, not resulting in death, hemodynamic compromise, myocardial infarction, coronary or aortic root injury, compromise in aortic valve prosthesis integrity, unplanned surgical or percutaneous intervention, or the inability to perform the intended procedure. |
| **Myocardial infarction** | Refer to the **Myocardial Infarction** definition in this Appendix |
| **Unstable angina** | Hospitalization for unstable angina defined as follows: |

| Cardiovascular Hospitalizations | |
|---|---|
| | 1. Ischemic discomfort (angina, or symptoms thought to be equivalent) ≥ 10 minutes in duration occurring at rest, or in an accelerating pattern with frequent episodes associated with progressively decreased exercise capacity, **AND**<br>2. Prompting an unscheduled hospitalization within 24 hours of the most recent symptoms. Hospitalization is defined as an admission to an inpatient unit or a visit to an emergency department that results in at least a 24 hour stay (or a change in calendar date if the hospital admission or discharge times are not available), **AND**<br>3. At least one of the following:<br>➢ New or worsening ST or T wave changes on resting ECG (in absence of confounders, such as LBBB or LVH)<br>- Transient ST elevation (duration < 20 minutes)<br>- New ST elevation at the J point in two contiguous leads with the cut-points:<br>- 0.1 mV in all leads other than leads V2-V3 where the following cut-points apply: ≥ 0.2 mV in men ≥ 40 years (≥ 0.25 mV in men < 40 years) or ≥ 0.15 mV in women.<br>- ST depression and T-wave changes<br>- New horizontal or down-sloping ST depression > 0.05 mV in two contiguous leads and/or new T-wave inversion > 0.3 mV in two contiguous leads with prominent R wave or R/S ratio > 1.<br>➢ Definite evidence of inducible myocardial ischemia as demonstrated by:<br>- an early positive exercise stress test, defined as ST elevation or ≥ 2 mm ST depression prior to 5 mets, **OR**<br>- stress echocardiography (reversible wall motion abnormality) **OR,**<br>- myocardial scintigraphy (reversible perfusion defect), **OR**<br>- MRI (myocardial perfusion deficit under pharmacologic stress) **AND** believed to be responsible for the myocardial ischemic symptoms/signs.<br>➢ Angiographic evidence of new or worse > 70% lesion (> 50% for left main lesion) and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs.<br>➢ Need for coronary revascularization procedure (PCI or CABG) for the presumed culprit lesion(s). This criterion would be fulfilled if revascularization was undertaken during the unscheduled hospitalization, or subsequent to transfer to another institution without interceding home discharge **AND,**<br>4. Negative cardiac biomarkers and no evidence of acute MI. |
| **Cardiogenic shock** | Hospitalization for cardiogenic shock, defined as follow: |

| Cardiovascular Hospitalizations | |
|---|---|
| | Sustained (>30 min) episode of hypoperfusion evidenced by systolic blood pressure <90 mm Hg and/or, if available, cardiac index <2.2 L/min per square meter determined to be secondary to cardiac dysfunction and/or the requirement for parenteral inotropic or vasopressor agents or mechanical support (e.g., IABP, extracorporeal circulation, VADs) to maintain blood pressure and cardiac index above those specified levels.<br>*Note: Transient episodes of hypotension reversed with IV fluid or atropine do not constitute cardiogenic shock. The hemodynamic compromise (with or without extraordinary supportive therapy) must persist for at least 30 min.* |
| **Other cardiovascular** | Hospitalization for any other cardiovascular-related reason that does not fit into one of the other categories.<br>Examples of "other cardiovascular" hospitalizations include suspicion or diagnosis of endocarditis, suspicion or diagnosis or prosthetic valve thrombosis, prosthetic valve leaflet thickening or immobility, bleeding event related to anti-thrombotic therapy, suspected or confirmed bioprosthetic valve dysfunction, new peripheral vascular or aortic disorders, etc. |

| Non-Cardiovascular Hospitalizations |
|---|
| Includes hospitalizations not due to cardiovascular causes as mentioned above. |

| Bleeding Complications | |
|---|---|
| **Life-threatening or disabling bleeding** | • Fatal bleeding *(BARC type 5)* OR<br>• Bleeding in a critical organ, such as intracranial, intraspinal,<br>• intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome *(BARC type 3b and 3c)* OR<br>• Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery *(BARC type 3b)* OR<br>• 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<br>2) Does not meet criteria of life-threatening or disabling bleeding |
| **Minor bleeding** *(BARC type 2 or 3a, depending* | Any bleeding worthy of clinical mention (e.g. access site hematoma) that does not qualify as life-threatening, disabling, or major |

| Bleeding Complications | |
|---|---|
| *on the severity)* | |
| *Given one unit of packed RBC typically will raise hemoglobin concentration by 1 g/dL, an estimated decrease in hemoglobin will be calculated; BARC: Bleeding Academic Research Consortium; RBC: red blood cell | |

*Notes:*

1. 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.
2. Pre-operative hemoglobin will be used to determine severity of bleeding events
3. Minor bleeding (VARC-2) can be categorized to VARC-3 Type 1; Major bleeding (VARC-2) can be categorized to VARC-3 Type 2; Life-threatening or disabling bleeding (VARC-2) can be categorized to VARC-3 Type 3 and Type 4.

| 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<br>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<br>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<br>2) Urine output <0.3 ml/kg/h for ≥24 h OR<br>3) Anuria for ≥12 h |

*Note:* *Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.

| 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<br>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<br>3) Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR<br>4) The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischemia or neurological impairment OR |

| Vascular Access Site and Access Related Complications | |
|---|---|
| | 5) Any new ipsilateral lower extremity ischemia documented by subject symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR<br>6) Surgery for access site-related nerve injury OR<br>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, pseudoaneurysms, hematomas, percutaneous closure device failure) *not leading to* death, life-threatening or major bleeding*, visceral ischemia, or neurological impairment OR<br>2) Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR<br>3) Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR<br>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) |

*Note:* *Refer to Bleeding Complications definitions

| Valve Dysfunction Requiring Repeat Procedure |
|---|
| Any valve dysfunction that requires repeat procedure (e.g. balloon valvuloplasty, TAVR, or surgical AVR) |

*Note*: Repeat procedures are reported on the appropriate eCRF

| Other TAVR Related Complications | |
|---|---|
| Conversion to open surgery | Conversion to open sternotomy during the TAVR procedure secondary to any procedure-related complications<br>Conversions to open surgery will be considered serious adverse events regardless of reason for the surgical conversion. |
| Unplanned use of cardiopulmonary bypass | Unplanned use of CPB for hemodynamic support at any time during the TAVR procedure |
| Coronary artery obstruction | Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary ostium, either by the TAV prosthesis itself, the native leaflets, calcifications, or dissection, occurring during or after the TAVR procedure. |

| Other TAVR Related Complications | |
|---|---|
| Ventricular septal perforation | Angiographic or echocardiographic evidence of a new septal perforation during or after the TAVR 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 TAV prosthesis) of the mitral valve during or after the TAVR procedure |
| Cardiac tamponade | Evidence of new pericardial effusion associated with hemodynamic instability and clearly related to the TAVR procedure |
| Valve Thrombosis (Clinical) | Any thrombus not caused by infection attached to or near the trial valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment which is associated with any of the following clinical sequelae.:<br>• Thromboembolic complications including<br>  ○ Any ischemic stroke<br>  ○ Any peripheral embolic event<br>  ○ ST segment elevation or Non-ST elevation myocardial infarction<br>• Hemodynamic impairment associated with a worsening of heart failure<br><br>Note: valve thrombus found at autopsy in a subject whose cause of death was not valve-related or found at operation for an unrelated indication should not be reported as valve thrombosis |
| Valve Thrombosis (Sub-Clinical) | Any thrombus not caused by infection attached to or near the trial valve that occludes part of the blood flow path or interferes with valve function, without evident clinical sequelae, causing a hemodynamic impediment meeting the following criteria:<br>• Increase in aortic regurgitation to moderate to severe.<br>An increase by more than 50% of discharge mean aortic valve gradient (with the post discharge mean gradient being ≥ 20 mmHg) or a decrease in the Doppler Velocity Index by more than 50% |
| Leaflet Motion Abnormality (With Treatment) | Possible leaflet motion abnormality identified by any imaging modality with medical therapy (e.g. anticoagulation therapy, fibrinolytic therapy or valve-related medical intervention) initiated and without significant negative change in valve function (i.e. increasing obstruction or central regurgitation). |

| Other TAVR Related Complications | |
|---|---|
| Leaflet Motion Abnormality (Without Treatment) | Possible leaflet motion abnormality identified by any imaging modality without medical therapy (e.g. anticoagulation therapy, fibrinolytic therapy or valve-related medical intervention) initiated but without significant negative change in valve function (i.e. increasing obstruction or central regurgitation). |
| Valve migration | After initial correct positioning, any observed movement (upward or downward) of the TAV implant within the aortic annulus from its initial position, with or without consequences. |
| Valve embolization | The trial device moves during or after deployment such that it loses contact within the aortic annulus* |
| Ectopic valve deployment | Permanent deployment of the TAV implant in a location other than the aortic root |
| Valve in Valve deployment | Additional valve prosthesis is implanted within a previously implanted trial device 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<br>**Minor hemolysis:** No intervention required<br>**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.<br>**Minor frame fracture:** Does not require intervention or is not associated with prosthetic valve dysfunction.<br>**Major frame fracture:** Intervention required (e.g. reoperation, catheter re-intervention) or is associated with prosthetic valve dysfunction |
| TAVR Conversion to Other Percutaneous Procedure | Any conversion of the intended TAVR procedure, prior to closure to other percutaneous intervention due to technical challenges, technical contraindications to the intended procedure identified intra-procedurally or complications. |
| Aborted Procedure | Termination of the procedure prior to implantation of the valve due to identification of a technical contraindication, intraprocedural complications of a concomitant procedure prior to valve implantation or radiation dosage.<br>Aborted procedures will be considered serious adverse events regardless of reason for termination of the procedure. |

| Other TAVR Related Complications | |
|---|---|
| Reintervention – Surgical or Percutaneous | Any surgical or percutaneous interventional catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve. In addition to surgical reoperations, balloon dilatation, interventional manipulation, repositioning, or retrieval, and other catheter-based interventions for valve-related complications are also considered reinterventions. Reintervention is further subdivided into surgical and percutaneous.<br>Relationship to the trial valve will be assessed for the most current valve implanted or attempted to be implanted. |

*Valve embolizations are not applicable to a valve that moves during the procedure but are able to be recaptured and repositioned.

**Prosthetic Valve Endocarditis**

Any of the following:

1) Fulfillment of the following Duke criteria[56] for definite endocarditis:
   - Histologic and/or microbiologic evidence of infection at surgery or autopsy, or
   - 2 major criteria, or
   - 1 major criterion 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:

| Prosthetic Valve Endocarditis |
|---|
| • 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<br>• Abscess, or<br>• New partial dehiscence of a valvular prosthesis<br>• New valvular regurgitation (worsening or changing or pre-existing murmur not sufficient)<br><br>**Minor Criteria:**<br>• Predisposition: predisposing heart condition or intravenous drug use<br>• Fever: temperature >38°C<br>• Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions<br>• Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor<br>• 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.<br>• Echocardiographic findings: consistent with IE but do not meet a major criterion as noted above<br>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"<br>2) Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during a re-operation<br>3) Findings of abscess, pus, or vegetation involving the trial device at autopsy |

| 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<br>**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<br>**For subjects with BSA < 1.6 $m^2$:** Mean aortic gradient > 40 mmHg, EOA < 0.6 $cm^2$ AND/OR DVI < 0.25 |

| Prosthetic Valve Dysfunction | |
|---|---|
| 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 transvalvular regurgitation (per echo criteria in CIP) |
| Transvalvular regurgitation: severe | Severe transvalvular regurgitation (per echo criteria in CIP) |

*Notes:*

- DVI = Doppler Velocity Index (LVOT VTI/valve VTI)
- For subjects LVOT diameter > 2.5 cm, the DVI criteria for significant (moderate or severe) stenosis is 0.2
- Reporting of prosthetic valve dysfunction will be based on core lab values (if available).
- 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.

| Device Success at 30 days |
|---|
| All the following<br>• Freedom from mortality AND<br>• Correct positioning of a single prosthetic heart valve into the proper anatomical location AND<br>• Intended performance of the prosthetic heart valve (no prosthesis-patient mismatch and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s) AND<br>• No moderate or severe prosthetic valve regurgitation) |

| Prosthesis-Patient Mismatch (PPM)[64] |
|---|
| For subjects with BMI < 30 kg/$m^2$<br>• **Moderate PPM:** EOAI = 0.85 – 0.65 $cm^2/m^2$<br>• **Severe PPM:** EOAI = ≤ 0.65 $cm^2/m^2$<br>For subjects with BMI ≥ 30 kg/$m^2$<br>• **Moderate PPM:** EOAI = 0.70 – 0.55 $cm^2/m^2$<br>• **Severe PPM:** EOAI = ≤ 0.55 $cm^2/m^2$ |

| Bioprosthetic Valve Dysfunction |
|---|
| Any of the following<br>• Hemodynamic structural valve dysfunction (HSVD): Mean gradient ≥ 20mmHg<br>• Non-structural valve dysfunction (NSVD): severe PPM or ≥ moderate aortic regurgitation<br>• Thrombosis<br>• Endocarditis<br>• Aortic valve reintervention |

*HSVD and NVSD are based on Echo core lab data, and events thrombosis, endocarditis and aortic valve reintervention are from CEC adjudications.

| Early Safety (at 30 days)[65] |
|---|
| A composite of<br>• All-cause mortality<br>• All stroke (disabling and non-disabling)<br>• Life-threatening bleeding<br>• Acute kidney injury—Stage 2 or 3 (including renal replacement therapy)<br>• Coronary artery obstruction requiring intervention<br>• Major vascular complication<br>• Valve-related dysfunction requiring repeat procedure (BAV, TAVI, or SAVR) |

| Clinical Efficacy (after 30 days) |
|---|
| A composite of<br>• All-cause mortality<br>• All stroke (disabling and non-disabling)<br>• Requiring hospitalizations for valve-related symptoms or worsening congestive heart failure<br>• NYHA class III or IV<br>• Valve-related dysfunction (mean aortic valve gradient ≥20 mmHg, EOA ≤0.9-1.1 $cm^2$ and/or DVI<0.35m/s, AND/OR moderate or severe prosthetic valve regurgitation) |

### 18.5.2 Classification of Causality Relatedness

The following definitions are intended as guidelines for classifying causality relatedness between the event and the TAV, the catheter delivery system, the loading system (applicable to the Evolut PRO/PRO+/FX Systems), and the TAVR implant procedure.

**Causality relatedness between event and the TAV**

| | |
|---|---|
| **Not related** to the TAV | The relationship to TAV can be excluded when:<br>• the event is not a known side effect of the TAV or product category the device belongs to or of similar devices;<br>• The event has no temporal relationship with the TAV<br>• The event does not follow a known response pattern to the TAV and is biologically implausible;<br>• The event involves a body-site or an organ not expected<br>In order to establish non-relatedness, not all the criteria listed above might be met at the same time. |
| **Unlikely to be related** to the TAV | The relationship with the TAV seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained. |
| **Possibly related** to the TAV | The relationship with the TAV is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible. |
| **Probably related** to the TAV | The relationship with TAV seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained. |
| **Causal relationship "Related"** to the TAV | The event is associated with the TAV beyond reasonable doubt when:<br>• the event is a known side effect of the TAV or product category the device belongs to or of similar devices;<br>• the event has a temporal relationship with investigational device use/application or procedures;<br>• the event involves a body-site or organ that<br>- the TAV is applied to;<br>- the TAV of has an effect on;<br>• the event follows a known response pattern to the TAV;<br>• other possible causes (e.g. an underlying or concurrent illness/clinical condition or an effect of another device, drug, or treatment) have been adequately ruled out<br>• harm to the subject is due to error in use<br>In order to establish relatedness, not all the criteria listed above might be met at the same time. |

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

**Causality relatedness between event and the TAVR delivery system**

| | |
|---|---|
| **Not related** to the TAVR delivery system | The relationship with the TAVR delivery system can be excluded when:<br>• the event is not a known side effect of the TAVR delivery system product category the device belongs to or of similar devices;<br>• The event has no temporal relationship with the use of the TAVR delivery system<br>• The event does not follow a known response pattern to the TAVR delivery system and is biologically implausible;<br>• The event involves a body-site or an organ not expected<br>In order to establish non-relatedness, not all the criteria listed above might be met at the same time |
| **Unlikely to be related** to the TAVR delivery system | The relationship with the TAVR delivery system seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained. |
| **Possibly related** to the TAVR delivery system | The relationship with the TAVR delivery system is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible. |
| **Probably related** to the TAVR delivery system | The relationship with the TAVR delivery system seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained. |
| **Causal relationship "Related"** to the TAVR delivery system | The event is associated with the TAVR delivery system reasonable beyond doubt when:<br>• the event is a known side effect of the product category the device belongs to or of similar devices;<br>• the event has a temporal relationship with the TAVR delivery system use/application;<br>• the event involves a body-site or organ that<br>- the TAVR delivery system is applied to;<br>- the TAVR delivery system has an effect on;<br>• the event follows a known response pattern to the TAVR delivery system;<br>• other possible causes (e.g. an underlying or concurrent illness/clinical condition or an effect of another device, drug, or treatment) have been adequately ruled out<br>• harm to the subject is due to error in use<br>In order to establish relatedness, not all the criteria listed above might be met at the same time. |

**Causality relatedness between event and the loading system *(Applicable to the Evolut PRO/PRO+/FX Systems)***

| | |
|---|---|
| **Not related** to the loading system | The relationship with the loading system can be excluded when:<br>• the event is not a known side effect of the loading system product category the device belongs to or of similar devices;<br>• The event has no temporal relationship with the use of the loading system<br>• The event does not follow a known response pattern to the loading system and is biologically implausible;<br>• The event involves a body-site or an organ not expected<br>In order to establish non-relatedness, not all the criteria listed above might be met at the same time |
| **Unlikely to be related** to the loading system | The relationship with the system seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained. |
| **Possibly related** to the loading system | The relationship with the loading system is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible. |
| **Probably related** to the loading system | The relationship with the loading system seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained. |
| **Causal relationship "Related"** to the loading system | The event is associated with the loading system reasonable beyond doubt when:<br>• the event is a known side effect of the product category the device belongs to or of similar devices;<br>• the event has a temporal relationship with the Loading system use/application;<br>• the event involves a body-site or organ that<br>- the Loading system is applied to;<br>- the Loading system has an effect on;<br>• the event follows a known response pattern to the Loading system;<br>• other possible causes (e.g. an underlying or concurrent illness/clinical condition or an effect of another device, drug, or treatment) have been adequately ruled out<br>• harm to the subject is due to error in use<br>In order to establish relatedness, not all the criteria listed above might be met at the same time. |

**Causality relatedness between event and the TAVR implant procedure**

| | |
|---|---|
| **Not related** to the TAVR implant procedure | The relationship with the TAVR implant procedure can be excluded when:<br>• the event is not a known side effect of the TAV implant procedure;<br>• The event has no temporal relationship with the TAVR implant relationship<br>• The event does not follow a known response pattern to the TAVR implant procedure and is biologically implausible;<br>• The event involves a body-site or an organ not expected<br>In order to establish non-relatedness, not all the criteria listed above might be met at the same time. |
| **Unlikely to be related** to the TAVR implant procedure | The relationship with the TAVR implant procedure seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained. |
| **Possibly related** to the TAVR implant procedure | The relationship with the TAVR implant procedure is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible. |
| **Probably related** to the TAVR implant procedure | The relationship with TAVR implant procedure seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained. |
| **Causal relationship "Related"** to the TAVR implant procedure | The event is associated with the TAVR implant procedure beyond reasonable doubt when:<br>• the event is a known side effect of the TAVR implant procedure;<br>• the event has a temporal relationship with the TAVR implant procedure;<br>• the event involves a body-site or organ that<br>- the TAVR is applied to;<br>- the TAVR implant procedure has an effect on;<br>• the event follows a known response pattern to the TAVR implant procedure;<br>• other possible causes (e.g. an underlying or concurrent illness/clinical condition or an effect of another device, drug, or treatment) have been adequately ruled out<br>• harm to the subject is due to error in use<br>In order to establish relatedness, not all the criteria listed above might be met at the same time. |

Note: Procedure related events refers to the procedure related to the initial application of the device only and therefore not to any other procedures or treatments applied later throughout the clinical investigation, for instance to treat serious adverse events.

# 18.6 Appendix VI: Procedural Checklists

## 18.6.1 Case Evaluation Checklist (Evolut)

| # | Procedural Step | Yes = 1 pt |
|---|---|---|
| 1. | Initial deployment performed using cusp overlap or near cusp overlap projection | ☐ Yes ☐ No<br>☐ NA ☐ NC |
| 2. | Guidewire properly positioned within the ventricle<br>Guidewire used (Procedure form): _____ | ☐ Yes ☐ No<br>☐ NA ☐ NC |
| 3. | Began deployment with marker band positioned mid-pigtail or higher | ☐ Yes ☐ No<br>☐ NA ☐ NC |
| 4. | Not exceeding 3 mm depth at the NCC prior to full annular contact | ☐ Yes ☐ No<br>☐ NA ☐ NC |
| 5. | Paced from annular contact to 80% deployment | ☐ Yes ☐ No<br>☐ NA ☐ NC |
| 6. | Assessed depth in cusp overlap view at 80% deployment | ☐ Yes ☐ No<br>☐ NA ☐ NC |
| 7. | Verified depth at LCC in LAO view at 80% deployment | ☐ Yes ☐ No<br>☐ NA ☐ NC |
| 8. | Appropriate determination to deploy or recapture (less than 1mm or greater than 5mm at NCC)? | ☐ Yes ☐ No<br>☐ NA ☐ NC |
| 9. | Retraction of the wire prior to release | ☐ Yes ☐ No<br>☐ NA ☐ NC |
| 10. | Centralization of the nosecone prior to withdrawal of delivery catheter | ☐ Yes ☐ No<br>☐ NA ☐ NC |
| 11. | Assessed final implant depth at the NCC by aortography in the original cusp overlap projection. | ☐ Yes ☐ No<br>☐ NA ☐ NC |
| | Total | |

NA- Not applicable

NC- Not captured

### 18.6.2 Case Evaluation Checklist (SAPIEN)

| # | Procedural Step | Yes = 1 pt |
|---|---|---|
| 1. | Performed an angiogram with fluoroscopic view perpendicular to the valve | ☐ Yes ☐ No ☐ NA ☐ NC |
| 2. | Evaluated the distance of the left and right coronary ostia from the aortic annulus in relation to the valve frame height. | ☐ Yes ☐ No ☐ NA ☐ NC |
| 3. | Position of the Pigtail in the Non-Coronary or Right Coronary Cusp | ☐ Yes ☐ No ☐ NA ☐ NC |
| 4. | Cross the aortic valve and place the bioprosthesis relatively to the annulus to ensure a position not to exceed 20% ventricular | ☐ Yes ☐ No ☐ NA ☐ NC |
| 5. | Retract the tip of the Flex Catheter to the center of the Triple Marker | ☐ Yes ☐ No ☐ NA ☐ NC |
| 6. | Verify coaxial position of bioprosthesis using flex on the catheter | ☐ Yes ☐ No ☐ NA ☐ NC |
| 7. | Rapid ventricular pacing | ☐ Yes ☐ No ☐ NA ☐ NC |
| 8. | Deploy THV with a slow controlled inflation, hold for 3 sec, completely deflate and then stop pacing and withdraw the balloon. | ☐ Yes ☐ No ☐ NA ☐ NC |
| 9. | Appropriate position of the Sapien valve within the annulus with ventricular position >0% and < 20% depth relative to annulus | ☐ Yes ☐ No ☐ NA ☐ NC |
| 10. | Complete angiography in the cusp overlap projection after deployment (for depth assessment) | ☐ Yes ☐ No ☐ NA ☐ NC |
| | Total | |

NA- Not applicable

NC- Not captured

## 19. Version History

| Version | Summary of changes | Justification of changes | Potential impact of the change on performance, effectiveness, or safety or other endpoints | Identification of the affected trial documents | Author(s)/Title |
|---|---|---|---|---|---|
| 1.0 | • New Document | N/A | N/A | N/A | [redacted] |

| | | | | | |
|---|---|---|---|---|---|
| 2.0 | Changes include the list below:<br>1. Removed TAV-in-SAV Cohort and references to the cohort<br>2. Removed references to the TAV Native Cohort<br>3. Increased trial sample size of TAV native subjects<br>4. Added powered secondary endpoints<br>5. Added exclusion criteria<br>6. Updated Figure 3<br>7. Updated Section 10.5 Healthcare Utilization<br>8. Revised/updated Section 12 Adverse Events and Device Deficiencies including Table 7<br>9. Updated Section 14 Statistical Design and Methods<br>10. Added sections related to records and reports<br>11. Added Section 16.10.1 Planned Trial Closure<br>12. Revised/removed data collection parameters including echo parameters in Appendix IIII: Echocardiography Procedures<br>13. Formatting and administrative updates | 1. Trial design change to remove cohort<br>2. Removal of the TAV-in-SAV Cohort; trial population will only consist of subjects with native aortic stenosis<br>3. TAV native sample size increased for additional follow-up data and increase power for the trial endpoints<br>4. Additional valve performance endpoints to compare SE and BE TAVR<br>5. To exclude subjects with active COVID-19 infection/ relevant history. To exclude subjects with prior aortic valve replacement.<br>6. Figure 3 updated to reflect current trial design and subject flow<br>7. To clarify Healthcare Utilization applicable to all geographies<br>8. Section 12 reformatted to clarify AE and DD definitions and reporting requirements | • Change in sample size will increase power for the trial endpoints | • Case Report Forms and Informed Consent Form | [redacted] |

| Version | Summary of changes | Justification of changes | Potential impact of the change on performance, effectiveness, or safety or other endpoints | Identification of the affected trial documents | Author(s)/Title |
|---|---|---|---|---|---|
| | | 9. Section 14 updated to reflect current trial design and additional endpoints<br>10. Sections related to records and reports added for Investigator and Sponsor requirements<br>11. To clarify planned trial closure process<br>12. To align CIP with eCRF data collection parameters/ variables<br>13. To ensure consistency throughout document | | | |

| Version | Summary of changes | Author(s)/Title |
|---|---|---|
| 3.0 | • Changed CIP template to current version C<br>• References throughout updated to reflect current Medtronic operating unit of Structural Heart and Aortic<br>• Evolut PRO + product status updated to reflect commercial availability<br>• Primary endpoint for heart failure rehospitalization updated throughout<br>• References to VARC-2 removed throughout<br>• Update language throughout to clarify electronic ICF will only be applicable to US/Canada per IRB/REB approval<br>• Exclusion criteria E2: Added clarification of Syntax score requirements in relation to patients with a history of previous revascularization<br>• Section 6.1 Duration: Enrollment period updated from 17 to 20 months based on current forecast<br>• Section 6.3 Trial Oversight:<br>  ○ Updated language to inform that the CPC membership list 'can be made available upon request'<br>  ○ Added description of the role of TEC and inform that the TEC membership list 'can be made available upon request'<br>• Section 7.8 Product Return for Device Malfunction or Explant:<br>  ○ Added language 'Subjects with explanted devices due to reintervention should be followed through the duration of the study'<br>  ○ Removed language that Medtronic devices explanted due to autopsy should be returned to Medtronic and replaced with 'In the event of a subject's death, it is recommended that the implanted system will be explanted and returned to the manufacturer for analysis wherever possible per local process'<br>• Section 8.3 Role of the Sponsor Representatives: Removed requirements to collect technical support list<br>• Section 10.1 Schedule of Events: Clarified examinations and procedures outside of the standard of care at certain sites | [redacted] |

| Version | Summary of changes | Author(s)/Title |
|---|---|---|
| | • Section 10.1.1 Screening Procedures, Enrollment and Randomization:<br>  ○ Removed language that the local Heart Team assessment would be completed after enrollment and update Figure 3 to clarify timing of the Heart Team decision can differ from the figure but must occur before submission of the subject for Confirmation of Qualification<br>  ○ Added 'Subjects with questionable anatomical suitability due to exclusion criteria for the trial, warnings, precautions, or contraindications in the Instructions for Use, or risk factors for TAVR implantation per product training will be reviewed and discussed between the site and the independent Case Planning Committee. Questionable anatomical suitability includes valve area out of range, small sinus of Valsalva (SoV), small femoral, low coronary height, severe left ventricular outflow tract (LVOT) calcification, narrow sinotubular junction (STJ), horizontal aorta, and challenging bicuspid morphology'<br>  ○ Added 'In the event a crossover occurs, a protocol deviation will be reported, and the subject should continue to be followed through the duration of the trial'<br>• Section 10.1.3 Implant Procedure (TAVR):<br>  ○ Added 'Subjects must be treated via percutaneous transfemoral access only'<br>  ○ Updated language to reflect expectations for the cusp overlap technique during the implant procedure.<br>  ○ Added review process for procedural angiograms and TEC review for cases with questions or concerns<br>• Section 10.3.1 Procedural Data: Added Implant depth percentage ratio, balloon inflation volume, procedural angiogram views and degrees, assessment of implant depth, and 'was the cusp overlap technique applied in the valve deployment' as collected variables<br>• Section 10.9.1.1 Time window for completion and submission of Case Report Forms: Added that sites should complete eCRFs no later than 5 working days following procedure<br>• Section 11.1 Potential Risks: Added language that the stress echocardiogram documents (ICF and CIP) will be provided under a separate cover<br>• Section 12.2: Added definition of DD for clarity | |

| Version | Summary of changes | Author(s)/Title |
|---|---|---|
| | • Table 5 Adverse Event Definitions for Reporting Requirements: SAE definition corrected from 'in-subject' to 'in-patient or prolonged hospitalization'.<br>• Section 12.5 Reporting of Adverse Events and Device Deficiencies:<br>  ○ Removed reference to MEDDEV 2.7/3 requirements and replaced with current requirements (EU MDR per MDCG 1010-10, local law, and the study site's EC).<br>  ○ Added Art. 32-34 ClinO-MD obligation for sites in Switzerland<br>• Section 12.7 Subject Death: Added autopsy is conducted per standard practice if applicable.<br>• Section 15.1 Statements of Compliance: Updated compliance standards to 'In the EU/EEA region the trial will be conducted in compliance with EU MDR and applicable data protection law' per current requirements.<br>• Section 16.7.1 and Section 16.7.2 Investigator Records and Sponsor Records: Removed requirement to collect insurance statements for Canada and update language to 'if applicable' for EMEA.<br>• Section 17 References: Added references 62 and 63<br>• Section 18.4.1 Anatomic Suitability and Valve Size Selection: Added footnote to SAPIEN 3 and SAPIEN 3 Ultra sizing table<br>• Section 18.5 Appendix V Endpoint Definitions:<br>  ○ Updated definition of Myocardial Infarction<br>  ○ Updated definition Rehospitalization<br>  ○ Updated definition of Heart Failure Hospitalization<br>  ○ Removed Signs and Symptoms of Aortic Valve Disease<br>  ○ Added footnote to definition of Acute Kidney Injury<br>• Section 18.6 Appendix VI Procedural Checklist: Added section<br>• Formatting and administrative updates throughout<br>• Revised the version history to remove 'Justification of changes', Potential impact of the change', and 'Identification of the affected documents' columns as columns are not required | |
| Version 4.0 | • Updated throughout to include Evolut FX as an acceptable device in regions where it is commercially available<br>• Section 3.0 Synopsis:<br>  ○ Added components of the Evolut FX system, statement regarding commercial availability in the United States, and clarification that the Evolut FX System may be used upon commercial availability in Canada.<br>  ○ Added clarification that Evolut PRO+ is recapturable | [redacted] |

| Version | Summary of changes | Author(s)/Title |
|---|---|---|
| | ○ I4 and E5 updated with generic language for the TAV systems; specific device names removed.<br>• Section 7.1.1.3 Medtronic Evolut FX System: Section added to clarify the components (figure 3), model numbers, sizes, associated aortic annulus diameters for the Evolut FX System.<br>• Section 9.3 Inclusion Criteria: Updated I4 with generic language for the TAV systems; specific device names removed<br>• Section 9.4 Exclusion Criteria: Updated E5 with generic language for the TAV systems; specific device names removed<br>• Section 10.1.2 Baseline: Added language to confirm TTE meets eligibility if not determined at Screening Visit<br>• Section 10.8 Assessment of Safety: Added Evolut FX System and system components<br>• Section 11.4 Risk-Benefit Rationale: Added equivalency statement for Evolut FX<br>• Section 12.4 Definitions/Classifications: Updated footnote to current hospitalization definition<br>• Section 12.4.1 Unavoidable Adverse Events: Added clarification that suspected or confirmed device-related SAEs must be reported.<br>• Section 16.5.1 Warranty: Removed warranty statement, as it is not required language and is not applicable for the study.<br>• Section 18.5 Appendix V: Endpoint Definitions: Expanded the types of cardiovascular hospitalizations for data collection and event adjudication<br>• Administrative updates throughout | |