Outcomes in the CoreValve US Pivotal High Risk Trial in Patients With a Society of Thoracic Surgeons Risk Score of Less than or Equal to 7
Reardon MJ, et al.

This supplement contains the following items:

1. US IDE High Risk Protocol Version 1.0
2. US IDE High Risk Protocol Version 12.0
3. US IDE High Risk Protocol Summary of Changes
4. Statistical Analysis Plan V 1.0
5. Statistical Analysis Plan V 2.0
6. Statistical Analysis Plan V 3.0 Addendum 23 mm Valve
7. Statistical Analysis Plan Summary of changes
Medtronic CoreValve® U.S. Pivotal Trial
(High Risk Surgical Patients)

Clinical Investigational Plan

Version 1.0
August 26, 2010

Sponsor:
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### 1. SYNOPSIS

<table>
<thead>
<tr>
<th>Title of Trial:</th>
<th>Medtronic CoreValve® U.S. Pivotal Trial</th>
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<tbody>
<tr>
<td>Title of Protocol:</td>
<td>Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients)</td>
</tr>
<tr>
<td>Name of Product:</td>
<td>Medtronic CoreValve® System (MCS)</td>
</tr>
<tr>
<td>Purpose:</td>
<td>To evaluate the safety and efficacy of the Medtronic CoreValve® System in the treatment of symptomatic severe aortic stenosis in subjects who have a predicted high risk for aortic valve surgery.</td>
</tr>
<tr>
<td>Design:</td>
<td>Subjects will be randomized on a 1:1 basis to either transcatheter aortic valve implant (TAVI) with the Medtronic CoreValve® System (MCS) or to surgical aortic valve replacement (SAVR).</td>
</tr>
<tr>
<td>Primary Objective:</td>
<td>The primary objective is to demonstrate that the safety and effectiveness of the Medtronic CoreValve® System (MCS) as measured by all-cause mortality rates at 12 months is non-inferior to surgical aortic valve replacement (SAVR) in the treatment of symptomatic severe aortic stenosis in subjects who have a predicted high risk for aortic valve surgery.</td>
</tr>
<tr>
<td>Primary Endpoint:</td>
<td>All-cause mortality at 12 months.</td>
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</table>
| Secondary Endpoints: | The following secondary endpoints will be compared between MCS TAVI and SAVR subject cohorts:  
1. Major Adverse Cardiovascular and Cerebrovascular Event (MACCE)-free survival at 30 days, 6 months, 12 months and annually thereafter up to 5 years. MACCE is defined as a composite of:  
   - all-cause death  
   - myocardial infarction (MI)  
   - major stroke, and  
   - reintervention (defined as any cardiac surgery or percutaneous reintervention catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve)  
2. The occurrence of individual MACCE components at 30 days, 6 months, 12 months and annually thereafter up to 5 years. |
### Secondary Endpoints (Continued):

3. Major Adverse Events (MAE) at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

4. Conduction disturbance requiring permanent pacemaker implantation at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

5. Change in NYHA class from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

6. Change in distance walked during 6-minute walk test (6MWT) from baseline to 30 days and baseline to 12 months.

7. Ratio of days alive out of hospital versus total days alive assessed at 12 months follow-up.

8. Quality of Life (QoL) change from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years using the following measures:
   - Kansas City Cardiomyopathy Questionnaire (KCCQ)
   - SF-12, and
   - EuroQoL

9. Echocardiographic assessment of prosthetic valve performance at discharge, 30 days, 6 months, 12 months and annually thereafter up to 5 years using the following measures:
   - transvalvular mean gradient
   - effective orifice area
   - degree of prosthetic aortic valve regurgitation (transvalvular and paravalvular)

10. Repeat hospitalization.

11. Cardiovascular deaths and valve-related deaths

12. Strokes (of any severity) and TIsAs at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

13. Index procedure related MAEs.

14. Length of index procedure hospital stay.

15. Device success defined as follows:
   - successful delivery and placement of the device, and successful retrieval of the delivery system,
### Secondary Endpoints (Continued):

- Correct position of the device within the aortic annular region (placement in the annulus with no impedance on device function),
- Successful device function assessed acutely (within 24 to 48 hours post-implantation or prior to hospital discharge), where successful device function is defined as follows:
  - Absence of device migration (device within aortic annular region) assessed qualitatively by echocardiography
  - Less than moderate (2+) aortic regurgitation by echocardiography
  - Effective orifice area > 1.2 cm² by echocardiography using the continuity equation.
- Only one valve implanted in the proper anatomical location

16. Procedural success, defined as device success and absence of in-hospital MACCE.
17. Evidence of prosthetic valve dysfunction at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

| Principal Investigators: | Jeffrey J. Popma, M.D. – Interventional Cardiologist  
| David H. Adams, M.D. – Cardiothoracic Surgeon |
| Trial Sites: | The trial will be conducted at up to 40 sites in the United States. |
| Sample Size: | 790 (395 MCS TAVI & 395 Surgical Aortic Valve Replacement (SAVR)) |
| Patient Population: | Subjects with symptomatic severe aortic stenosis (AS), necessitating aortic valve replacement whose predicted risk of operative mortality is ≥15% (and predicted operative mortality or serious, irreversible morbidity risk of < 50%) at 30 days. |
| Inclusion Criteria: | 1. Subject must have co-morbidities such that one cardiologist and two cardiac surgeons agree that predicted risk of operative mortality is ≥15% (and predicted operative mortality or serious, irreversible morbidity risk of < 50%) at 30 days.  
2. Subject has senile degenerative aortic valve stenosis with mean gradient > 40 mmHg jet velocity greater than 4.0 m/s, or an initial aortic valve area of ≤ 0.8 cm² (or aortic valve area |
<table>
<thead>
<tr>
<th>Inclusion Criteria (Continued):</th>
</tr>
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| 3. Subject is symptomatic from his/her aortic valve stenosis, as demonstrated by NYHA Functional Class II or greater.  
4. The subject or the subject’s legal representative has been informed of the nature of the trial, agrees to its provisions and has provided written informed consent as approved by the IRB of the respective clinical site.  
5. The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits.  

<table>
<thead>
<tr>
<th>Exclusion Criteria:</th>
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| **Clinical**  
1. Evidence of an acute myocardial infarction ≤ 30 days before the intended treatment.  
2. Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to the index procedure with bare metal stents and 6 months with drug eluting stents.  
3. Blood dyscrasias as defined: leukopenia (WBC < 1000mm³), thrombocytopenia (platelet count <50,000 cells/mm³), history of bleeding diathesis or coagulopathy, or hypercoagulable states.  
4. Untreated clinically significant coronary artery disease requiring revascularization.  
5. Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support.  
7. Severe ventricular dysfunction with left ventricular ejection fraction (LVEF) < 20% as measured by resting echocardiogram.  
8. Recent (within 6 months) cerebrovascular accident (CVA) or transient ischemic attack (TIA).  
9. End stage renal disease requiring chronic dialysis or creatinine clearance < 20 cc/min.  
10. GI bleeding within the past 3 months.  
11. A known hypersensitivity or contraindication to any of the following which cannot be adequately pre-medicated:  
   - aspirin  
   - heparin (HIT/HITTS)
Exclusion Criteria (Continued):

- nitinol (titanium or nickel)
- ticlopidine and clopidogrel
- contrast media

12. Ongoing sepsis, including active endocarditis.
13. Subject refuses a blood transfusion.
14. Life expectancy < 12 months due to associated non-cardiac co-morbid conditions.
15. Other medical, social, or psychological conditions that in the opinion of an Investigator precludes the subject from appropriate consent.
16. Severe dementia (resulting in either inability to provide informed consent for the trial/procedure, prevents independent lifestyle outside of a chronic care facility, or will fundamentally complicate rehabilitation from the procedure or compliance with follow-up visits).
17. Currently participating in an investigational drug or another device trial.
18. Symptomatic carotid or vertebral artery disease.
19. Subject has been offered surgical aortic valve replacement but declined.

Anatomical

20. Native aortic annulus size < 20 mm or > 27 mm per the baseline diagnostic imaging.
21. Pre-existing prosthetic heart valve in any position.
22. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation (3-4+)).
23. Severe mitral (3-4+) or severe tricuspid regurgitation.
24. Moderate to severe mitral stenosis.
25. Hypertrophic obstructive cardiomyopathy.
26. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
27. Severe basal septal hypertrophy with outflow gradient.
28. Aortic root angulation > 70°.
29. Ascending aorta diameter > 43 mm unless the aortic annulus is 20-23 mm in which case the ascending aorta diameter > 40 mm.
| Exclusion Criteria (Continued): | 30. Congenital bicuspid or unicuspid valve verified by echocardiography.  
**Vascular**  
31. Transarterial access not able to accommodate an 18Fr sheath. |
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<tr>
<td><strong>Enrollment Phase:</strong></td>
<td>The enrollment phase is expected to last 20 months.</td>
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<tr>
<td><strong>Follow-up Evaluations:</strong></td>
<td>Subjects will be followed through 5 years with assessments at 30 days, 6 months, and 12 months as well as 2, 3, 4 and 5 years post MCS TAVI or post SAVR.</td>
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2. PURPOSE

2.1 Background

The management of heart disease in the elderly has been affected by the dramatic increase in life expectancy. With the number of persons over age 80 expected to increase to approximately 25 million by the year 2050, degenerative heart disease is likely to become an increasing problem. Calcific or degenerative aortic valve disease is considered the most common valvular lesion among elderly subjects. Aortic stenosis (AS) causes left ventricular outflow obstruction in adults, with severe AS defined as a combination of echocardiographic parameters: an aortic jet velocity >4 m/s, a mean gradient >40 mmHg, and a valve area <1.0 cm², according to the ACC/AHA guidelines for the management of valvular heart disease. Severe aortic stenosis is also considered to be present if the valve area index is < 0.6 cm²/m². However, in patients with severe AS who also have a low cardiac output state, the aortic jet velocity and mean gradient may be lower, a condition known as low-gradient stenosis. Subjects with AS can remain asymptomatic for a prolonged period, although once symptoms develop, prompt intervention is required. The classic symptoms associated with AS typically occur with exertion and include heart failure, syncope, and angina. Surgical replacement of the aortic valve is the only effective treatment for severe AS currently approved in the United States.

For those subjects ineligible for open-heart surgery, however, therapeutic options include only the palliative measures of medical therapy or percutaneous aortic valvuloplasty. Percutaneous balloon aortic valvuloplasty (BAV) has been suggested as an alternative to aortic valve replacement in subjects with AS and can result in improved symptoms. However, the high incidence of residual or recurrent stenosis and serious complications have limited the utility of this technique in the elderly. Subjects deemed too high risk to undergo aortic valve replacement (AVR) experience very high mortality rates, with average survival only two to three years.

In order to identify “high-risk” subjects for mortality following AVR, a number of scoring systems have been developed. The Society of Thoracic Surgeons (STS) Predicted Risk of Mortality appears to be the most accurate score for predicting perioperative and long-term mortality and morbidity in subjects undergoing aortic valve replacement. Dewey and colleagues compared the mean and logistic Euro System for Cardiac Operative Risk Evaluation (EuroSCORE), the Society of Thoracic Surgeons (STS) risk score, and the Ambler Risk Score in 638 subjects who underwent isolated aortic valve replacement. Subjects at or above the 90th percentile of risk (8.38% for STS, 33.47% for logistic, 12% for additive, 14.3% for Ambler) were identified as “high-risk” subjects for aortic valve replacement. Long-term mortality, per high-risk group, was 64.1% in the STS Predicted Risk of Mortality, 45.3% in the logistic, 45.2% in the additive, and 40.2% in Ambler Risk Score, and logistic regression showed that the STS algorithm was the most sensitive in defining the subjects most at risk for long-term mortality. There are
also potential risks associated with cardiopulmonary bypass in high-risk subjects, and minimally invasive surgical approach has lessened but not eliminated these risks. 

Moreover, there are subjects who are deemed non-surgical due to prohibitive medical and anatomical conditions including highly compromised respiratory disease, severe immunosuppressive diseases, “true” porcelain aorta, chest wall radiation or deformity and multiple previous interventions in the presence of advanced multi-system dysfunction. Most of these characteristics are not included in the STS or other risk assessment systems (often such subjects will score less than an STS of 10). Despite the limitations noted, subjects with severe aortic stenosis who are not candidates for aortic valve replacement may undergo balloon valvuloplasty as a palliative procedure. In a series reported by Shareghi and colleagues, 80 consecutive subjects with symptomatic severe aortic stenosis underwent 104 balloon aortic valvuloplasty procedures and were followed for a mean of 3±2 years. Repeated valvuloplasty was needed in 15 subjects over the course of follow-up, including 5 balloon valvuloplasties in one subject. Nine percent of subjects had vascular complications. In-hospital, 1, 2- and 3-year mortality rates were 6%, 44%, 62% and 71%, respectively. In another series reported by Sack and colleagues, BAV was performed in 75 subjects who were not candidates for surgical aortic valve replacement. Serious adverse events occurred in 17% of the BAV procedures. The mortality rates at 6 months and 12 months were 25% and 29%, respectively. Contemporary BAV has acceptable short- and mid-term results and can effectively be used for subjects deemed unsuitable surgical candidates and those at highest operative risk, such as subjects with cardiogenic shock, but these therapies should be considered only palliative in nature.

A more viable long-term solution for high or extreme risk subjects for AS may be the development of transcatheter aortic valve implant (TAVI), which would provide the benefit of valve replacement without the associated risks of open-heart surgery. Recent advances in both percutaneous techniques and concurrent technological advances in the evolution of collapsible bioprosthetic aortic valves have led to cautious optimism about this emerging approach. Less invasive percutaneous aortic valve procedures have emerged. Medtronic CoreValve® has developed the Medtronic CoreValve® System (MCS) which consists of a porcine pericardial bioprosthetic valve mounted and sutured in a self-expanding Nitinol frame. The bioprosthesis is housed in a collapsed position for percutaneous delivery via a catheter-based technique, and implanted within the diseased aortic valve. At the discretion of the participating physician (in accordance with the local standard of care), the procedure is performed utilizing local anesthesia (with or without conscious sedation) or under general anesthesia (with or without hemodynamic support or cardiac assistance).

The purpose of this protocol is to evaluate the safety and efficacy of the Medtronic CoreValve® System in the treatment of symptomatic severe aortic stenosis in subjects who have a predicted high risk for aortic valve surgery. High risk surgical subjects will be randomized to receive either transcatheter aortic
valve implant (TAVI) with the Medtronic CoreValve® System (MCS) or SAVR in a 1:1 ratio.

The primary endpoint is all cause mortality at 12 months. The assumption for 12 month mortality for the SAVR arm is an estimate based on 12-month mortality as reported in the surgical literature for high risk AVR (table below). The subjects enrolled in this study are expected to have a higher mortality than observed in the surgical literature, as subjects enrolled in the High Risk Surgical Cohort must have an expected perioperative mortality of 15% (based on Investigator-estimated mortality or STS score >10). Therefore, the assumption of 20% mortality at one year is likely conservative for this subject population. The complete references to the studies used to estimate the rates for the BAV and AVR comparator arms can be found in Section 16.

Table 1. Mortality rates of high risk population from published data.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Mortality at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elayda et al. xviii</td>
<td>1993</td>
<td>77</td>
<td>16%</td>
</tr>
<tr>
<td>Sundt et al. xix</td>
<td>2000</td>
<td>133</td>
<td>20%</td>
</tr>
<tr>
<td>Chiappini et al. xx</td>
<td>2004</td>
<td>71</td>
<td>10%</td>
</tr>
<tr>
<td>Collart et al. xxi</td>
<td>2005</td>
<td>215</td>
<td>16%</td>
</tr>
<tr>
<td>Varadarajan et al. xxi</td>
<td>2006</td>
<td>80</td>
<td>13%</td>
</tr>
<tr>
<td>Melby et al. xxiii</td>
<td>2007</td>
<td>105</td>
<td>18%</td>
</tr>
</tbody>
</table>

Currently, the average patient undergoing surgery is older and has a greater number of comorbidities than the previously studied population. Given that the expected High Risk Surgical population will be older and at higher risk for surgery, it is estimated that the 12-month mortality rate among high risk SAVR subjects in the current study will be 20%.

Sundt et al. xix, Collart et al. xxi, and Melby et al. xxiii reported MACCE rates at 30 days. From these studies, the MACCE (defined as a composite of all cause death, MI (Q-wave and non-Q-wave), emergent cardiac surgery, stroke, and reintervention) rate ranged from 15% to 31% with meta-analytic average of 20.1% (95% CI 16.5-23.8%). Thus, for the current study it is assumed that the expected MACCE rate at 30 days will be 20%.

2.2 Medtronic CoreValve® System and Intended Use

The Medtronic CoreValve® System is intended for use in subjects with severe symptomatic Aortic Stenosis (AS), necessitating aortic valve replacement whose predicted risk of operative mortality is ≥15% (and predicted operative mortality or serious, irreversible morbidity risk of < 50%) at 30 days.
2.3 Primary Objective

The primary objective is to demonstrate that the safety and effectiveness of the Medtronic CoreValve® System (MCS), as measured by all cause mortality rates at 12 months, is non-inferior to surgical aortic valve replacement (SAVR) in the treatment of symptomatic severe aortic stenosis in subjects who have a predicted high risk for aortic valve surgery.

3. TRIAL PROTOCOL

3.1 Ethics & Regulatory Compliance

3.1.1 Applicable Regulations

This trial will be conducted in compliance with the protocol, the Sponsor’s standard operating procedures and/or guidelines, the United States Food and Drug Administration (FDA) and local regulations where applicable, the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki.

3.1.2 Institutional Review Board (IRB)

The trial will be conducted in accordance with 21 CFR 56 Institutional Review Boards. The trial protocol and consent must be approved by the responsible Institutional Review Board (IRB) at each investigational site. Trial activities must not commence prior to receipt of documentation of IRB approval by the site and Medtronic. The Investigator and trial staff must comply with the requirements of their IRB.

3.1.3 Ethical Conduct of the Trial

The trial will be conducted in accordance with the design and specific provisions of this protocol, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable regulatory requirements.

3.1.4 Subject Information and Consent

All subjects must provide written informed consent in accordance with the site’s IRB, using an IRB-approved informed consent form. Trial-specific procedures beyond standard of care must not be performed until a signed informed consent has been obtained. The Investigator/designee, who has been trained on the protocol, will explain the nature and scope of the trial, potential risks and benefits of participation, and answer questions for the patient. If the patient agrees to participate, the informed consent form must be signed and personally dated by the patient or legally authorized representative. The person obtaining informed consent must also sign the informed consent form prior to any trial-related procedures. Any additional persons required by the site’s IRB to sign the informed consent form must also comply. The consent process should be documented in the patient’s medical record.
All subjects are to be fully informed and trial conduct must be in accordance with the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.

Subject confidentiality will be maintained throughout the clinical trial in a way that assures that data can always be tracked back to the source data. For this purpose, a unique subject identification code will be used that allows identification of all data reported for each subject.

Data relating to the trial might be made available to third parties (for example in case of an audit performed by regulatory authorities), provided the data are treated as confidential and that the subject’s privacy is guaranteed. “Protected Health Information” will be maintained in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

3.2 Trial Administration

3.2.1 Operations Committee

An Operations Committee will provide oversight of the Medtronic CoreValve® U.S. Pivotal Trial as well as issues relating to study enrollment and quality performance at individual sites. The Operations Committee will consist of, at a minimum, the following individuals:

- Medtronic Membership:
  - Committee Chairperson
  - Clinical & Medical Leadership
  - Facilitator
- Non-Medtronic Membership:
  - National Principal Investigators (Interventional Cardiologist and Cardiac Surgeon)
  - Consulting Specialties
    - Medtronic CoreValve® Proctor
    - Heart Failure physician
    - Neurologist
    - Electrophysiologist
    - Interventional Cardiologist
    - Quality of Life Specialist
  - Selected Clinical Site Investigators
    - Cardiac Surgeon
    - Interventional Cardiologist

The functions of the Operations Committee include, but are not limited to the following:

- Provide oversight and direction for the trial
- Review of trial enrollment and trial progress
• Support site investigators in resolving any clinical or procedural issues that may impact patient well-being or integrity of the study

• Participate in investigator meetings with case review, protocol insights, etc.

• Review of Data Safety Monitoring Board (DSMB) recommendations

• Assist with publication efforts

Prior to the onset of the trial, the Operations Committee will establish a charter that outlines their roles and responsibilities and describes the planned frequency of meetings. The Operations Committee charter will be approved by Medtronic and the Operations Committee members.

### 3.2.2 Screening Committee

The Medtronic CoreValve® U.S. Pivotal Trial Screening Committee will ensure appropriate and consistent patient selection across all sites for the Medtronic CoreValve® U.S. Pivotal Trial. The Screening Committee will consist of Medtronic CoreValve® U.S. Pivotal Trial investigators (interventional cardiologists and cardiac surgeons) and Medtronic CoreValve® proctors. Final decisions on patient eligibility will be made by two cardiac surgeons and one interventional cardiologist on the Screening Committee.

Prior to the onset of the trial, the Screening Committee will establish a charter that outlines their roles and responsibilities and describes the Screening Committee process. The Screening Committee charter will be approved by Medtronic and the Screening Committee members.

### 3.2.3 Training and Education Committee

The Medtronic CoreValve® U.S. Pivotal Trial Training and Education Committee will review recommendations made by Medtronic field support and Medtronic CoreValve® proctors for transition of sites from the roll-in phase to the randomization phase of enrollment. The Committee will also review recommendations made by the Data Safety Monitoring Board (DSMB) after their scheduled reviews. It is the responsibility of the Training and Education Committee to make recommendations relative to the augmentation of physician training at a site level, as well as across the trial as a whole. The Training and Education Committee will consist of experienced Medtronic CoreValve® implanters and Medtronic CoreValve® U.S. Pivotal Trial investigators.

Prior to the onset of the trial, the Training and Education Committee will establish a charter that outlines their roles and responsibilities and describes the planned frequency of meetings. The Training and Education Committee charter will be approved by Medtronic and the Training and Education Committee members.

### 3.2.4 Publication Committee

The Medtronic CoreValve® U.S. Pivotal Trial Publication Committee will review and approve publication ideas and facilitate submissions, including abstracts and manuscripts. The Publication Committee will consist of Medtronic CoreValve®
U.S. Pivotal Trial investigators (interventional cardiologists and cardiac surgeons) and Medtronic representatives.

Prior to the onset of the trial, the Publication Committee will establish a plan that outlines their roles and responsibilities and describes the planned frequency of meetings. The Publication Committee plan will be approved by Medtronic and the Publication Committee members.

3.3 Methodology

3.3.1 Purpose
To evaluate the safety and efficacy of the Medtronic CoreValve® System in the treatment of symptomatic severe aortic stenosis in subjects who have a predicted high risk for aortic valve surgery. The total trial duration is expected to be approximately seven years.

3.3.2 Patient Population
Subjects with symptomatic severe aortic stenosis (AS), necessitating aortic valve replacement whose predicted risk of operative mortality is ≥15% (and predicted operative mortality or serious, irreversible morbidity risk of < 50%) at 30 days.

3.3.3 Design
Subjects will be randomized on a 1:1 basis to either transcatheter aortic valve implant (TAVI) with the Medtronic CoreValve® System (MCS) or to surgical aortic valve replacement (SAVR).

3.3.4 Investigational Sites
The trial will be conducted at up to 40 investigational sites in the United States.

3.3.5 Number of Subjects
Roll-in cases: 3 per implanting site (inclusive of both High Risk Surgical and Extreme Risk patient populations and separate from evaluable sample size)
Proctored cases: minimum of 5 per site (inclusive of the 3 roll-in cases)
Sample size: 790 (395 MCS TAVI : 395 Surgical Aortic Valve Replacement (SAVR))

3.3.6 Inclusion/Exclusion Criteria
To participate in this trial, the subject must meet ALL of the following inclusion criteria:
1. Subject must have co-morbidities such that one cardiologist and two cardiac surgeons agree predicted risk of operative mortality is ≥15% (and predicted operative mortality or serious, irreversible morbidity risk of < 50%) at 30 days.
2. Subject has senile degenerative aortic valve stenosis with mean gradient > 40 mmHg jet velocity greater than 4.0 m/s, or an initial aortic valve area of ≤ 0.8 cm² (or aortic valve area index ≤ 0.5 cm²/m²) by resting echocardiogram.

3. Subject is symptomatic from his/her aortic valve stenosis, as demonstrated by New York Heart Association (NYHA) Functional Class II or greater.

4. The subject or the subject’s legal representative has been informed of the nature of the trial, agrees to its provisions and has provided written informed consent as approved by the IRB of the respective clinical site.

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

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

**Clinical**

1. Evidence of an acute myocardial infarction ≤ 30 days before the intended treatment.

2. Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to the index procedure with bare metal stents and 6 months with drug eluting stents.

3. Blood dyscrasias as defined: leukopenia (WBC < 1000/mm³), thrombocytopenia (platelet count <50,000 cells/mm³), history of bleeding diathesis or coagulopathy, or hypercoagulable states.

4. Untreated clinically significant coronary artery disease requiring revascularization.

5. Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support.


7. Severe ventricular dysfunction with left ventricular ejection fraction (LVEF) < 20% as measured by resting echocardiogram.

8. Recent (within 6 months) cerebrovascular accident (CVA) or transient ischemic attack (TIA).

9. End stage renal disease requiring chronic dialysis or creatinine clearance < 20 cc/min.

10. Gastrointestinal (GI) bleeding within the past 3 months.

11. A known hypersensitivity or contraindication to any of the following which cannot be adequately pre-medicated:
   - aspirin
   - heparin (HIT/HITTS)
   - nitinol (titanium or nickel)
   - ticlopidine and clopidogrel
   - contrast media

12. Ongoing sepsis, including active endocarditis.
13. Subject refuses a blood transfusion.
14. Life expectancy < 12 months due to associated non-cardiac co-morbid conditions.
15. Other medical, social, or psychological conditions that in the opinion of an Investigator precludes the subject from appropriate consent.
16. Severe dementia (resulting in either inability to provide informed consent for the trial/procedure, prevents independent lifestyle outside of a chronic care facility, or will fundamentally complicate rehabilitation from the procedure or compliance with follow-up visits).
17. Currently participating in an investigational drug or another device trial.
18. Symptomatic carotid or vertebral artery disease.
19. Subject has been offered surgical aortic valve replacement but declined.

**Anatomical**
20. Native aortic annulus size < 20 mm or > 27 mm per the baseline diagnostic imaging.
21. Pre-existing prosthetic heart valve in any position.
22. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation (3-4+)).
23. Severe mitral (3-4+) or severe tricuspid regurgitation.
24. Moderate to severe mitral stenosis.
25. Hypertrophic obstructive cardiomyopathy.
26. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.
27. Severe basal septal hypertrophy with outflow gradient.
28. Aortic root angulation > 70°.
29. Ascending aorta diameter > 43 mm unless the aortic annulus is 20-23 mm in which case the ascending aorta diameter > 40 mm.
30. Congenital bicuspid or unicuspid valve verified by echocardiography.

**Vascular**
31. Transarterial access not able to accommodate an 18Fr sheath.

**3.3.7 Informed Consent**
Prior to enrolling in the trial, patients should be fully informed of the details of trial participation as required by applicable regulations, the site’s Institutional Review Board (IRB) and by Medtronic, Inc. Informed consent must be obtained from each patient or legally authorized representative prior to conducting any protocol-induced activities beyond standard of care, by using the informed consent form (ICF) approved by that site’s IRB and by Medtronic, Inc. The consent form must be signed and dated by the patient or legal representative and by the person obtaining the consent. Any additional persons required by the site’s IRB to sign the informed consent form must also comply.

Prior to the patient or legal representative signing the ICF, the Investigator or authorized designee will fully explain to the patient or legal representative 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 patient or legal representative to read and review the consent form and to ask questions.

Signing the ICF serves to document the written and verbal information that the Investigator or authorized delegate provides to the patient or legal representative, the patient or legal representative’s understanding of the information, and their agreement to participate. The Investigator or authorized delegate must document in the patient’s medical records that the patient was consented and the date on which the consent was obtained. The original signed consent form will be retained in the patient’s trial records. A copy of the informed consent will be provided to the patient or legal representative and a copy placed in the patient’s medical record.
3.3.8 Enrollment Flowchart for randomization to MCS TAVI vs. SAVR

Figure 1: Enrollment Flowchart

- Subjects with Symptomatic Aortic Stenosis
- Obtain Informed Consent
- Physician Screening Assessment
  - No → Subject Not Enrolled
  - Pass → Screening Committee Review
    - No → Subject Not Enrolled
    - Pass → Subject Enrolled Randomized 1:1
      - MCS TAVI N=395
      - SAVR N=395
3.3.9 Trial Training

Protocol-specific training and education of all site staff with roles in this trial will take place during the site initiation visit, and throughout the trial as needed. The sponsor will maintain documentation of attendance at each of these training opportunities. Training will include the specifics of trial conduct, product-specific information, and adverse event reporting. A Medtronic representative may be present at each site’s MCS TAVI procedures.

Training for the implanting investigators includes but is not limited to the following:

- On-line training, including
  - Good Clinical Practice
  - Pathophysiology and Natural History of Aortic Stenosis
  - General Product Description
  - Pre- and post-patient procedural care
  - Medtronic CoreValve® U.S. Pivotal Trial Inclusion/Exclusion Criteria

- Face-to-face didactic training, including
  - Aortic Anatomy and Current Procedures
  - Medtronic CoreValve® Technology Review
  - Procedure Steps
  - Patient selection
  - Implant procedure – Pre-Procedure, Anesthesia and Post-Procedure Patient Care
  - Device Preparation & Loading
  - Complication Management
  - Clinical Data Overview

- Case observations
- Case proctoring
  - A minimum of 5 procedures will be proctored by a Medtronic-trained physician.

- Training for the full team conducted on-site will include the following:
  - Product Use
  - Procedure Steps
  - Device Preparation & Loading
3.4 Trial Procedures

3.4.1 Screening Procedures

Prior to subject participation in this trial, the Investigator must obtain written IRB approval for the trial protocol, informed consent form, and Health Insurance Portability and Accountability Act (HIPAA) Authorization. The approved consent form should clearly reflect the IRB approval date.

All potential subjects for trial entry must be screened for eligibility. Prior to any trial-specific tests or procedures, written informed consent must be obtained from the subject.

Failure to obtain a signed and hand dated informed consent prior to the procedure constitutes a protocol violation, which is reportable to the IRB and the Food and Drug Administration (FDA).

The following tests and procedures must be performed prior to randomization to verify eligibility. The recommended timeframe for these tests and procedures is approximately 30 days prior to submission to the Screening Committee, unless otherwise specified:

- Physical examination including vital signs and all major systems findings, weight, height and body surface area (BSA); BSA will be calculated from height and weight by use of the formula by Dubois and Dubois (BSA = 0.007184 × weight [kg]^{0.425} × height [m]^{0.725}).
- NYHA classification
- STS Risk Score Assessment
- Medtronic CoreValve® Frailty Index
- Routine laboratory tests (most recent) including complete blood count (CBC), platelet count, cardiac enzymes (CK and CK-MB), international normalized ratio (INR), Partial Thromboplastin Time (PTT), liver panel and albumin.
- Subject demographics, medical history, risk factors targeted to cardiovascular disease
- 12-lead Electrocardiogram
- Cardiovascular imaging studies:
  - Comprehensive transthoracic 2D echocardiogram (TTE). The TTE must be performed within 45 days prior to submission to the Screening Committee. (Note: if patient recently underwent BAV, a TTE should be obtained post-BAV; within 45 days prior to submission to the Screening Committee). Echocardiograms will be performed according to the Echocardiography Procedures found in Appendix 17.8. All echocardiograms for enrolled subjects will be independently analyzed by the Echocardiographic Core Lab.
Screening thoracic and abdominal Computed Tomography (CT) angiograms with complete visualization of both iliacs, femorals and aorta, up to and including the aortic annulus. In the situation where subjects have compromised renal function that precludes contrast media, Magnetic Resonance (MR) imaging may be used as an alternative. CT angiograms will be performed according to the CT Angiography Acquisition Guidelines found in Appendix 17.20.

If the CT angiogram was conducted in the last 365 days and subject has not had a peripheral vascular intervention since the time of the image, a more recent exam is not required as long as visualization of both iliacs and femorals to the aorta can be viewed. However, if the subject had a peripheral vascular intervention, the exam must be more recent (within 90 days of being sent to the Screening Committee).

Selective coronary arteriography to assess the presence and severity of coronary artery disease which should include angiograms of both coronary arteries and all bypass grafts (if applicable).

If the coronary arteriogram has been performed within the last 365 days and the subject qualifies for the study (no significant coronary artery disease), a more recent exam is not required. However, if the subject had evidence of significant coronary artery disease and/or received a coronary intervention, the exam must be repeated within 90 days of being sent to the Screening Committee.

- B-type Natriuretic Peptide (BNP), hemoglobin, and plasma free hemoglobin
- National Institutes of Health Stroke Scale (NIHSS)
- Modified Rankin Scale (for subjects with history of stroke only)
- A six minute walk test per the American Thoracic Society Guidelines (detailed instructions can be found in Appendix 17.15), will be performed unless the subject is exempt due to any of the following conditions: postural hypotension, postural arrhythmia, resting systolic pressure less than 95 mmHg, non-ambulatory due to arthritis, neuromuscular disease or Peripheral Vascular Disease (PVD), Chronic Obstructive Pulmonary Disease (COPD) with O₂ desaturation upon ambulation or oxygen dependent, or unstable angina. Subjects with any of these conditions will not undergo the test, but the reasons for not performing the test must be completed on the six minute walk test case report form.
- Quality of Life Questionnaires (Kansas City Cardiomyopathy Questionnaire (KCCQ), SF-12, and EuroQoL)
- Assessment of concomitant medications. All medications administered during this trial will be recorded in the subject’s medical record. Use of relevant medications (diuretics, ACE-I, ARB, beta-blockers, statins and anti-platelets) must be reported on the electronic Case Report Form (eCRF).
• For patients with an existing permanent pacemaker or defibrillator only:
  Perform a full interrogation. Save the data on a diskette and retain the
  diskette in the subject's file for source verification.

The final eligibility for each subject will be confirmed by the Screening
Committee.

3.4.2 Screening Committee Procedures

The Medtronic CoreValve® U.S. Pivotal Trial Screening Committee will review
baseline information to make the final determination regarding eligibility of the
prospective subject to be enrolled in the Medtronic CoreValve® U.S. Pivotal Trial.

The following information should be submitted to the Screening Committee:

• Completed Patient Screening Worksheet including, but not limited to:
  o Demographics
  o Physical Measurements & Vital Signs
  o Surgical Risk Assessment
  o Case Planning
  o Medtronic CoreValve® Frailty Index
  o Medical History and Co-Morbidities
  o Anatomical Measurements

• DICOM-compatible images and cines of all screening exams:
  o Comprehensive transthoracic 2D echocardiogram (TTE). The TTE
    must be performed within 45 days prior to submission to the
    Screening Committee. (Note: if patient recently underwent BAV, a
    TTE should be obtained post-BAV; within 45 days prior to
    submission to the Screening Committee). Echocardiograms will be
    performed according to the Echocardiography Procedures found in
    Appendix 17.8.
  o Screening thoracic and abdominal CT angiograms with complete
    visualization of both iliacs, femorals and aorta, up to and including
    the aortic annulus. CT angiograms will be performed according to
    the CT Angiography Acquisition Guidelines found in Appendix
    17.20.
  o Selective coronary arteriography to assess the presence and
    severity of coronary artery disease which should include
    angiograms of both coronary arteries and all bypass grafts (if
    applicable).
3.4.3 Roll-in Cases

The first three successfully screened patients at each implanting site inclusive of both High Risk Surgical and Extreme Risk patient populations will be considered “roll-in” subjects, will not be randomized, and will automatically be assigned to MCS TAVI. A maximum of three roll-in subjects is allowed per site. The purpose of the roll-in subjects is to provide the investigators the time for training and familiarization with the protocol and devices. The Medtronic CoreValve® U.S. Pivotal Trial Training and Education Committee will review recommendations made by Medtronic field support and Medtronic CoreValve Proctors for transition of sites from the roll-in phase to the randomization phase of enrollment. The Training and Education Committee will review and document their decisions based on the technique of the investigators, as well as the frequency, severity and nature of events in the roll-in subjects.

Subjects enrolled as roll-in subjects will be followed for safety following the same schedule as subjects who are randomized to MCS TAVI. However, the results for the roll-in population will be analyzed separately from the Pivotal trial subjects.

3.4.4 Enrollment and Randomization

Prior to randomization of a subject, the following must occur:

- Obtain signed informed consent.
- Confirm patient meets all of the inclusion and none of the exclusion criteria, including approval by the Screening Committee.

Due to the inclusion/exclusion criteria, not all subjects that consent to the trial will be enrolled. All sites will be required to maintain a record of patients screened for the trial meeting general inclusion criteria who have signed the approved informed consent document. For subjects that do not meet trial criteria, the reason for not continuing in the trial must be documented on the screening log. Randomization will occur only if the patient meets all inclusion criteria and does not meet any exclusion criteria and has been assessed by the Screening Committee as being an appropriate candidate for enrollment in the Medtronic CoreValve® U.S. Pivotal Trial.

Subjects will be considered enrolled into the trial at the time of randomization. Subjects must have their MCS TAVI or SAVR procedure no later than 30 days post-randomization. Trial randomization will not be blinded. Once randomization is complete and a treatment arm is assigned, crossover from SAVR to TAVI treatment is not permitted. The sponsor will maintain strict device accountability to ensure that only those subjects randomized to the MCS TAVI treatment arm receive the Medtronic CoreValve® PAV.

Distribution of the subjects within the trial groups will be controlled at the implanting sites by means of central randomization using interactive voice/web randomization service (IXRS). The randomization scheme will be securely stored at the IXRS provider (Appendix 17.11).
Randomization with an assignment to the treatment arm or control arm (MCS TAVI or SAVR) will be executed in a 1:1 ratio. Stratified randomization by implanting site will be used to ensure subjects at each site will be allocated to each comparison group proportionately.

### 3.4.5 Medtronic CoreValve® System TAVI or Surgical Aortic Valve Replacement (SAVR) Procedure

#### 3.4.5.1 MCS TAVI

The following procedures are recommended for MCS TAVI subjects. The Instructions For Use (IFU) and Medtronic CoreValve® Proctors may also be consulted for additional guidance.

**Pre-Procedure**

- If the patient is currently on warfarin therapy prior to the procedure
  - Discontinue warfarin 3 days prior to the procedure
  - Confirm that the INR < 1.8 prior to the procedure
  - aspirin (81-325 mg) and clopidogrel (75 mg) daily or ticlopidine if clopidogrel is contraindicated) for 3 days prior to the procedure.
- If the patient is currently not on warfarin therapy prior to the procedure
  - aspirin (81-325 mg) on the day of the procedure, then
  - clopidogrel, 300 mg daily
- Consider adjunctive proton pump inhibitors, H₂ antagonists or antacids
- Routine laboratory tests including complete blood count (CBC), platelet count, international normalized ratio (INR), Partial Thromboplastin Time (PTT), liver panel and albumin.
- Cardiac enzymes (CK and CK-MB) obtained within 48 hours of the procedure.
- Perform 12-lead Electrocardiogram.
- Check serum creatinine and creatinine clearance.
  - If the GFR < 60 cc/min, consider:
    - Fluid hydration on the day prior to the procedure
    - Discontinuation of NSAIDs and ACE inhibitors

**MCS TAVI Procedure**

- **Medications**
  One hour prior to the procedure, prophylactic antibiotic therapy of the Investigator’s choice should be initiated:
  - Cefuroxime 750mg IV 1 hour pre-procedure, then 6 hours and 12 hours post-procedure
  - If allergic to Penicillin, prescribe Vancomycin 1g IV,
  - Consider holding anti-hypertensives

- **Anesthesia and Procedural Set Up**
  - Establish a central venous line.
\begin{itemize}
  \item Administer general anesthesia or conscious sedation per hospital protocol.
  \item Place a temporary 4-5 Fr. balloon-tip pacing wire in a stable location within the right ventricular (balloon-tip or screw in leads)
  \item Whenever possible, use the upper torso venous system (e.g., jugular, subclavian) for temporary pacing wire access.
  \item Use fluoroscopy to guide wire placement and stability.
  \item Set the back up pacing rate at a minimum rate
  \item Record ECG and angiogram during the procedure
\end{itemize}

\textbf{Vascular Access}
\begin{itemize}
  \item Insert 18 Fr Sheath using hospital protocol (either percutaneously or surgical cut down)
  \item Administer anticoagulant therapy according to hospital protocol. If heparin is administered as an anticoagulant, check activated clotting time (ACT) at five minutes and monitor every 30-60 minutes after initial bolus of heparin.
  \item Maintain ACT $\geq$ 250 seconds.
  \item Anticoagulant may be administered at any time prior to this point, but avoid delaying beyond this point.
\end{itemize}

\textbf{Crossing the native valve}
\begin{itemize}
  \item Advance the graduated pigtail catheter to the ascending aorta and position the distal tip in the noncoronary cusp of the native aortic valve.
  \item Identify the ideal annular viewing plane using contrast injections at various angiographic angles, preferably in the left anterior oblique (LAO) projection.
  \item Insert an angiographic catheter over a standard, J-tip guidewire into the primary access sheath and advance to the ascending aorta.
  \item Exchange the J-tip guidewire for a 0.035-in (0.889-mm) straight-tip guidewire. Advance the straight-tip guidewire across the aortic valve into the left ventricle.
  \item After crossing the native aortic valve with the guidewire, advance the angiographic catheter into the left ventricle.
  \item Exchange the straight-tip guidewires for an exchange-length J-tip guidewire.
  \item Exchange the angiographic catheter for a 6 Fr pigtail catheter.
  \item Remove the guidewire and connect the catheter to the transducer. Using both catheters, record the aortic pressure gradient.
  \item Using a right anterior oblique (RAO) projection, advance previously pigtail-shaped, 0.035-in (0.889-mm) high-support guidewire through the pigtail catheter and position in the apex of the left ventricle.
  \item Remove the pigtail catheter while maintaining guidewire position in the left ventricle.
\end{itemize}
• **Rapid Pacing and Pre-dilatation of the Implant site**
  
  o Insert the valvuloplasty balloon through the 18 Fr introducer sheath and advance it to the ascending aorta.
  
  o Perform a rapid pacing test. A successful test is defined as 1-to-1 pacing capture with an immediate drop in pressure and reduction of the systolic-diastolic waveform and reduction of peak systolic pressure < 60 mmHg, usually 180-200 bpm.
  
  o Reposition the angiographic equipment to the ideal viewing plane as previously described. Position the valvuloplasty balloon across the native valve, while maintaining strict fluoroscopic surveillance of the distal tip of the guidewire in the left ventricle (LV).
  
  o Perform BAV per hospital protocol and remove the valvuloplasty balloon while maintaining guidewire position across the native aortic valve.
  
  o Balloon sizing directed to 1:1 sizing of the minimal annular diameter by CTA or echocardiogram with maximum 25 mm balloon.
  
  o Perform full balloon expansion (high pressure).

• **Medtronic CoreValve® Implantation**
  
  o Insert the device over the 0.035-in (0.889-mm) guidewire and advance it to the descending aorta, while maintaining strict fluoroscopic surveillance of the guidewire in the LV.
  
  o When crossing the aortic arch, control the guidewire preventing it from moving forward.
  
  o Advance the device through the native valve. Perform an angiogram to confirm that the pigtail catheter is in position within the noncoronary cusp of the aortic root, preferably in the shallow LAO projection.
  
  o Use Fluoroscopy to identify the appropriate landmarks.
  
  o Place the bioprosthesis within the aortic annulus (less that 6 mm below the annulus). The annulus is defined as the angiographic floor of the cusps.
  
  o After attaining optimal catheter position, slowly turn the micro knob and begin to deploy the bioprosthesis. As the inflow aspect of the bioprosthesis starts to flare outward, monitor bioprosthesis position under fluoroscopy.
  
  o Caution: During implantation, if resistance to deployment is encountered (for example, the micro knob starts clicking or is tight or stuck), apply mild upward pressure to the macro slider while turning the micro knob. If the bioprosthesis still does not deploy, remove it from the patient and use another system.
  
  o Perform an angiogram. Once annular contact is made, the bioprosthesis should not be advanced into a lower position.
  
  o Continue deploying rapidly to the 2/3 deployment point; stop turning the micro knob.
Perform an angiogram to assess the location of the bioprosthesis. Optimal placement of the bioprosthesis is within the aortic annulus (approximately 6 mm below the annulus).

- If the bioprosthesis is positioned low, carefully pull the DCS to reposition the bioprosthesis.
- Evaluate the valve position and valve function using hemodynamic, aortography, and possible echocardiography.
- When satisfactory position is achieved, continue to turn the micro knob until both frame loops disengage.
- Use orthogonal views under fluoroscopy to confirm that the frame loops have detached from the catheter tabs. If a frame loop is still attached to a catheter tab, under fluoroscopy, advance the catheter slightly and, if necessary, gently rotate the handle clockwise (<180°) and counterclockwise (<180°) to disengage the loop from the catheter tab.
- Withdraw the DCS carefully into the ascending aorta avoiding contact with the inflow portion of the frame

**Post Deployment**

- Withdraw the DCS to the descending aorta, while maintaining guidewire position.
- Close the DCS capsule and remove the DCS through the 18 Fr introducer sheath.
- Advance a 6-Fr pigtail catheter over the guidewire into the left ventricle.
- Remove the guidewire and connect the pigtail catheter to the transducer.
- Using both pigtail catheters, record aortic pressure gradient.
- Withdraw 6-Fr pigtail.
- Perform postimplant aortogram with the 5-Fr reference pigtail to assure coronary patency and assess aortic regurgitations.
- Withdraw the 5-Fr reference pigtail to the aortic bifurcation.
- Remove the 18-Fr introducer sheath and complete the access site closure per hospital protocol.
- Perform contrast angiography of the primary iliac and femoral vessels to verify the absence of any vascular complications with the 5-Fr reference pigtail.
- Remove the 5-Fr reference pigtail catheter over a standard guidewire.
- Remove the 6 Fr introducer and close the access site per hospital protocol.

Ballooning as needed during the implant procedure is standard practice and should not be considered a reintervention.

**Immediate Post-Procedure**
The procedure is considered complete after final angiography has been performed, and the introducer sheath has been removed from the subject. Thereafter, if an introducer sheath is re-introduced, this is considered a repeat intervention, which must be documented on the reintervention eCRF.

- Anticoagulants should be discontinued per hospital standard.
- Activated clotting time (ACT) should be monitored per hospital standards but recommendation is >250 seconds.
- Cardiac Enzymes (CK and CK-MB) Note: CK within 8-12 hours post procedure and at any time when a clinical ischemic event is suspected. CK-MB is required if CK is elevated >2X the laboratory upper limit of normal. If a clinical event is confirmed, a total of 3 sets of cardiac enzymes within the first 24 hours (drawn every 8 hours) following the clinical event should be obtained.
- 12-lead Electrocardiogram (performed within 48 hours of MCS TAVI)
- NIHSS should be administered within 24 hours post-procedure
- Modified Rankin Scale (for subjects with a stroke only – to be performed at 30 days and 3 months post-stroke.)
- An echocardiogram should be done 24-48 hours post-procedure to assess device success.
- It is recommended that subjects are treated for a minimum of three months with dual anti-platelet medication.
  - if the patient is on warfarin therapy post-procedure:
    - it is recommended that subjects are prescribed daily aspirin (81 to 325 mg) and daily clopidogrel (75 mg) (or ticlopidine, if clopidogrel is contraindicated) for at least three months following the procedure.
  - If the patient will not be on warfarin therapy post-procedure:
    - it is recommended that subjects are prescribed either daily aspirin (81 to 325 mg) or daily clopidogrel (75 mg) (or ticlopidine, if clopidogrel is contraindicated) for at least three months following the procedure.
- Documentation of all adverse events/serious adverse events from enrollment to discharge including all unanticipated adverse device effects (UADE), reinterventions or repeat admissions to the catheterization suite.

**Post-Procedure Pacing guidelines**
- All patients should stay on telemetry until discharge
- Maintain temporary pacing until at least 48 hours post-implant in CV-ICU
- After 48 hours, obtain Electrocardiogram (ECG) and assess patient rhythm and condition
- Based on assessment, and with the consult of an electrophysiologist as needed, take one of the following actions:
  - Discontinue temporary pacing
- Continue temporary pacing for another 24 hours (longer if needed) to make further assessments
- Place a permanent pacemaker according to ACC/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities
- For complete heart block, review patient medications.
- Consider withholding some medications to assess for patient’s intrinsic rate and conduction.
- If heart block persists off medications, a permanent pacemaker should be considered.
- If a permanent pacemaker is required, a dual chamber system is recommended to optimize patient hemodynamics.
- If a permanent pacemaker is implanted, perform a device interrogation post insertion and prior to hospital discharge as well as at every follow-up visit to evaluate device utilization.

Assessments done at discharge

Prior to hospital discharge (or within 7 days post-MCS TAVI, whichever occurs first) the following tests and procedures must be performed and data collected:
- Brief physical examination including vital signs and all major systems findings
- Routine laboratory tests including CBC, platelet count, BNP, hemoglobin and plasma-free hemoglobin.
- 12-lead Electrocardiogram
- Comprehensive transthoracic 2D echocardiogram (TTE). The TTE should be performed as close to discharge (or 7 days, whichever is sooner) as possible. Echocardiograms will be performed according to the Echocardiography Procedures found in Appendix 17.8. All echocardiograms for enrolled subjects will be independently analyzed by the Echocardiographic Core Lab.
- NIH Stroke Scale (NIHSS also to be done within 24 hours of any reintervention.)
  - Any patient with evidence of a neurological event should have a neurology consult and an imaging study if deemed necessary.
- Modified Rankin Scale (for subjects with a stroke only – to be performed at 30 days and 3 months post-stroke.)
- Concomitant Medications Assessment
  - All medications administered during this trial will be recorded in the subject’s medical record.
  - Use of relevant medications (diuretics, aspirin, anticoagulants, ACE-I, ARB, beta-blockers, statins and anti-platelets) must be reported on the eCRF through at least the 12 month follow-up assessment.
o Documentation of all adverse events/serious adverse events from enrollment to discharge including all unanticipated adverse device effects (UADE), reinterventions or repeat admissions to the catheterization suite.

o For patients with permanent pacemakers or defibrillators only: Perform a full interrogation. Save the data on a diskette and retain the diskette in the subject’s file for source verification.

3.4.5.2 Surgical Aortic Valve Replacement
Subjects randomized to SAVR should be treated according to the surgeon and hospital’s standard practices. The SAVR procedure must be an isolated procedure (no concomitant procedures). The surgeon or co-surgeon performing the SAVR must be a trial investigator for the site.

All medications administered during this trial will be recorded in the subject’s medical record. Use of relevant medications (diuretics, aspirin, anticoagulants, ACE-I, ARB, beta-blockers, statins, and anti-platelets) must be reported on the eCRF through at least the 12-month follow up assessment.

Immediate Post-Procedure
Immediately post-procedure the following tests and procedures must be performed and data collected:

- Cardiac Enzymes (CK and CK-MB) Note: CK within 8-12 hours post procedure and at any time when a clinical ischemic event is suspected. CK-MB is required if CK is elevated ≥2X the laboratory upper limit of normal. If a clinical event is confirmed, a total of 3 sets of cardiac enzymes within the first 24 hours (drawn every 8 hours) following the clinical event should be obtained.
- 12-lead Electrocardiogram (performed within 48 hours of SAVR)
- NIHSS should be administered within 24 hours post-procedure
- Modified Rankin Scale (for subjects with a stroke only – to be performed at 30 days and 3 months post-stroke.)
- Comprehensive transthoracic 2D echocardiogram (TTE). The TTE will be performed according to the Echocardiography Procedure found in Appendix 17.8. All echocardiograms for enrolled subjects will be independently analyzed by the Echocardiographic Core Lab. A TTE should be performed 24-48 hours post-procedure to assess device success.

Assessments done at discharge

o Prior to hospital discharge (or within 7 days post-procedure, whichever occurs first) the following tests and procedures must be performed and data collected:
Brief physical examination including vital signs and all major systems findings

Routine laboratory tests including CBC, platelet count, BNP, hemoglobin, and plasma-free hemoglobin

12-lead Electrocardiogram

Comprehensive transthoracic 2D echocardiogram (TTE) The TTE will be performed according to the Echocardiography Procedure found in Appendix 17.8. All echocardiograms for enrolled subjects will be independently analyzed by the Echocardiographic Core Lab. The TTE should be performed as close to discharge (or 7 days, whichever is sooner) as possible.

NIH Stroke Scale (NIHSS also to be done within 24 hours of any reintervention.)  
  - Any patient with evidence of a neurological event should have a neurology consult and an imaging study if deemed necessary.

Modified Rankin Scale (for subjects with a stroke only – to be performed at 30 days and 3 months post-stroke.)

Concomitant Medications Assessment  
  - All medications administered during this trial will be recorded in the subject’s medical record.

Use of relevant medications (diuretics, aspirin, anticoagulants, ACE-I, ARB, beta-blockers, statins, and anti-platelets) must be reported on the eCRF through at least the 12 month follow-up assessment.

Documentation of all adverse events/serious adverse events from enrollment to discharge including all unanticipated adverse device effects (UADE), reinterventions or repeat admissions to the catheterization suite.

For patients with permanent pacemakers or defibrillators only: Perform a full interrogation. Save the data on a diskette and retain the diskette in the subject’s file for source verification.

3.4.6 Follow-up Evaluations

All trial subjects will undergo follow-up evaluations at the following time points post implant (MCS TAVI or SAVR): 30 days (± 7 days), 6 months (180 ± 14 days), 12 months (360 ± 45 days), and annually at 2 years (720 days ± 60 days), 3 years (1080 ± 60 days), 4 years (1440 days ± 60 days) and 5 years (1800 ± 60 days). All of these visits will require the subject to return to the clinic.

The following assessments are required at the 30 day, 6 month and 12 month clinic visits.
• Brief physical examination including vital signs and all major systems findings
• NYHA classification
• 12-lead Electrocardiogram
• Rotational x-ray (12-month visit only and for MCS TAVI patients only)
• Comprehensive transthoracic 2D echocardiogram (TTE). The TTE will be performed according to the Echocardiography Procedure found in Appendix 17.8. All echocardiograms for enrolled subjects will be independently analyzed by the Echocardiographic Core Lab.
• BNP, hemoglobin, and plasma free hemoglobin
• NIH Stroke Scale (NIHSS also to be done within 24 hours of any re-intervention.)
• Modified Rankin Scale (for subjects with a stroke only – to be performed at 30 days and 3 months post-stroke.)
• A six minute walk test per the American Thoracic Society Guidelines (detailed instructions can be found in Appendix 17.15), will be performed unless the subject is exempt due to any of the following conditions: postural hypotension, postural arrhythmia, resting systolic pressure less than 95 mmHg, non-ambulatory due to arthritis, neuromuscular disease or Peripheral Vascular Disease, Chronic Obstructive Pulmonary Disease with O₂ desaturation upon ambulation or oxygen dependent, or unstable angina. Subjects with any of these conditions will not undergo the test, but the reasons for not performing the test must be documented on the six minute walk test case report form. The six minute walk test is not required at the 6-month visit interval.
• Quality of Life Questionnaires (Kansas City Cardiomyopathy Questionnaire (KCCQ), SF-12, and EuroQoL)
• Assessment of concomitant medications
• Documentation of all adverse events, technical observations, and deaths, including all unanticipated adverse device effects (UADE), re-interventions or repeat admission to the catheterization suite.
  • Any patient with evidence of a neurological event should have a neurology consult and subsequently an imaging study if deemed necessary by the neurologist.
• For patients with permanent pacemakers or defibrillators only (existing or new): Perform a full interrogation at the beginning of each follow-up visit. Save the data on a diskette and retain the diskette in the subject’s file for source verification.

The following assessments are required at the annual clinic visits at 2, 3, 4 and 5 years.
• Brief physical examination including vital signs and all major systems findings
• NYHA classification
• 12-lead Electrocardiogram
• Rotational x-ray (for MCS TAVI only)
• Comprehensive transthoracic 2D echocardiogram (TTE). The TTE will be performed according to the Echocardiography Procedure found in Appendix 17.8  All echocardiograms for enrolled subjects will be independently analyzed by the Echocardiographic Core Lab.
• BNP, hemoglobin, and plasma free hemoglobin
• NIH Stroke Scale (NIHSS also to be done within 24 hours of any reintervention.)
• Modified Rankin Scale (for subjects with a stroke only – to be performed at 30 days and 3 months post-stroke.)
• Quality of Life Questionnaires (Kansas City Cardiomyopathy Questionnaire (KCCQ), SF-12, and EuroQoL)
• Documentation of serious adverse events, major adverse events, device-related events, including device-related technical observations, unanticipated adverse device effects (UADE), all strokes (CVAs) and deaths. Data related to pre-existing adverse events should be reconciled and resolved.
  o Any patient with evidence of a neurological event should have a neurology consult and an imaging study if deemed necessary.
• For patients with permanent pacemakers or defibrillators only (existing or new): Perform a full interrogation at the beginning of each follow-up visit. Save the data on a diskette and retain the diskette in the subject’s file for source verification.

3.4.7 Data Collection
All scheduled testing and procedures to be conducted during the screening, index procedure and follow-up assessments are summarized in Table 2.
<table>
<thead>
<tr>
<th>Testing</th>
<th>Screening/Baseline</th>
<th>Implant Procedure/Valve Surgery</th>
<th>Immediate Post-Procedure</th>
<th>Discharge (or at 7 days post-procedure, whichever occurs first)</th>
<th>1 month (30 days)</th>
<th>6 month (120 days)</th>
<th>Month 12 (360 days)</th>
<th>Months 24, 36, 48 &amp; 60 (± 60 Days)</th>
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<tbody>
<tr>
<td>Informed Consent and HIPAA Authorization</td>
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<td></td>
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<td>Inclusion/Exclusion Criteria</td>
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<tr>
<td>Clinical Assessment &amp; Physical Exam</td>
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<td>Demographics and Medical History</td>
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<td>Medtronic CoreValve® Frailty Index</td>
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<td>X</td>
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<td>X</td>
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<td>STS Risk Score</td>
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<td>Routine Laboratory Tests including Complete Blood Count, &amp; Platelet Count</td>
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<td>Cardiac Enzymes (CK/CK MB)^2</td>
<td>X^1</td>
<td>X^3</td>
<td>X^2</td>
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<td>B-type Natriuretic Peptide, Hemoglobin, Plasma Free Hemoglobin</td>
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<td>X</td>
<td>X</td>
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<td></td>
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<tr>
<td>International Normalized Ratio, Partial Thromboplastin Time, Liver Panel, Albumin</td>
<td>X^1</td>
<td>X^3</td>
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<td>Electrocardiogram</td>
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<td>Transthoracic Echocardiogram (TTE)</td>
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<td>Computed Tomography (CT) Angiogram^6</td>
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<td>Coronary Arteriogram)</td>
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<td>NIH Stroke Scale^7</td>
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<td>X^8</td>
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<td>Quality of Life Questionnaires</td>
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<td>Adverse Events</td>
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<td>X</td>
<td>X</td>
<td>X^11</td>
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<tr>
<td>Pacemaker/defibrillator interrogation^12</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

(X) MCS TAVI subjects only (SAVR subjects will not have these assessments)

^1 Results may be sent to the Screening Committee for confirmation of eligibility.

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2 CK within 48 hours of procedure and 8-12 hours post-procedure and at any time when a clinical ischemic event is suspected. CK-MB is required if CK is elevated (≥ 2X the laboratory upper limit of normal). If a clinical event is confirmed, a total of 3 sets of cardiac enzymes within the first 24 hours (drawn every 8 hours) following the clinical event should be obtained.

3 Laboratory test results must be performed pre-procedure for subjects randomized to the MCS TAVI or SAVR.

4 Electrocardiogram will be obtained within 48 hours of surgery.

5 TTE should be done 24-48 hours post-procedure to assess device success.

6 All subjects should have screening thoracic and abdominal CT angiograms with complete visualization of both iliacs, femorals and aorta, up to and including the aortic annulus. (MRI may be used as an alternative in situations where subjects have compromised renal function)

7 NIHSS to be done within 24 hours of any reintervention.

8 NIHSS to be done within 24 hours of the procedure

9 For any patient that has a stroke, Modified Rankin scale must be performed at 30 days (±7 days) and 3 months (±7 days) post-stroke.

10 Modified Rankin to be performed at baseline for patients with a previous history of stroke only

11 SAE, MAE, device-related events, including device-related technical observations, UADEs, all strokes (CVAs) and death reports.

12 For patients with permanent pacemakers or defibrillators only.

3.4.8 Unscheduled Follow-up Assessments
If a subject returns to the institution between their scheduled follow-up visits the visit will be treated as an unscheduled visit and the assessments completed at this visit will be done at the discretion of the investigator. eCRFs are provided for unscheduled visits.

3.4.9 Investigational Product Handling and Accountability
The Investigator shall maintain adequate records of the receipt and disposition of all investigational devices. At the trial closeout visit, the Investigator must return to the Sponsor any unused devices and a copy of the completed device inventory. The Investigator’s copy of the device reconciliation records must document any unused devices that have been returned to the Sponsor as well as all product usage including opened but unimplanted devices.

In the event that a Medtronic CoreValve® PAV is explanted (due to reintervention or autopsy), the Medtronic CoreValve® PAV should be returned per the Explanted Device/Pathology Core Lab Protocol in Appendix 17.12.

In the event of a device malfunction of the Medtronic CoreValve® System (MCS) prior to implant, affect MCS components should be returned to:
Explant Laboratory
Medtronic, Inc. SS-84
1851 E. Deere Avenue
Santa Ana, CA 92705-5720

Additional details surrounding the device return process are contained within the Medtronic explant kit.
3.4.10 Protocol Deviations

A protocol deviation is defined as an event where the clinical investigator or site personnel did not conduct the trial according to the protocol or the Investigator agreement. Deviations will be reported regardless of whether medically justifiable, pre-approved by Medtronic, or taken to protect the patient in an emergency.

A protocol deviation form is to be completed for each trial protocol deviation, including, but not limited to:

- Failure to obtain informed consent
- Incorrect version of consent provided to patient
- Failure to obtain IRB protocol review and approval before starting the trial
- Enrollment of patient during an IRB approval lapse
- Clinical investigator exceeding enrollment limits specified by sponsor
- Patient did not meet inclusion/exclusion criteria
- Incorrectly performed testing
- Protocol-required testing and/or measurements not done or performed outside of window
- Source data permanently missing
- UADE not reported in the required timeframe

FDA regulations [21 CFR 812.140] require that the Investigator maintain accurate, complete, and current records, including documents showing the dates of and reasons for each deviation from the protocol. Relevant information for each deviation will be documented on a deviation form completed by site personnel and reviewed by the Investigator.

Federal regulations [21 CFR 812.150] require Investigators to obtain prior approval from the sponsor before initiating changes in or deviations from the protocol, except when necessary to protect the life or physical well being of a patient in an emergency.

Prior approval by the sponsor is expected in those situations in which the Investigator anticipates, contemplates or makes a conscious decision to depart from procedures specified in the protocol. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator’s control, but is still considered a deviation (e.g. a trial subject who fails to attend a scheduled follow-up visit, a trial subject too ill to perform a protocol-required test). To obtain approval, the Investigator must call or email and discuss the potential deviation with the Medtronic trial manager or designee prior to initiating any changes.

FDA regulations require the Investigator to notify the sponsor and the reviewing IRB within 5 working days of the following deviations [21 CFR 812.150]:

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• a deviation from protocol to protect the life or physical well being of a patient in an emergency
• failure to obtain an informed consent.

Investigators or an authorized designee must notify Medtronic as soon as possible by calling the trial manager or designee and completing the protocol deviation form.

The Investigator is required to adhere to local IRB procedures for reporting deviations.

The DSMB may review protocol deviations to ensure compliance and overall study integrity.

3.4.11 Subject Withdrawal or Discontinuation

All subjects will be encouraged to remain in the trial through the last follow-up visit at month 60. Subjects who discontinue participation prematurely after randomization will be included in the analysis of results (as appropriate) but they will not be replaced in the enrollment of total trial subjects. If a trial subject is discontinued from the trial early, a Study Exit eCRF must be completed describing the reason for discontinuation. The trial site and Sponsor 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 three attempts to make contact via telephone and if contact via phone is not successful, a certified letter from the Principal Investigator must be sent to the subject’s last known address. Should both telephone and mail efforts to contact the subjects be unsuccessful, the subject’s primary physician should be contacted. 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 in the trial eCRFs.

3.4.12 Early Termination or Discontinuation of Trial

Possible reasons for early trial termination include:

• Unanticipated Adverse Device Effects (UADE) present an unreasonable risk to patients.
• Recommendation from DSMB.

If the trial is terminated early, the Sponsor will provide a written statement to the Investigators to enable notification of the IRBs. The Sponsor will also inform the FDA. If the trial enrollment is terminated early, the follow-up visits will continue for all enrolled subjects.

3.5 Adverse Events

3.5.1 Definitions

The definitions presented in this section allow for a clear understanding of adverse event data collection and subsequent analysis.
3.5.1.1 Adverse Event
An adverse event (AE) is any undesirable experience (sign, symptom, illness, or other medical event) occurring to the subject, and that appears or worsens during the clinical trial, whether or not associated with the investigational products or related procedures.
The following events are expected to occur with any surgical implant and therefore should not be reported as AEs, unless they occur outside of the stated timeframe:

<table>
<thead>
<tr>
<th>Description of the Event</th>
<th>Timeframe (hours) from the Surgical Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthesia-related nausea and/or vomiting</td>
<td>24</td>
</tr>
<tr>
<td>Low-grade fever (&lt;100°F or &lt;37.8°C)</td>
<td>48</td>
</tr>
<tr>
<td>Back pain related to laying on the procedure table</td>
<td>72</td>
</tr>
<tr>
<td>Incisional pain (pain at access site)</td>
<td>72</td>
</tr>
<tr>
<td>Sleep problems or insomnia</td>
<td>72</td>
</tr>
<tr>
<td>Mild to moderate bruising or ecchymosis</td>
<td>168</td>
</tr>
</tbody>
</table>

3.5.1.2 Serious Adverse Event
A serious adverse event (SAE) is an event that meets any of the following criteria:

- Results in subject death
- Is life threatening* (i.e., the subject was at risk of death at the time of the event)
- Results in inpatient hospitalization
- Results in prolonged existing hospitalization
- Results in persistent or significant disability**/incapacity
- Results in congenital anomaly/birth defect
- Results in permanent impairment of a body function or permanent damage to a body structure
- Necessitated medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

*A life-threatening adverse event is any adverse event that places the subject, in the opinion of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.
**The definition of disability is a substantial disruption of a person’s ability to conduct normal life functions.
Events that do not meet these criteria are considered non-serious.

3.5.1.3 Major Adverse Cardiovascular and Cerebrovascular Events
Major adverse cardiovascular and cerebrovascular events (MACCE) is defined as a composite of:
- all-cause death
- myocardial infarction (MI)
- major stroke, and
- reintervention (defined as any cardiac surgery or percutaneous reintervention catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve)

3.5.1.4 Major Adverse Event
Major adverse event (MAE) includes:
- MACCE
- Acute kidney Injury
- Cardiac tamponade
- Prosthetic valve dysfunction
- Cardiogenic shock
- Valve endocarditis
- Embolism
- Life-threatening, disabling or major bleeding
- Major vascular complication

3.5.1.5 Adverse Device Effect (ADE) or Device-Related Adverse Event
An ADE is an adverse event with a reasonable possibility that the device caused or contributed to the event. During this clinical investigation an event should be considered related to the device when it is the result of the Medtronic CoreValve® System (MCS):
- The percutaneous aortic valve (PAV)
- The delivery catheter system (DCS)
- The compression loading system (CLS)
- The implant procedure
An event should be considered not related to the device when it is the result of:
- A pre-existing medical condition
- A new illness, injury or condition
- Medication
3.5.1.6 Unanticipated Adverse Device Effect (UADE)
An unanticipated adverse device effect or UADE is defined as “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol or application (including a supplementary plan or application), or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects” [21 CFR 812.3 (s)].
Those known adverse events related to the device, procedure or therapy are listed in Section 3.5.2.3 and in the Risk/Benefit Analysis section of this document (Section 4).

3.5.1.7 Technical Observation
A technical observation is a defect, malfunction, or failure of any part of the Medtronic CoreValve® System. This may pertain to the device or system not functioning according to its design intent. Technical observations may or may not be related to an adverse event in a subject. Technical observations (whether or not associated with any untoward medical occurrence in a subject) will be reported on the Adverse Event (AE) eCRF.

3.5.2 Reporting
Investigators are required to keep records on "all relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated)" [21 CFR 812.140]. All new or worsening (from baseline) adverse events and technical observations will be captured on the AE eCRF. It is the responsibility of the Investigator to assess the subject for adverse events and capture the required adverse event information on the AE eCRF. Once a subject has completed their 12-month scheduled follow-up visit, serious adverse events, major adverse events, device-related adverse events, including device related technical observations, unanticipated adverse device effects (UADE), all strokes (CVAs) and deaths will be required to be reported.
Medtronic representatives or their designees will conduct monitoring visits to review source documentation and verify the complete and accurate capturing of adverse events.
The Investigator must also notify the responsible IRB regarding new and significant safety information and any event identified by Medtronic that require expedited FDA reporting as serious, unexpected, and related to the investigational device.
Medtronic Clinical will ensure all device-related adverse events and all procedure-related SAEs are processed according to internal policies and procedures. When necessary, Medtronic Field Assurance will respond to sites in writing with the findings related to the product experiences.
The general procedure for investigators reporting any adverse event is as follows:
• If an adverse event occurs, complete all sections of the Adverse Event eCRF.
• Each unique event/diagnosis must be documented separately.
• Documented pre-existing conditions are not considered to be reportable AEs unless there is a change in the nature or severity of the condition.
• The Adverse Event eCRF must be reviewed by the Investigator

Reporting guidelines related to specific types of adverse events are outlined below.

3.5.2.1 Serious Adverse Events (SAEs)
Medtronic requests that the Investigator notify the sponsor within 3 working days of learning of any SAE using the electronic data capture (eCRF) system. If necessary, the Investigator may be requested to provide copies of source documentation regarding the event (e.g., physician/nurse notes or summaries). Medtronic will conduct an evaluation of the event and if it is determined by Medtronic to be a UADE, it will be reported as described in the following sections.

3.5.2.2 Unanticipated Adverse Device Effects
Investigators must report any (potential) unanticipated adverse device effects to Medtronic and their IRB as soon as possible but no later than within 10 working days after the Investigator first learns of the event [21 CFR 812.150]. UADEs should be reported immediately via telephone as well as on an eCRF. The Investigator should consider the device labeling and the Risk/Benefit Analysis section of this document (Section 4) when determining whether an event is unanticipated or not.

If an event is determined by Medtronic to be a UADE, Medtronic will report the event to all investigators to enable reporting to their respective IRBs. Medtronic will provide this notification within 10 working days after Medtronic first receives notice of the effect. [21 CFR 812.150]

If Medtronic and the DSMB determine that the event presents an unreasonable risk to the participating subjects, Medtronic must terminate all investigations or parts of investigations presenting the risk in the clinical trial 5 working days after making that determination and not later than 15 working days after Medtronic first receives notice of the effect. [21 CFR 812.46] Follow-up visits for enrolled subjects will continue according the schedule of assessments.

3.5.2.3 Anticipated Adverse Events
Potential risks associated with MCS TAVI may include, but are not limited to, the following:
• Death
• Acute myocardial infarction
• Stroke
• Urgent need for surgery
  o Coronary artery bypass
Heart valve replacement
Valve explant

- Urgent need for balloon valvuloplasty (note that BAV during implantation is expected)
- Urgent need for Percutaneous Coronary Intervention (PCI)
- Cardiogenic shock
- Perforation of the myocardium or vessel
- Cardiac Tamponade
- Ascending aorta trauma
- Myocardial ischemia
- Acute coronary artery occlusion
- Disturbances in the electrical system of the heart that may result in the permanent placement of a device (pacemaker)
  - Atrio-ventricular node block
  - Bundle branch block
  - Asystole
- Ventricular arrhythmias
- Embolization
- Thrombosis
- Hemorrhage requiring transfusion
- Arteriovenous fistula
- Vessel dissection or spasm
- Valve migration
- Prosthetic valve dysfunction including but not limited to:
  - Fracture
  - Bending of the valve frame
  - Under-expansion of the valve frame
  - Calcification
  - Wear or tear in the valve leaf
  - Poor valve coaptation
  - Suture breaks or disruption
  - Leak
  - Mal-sizing
  - Malposition (either too high or too low)
  - Regurgitation
  - Stenosis
- Mitral valve regurgitation
- Hypotension or hypertension
- Acute renal injury
- Allergic reaction to antiplatelet agents or contrast medium
- Infection
- Bowel ischemia
- Complications at the area where the doctor opened the skin, including
  - pain
  - bleeding
  - hematoma
3.5.2.4 Deaths
The Investigator should notify Medtronic and his/her IRB within 3 working days of learning of a subject’s death, whether or not the death is related to the investigational device. The Investigator should also attempt to determine, as conclusively as possible, whether such deaths are related to the Medtronic CoreValve® System. When an autopsy is conducted, a copy of the report should be provided to Medtronic. Medtronic will evaluate the event and if device-related and unexpected, the event will be reported as a UADE.

Any subject death will be reported on an eCRF and accompanied by an adverse event form identifying the cause of death.

3.5.3 Clinical Events Committee (CEC)
An independent Clinical Events Committee (CEC) will review and adjudicate, at a minimum, all deaths and endpoint related adverse events. The CEC will consist of interventional cardiologists, cardiologists and cardiovascular surgeons, including a chairperson, who are not participants in the trial.

The purpose of the CEC is to conduct a medical review and classify/adjudicate, at a minimum, all deaths and/or clinical endpoints collected in the trial according to definitions and processes outlined in the Medtronic CoreValve® U.S. Pivotal Trial protocol and the CEC charter, which will be developed and approved by Medtronic and the CEC members.

Events will be reviewed and adjudicated by a minimum of three CEC members, who will meet at regular intervals, via teleconference or in person, as deemed necessary. All other events will be reviewed and adjudicated by qualified internal Medtronic safety individual(s) to ensure they should not be adjudicated by the full CEC and that the events are appropriately classified by the investigator.

Prior to the onset of the trial, the CEC will establish explicit rules outlining the minimum amount of data required and the algorithm followed in order to classify/adjudicate a trial endpoint related clinical event. CEC decisions will be documented in meeting minutes, which will be maintained in the trial file.

3.5.4 Data Safety Monitoring Board (DSMB)
An independent, unblinded DSMB will be established and will be comprised of at least 3 experts, including a chairperson. The DSMB will have a minimum of one cardiac surgeon, one interventional cardiologist and one statistician, and will be independent of Medtronic and the trial investigators. Investigators participating in the trial may participate in the meetings to offer clarification surrounding events, but will not have voting privileges. Medtronic personnel may facilitate the DSMB meeting but will not have voting privileges. The DSMB will meet (via teleconference or in person) prior to first subject enrollment to establish procedures for DSMB review, chairman appointment and guidelines for trial recommendation. The full DSMB will meet on a periodic basis to perform a comprehensive data review, including at a minimum, all adverse events and
deaths, and will meet more frequently when needed. Primary and safety-related secondary endpoints may also be reviewed at these meetings. Meetings will consist of both open and closed sessions.

The DSMB will also perform a supplemental review of, at a minimum, serious adverse events and deaths and any other data requested by the DSMB on a more frequent periodic basis to ensure patient safety. DSMB members would review the report, and when necessary provide recommendations about the conduct of the study and/or request a full DSMB meeting.

A DSMB charter will be developed and approved by Medtronic. The committee and will outline the criteria for both the full DSMB meeting and supplemental DSMB reviews.

Following each full DSMB meeting, the board will report to Medtronic in writing and may recommend changes in the conduct of the trial. These DSMB recommendations may include recommendations on trial status such as continuing the trial without modifications, continuing the trial with modifications, stopping the enrollment in the trial or a specific trial arm, or recommendations about trial conduct including recommendations around enrollment or protocol deviations.

In the case of UADEs, if Medtronic and the DSMB determine that the event presents an unreasonable risk to the participating subjects, Medtronic must terminate the clinical trial 5 working days after making that determination and not later than 15 working days after Medtronic first receives notice of the effect. [21 CFR 812.46].

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 and returned to the trial statistician at the closure of the DSMB meeting.

Additional details about the DSMB can be found in the DSMB charter.

3.6 Statistical Methods and Analysis

The statistical analyses will be performed by Medtronic employed statisticians and independently verified by the staff of the Biostatistics Department at the Harvard Clinical Research Institute. All randomized subjects will be analyzed following the intent-to-treat (ITT) approach.

3.6.1 Description of Baseline Variables

Baseline demographic and clinical variables will be summarized for each of the treatment groups for both the intent-to-treat and per protocol populations. All continuous variables will be summarized as means, medians, standard deviations and interquartile ranges and compared between treatment groups using a two-sample t-test or the non-parametric Wilcoxon rank sum test. Categorical variables will be summarized as frequencies and percentages and compared between treatment groups using Pearson’s \( \chi^2 \) test or Fisher’s exact test, as appropriate. Ordinal variables will be compared using Cochran-Mantel-Haenszel test with row mean scores.
3.6.2 Missing Data
Every effort will be undertaken to minimize missing data. In time-to-event outcomes drop-outs 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 for continuous or categorical outcomes. The number of subjects included in each analysis will be reported so that the reader can assess the potential impact of missing data.

For the primary endpoint, a sensitivity analysis will be conducted to assess the impact of censored data and will include a worst-case analysis.

3.6.3 Reports
Medtronic is responsible for the reports cited in Table 3. These reports are subject to regulatory retention and inspection requirements. In addition to the reports listed in Table 3, FDA or the reviewing IRB may request reports pertaining to any aspect of the clinical trial.

3.6.4 Primary Endpoint
The primary endpoint for the trial is all cause mortality at 12 months.

3.6.5 Primary Hypothesis and Sample Size Determination

3.6.5.1 Primary Hypothesis
Primary Hypothesis: TAVI with the Medtronic CoreValve® System is non-inferior to surgical aortic valve replacement (SAVR) in 12 month mortality:

\[ H_0: \pi_{MCS \ TAVI} \geq \pi_{SAVR} + 7.5\% \]
\[ H_A: \pi_{MCS \ TAVI} < \pi_{SAVR} + 7.5\% \]

In the above expression \( \pi_{MCS \ TAVI} \) and \( \pi_{SAVR} \) denote binary rates of all cause mortality during a fixed follow-up of 12 months. The one-sided Farrington and Manning test\textsuperscript{xxiv} for non-inferiority of two binomial proportions will be carried out to assess statistical significance.

Powered Secondary Hypothesis: TAVI with the Medtronic CoreValve® System is superior to SAVR in binary rate of mortality at 30 days:

\[ H_0: \pi_{MCS \ TAVI} = \pi_{SAVR} \]
\[ H_A: \pi_{MCS \ TAVI} < \pi_{SAVR} \]

This one-sided test will be carried out at the 0.025 level using the pooled z-test without correction for continuity.
3.6.5.2 Sample Size Determination

Primary Hypothesis

Assumptions:

1:1 treatment allocation ratio
One-sided alpha = 0.05

$\pi_{SAVR} = 20.0\%$

$\pi_{MCS\ TAVI} = 20.0\%$

Power = $>80\%$

Evaluable sample size: 710 (355 MCS TAVI : 355 SAVR)

Assuming 1:1 treatment allocation ratio between study device and surgical valve replacement and assuming the proportion of all cause mortality at 12 months equal to 20% for both arms and a non-inferiority margin of 7.5%, a total of 355 subjects in each arm is required to attain 80% power in a test of non-inferiority of the study device at the 0.05 level of significance. Accounting for 10% loss to follow-up, a total of 395+395 = 790 subjects is required.

Powered Secondary Hypothesis

Assumptions:

1:1 treatment allocation ratio
One-sided alpha = 0.025

$\pi_{SAVR} = 20.0\%$

$\pi_{MCS\ TAVI} = 12.1\%$

For the secondary superiority hypothesis, assuming 1:1 treatment allocation ratio between study device and surgical valve replacement and assuming the proportion of MACCE at 30 days equal to 20% in the surgical valve replacement arm and equal to 12.1% in the study device arm (39.5% relative treatment effect), 355 evaluable subjects per arm would yield 81.9% power for a one-sided test at the 0.025 level of significance.
3.6.6 Secondary Endpoints

The secondary endpoints are as follows:

The following secondary endpoints will be compared between MCS TAVI and SAVR subject cohorts:

1. MACCE-free survival at 30 days, 6 months, 12 months and annually thereafter up to 5 years.
   MACCE-free survival estimates will be provided for the randomized groups at 30 days, 6 months, 12 months and annually through five years. All subjects will be included in the analysis.
   The endpoint will be evaluated using life table Kaplan-Meier survival analysis and the log-rank test.

2. The occurrence of individual MACCE components at 30 days, 6 months, 12 months and annually thereafter up to 5 years.
   MACCE components will be summarized and MACCE component event-free rates will be provided at 30 days, 6 months, 12 months and annually through 5 years. All subjects will be included in the analysis.
   The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.

3. MAE at 30 days, 6 months, 12 months and annually thereafter up to 5 years.
   MAE events will be summarized and MAE event-free rates will be provided at 30 days, 6 months, 12 months, and annually through five years. All subjects will be included in the analysis.
   The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.

4. Conduction disturbance requiring permanent pacemaker implantation at 30 days, 6 months, 12 months and annually thereafter up to 5 years.
   The incidence of conduction disturbance requiring permanent pacemaker implantation will be provided at 30 days, 6 months, 12 months and annually through five years, separately for new onset and pre-existing conduction disturbance. All subjects will be included in the analysis.
   The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.

5. Change in NYHA class from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years.
   For each subject with paired data, the number of classes changed from baseline (-2, -1, 0, 1, 2, or 3) will be calculated at 30 days, 6 months, 12 months and annually through five years.
   The endpoint will be evaluated using a two-sample t-test or Wilcoxon rank sum test as appropriate.
6. Change in distance walked during 6-minute walk test (6MWT) from baseline to 30 days and baseline to 12 months
   All subjects who are able to perform the six-minute walk evaluation; and those subjects who are unable to perform the walk evaluation due to heart failure symptoms at the time of the follow-up visit will be included in the analysis.
   The six-minute walk evaluation will be evaluated at 30 days and at 12 months using a two-sample t-test or Wilcoxon rank sum test as appropriate.

7. Ratio of days alive out of hospital versus total days alive assessed at 12 months follow-up.
   The proportion of post randomization days alive out of hospital against total days alive will be compared at twelve months. The numerator will be the number of days alive out of hospital, and the denominator will be the number of days alive as of the follow-up visit date. All hospitalizations will be included in this analysis, including hospitalization for device implant. All subjects will be included in the analysis.
   The endpoint will be evaluated using continuous data analyses such as a two-sample t-test or Wilcoxon rank sum test.

8. Quality of Life (QoL) change from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years.
   The Kansas City Cardiomyopathy Questionnaire (KCCQ), SF-12, and EuroQoL will be assessed at baseline, 30 days, 6 months, 12 months and annually through five years. All subjects completing the questionnaires will be evaluated and the reasons for missing data will be provided.
   The changes in QoL scores will be evaluated using a two-sample t-test or Wilcoxon rank sum test as appropriate.

9. Echocardiographic assessment of prosthetic valve performance at discharge, 30 days, 6 months, 12 months, and annually thereafter up to 5 years using the following measures:
   - transvalvular mean gradient
   - effective orifice area
   - degree of prosthetic aortic valve regurgitation (transvalvular and paravalvular)

   The four echocardiographic measurements will be evaluated at discharge, 6 months, 12 months and annually through five years. All subjects undergoing echocardiography procedures will be evaluated.
   All measures will be evaluated using a two-sample t-test or the Wilcoxon rank sum test for continuous variables, and the Mantel-Haenszel test for categorical variables, as appropriate.
10. Repeat hospitalization
The number of subjects re-hospitalized after the initial index procedure will be compared at 30 days, 6 months, 12 months and annually through five years. All subjects will be included in the analysis. Hospitalization-free rates will be provided at 30-days, 6 months, 12 months and annually through five years. All subjects will be included in the analysis. The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.

11. Cardiovascular deaths and valve-related deaths
The number of cardiovascular deaths and valve-related deaths at 30 days, 6 months, 12 months, and annually through five years will be reported. All subjects will be included in the analysis. The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.

12. Strokes
The number of strokes (of any severity) and TIAs at 30 days, 6 months, 12 months and annually through five years will be reported. All subjects will be included in the analysis. The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.

13. Index procedure related MAEs
Index procedure-related MAE events will be summarized and event rates will be provided at 30 days. The numerator will be the number of procedure-related MAE events experienced by the end of the follow-up visit, and the denominator will be the number of subjects evaluated at the follow-up visit plus the number of subjects not evaluated but who experienced a procedure-related MAE event prior to the end of the follow-up visit window. The endpoint is descriptive and no statistical hypothesis test will be performed.

14. Length of index procedure hospital stay
The length of TAVI or SAVR hospital stay will be summarized for all subjects. Descriptive statistics will be provided. The endpoint is descriptive and no statistical hypothesis test will be performed.

15. Device success defined as follows:
- successful delivery and placement of the device, and successful retrieval of the delivery system,
- correct position of the device within the aortic annular region (placement in the annulus with no impedance on device function),
- successful device function assessed acutely (within 24 to 48 hours post-implantation or prior to hospital discharge), where successful device function is defined as follows:
- absence of device migration (device within aortic annular region) assessed qualitatively by echocardiography
- less than moderate (2+) aortic regurgitation by echocardiography
- effective orifice area > 1.2 cm² by echocardiography using the continuity equation.

- Only one valve implanted in the proper anatomical location

Device success, as defined above, will be calculated for all subjects undergoing the TAVI procedure.
The endpoint is descriptive and no statistical hypothesis test will be performed.

16. Procedural success, defined as device success and absence of in-hospital MACCE.
Procedure success, as defined above, will be calculated for all subjects undergoing the TAVI procedure.
The endpoint is descriptive and no statistical hypothesis test will be performed.

17. Evidence of prosthetic valve dysfunction at 30 days, 6 months, 12 months and annually thereafter up to 5 years.
The number of subjects with evidence of prosthetic valve dysfunction will be evaluated at 30 days, 6 months, 12 months and annually through five years. All subjects will be included in the analysis.
A Kaplan-Meier survival analysis will be performed. The endpoint is descriptive and no statistical hypothesis test will be performed.

3.6.7 Relevant Statistical Analysis Considerations
All statistical tests and/or confidence intervals, as appropriate, will be performed at $\alpha=0.05$ (2-sided), except when specified otherwise. All reported p-values greater than or equal to 0.0001 will be rounded to three decimal places. P-values less than 0.001 will be displayed as “<0.001.”

Provided the 12-month mortality primary objective and the 30-day MACCE powered secondary hypothesis are met with significant p-values, to keep the overall (familywise) Type I error rate at 0.05, a hierarchical test procedure will be applied to five of the secondary objective hypothesis tests. The goal of this hierarchical procedure is to make statistically valid claims of significance in the device labeling.
In this hierarchical test procedure, each objective is examined in the pre-specified order. The hierarchical testing order will be:

1. Change in transvalvular mean gradient from baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #9. The one-sided two-sample t-test will be used to test non-inferiority at a level of 0.05 the hypotheses:

   \[ H_0: \mu_{MCS\ TAVI} \leq \mu_{SAVR} -15 \]
   \[ H_A: \mu_{MCS\ TAVI} > \mu_{SAVR} -15 \]

   In the above expression \( \mu_{MCS\ TAVI} \) and \( \mu_{SAVR} \) denote the mean improvements in mean gradient from baseline to 12 months measured in mmHg.

2. Change in effective orifice area baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #9. The one-sided two-sample t-test will be used to test non-inferiority at a level 0.05 the hypotheses:

   \[ H_0: \mu_{MCS\ TAVI} \leq \mu_{SAVR} -0.375 \]
   \[ H_A: \mu_{MCS\ TAVI} > \mu_{SAVR} -0.375 \]

   In the above expression \( \mu_{MCS\ TAVI} \) and \( \mu_{SAVR} \) denote the mean improvements in effective orifice area from baseline to 12 months measured in cm\(^2\).

3. Change in NYHA classification from baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #5. The one-sided two-sample t-test will be used to test non-inferiority at a level 0.05 the hypotheses:

   \[ H_0: \mu_{MCS\ TAVI} \leq \mu_{SAVR} -0.375 \]
   \[ H_A: \mu_{MCS\ TAVI} > \mu_{SAVR} -0.375 \]

   In the above expression \( \mu_{MCS\ TAVI} \) and \( \mu_{SAVR} \) denote the mean number of classification improvements in NYHA from baseline to 12 months.

4. Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score from baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #8. The one-sided two-sample t-test will be used to test non-inferiority at a level 0.05 the hypotheses:

   \[ H_0: \mu_{MCS\ TAVI} \leq \mu_{SAVR} -5 \]
   \[ H_A: \mu_{MCS\ TAVI} > \mu_{SAVR} -5 \]

   In the above expression \( \mu_{MCS\ TAVI} \) and \( \mu_{SAVR} \) denote the mean improvements in the KCCQ score from baseline to 12 months.

5. Change in SF-12 Physical Summary Scale from baseline to 30 days: TAVI vs. SAVR from secondary objective #8. The two-sided two-sample t-test will be used to test at a level 0.05 the hypotheses:

   \[ H_0: \mu_{MCS\ TAVI} = \mu_{SAVR} \]
   \[ H_A: \mu_{MCS\ TAVI} \neq \mu_{SAVR} \]
In the above expression $\mu_{MCS \text{TAVI}}$ and $\mu_{SAVR}$ denote the mean improvements in the SF-12 Physical Summary Scale from baseline to 30 days.

As the trial confirmation is not dependent on the secondary endpoints, multiplicity adjustments will not be made in the analyses of the secondary endpoints. Summary data from other secondary objectives, such as device success and procedural success from secondary objectives #16 and #17, respectively, may be provided in the device labeling. However, no claims of statistical significance or other statistical inference will be made.

A poolability analysis between investigational centers and primary baseline demographics will be performed for the primary endpoint and will be described in the Statistical Analysis Plan. In particular, the primary endpoint and key secondary endpoints such as MACCE- and MAE-free survival will be examined for differences in outcome between genders. Additionally, tests for these outcomes will be performed to evaluate potential interactions between treatment and gender.

### 3.7 Data and Quality Management

#### 3.7.1 Electronic Data Capture

Medtronic will use the Oracle Clinical Remote Data Capture database system for data collection.

#### 3.7.2 Data Collection

Required data will be recorded on electronic case report forms (eCRFs) by authorized site personnel as indicated on the Delegation of Authority Log. 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.

The sponsor and/or assigned designee will be responsible for the processing and quality control of the data. All trial-related documents must be retained for a period of at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational device. 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 the Sponsor and the investigator. Should the investigator wish to assign the trial records to another party or move them to another location, advance written notice should be given to the Sponsor.
3.7.3 Core Laboratories Procedures

Data from the core lab will be transferred to Medtronic and stored in the Oracle Clinical Remote Data Capture system as described in the Medtronic CoreValve® U.S. Pivotal Trial Data Management Plan.

3.7.4 Source Documents

Source documentation is defined as the first time the data appear and may include all clinical records, hospital records, surgery reports, autopsy reports, and any other material that contains original information used for trial data collection or adverse event reporting. No eCRFs may serve as source documents. Source documentation may vary from site to site.

The source documents must be retained by the investigational site for a period of 2 years after trial conclusion and made available for monitoring or auditing by the sponsor’s representative or representatives of the FDA and other applicable regulatory agencies. The Investigator must ensure the availability of source documents from which the information on the eCRFs was derived.

3.8 Records and Reports

3.8.1 Responsibilities of the Sponsor

The Sponsor must maintain the following records:

- All essential correspondence related to the clinical trial
- Signed Investigator Agreement
- Curriculum vitae for each Investigator
- Records of device shipment and disposition (shipping receipts, material destruct records, etc.)
- Adverse event information
- Complaint documentation
- All data forms, prepared and signed by the Investigators and received source documentation and core lab reports
- Protocol and report of prior investigations
- Site monitoring reports
- Financial disclosure information
The Sponsor is responsible for the preparation of, the accuracy of the data contained in, the review of and the submission of the reports listed in Table 3.

### Table 3. Sponsor Reporting Responsibilities

<table>
<thead>
<tr>
<th>Report</th>
<th>Submit to</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unanticipated Adverse Device Effects</td>
<td>IRB, Investigators, FDA</td>
<td>Medtronic will report on any unanticipated adverse device effect evaluation within 10 working days after first receiving notice of the effect.</td>
</tr>
<tr>
<td>Withdrawal of IRB approval</td>
<td>IRB, Investigators, FDA</td>
<td>Notification, when appropriate, will be made within 5 working days after Medtronic receives notice of withdrawal of IRB approval.</td>
</tr>
<tr>
<td>Withdrawal of FDA approval</td>
<td>IRB, Investigators</td>
<td>Notification will be made within 5 working days after Medtronic receives notice of withdrawal of FDA approval.</td>
</tr>
<tr>
<td>Current Investigator List</td>
<td>FDA</td>
<td>Medtronic will submit a current list of the names and addresses of all participating Investigators at six-month intervals, beginning six months after FDA approval of IDE.</td>
</tr>
<tr>
<td>Progress Report</td>
<td>IRB, Investigators, FDA</td>
<td>A progress report will be submitted at least yearly.</td>
</tr>
<tr>
<td>Recall and Device Disposition</td>
<td>IRB, Investigators, FDA</td>
<td>Notification will be made within 30 working days of Medtronic’s request that an Investigator return, repair or otherwise dispose of any devices. Such notification will state why the request was made.</td>
</tr>
<tr>
<td>Final Report</td>
<td>IRB, Investigators, FDA</td>
<td>Notification will be made within 30 working days of the completion or termination of the investigation. A final report will be submitted within six months after trial completion or termination.</td>
</tr>
<tr>
<td>Failure to obtain Informed Consent</td>
<td>FDA</td>
<td>Notification will be made within 5 working days after Medtronic’s receipt of such notification indicating Informed Consent was not obtained.</td>
</tr>
<tr>
<td>Emergency Deviations from Investigational Plan</td>
<td>FDA</td>
<td>Notification will be made within 5 working days after Medtronic learns of an emergency deviation from the Investigational Plan where the deviation was made to protect the life or physical well being of a subject.</td>
</tr>
</tbody>
</table>
3.8.2 Responsibilities of the Investigator

The Investigator is responsible for the preparation, review, signature, and retention of the records listed below:

- All essential correspondence that pertains to the investigation
- Device use/disposition records
- Records of each subject’s case history and exposure to the device. Case histories include the CRFs and supporting data (source documentation), including, for example:
  - Signed and dated consent forms
  - Medical records, including, for example, progress notes of the physicians, the subject’s hospital chart(s) and the nurses’ notes
- All adverse event information
- A record of the exposure of each subject to the investigational device (e.g., date of implant procedure and follow-up assessment dates)
- Documentation of any deviation from the protocol, including the date and the rationale for such deviation
- Signed Investigator Agreement and curriculum vitae
- The protocol and any amendments

The Investigator may withdraw from responsibility to maintain records by transferring custody to another person, who will accept responsibility for record and report maintenance.

The Investigator is responsible for the preparation, review, signature, and submission of the reports listed below in Table 4. These are also subject to inspection by government agencies and must be retained as specified above.

Table 4. Investigator Reporting Responsibilities

<table>
<thead>
<tr>
<th>Report</th>
<th>Submitted to</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unanticipated Adverse Device Effects</td>
<td>Sponsor, IRB</td>
<td>The Investigator’s report on any unanticipated adverse effect must be submitted as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect.</td>
</tr>
<tr>
<td>Serious Adverse Events and Deaths</td>
<td>Sponsor</td>
<td>Medtronic requests that the Investigator’s report on all serious adverse events and deaths be submitted within 3 working days after the Investigator first learns of the event.</td>
</tr>
<tr>
<td>Withdrawal of IRB approval</td>
<td>Sponsor</td>
<td>The Investigator must report a withdrawal of the reviewing IRB, approval within 5 working days.</td>
</tr>
<tr>
<td>Progress Report</td>
<td>Sponsor, IRB</td>
<td>The Investigator must submit a progress report on an annual basis if the trial lasts longer than one year.</td>
</tr>
</tbody>
</table>
### Deviations from Investigational Plan (CFR 812.150)

<table>
<thead>
<tr>
<th>Report</th>
<th>Submitted to</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure to obtain Informed Consent</td>
<td>Sponsor, IRB</td>
<td>The Investigator must make notification within 5 working days after device implant.</td>
</tr>
<tr>
<td>Final Report</td>
<td>Sponsor, IRB</td>
<td>This report must be submitted within 3 months after termination or completion of the investigation.</td>
</tr>
<tr>
<td>Emergency Use</td>
<td>Sponsor, IRB</td>
<td>Notification must be made within 5 working days of the occurrence of an emergency deviation made to protect the life or physical well-being of a subject.</td>
</tr>
<tr>
<td>Planned deviation</td>
<td>Sponsor, IRB, FDA</td>
<td>If the deviation affects scientific soundness of the trial or the rights, safety, or welfare of the subject and is not an emergency, prior approval must be obtained from Medtronic, the reviewing IRB, and FDA.</td>
</tr>
<tr>
<td>Other Deviations</td>
<td>Sponsor</td>
<td>Deviations that are beyond the control of the investigator (such as patient who fails to return to follow-up visit) or deviations that do not affect the scientific soundness of the trial or the rights, safety, or welfare of the subject and are not an emergency, should be submitted as they are identified by the site or Medtronic staff.</td>
</tr>
</tbody>
</table>

## 4. RISK / BENEFIT ANALYSIS

### 4.1 Potential Risks and Discomforts

There are risks for participants in this trial. However, it should be noted that most of the risks of trial participation are not materially different than those entailed by an individual who undergoes the same treatment outside of the context of this trial.

Known adverse events that may result from TAVI include but may not be limited to:

- Death
- Acute myocardial infarction
- Stroke
- Urgent need for surgery
  - Coronary artery bypass
  - Heart valve replacement
  - Valve explant
- Urgent need for balloon valvuloplasty
- Urgent need for Percutaneous Coronary Intervention (PCI)
- Cardiogenic shock
- Perforation of the myocardium or vessel
- Cardiac Tamponade
- Ascending aorta trauma
- Myocardial ischemia
- Acute coronary artery occlusion
- Disturbances in the electrical system of the heart that may result in the permanent placement of a device (pacemaker)
  - Atrio-ventricular node block
  - Bundle branch block
  - Asystole
- Ventricular arrhythmias
- Embolization
- Thrombosis
- Hemorrhage requiring transfusion
- Arteriovenous fistula
- Vessel dissection or spasm
- Valve migration
- Prosthetic valve dysfunction including but not limited to:
  - Fracture
  - Bending of the valve frame
  - Under-expansion of the valve frame
  - Calcification
  - Wear or tear in the valve leaf
  - Poor valve coaptation
  - Suture breaks or disruption
  - Leak
  - Mal-sizing
  - Malposition (either too high or too low)
  - Regurgitation
  - Stenosis
- Mitral valve regurgitation
- Hypotension or hypertension
- Acute renal injury
- Allergic reaction to antiplatelet agents or contrast medium
- Infection
- Bowel ischemia
- Complications at the area where the doctor opened the skin, including
  - pain
  - bleeding
• hematomas
• pseudoaneurysm

There have been no voluntary or involuntary regulatory recalls of the Medtronic
CoreValve® System to date. The original 18Fr Delivery Catheter System has
been improved with the addition of the AccuTrak™ stability layer which has been
added to aid in accuracy in the deployment of the Medtronic CoreValve® PAV.
There are no design changes anticipated for the Medtronic CoreValve® System
during the clinical trial.

4.2 Methods to Minimize Risks
The investigational plan is specifically designed to manage and minimize risks
through careful subject selection, thorough training of investigators, adherence to
the pre-determined time points to assess subject clinical status and regular
clinical monitoring visits by Sponsor appointed monitoring personnel.
In addition, an independent Data Safety Monitoring Board will monitor safety of
the subjects throughout the trial.

4.3 Potential Benefits
The targeted trial population (generally elderly patients of both genders) has
been shown to have high mortality if the severe aortic stenosis is left untreated.
This population also has high risk for mortality and morbidity if treated surgically
or are managed medically. The less invasive investigational treatment of
transcatheter aortic valve implantation has shown in research to reduce mortality
and morbidity.
5. DESCRIPTION OF MEDTRONIC COREVALVE® SYSTEM

5.1 Investigational Product Description
The Medtronic CoreValve® System (MCS) consists of 3 components: the Percutaneous Aortic Valve Bioprosthesis (PAV) in Figures 2 & 3 and Table 5 below, the Delivery Catheter System (DCS) in Figure 4, and the Compression Loading System (CLS) in Figure 5.

Percutaneous Aortic Valve Bioprosthesis
Figure 2: Percutaneous Aortic Valve (PAV)    Figure 3: PAV

Table 5. Device Size

<table>
<thead>
<tr>
<th>MCS-P3-640</th>
<th>MCS-P3-943</th>
</tr>
</thead>
<tbody>
<tr>
<td>A = 26 mm</td>
<td>A = 29 mm</td>
</tr>
<tr>
<td>B = 22 mm</td>
<td>B = 24 mm</td>
</tr>
<tr>
<td>C = 40 mm</td>
<td>C = 43 mm</td>
</tr>
<tr>
<td>D = 55 mm</td>
<td>D = 53 mm</td>
</tr>
</tbody>
</table>

The PAV is manufactured by suturing valve leaflets and a skirt, made from a single layer of porcine pericardium, into a tri-leaflet configuration. The PAV is designed to replace the native aortic heart valve without open heart surgery and without concomitant surgical removal of the failed native valve.

The self-expanding multi-level frame is made of Nitinol and is radiopaque.

The PAV is available for a range of aortic annulus and ascending aortic diameters as shown in Table 6 below.
### Table 6. Patient Anatomical Diameters

<table>
<thead>
<tr>
<th>Model</th>
<th>Size (mm)</th>
<th>Aortic Annulus Diameter (range in mm)</th>
<th>Ascending Aortic Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCS-P3-640</td>
<td>26</td>
<td>20-23</td>
<td>≤40</td>
</tr>
<tr>
<td>MCS-P3-943</td>
<td>29</td>
<td>23-27</td>
<td>≤43</td>
</tr>
</tbody>
</table>

### Delivery Catheter System

The AccuTrak™ DCS (DCS-C4-18FR) is compatible with a 0.889-mm (0.035-in) guidewire. The working length of the AccuTrak™ DCS is 112.5 cm. It incorporates a protective deployment sheath that houses and deploys the PAV. The AccuTrak™ DCS can be used to house and deliver both the commercially available sizes of the PAV (26mm and 29mm PAV). The outer diameter of the DCS is 12Fr, the stability layer is 15Fr and the outer diameter of the valve capsule is 18 Fr.

### Compression Loading System (Model CLS-3000-18 FR)

The AccuTrak™ DCS features an integrated handle designed to provide the user with accurate and controlled deployment. After the DCS is placed in the vicinity of the aortic annulus, the user retracts the deployment sheath, thereby deploying the PAV to the desired location. In use, the deployment sheath can be partially pulled back to evaluate the PAV location prior to fully releasing the PAV. In this way, the user can make slight adjustments to the PAV location if needed prior to release.
The CLS (Model CLS-3000-18FR) compresses the PAV into the DCS. The CLS is comprised of the following elements:

- inflow cone
- inflow tube (straight tube)
- outflow cap
- outflow cone
- outflow tube (tube with flared ends)

Medtronic may incorporate additional devices into this clinical study providing they receive regulatory approval and the scientific soundness of the study is not adversely affected.

5.2 Medtronic CoreValve® Ordering, Storage, and Disposition

Devices will be ordered through Medtronic.

As stated in the Instructions for Use (IFU), the PAV should be stored at 15°C to 25°C (59°F to 77°F). Avoid exposing the PAV to extreme fluctuations of temperature. Avoid freezing the PAV. Appropriate inventory control should be maintained so that PAVs with earlier Use By dates are implanted preferentially. Store the delivery system and compression loading system in a cool, dry environment.

All implanting sites will maintain device logs to document the disposition of all components of the Medtronic CoreValve® System.
6. MONITORING AND AUDITING

6.1 Monitoring

The investigational site will be monitored to ensure compliance with the trial protocol, adherence to applicable regulations, and accuracy of trial data. A monitoring visit will be conducted primarily to ensure the safety and wellbeing of the subjects is preserved. Monitoring visits will also be used to verify that trial data submitted on case report forms are complete and accurate with respect to the subject records and to verify device accountability. Site personnel will complete eCRFs following each subject visit. Trial data submitted will be reviewed against patient charts and other sources containing original records of patient data. There will be 100% source document verification.

The responsible individual for this trial is included on the title page of the CIP. The progress of the trial will be monitored by:

- On-site review, as deemed appropriate by the sponsor
- Telephone communications between the site personnel (e.g., Investigator, Trial Coordinator) and trial monitors
- Review of eCRFs and the associated clinical records
- Review of regulatory documents

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

6.2 Auditing

Medtronic may conduct audits at participating clinical sites. The purpose of an audit is to verify the performance of the monitoring process and the trial conduct, independently of the personnel directly involved in the trial. Regulatory bodies, such as the Food and Drug Administration, may also perform inspections at participating sites. The investigator and/or institution shall permit Medtronic and regulatory bodies direct access to source data and documents.

7. LABELING

Instructions for Use and additional labeling are attached in Appendix 17.1.

8. CONSENT MATERIALS

The template consents for the trial are attached in Appendix 17.2.
9. IRB INFORMATION

IRB information is attached in Appendix 17.3.

10. OTHER INSTITUTIONS

Information regarding other institutions involved in this trial is located in Appendices 17.4, 17.8, 17.9, 17.10, 17.11, 17.12, and 17.13.

11. ADDITIONAL RECORDS AND REPORTS

Information regarding additional Records and Reports can be found in Appendix 17.5.

12. REPORT OF PRIOR INVESTIGATIONS

The Report of Prior Investigations is attached in Appendix 17.18.

13. PUBLICATION POLICY

Medtronic, as the Sponsor of this trial, recognizing the seminal importance of this investigation, is committed to the widespread dissemination of all primary and secondary endpoint results. A publication plan will be implemented and followed. At the conclusion of the trial, a multisite abstract reporting the primary results will be prepared by the National Principal Investigators (in collaboration with others including but not limited to the Operations Committee, directors of the core laboratories, CEC, and Lead Investigators from high enrolling sites) and presented at an annual scientific meeting (e.g., Transcatheter Cardiovascular Therapeutics, EuroPCR, the American Heart Association, or the American College of Cardiology). 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 both the preparation and publication of the multisite results, and then only with written permission from Medtronic.

Following analysis and presentation of the primary endpoint results, active participation of all committee members, Investigators from high enrolling sites, 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 Operations Committee. A separate publication plan will provide detailed information about the publication committee, authorship, publication proposals, and requests for data.
14. **AMENDMENTS TO THE CLINICAL INVESTIGATIONAL PLAN**

All amendments to the CIP shall be agreed between the sponsor and the clinical investigator(s). Amendments will be recorded with a justification for the amendments in the log below:

<table>
<thead>
<tr>
<th>Version</th>
<th>Description of change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
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<td></td>
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<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 15. ABBREVIATIONS AND DEFINITIONS

#### 15.1 List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D</td>
<td>Two dimensional</td>
</tr>
<tr>
<td>3D</td>
<td>Three dimensional</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ACT</td>
<td>Active Clotting Time</td>
</tr>
<tr>
<td>ADE</td>
<td>Adverse Device Effect</td>
</tr>
<tr>
<td>AR</td>
<td>Aortic regurgitation</td>
</tr>
<tr>
<td>AS</td>
<td>Aortic stenosis</td>
</tr>
<tr>
<td>AVR</td>
<td>Aortic valve replacement</td>
</tr>
<tr>
<td>BAV</td>
<td>Balloon Aortic Valvuloplasty</td>
</tr>
<tr>
<td>BSA</td>
<td>Body Surface Area</td>
</tr>
<tr>
<td>BNP</td>
<td>B-type Natriuretic Peptide</td>
</tr>
<tr>
<td>CEC</td>
<td>Clinical Events Committee</td>
</tr>
<tr>
<td>CIP</td>
<td>Clinical Investigational Plan</td>
</tr>
<tr>
<td>CLS</td>
<td>Compression loading system</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CVA</td>
<td>Cerebrovascular accident</td>
</tr>
<tr>
<td>DCS</td>
<td>Delivery catheter system</td>
</tr>
<tr>
<td>DSMB</td>
<td>Data Safety Monitoring Board</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case report form</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>European System for Cardiac Operative Risk Evaluation</td>
</tr>
<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration</td>
</tr>
<tr>
<td>GCP</td>
<td>Good clinical practice</td>
</tr>
<tr>
<td>HIPAA</td>
<td>Health Insurance Portability and Accountability Act</td>
</tr>
<tr>
<td>HIT/HITTS</td>
<td>Heparin-Induced Thrombocytopenia / Heparin-Induced Thrombocytopenia and Thrombosis</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
</tbody>
</table>
IFU Instructions for use
ITT Intent-to-treat
IXRS Interactive Voice/Web Response System
LBBB Left Bundle Branch Block
LVEF Left ventricular ejection fraction
LVOT Left ventricular outflow tract
MACCE Major adverse cardiovascular and cerebrovascular event
MAE Major Adverse Event
MCS Medtronic CoreValve® System
MI Myocardial infarction
NYHA New York Heart Association
PAV Percutaneous aortic valve
PCI Percutaneous Coronary Intervention
TAVI Transcatheter aortic valve implant
QoL Quality of Life
RBBB Right Bundle Branch Block
SAE Serious adverse event
SAVR Surgical Aortic Valve Replacement
STS Society of Thoracic Surgeons
TEE Transesophageal echocardiography
TIA Transient Ischemic Attack
TTE Transthoracic echocardiography
UADE Unanticipated adverse device effect
15.2 Definition of Terms

ACUTE KIDNEY INJURY

Acute Kidney Injury will be defined according to the definition proposed by the Valve Academic Research Consortium (VARC) Consensus Report for Transcatheter Aortic Valve Implantation (TAVI); 2010-06-15.

<table>
<thead>
<tr>
<th>Stages</th>
<th>Change in Serum Creatinine (up to 72 hours) compared to Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Increase in serum creatinine to 150-200% (1.5-2.0 x increase compared with baseline) or increase of ≥ 0.3 mg/dl (≥26.4 μmol/L)</td>
</tr>
<tr>
<td>Stage 2*</td>
<td>Increase in serum creatinine to 200-300% (&gt; 2-3 x increase compared with baseline)</td>
</tr>
<tr>
<td>Stage 3*/**</td>
<td>Increase in serum creatinine to ≥300% (&gt; 3 x increase compared with baseline) or serum creatinine of ≥ 4.0 mg/d (≥354 μmol/L) with an acute increase of at least 0.5 mg/dl (44 μmol/L)</td>
</tr>
</tbody>
</table>

* Stage 2 and 3 acute renal injuries will be considered to be serious adverse events.

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

ACUTE VESSEL OCCLUSION

The state of complete luminal obstruction with no antegrade blood flow.

ADVERSE EVENT (AE)

An adverse event is any undesirable experience (sign, symptom, illness, or other medical event) occurring to the subject, and that appears or worsens during the clinical trial, whether or not associated with the investigational products or related procedures.

AORTIC DISSECTION

Intimal tear resulting in blood splitting the aortic media and producing a false lumen that can progress in an antegrade or retrograde direction. Aortic dissection is further classified using Stanford classification (Types A and B depending on whether ascending or descending aorta involved) or DeBakey classification (Types I, II and III) as shown below.

- Major Aortic Dissection: Type A and Types I and II.
  - Major aortic dissections will be considered to be serious adverse events.
- Minor Aortic Dissection: Type B and Type III
AORTIC REGURGITATION (AR)

Aortic valve incompetence resulting in backward flow of blood. Further information can be found in the Echocardiography Procedures in Appendix 17.8.

Moderate or severe aortic regurgitation (AR) via echo assessment and a grade ≥ 2 using angiographic assessment, will be considered a serious adverse event.

AORTIC STENOSIS (AS)

A narrowing, stiffening or stricture of the aortic valve.

Moderate or severe AS will be considered a serious adverse event.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jet velocity (m/s)</td>
<td>Less than 3.0</td>
<td>3.0-4.0</td>
<td>Greater than 4.0</td>
</tr>
<tr>
<td>Mean gradient (mmHg)</td>
<td>Less than 25</td>
<td>25-40</td>
<td>Greater than 40</td>
</tr>
<tr>
<td>Valve area (cm²)</td>
<td>Greater than 1.5</td>
<td>1.0-1.5</td>
<td>Less than 1.0</td>
</tr>
<tr>
<td>Valve area index (cm²/m²)</td>
<td></td>
<td></td>
<td>Less than 0.6</td>
</tr>
</tbody>
</table>

ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease (published in the August 1, 2006, issues of Journal of the American College of Cardiology and Circulation)

ARRHYTHMIA

Any variation from the normal rhythm of the heart beat, including sinus arrhythmia, premature beat, heart block, atrial fibrillation, atrial flutter and tachycardia.

- Major Arrhythmias: Complete heart block, ventricular tachycardia and ventricular fibrillation
- Serious Arrhythmias: Any arrhythmia requiring surgical or invasive intervention or DC cardioversion
BLEEDING EVENT

Bleeding event will be defined according to the definition proposed by the Valve Academic Research Consortium (VARC) Consensus Report for Transcatheter Aortic Valve Implantation (TAVI); 2010-06-15.

<table>
<thead>
<tr>
<th>Life-threatening or Disabling Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fatal bleeding OR</td>
</tr>
<tr>
<td>• Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome OR</td>
</tr>
<tr>
<td>• Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery OR</td>
</tr>
<tr>
<td>• Overt source of bleeding with drop in hemoglobin of ≥5 g/dL or whole blood or packed red blood cells (RBC) transfusion ≥4 units*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0g/dL or requiring transfusion of 2-3 units of whole blood/RBC AND</td>
</tr>
<tr>
<td>• Does not meet criteria of life-threatening or disabling bleeding</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Any bleeding worthy of clinical mention (e.g. access site hematoma) that does not qualify as life-threatening, disabling or major</td>
</tr>
</tbody>
</table>

* Given one unit of packed RBC typically will raise blood hemoglobin concentration by 1 g/dL, an estimated decrease in hemoglobin will be calculated.

Life-threatening and Major bleeding events are considered to be serious.

BUNDLE BRANCH BLOCK


Left Bundle Branch Block (LBBB)

• QRS duration ≥120 ms or longer
• Delayed onset of intrinsicsoid deflection in I, V5, and V6 ≥60 ms
• Broad and notched or slurred R waves in I, aVL, V5, and V6
• rS or QS complexes in right precordial leads
• ST-segment and T waves in opposite polarity to the major QRS deflection

Right Bundle Branch Block (RBBB)

• QRS duration ≥120 ms
• rsR= or rSR= complexes in V1 and V2
• Delayed onset of intrinsicsoid deflection in V1 and V2 ≥50 ms
• Broad, slurred S wave in 1, V5,

Any new or worsening LBBB or RBBB that requires the placement of a permanent pacemaker and/or other surgical or invasive intervention will be considered to be serious.
CARDIAC TAMponade
Clinical syndrome caused by the accumulation of fluid in the pericardial space, resulting in reduced ventricular filling and subsequent hemodynamic compromise.

CARDIOGENIC SHOCK
An insufficient forward cardiac output to maintain adequate perfusion of vital organs to meet ongoing demands for oxygenation and metabolism. Cardiogenic shock is due to either inadequate left ventricular pump function (such as in congestive heart failure) or inadequate left ventricular filling (such as in cardiac tamponade). Cardiogenic shock is defined as sustained hypotension (>30 minutes) with evidence of tissue hypoperfusion including oliguria (<30 mL/h), cool extremities, cyanosis and altered mental status.

CHRONIC RENAL INSUFFICIENCY
Kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m² for or ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine test or imaging studies.

DEATH
A serious adverse event that is classified by the following:

All-cause death: All deaths from any cause after a valve intervention or randomization to optimal medical management. This includes all cardiovascular and non-cardiovascular deaths.

Cardiovascular Death:
(Cardiovascular death will be defined according to the definition proposed by the Valve Academic Research Consortium (VARC) Consensus Report for Transcatheter Aortic Valve Implantation (TAVI); 2010-06-15)

Any one of the following criteria:

- Any death due to proximate cardiac cause (e.g. MI, cardiac tamponade, worsening heart failure)
- Unwitnessed death and death of unknown cause
- All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure
- Death caused by non-coronary vascular conditions such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease

Note: All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in subjects with coexisting potentially fatal non-cardiac disease (e.g., cancer, infection) should be classified as cardiac.

Non-cardiovascular death: Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.

Valve-related death:
- Any death caused by prosthetic valve dysfunction, valve thrombosis, embolism, bleeding event, or implanted valve endocarditis;
- Death related to reintervention on the operated valve
DEVICE FAILURE
- Inability to successfully deliver and place the device in stable position
- Failure to retrieve the delivery catheter
- More than one Medtronic CoreValve® PAV is implanted
- Unsuccessful device function as assessed acutely (within 24-48 hours post-implantation or prior to hospital discharge), where unsuccessful device function is defined as follows:
  - Device migration assessed qualitatively by echocardiography
  - Greater than or equal to moderate (2+) aortic regurgitation by echocardiography
  - Effective orifice area ≤ 1.2 cm² by echocardiography using the continuity equation

DEVICE MIGRATION
Obvious movement of the Medtronic CoreValve® PAV from its documented original implant position, after access site closure, as confirmed by X-ray, echocardiography, CT scan or direct assessment during open heart surgery or autopsy.

DEVICE MALPLACEMENT
Placement of the Medtronic CoreValve® PAV in a non-therapeutic location, either inadvertently, or possibly intentionally due to unintended problems during the Medtronic CoreValve® System (MCS) delivery that necessitates placement in the non-therapeutic location.

DEVICE RELATED
Events that occur as the direct result of the Medtronic CoreValve® System (MCS) as it relates to delivery, placement, efficacy or durability; these may involve the implanted device or the delivery system components.

DEVICE RELATED COMPLICATIONS
Complications associated with the device as it relates to delivery, placement, efficacy or durability; these may involve the implanted device or the delivery system.

DEVICE SUCCESS
Device success is defined as follows:
- successful delivery and placement of the device, and successful retrieval of the delivery system,
- correct position of the device within the aortic annular region (placement in the annulus with no impedance on device function),
- successful device function assessed acutely in a resting state, either within 24-48 hours after the index procedure or before hospital discharge, where successful device function is defined as follows:
  - absence of device migration (device within aortic annular region) assessed qualitatively by echocardiography
  - less than moderate (2+) aortic regurgitation by echocardiography
  - effective orifice area > 1.2 cm² by echocardiography using the continuity equation.
- Only one valve implanted in the proper anatomical location
EMBOLISM
Free flowing blood clot or lesion material that is located in the systemic or pulmonary circulation that occurs in the absence of infection after the immediate perioperative period. Embolism may be manifested by a neurological event or a noncerebral embolic event.

ENDOCARDITIS
Implanted valve endocarditis: Any infection involving an implanted valve. The diagnosis of operated valvular endocarditis is based on one of the following criteria:
- re-operation with evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriologic studies;
- autopsy findings of abscess, pus, or vegetation involving a replaced valve; or
- in the absence of reoperation or autopsy, meeting of the Duke Criteria for endocarditis.
Infective endocarditis is diagnosed based on Duke criteria and necessitates 2 major criteria, or 1 major and 3 minor criteria, or 5 minor criteria

Major criteria 1: Positive blood culture for infective endocarditis
Typical microorganism consistent with infective endocarditis from 2 separate blood cultures, as noted below:
- Viridans streptococci, Streptococcus bovis, or HACEK group (Haemophilus. Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella or
- Community-acquired Staphylococcus aureus or enterococci, in the absence of a primary focus

-OR-
Microorganisms consistent with infective endocarditis from persistently positive blood cultures defined as:
- Two positive cultures of blood samples drawn >12 hours apart, or
- All of 3 or a majority of 4 separate cultures of blood (with first and last sample drawn 1 hour apart)

Major criteria 2: Evidence of endocardial involvement
Positive echocardiogram for infective endocarditis defined as:
- oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, or
- abscess, or
- new partial dehiscence of prosthetic valve

-OR-
New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)

Minor criteria 1: Predisposition: predisposing heart condition or intravenous drug use
Minor criteria 2: Fever: temperature > 38.0° C (100.4° F)
Minor criteria 3: Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
Minor criteria 4: Immunologic phenomena: glomerulonephritis, Osler’s nodes, Roth spots, and rheumatoid factor
Minor criteria 5: 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 infective endocarditis
Minor criteria 6: Echocardiographic findings: consistent with infective endocarditis but do not meet a major criterion as noted above

EXPLANT
Removal of the investigational valve implant for any reason, including post-mortem.
HEMOLYSIS
Two plasma free hemoglobin values > 40 mg/dL with the two readings taken within a single forty-eight (48) hour period. If the second plasma free hemoglobin assessment is not performed within 48 hours following an initial determination of > 40 mg/dL, this would qualify as an adverse event.

- Major hemolysis: red cell destruction as evidenced by a positive finding of urobilinogen in the urine that requires intervention (e.g. iron supplements, transfusion, invasive intervention). Major hemolysis events will be considered to be serious adverse events.
- Minor hemolysis: red cell destruction as evidenced by a positive finding of urobilinogen in the urine that does not require intervention.

HOSPITALIZATION FOR SIGNS AND SYMPTOMS RELATED TO AORTIC VALVE DISEASE
Aortic valve disease hospitalizations are defined as a non-elective hospital admission for signs and symptoms related to aortic valve disease (as described below) that results in at least a two-night stay (i.e., where the admission date and the discharge date differ by at least two calendar days). For the purpose of the protocol, overnight stays at nursing home facilities or extended care facilities do not meet the protocol definition of hospitalization. This does include the administration or augmentation of intravenous heart failure therapy (e.g., inotropes, diuretics, and/or vasodilators).

Patients with signs and symptoms related to aortic valve disease (as described below) who are hospitalized for less than two days or who are treated and released from the emergency department or an outpatient clinic (including treatment for intravenous heart failure therapy (e.g., inotropes, diuretics, and/or vasodilators)), will not be counted as aortic valve disease hospitalizations.

Aortic valve disease will be evaluated using documented evidence of the following signs and symptoms. An independent Clinical Events Committee (CEC) will review all available source documentation for all hospitalizations to determine if they are aortic valve disease hospitalizations. The CEC adjudication will be used for final analysis.

<table>
<thead>
<tr>
<th>Signs and Symptoms of Aortic Valve Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sign/Symptom</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td><strong>Aortic Valve Dysfunction</strong></td>
</tr>
<tr>
<td>Shortness of breath/dyspnea</td>
</tr>
<tr>
<td>Exercise intolerance</td>
</tr>
<tr>
<td>Dizziness/syncope</td>
</tr>
<tr>
<td>Chest pain</td>
</tr>
<tr>
<td><strong>Worsening Heart Failure</strong></td>
</tr>
<tr>
<td><strong>Volume Overload</strong></td>
</tr>
<tr>
<td>Orthopnea</td>
</tr>
<tr>
<td>Paroxysmal nocturnal dyspnea</td>
</tr>
<tr>
<td>Jugular venous distension</td>
</tr>
</tbody>
</table>
more than 3 centimetres above the sternal angle.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatomegaly</td>
<td>Palpation of the edge of the liver below the edge of the ribs without inspiration</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>Swelling of tissues, usually in the lower limbs, due to the accumulation of fluids.</td>
</tr>
<tr>
<td>Pulmonary rales</td>
<td>Small clicking, bubbling, or rattling sounds in the lung associated with inspiration</td>
</tr>
<tr>
<td>Abdominal-jugular reflux</td>
<td>An elevation of venous pressure visible in the jugular veins and measurable in the veins of the arm, produced in active or impending congestive heart failure by firm pressure with the flat hand over the abdomen.</td>
</tr>
<tr>
<td>Radiographic evidence of pulmonary edema</td>
<td>NA</td>
</tr>
<tr>
<td>Elevated B-type natriuretic peptide level</td>
<td>NA</td>
</tr>
<tr>
<td>Hypoperfusion</td>
<td>- Narrow pulse pressure: Pulse pressure &lt; 30 mmHg</td>
</tr>
<tr>
<td></td>
<td>- Hypotension: Systolic BP &lt; 90 systolic</td>
</tr>
<tr>
<td></td>
<td>- Renal or hepatic dysfunction:</td>
</tr>
<tr>
<td></td>
<td>- Rise in baseline creatinine by 25%</td>
</tr>
<tr>
<td></td>
<td>- Increase in LFT (SGOT, SGPT) &gt; 2 times normal</td>
</tr>
<tr>
<td>Low serum sodium concentration</td>
<td>Serum sodium &lt; 130 mEq/dL</td>
</tr>
</tbody>
</table>

**INFECTION**

Elevated body temperature (fever), and White Blood Count (WBC) > 12,000/ml, and Significant leftward shift on Differential.

**MAJOR ADVERSE CARDIOVASCULAR AND CEREBROVASCULAR EVENTS (MACCE)**

Defined as a composite rate of
- all-cause death
- myocardial infarction (MI)
- major stroke, and
- reintervention (defined as any cardiac surgery or percutaneous reintervention catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve)

**MAJOR ADVERSE EVENT (MAE)**

Major Adverse events include the following:
- MACCE
- Acute kidney Injury
- Cardiac tamponade
- Prosthetic valve dysfunction
- Cardiogenic shock
- Valve endocarditis
- Embolism
- Life-threatening, disabling or major bleeding
- Major vascular complication
MITRAL STENOSIS

A narrowing, stiffening or stricture of the mitral valve.

<table>
<thead>
<tr>
<th>Mitral Stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>Mean gradient (mm Hg)*</td>
</tr>
<tr>
<td>Pulmonary artery systolic pressure (mm Hg)</td>
</tr>
<tr>
<td>Valve area (cm²)</td>
</tr>
</tbody>
</table>

ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease (published in the August 1, 2006, issues of Journal of the American College of Cardiology and Circulation)

MYOCARDIAL INFARCTION (MI)

Myocardial infarction will be defined according to the definition proposed by the Valve Academic Research Consortium (VARC) Consensus Report for Transcatheter Aortic Valve Implantation (TAVI); 2010-06-15.

<table>
<thead>
<tr>
<th>Peri-Procedural MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(≤ 72 hours after the index procedure)</td>
</tr>
<tr>
<td>1. New ischemic symptoms (e.g. chest pain or shortness of breath), or new ischemic signs (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, or imaging evidence of new loss of viable myocardium or new wall motion abnormality)</td>
</tr>
<tr>
<td>2. Elevated cardiac biomarkers (preferably CK-MB) within 72 hours after the index procedure, consisting of two or more post-procedure samples that are ≥ 6-8 hours apart with a 20% increase in the second sample and a peak value exceeding 10x the 99th percentile upper reference limit (URL) or a peak value exceeding 5x the 99th percentile URL and with new pathological Q waves in at least 2 contiguous leads.</td>
</tr>
</tbody>
</table>
MYOCARDIAL INFARCTION (MI) – continued

<table>
<thead>
<tr>
<th>Spontaneous MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&gt; 72 hours after the index procedure)</td>
</tr>
</tbody>
</table>

Any one of the following criteria:

1. Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with evidence of myocardial ischemia with at least one of the following:
   - ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]);
   - New pathological Q waves in at least 2 contiguous leads;
   - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
2. Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
3. Pathological findings of an acute myocardial infarction.

All myocardial infarctions will be considered serious adverse events.

NEUROLOGICAL EVENT

Any central, new neurological deficit, whether temporary or permanent and whether focal or global, that occurs after the subject emerges from anesthesia.

NEW YORK HEART ASSOCIATION CLASSIFICATION (NYHA)

Classification system for defining cardiac disease and related functional limitations into four broad categorizations:

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

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26-August-2010
PARAVALVULAR LEAK (as measured by echocardiogram)
Leakage due to a separation of the prosthetic valve from the annulus. Any evidence of leakage of blood around the device. Diagnosis of paravalvular leak may be obtained from echocardiogram; however definitive diagnosis is obtained at reoperation, explant, or autopsy.

**Primary paravalvular leak**
Defined as any evidence of leakage of blood around the prosthesis between the device and the native annulus. Primary paravalvular leaks will be stratified by the following:

- **All leaks:** evidence of moderate to severe paravalvular regurgitation by echocardiography
- **Minor leaks:** A paravalvular leak graded < 2+ aortic regurgitation and does not require surgical intervention
- **Major leaks:** A paravalvular leak graded ≥2+ aortic regurgitation or requires surgical intervention

Paravalvular leaks (≥ 2+) will be classified as Serious Adverse Events.

PATIENT PROSTHESIS MISMATCH (PPM)

- **Severe PPM** will be defined as an EOA ≤ 0.65 cm² /m² BSA
- **Moderate PPM** defined as a patient with an EOA ≤ 0.85 cm² /m² BSA

PERMANENT PACEMAKER IMPLANTATION
Implantation of permanent pacemaker after the index procedure due to occurrence of conduction disturbances.

- **Procedure-related:** Permanent Pacemaker is implanted in subjects with new onset conduction disturbances or worsening of existing conduction disturbances
- **Not related to procedure:** Permanent Pacemaker is implanted in subjects with known conduction disturbances that did not advance after the index procedure.

PROCEDURE RELATED COMPLICATIONS
Complications associated with any part of the vascular access procedure, associated treatments or necessary secondary interventions that do not necessarily involve the device. This includes morbidity associated with either pre-medication, or anesthesia, or other adjunct to the surgical procedure. Other technical errors including inappropriate patient selection, inappropriate operator techniques, measurements, or judgment that do not involve the device itself are also included.

PROCEDURAL SUCCESS
Defined as device success without occurrence of in-hospital MACCE.

PROCEDURE-RELATED EVENTS
Events occurring during or as a direct result of the index procedure. Events that occur before extubation and before access site closure are classified as procedural.
PROSTHETIC VALVE DYSFUNCTION

Prosthetic Valve Dysfunction will be defined according to the definition proposed by the Valve Academic Research Consortium (VARC) Consensus Report for Transcatheter Aortic Valve Implantation (TAVI); 2010-06-15

Failure modes of prosthetic valve dysfunction include, but are not limited to, the following:

- Aortic Stenosis
  - Stent creep
  - Pannus
  - Calcification
  - Support structure deformation (out-of-round configuration), under-expansion, fracture, or trauma (cardi-pulmonary resuscitation, blunt chest trauma)
  - Mal-sizing (prosthesis-patient mismatch(PPM))
  - Endocarditis
  - Prosthetic valve thrombosis
  - Native leaflet prolapse impeding prosthetic leaflet motion

- Aortic Regurgitation
  - Pannus
  - Calcification
  - Support structure deformation (out-of-round configuration), under-expansion, fracture, or trauma (cardi-pulmonary resuscitation, blunt chest trauma)
  - Endocarditis
  - Prosthetic valve thrombosis
  - Mal-position (too high, too low)
  - Acute mal-coaptation
  - Leaflet wear, tear/perforation, prolapse or retraction
  - Suture breakage or disruption
  - Native leaflet prolapse impeding prosthetic leaflet motion

Prosthetic valve dysfunction will be considered serious when it meets the definition of a serious adverse event (SAE).

REINTERVENTION

Any surgical or percutaneous interventional catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve. In addition to surgical reoperations, enzymatic, 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.

RESPIRATORY INSUFFICIENCY

Post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) ratio \( [\text{FEV1/FVC}] \) less than 70%.

Post-bronchodilator FEV1 less than 80% predicted, with or without chronic symptoms (i.e., cough or sputum production).

RESPIRATORY FAILURE

The need for ventilatory support for > 72 hours associated with an inability to wean from the respirator for any reason.
RIGHT VENTRICULAR INSUFFICIENCY
Defined as sequelae of right ventricular failure including the following:
- Significantly decreased right ventricular systolic and/or diastolic function
- Tricuspid valvular regurgitation secondary to elevated pressure
Clinical symptoms to include:
- Hepatic congestion
- Ascites
- Anasarca
- Presence of “hepato-jugular reflux”
- Edema

SERIOUS ADVERSE EVENT (SAE)
A serious adverse event (SAE) is an event that meets any of the following criteria:
- Results in subject death
- Is life threatening* (i.e., the subject was at risk of death at the time of the event)
- Results in inpatient hospitalization
- Results in prolonged existing hospitalization
- Results in persistent or significant disability**/incapacity
- Results in congenital anomaly/birth defect
- Results in permanent impairment of a body function or permanent damage to a body structure
- Necessitated medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

*A life-threatening adverse event is any adverse event that places the subject, in the opinion of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

**The definition of disability is a substantial disruption of a person’s ability to conduct normal life functions.
Events that do not meet these criteria are considered non-serious.

STROKE (CVA)
Stroke and TIA will be defined according to the definition proposed by the Valve Academic Research Consortium (VARC) Consensus Report for Transcatheter Aortic Valve Implantation (TAVI); 2010-06-15

<table>
<thead>
<tr>
<th>Stroke Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke</td>
</tr>
<tr>
<td>- Duration of a focal or global neurological deficit ≥ 24 hours; OR &lt; 24 hours, if therapeutic intervention(s) were performed (e.g. thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; OR the neurologic deficit results in death</td>
</tr>
<tr>
<td>- No other readily identifiable non-stroke cause for the clinical presentations (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences)*</td>
</tr>
<tr>
<td>- Confirmation of the diagnosis by at least one of the following:</td>
</tr>
</tbody>
</table>
  - Neurology or neurosurgical specialist |
Neuroimaging procedure (MR or CT scan or cerebral angiography)
Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)

Stroke Definitions

- Transient Ischemic Attack
  - New focal neurologic deficit with rapid symptom resolution (usually 1-2 hours), always within 24 hours
  - Neuroimaging without tissue injury

- Stroke: (diagnosis as above, preferably with positive neuroimaging study)+
  - Minor (non-clinically important disability) - modified Rankin score < 2 at 7 days or prior to discharge AND NIHSS score < 3 (above baseline) at 7 days or prior to discharge and at 30-day assessment
  - Major (clinically important disability) - modified Rankin score ≥ 2 at 7 days or prior to discharge AND NIHSS score ≥ 3 (above baseline) at 7 days or prior to discharge and at 30-day assessment

*Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies

+ If there is discordance between modified Rankin and NIHSS determination of major versus minor stroke, final adjudication is made by a qualified neurologist

Modified Rankin Scale

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

Clinically important disabilities will be considered to be serious adverse events.
Strokes will be further categorized to the following:

- Ischemic stroke is defined as an acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.
Hemorrhagic stroke is defined as an acute symptomatic episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.

Undetermined stroke is defined as a stroke with insufficient information to allow categorization as A or B.

TRANSIENT ISCHEMIC ATTACK (TIA)
(Refer to the definition of TIA under stroke above.)

• New focal neurologic deficit with rapid symptom resolution (usually 1-2 hours), always within 24 hours
• Neuroimaging without tissue injury

VALVE THROMBOSIS
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. 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 also be counted as valve thrombosis.

VASCULAR COMPLICATIONS
Vascular Complications will be defined according to the definition proposed by the Valve Academic Research Consortium (VARC) Consensus Report for Transcatheter Aortic Valve Implantation (TAVI); 2010-06-15.

<table>
<thead>
<tr>
<th>Vascular Access Site and Access Related Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Vascular Complications</strong></td>
</tr>
<tr>
<td>1. Any thoracic aortic dissection</td>
</tr>
<tr>
<td>2. Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, or compartment syndrome) leading to either death, need for significant blood transfusions (≥ 4 units), unplanned percutaneous or surgical intervention, or irreversible end-organ damage (e.g. hypogastric artery occlusion causing visceral ischemia or spinal artery injury causing neurologic impairment)</td>
</tr>
<tr>
<td>3. Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage</td>
</tr>
<tr>
<td>4. Failure of percutaneous access site closure leading to either death, need for significant blood transfusions (≥ 4 units), unplanned percutaneous or surgical intervention, or irreversible end-organ damage.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor Vascular Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula or pseudoaneuysms requiring compression or thrombin injection therapy, or hematomas requiring transfusion of ≥ 2 but &lt; 4 units) not requiring unplanned percutaneous or surgical intervention and not resulting in irreversible end-organ damage</td>
</tr>
<tr>
<td>2. Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage</td>
</tr>
<tr>
<td>3. Failure of percutaneous access site closure that did not result in an interventional or surgical correction and is not associated with death, need for significant blood transfusions (≥4 units), or irreversible end-organ damage.</td>
</tr>
</tbody>
</table>

Major vascular complications will be considered to be serious adverse events.
16. BIBLIOGRAPHY / LITERATURE REVIEW


Medtronic CoreValve® U.S. Pivotal Trial
(High Risk Surgical Patients)

Clinical Investigational Plan

Version 12.0
August 22, 2012

Sponsor:
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Clinical Research
Mailstop: MVS66
Mounds View South
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Mounds View, MN 55112
Trial Title: Medtronic CoreValve® U.S. Pivotal Trial

IDE No.  G100012

CIP No.  MCV-US-2009-01 (High Risk Surgical)
10008960DOC REV 1H

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### 1. SYNOPSIS

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<th>Medtronic CoreValve® U.S. Pivotal Trial</th>
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<tbody>
<tr>
<td>Title of Protocol:</td>
<td>Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients)</td>
</tr>
<tr>
<td>Name of Product:</td>
<td>Medtronic CoreValve® System (MCS)</td>
</tr>
<tr>
<td>Purpose:</td>
<td>To evaluate the safety and efficacy of the Medtronic CoreValve® System in the treatment of symptomatic severe aortic stenosis in subjects who have a predicted high risk for aortic valve surgery.</td>
</tr>
<tr>
<td>Design:</td>
<td>Subjects will be randomized on a 1:1 basis to either transcatheter aortic valve implant (TAVI) with the Medtronic CoreValve® System (MCS) or to surgical aortic valve replacement (SAVR).</td>
</tr>
<tr>
<td>Primary Objective:</td>
<td>The primary objective is to demonstrate that the safety and effectiveness of the Medtronic CoreValve® System (MCS) as measured by all-cause mortality rates at 12 months is non-inferior to surgical aortic valve replacement (SAVR) in the treatment of symptomatic severe aortic stenosis in subjects who have a predicted high risk for aortic valve surgery.</td>
</tr>
<tr>
<td>Primary Endpoint:</td>
<td>All-cause mortality at 12 months.</td>
</tr>
</tbody>
</table>
| Secondary Endpoints: | The following secondary endpoints will be compared between MCS TAVI and SAVR subject cohorts:  
1. Major Adverse Cardiovascular and Cerebrovascular Event (MACCE)-free survival at 30 days, 6 months, 12 months and annually thereafter up to 5 years. MACCE is defined as a composite of:  
   - all-cause death  
   - myocardial infarction (MI)  
   - all stroke, and  
   - reintervention (defined as any cardiac surgery or percutaneous reintervention catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve)  
2. The occurrence of individual MACCE components at 30 days, 6 months, 12 months and annually thereafter up to 5 years. |
<table>
<thead>
<tr>
<th>Secondary Endpoints (Continued):</th>
<th>3. Major Adverse Events (MAE) at 30 days, 6 months, 12 months and annually thereafter up to 5 years.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4. Conduction disturbance requiring permanent pacemaker implantation at 30 days, 6 months, 12 months and annually thereafter up to 5 years.</td>
</tr>
<tr>
<td></td>
<td>5. Change in NYHA class from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years.</td>
</tr>
<tr>
<td></td>
<td>6. Change in distance walked during 6-minute walk test (6MWT) from baseline to 30 days and baseline to 12 months.</td>
</tr>
<tr>
<td></td>
<td>7. Ratio of days alive out of hospital versus total days alive assessed at 12 months follow-up.</td>
</tr>
<tr>
<td></td>
<td>8. Quality of Life (QoL) change from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years using the following measures:</td>
</tr>
<tr>
<td></td>
<td>- Kansas City Cardiomyopathy Questionnaire (KCCQ)</td>
</tr>
<tr>
<td></td>
<td>- SF-12, and</td>
</tr>
<tr>
<td></td>
<td>- EuroQoL</td>
</tr>
<tr>
<td></td>
<td>9. Echocardiographic assessment of prosthetic valve performance at discharge, 30 days, 6 months, 12 months and annually thereafter up to 5 years using the following measures:</td>
</tr>
<tr>
<td></td>
<td>- transvalvular mean gradient</td>
</tr>
<tr>
<td></td>
<td>- effective orifice area</td>
</tr>
<tr>
<td></td>
<td>- degree of prosthetic aortic valve regurgitation (transvalvular and paravalvular)</td>
</tr>
<tr>
<td></td>
<td>10. Aortic valve disease hospitalization at 30 days, 6 months, 12 months and annually thereafter up to 5 years.</td>
</tr>
<tr>
<td></td>
<td>11. Cardiovascular deaths and valve-related deaths at 30 days, 6 months, 12 months and annually thereafter up to 5 years.</td>
</tr>
<tr>
<td></td>
<td>12. Strokes (of any severity) and TIAs at 30 days, 6 months, 12 months and annually thereafter up to 5 years.</td>
</tr>
<tr>
<td></td>
<td>13. Index procedure related MAEs.</td>
</tr>
<tr>
<td></td>
<td>14. Length of index procedure hospital stay.</td>
</tr>
</tbody>
</table>
### Secondary Endpoints (Continued):

The following secondary endpoints will be assessed for the MCS TAVI cohort subjects only:

#### 15. Device success defined as follows:
- successful vascular access, delivery and deployment of the device, and successful retrieval of the delivery system,
- correct position of the device in the proper anatomical location (placement in the annulus with no impedance on device function),
- Intended performance of the prosthetic valve (aortic valve area > 1.2 cm² for 26, 29 and 31mm valves, ≥ 0.9 cm² for 23mm valve (by echocardiography using the continuity equation) and mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/sec, without moderate or severe prosthetic valve AR)
- Only one valve implanted in the proper anatomical location

1 assessed acutely in a resting state, either within 24-48 hours after the index procedure or before hospital discharge

#### 16. Procedural success, defined as device success and absence of in-hospital MACCE.

#### 17. Evidence of prosthetic valve dysfunction at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

### Principal Investigators:

| Jeffrey J. Popma, M.D. – Interventional Cardiologist |
| David H. Adams, M.D. – Cardiothoracic Surgeon |

### Trial Sites:
The trial will be conducted at up to 45 sites in the United States.

### Sample Size:

790 (395 MCS TAVI & 395 SAVR) and up to 40 additional subjects enrolled with approximately 20 subjects randomized to TAVI and receiving a 23mm valve

Non-ilio-femoral will be limited to no more than 30% (249) of the 830 randomized subjects.

### Patient Population:

Subjects with symptomatic severe aortic stenosis (AS), necessitating aortic valve replacement whose predicted risk of operative mortality is ≥15% (and predicted operative mortality or serious, irreversible morbidity risk of < 50%) at 30 days.

### Inclusion Criteria:

1. Subject must have co-morbidities such that one cardiologist and two cardiac surgeons agree that predicted risk of operative mortality is ≥15% (and
### Inclusion Criteria (Continued):

1. Predicted operative mortality or serious, irreversible morbidity risk of < 50% at 30 days.
2. Subject has senile degenerative aortic valve stenosis with:
   - mean gradient > 40 mmHg or jet velocity greater than 4.0 m/s by either resting or dobutamine stress echocardiogram, or simultaneous pressure recordings at cardiac catheterization (either resting or dobutamine stress), AND
   - an initial aortic valve area of ≤ 0.8 cm² (or aortic valve area index ≤ 0.5 cm²/m²) by resting echocardiogram or simultaneous pressure recordings at cardiac catheterization
3. Subject is symptomatic from his/her aortic valve stenosis, as demonstrated by NYHA Functional Class II or greater.
4. The subject or the subject's legal representative has been informed of the nature of the trial, agrees to its provisions and has provided written informed consent as approved by the IRB of the respective clinical site.
5. The subject and the treating physician agree that the subject will return for all required post-procedure follow-up visits.

### Exclusion Criteria:

<table>
<thead>
<tr>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Evidence of an acute myocardial infarction ≤ 30 days before the intended treatment.</td>
</tr>
<tr>
<td>2. Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to the index procedure including bare metal stents. Additionally, any drug eluting stents placed within 6 months prior to the index procedure.</td>
</tr>
<tr>
<td>3. Blood dyscrasias as defined: leukopenia (WBC &lt; 1000/mm³), thrombocytopenia (platelet count &lt;50,000 cells/mm³), history of bleeding diathesis or coagulopathy.</td>
</tr>
<tr>
<td>4. Untreated clinically significant coronary artery disease requiring revascularization.</td>
</tr>
<tr>
<td>5. Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support.</td>
</tr>
</tbody>
</table>
Exclusion Criteria (Continued):

7. Severe ventricular dysfunction with left ventricular ejection fraction (LVEF) < 20% as measured by resting echocardiogram.
8. Recent (within 6 months) cerebrovascular accident (CVA) or transient ischemic attack (TIA).
9. End stage renal disease requiring chronic dialysis or creatinine clearance < 20 cc/min.
10. Active GI bleeding within the past 3 months.
11. A known hypersensitivity or contraindication to any of the following which cannot be adequately pre-medicated:
   - aspirin
   - heparin (HIT/HITTS)
   - nitinol (titanium or nickel)
   - ticlopidine and clopidogrel
   - contrast media
12. Ongoing sepsis, including active endocarditis.
13. Subject refuses a blood transfusion.
14. Life expectancy < 12 months due to associated non-cardiac co-morbid conditions.
15. Other medical, social, or psychological conditions that in the opinion of an Investigator precludes the subject from appropriate consent.
16. Severe dementia (resulting in either inability to provide informed consent for the trial/procedure, prevents independent lifestyle outside of a chronic care facility, or will fundamentally complicate rehabilitation from the procedure or compliance with follow-up visits).
17. Currently participating in an investigational drug or another device trial.
18. Symptomatic carotid or vertebral artery disease.
19. Subject has been offered surgical aortic valve replacement but declined.

Anatomical

20. Native aortic annulus size < 18 mm or > 29 mm per the baseline diagnostic imaging.
21. Pre-existing prosthetic heart valve in any position.
22. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation (3-4+)).
23. Moderate to severe (3-4+) or severe (4+) mitral or
Exclusion Criteria (Continued):

- 22. Severe (4+) tricuspid regurgitation.
- 24. Moderate to severe mitral stenosis.
- 26. New or untreated echocardiographic evidence of intracardiac mass, thrombus or vegetation.
- 27. Severe basal septal hypertrophy with an outflow gradient.
- 28. Aortic root angulation (angle between plane of aortic valve annulus and horizontal plane/vertebrae) > 70° (for femoral and left subclavian/axillary access) and > 30° (for right subclavian/axillary access).
- 29. Ascending aorta that exceeds the maximum diameter for any given native aortic annulus size (see table below)

<table>
<thead>
<tr>
<th>Aortic Annulus Diameter</th>
<th>Ascending Aorta Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 mm – 20 mm</td>
<td>&gt;34 mm</td>
</tr>
<tr>
<td>20 mm – 23 mm</td>
<td>&gt;40 mm</td>
</tr>
<tr>
<td>23 mm – 27 mm</td>
<td>&gt;43 mm</td>
</tr>
<tr>
<td>27 mm – 29 mm</td>
<td>&gt;43 mm</td>
</tr>
</tbody>
</table>

- 30. Congenital bicuspid or unicuspid valve verified by echocardiography.
- 31. Sinus of valsalva anatomy that would prevent adequate coronary perfusion

**Vascular**

- 32. Transarterial access not able to accommodate an 18Fr sheath.

<table>
<thead>
<tr>
<th>Enrollment Phase:</th>
<th>The enrollment phase is expected to last 20 months.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up Evaluations:</td>
<td>Subjects will be followed through 5 years with assessments at 30 days, 6 months, and 12 months as well as 2, 3, 4 and 5 years post MCS TAVI or post SAVR.</td>
</tr>
</tbody>
</table>
2. PURPOSE

2.1 Background

The management of heart disease in the elderly has been affected by the dramatic increase in life expectancy. With the number of persons over age 80 expected to increase to approximately 25 million by the year 2050, degenerative heart disease is likely to become an increasing problem. Calcific or degenerative aortic valve disease is considered the most common valvular lesion among elderly subjects. Aortic stenosis (AS) causes left ventricular outflow obstruction in adults, with severe AS defined as a combination of echocardiographic parameters: an aortic jet velocity >4 m/s, a mean gradient >40 mmHg, and a valve area <1.0 cm², according to the ACC/AHA guidelines for the management of valvular heart disease. Severe aortic stenosis is also considered to be present if the valve area index is < 0.6 cm²/m². However, in patients with severe AS who also have a low cardiac output state, the aortic jet velocity and mean gradient may be lower, a condition known as low-gradient stenosis. Subjects with AS can remain asymptomatic for a prolonged period, although once symptoms develop, prompt intervention is required. The classic symptoms associated with AS typically occur with exertion and include heart failure, syncope, and angina. Surgical replacement of the aortic valve is the only effective treatment for severe AS currently approved in the United States.

For those subjects ineligible for open-heart surgery, however, therapeutic options include only the palliative measures of medical therapy or percutaneous aortic valvuloplasty. Percutaneous balloon aortic valvuloplasty (BAV) has been suggested as an alternative to aortic valve replacement in subjects with AS and can result in improved symptoms. However, the high incidence of residual or recurrent stenosis and serious complications have limited the utility of this technique in the elderly. Subjects deemed too high risk to undergo aortic valve replacement (AVR) experience very high mortality rates, with average survival only two to three years.

In order to identify “high-risk” subjects for mortality following AVR, a number of scoring systems have been developed. The Society of Thoracic Surgeons (STS) Predicted Risk of Mortality appears to be the most accurate score for predicting perioperative and long-term mortality and morbidity in subjects undergoing aortic valve replacement. Dewey and colleagues compared the mean and logistic Euro System for Cardiac Operative Risk Evaluation (EuroSCORE), the Society of Thoracic Surgeons (STS) risk score, and the Ambler Risk Score in 638 subjects who underwent isolated aortic valve replacement. Subjects at or above the 90th percentile of risk (8.38% for STS, 33.47% for logistic, 12% for additive, 14.3% for Ambler) were identified as “high-risk” subjects for aortic valve replacement. Long-term mortality, per high-risk group, was 64.1% in the STS Predicted Risk of Mortality, 45.3% in the logistic, 45.2% in the additive, and 40.2% in Ambler Risk Score, and logistic regression showed that the STS algorithm was the most sensitive in defining the subjects most at risk for long-term mortality. There are also potential risks associated with cardiopulmonary bypass in high-risk subjects,
and minimally invasive surgical approach has lessened but not eliminated these risks.

Moreover, there are subjects who are deemed non-surgical due to prohibitive medical and anatomical conditions including highly compromised respiratory disease, severe immunosuppressive diseases, “true” porcelain aorta, chest wall radiation or deformity and multiple previous interventions in the presence of advanced multi-system dysfunction. Most of these characteristics are not included in the STS or other risk assessment systems (often such subjects will score less than an STS of 10). Despite the limitations noted, subjects with severe aortic stenosis who are not candidates for aortic valve replacement may undergo balloon valvuloplasty as a palliative procedure. In a series reported by Shareghi and colleagues, 80 consecutive subjects with symptomatic severe aortic stenosis underwent 104 balloon aortic valvuloplasty procedures and were followed for a mean of 3±2 years. Repeated valvuloplasty was needed in 15 subjects over the course of follow-up, including 5 balloon valvuloplasties in one subject. Nine percent of subjects had vascular complications. In-hospital, 1, 2- and 3-year mortality rates were 6%, 44%, 62% and 71%, respectively. In another series reported by Sack and colleagues, BAV was performed in 75 subjects who were not candidates for surgical aortic valve replacement. Serious adverse events occurred in 17% of the BAV procedures. The mortality rates at 6 months and 12 months were 25% and 29%, respectively. Contemporary BAV has acceptable short- and mid-term results and can effectively be used for subjects deemed unsuitable surgical candidates and those at highest operative risk, such as subjects with cardiogenic shock, but these therapies should be considered only palliative in nature.

A more viable long-term solution for high or extreme risk subjects for AS may be the development of transcatheter aortic valve implant (TAVI), which would provide the benefit of valve replacement without the associated risks of open-heart surgery. Recent advances in both percutaneous techniques and concurrent technological advances in the evolution of collapsible bioprosthetic aortic valves have led to cautious optimism about this emerging approach.

Less invasive percutaneous aortic valve procedures have emerged. Medtronic CoreValve® has developed the Medtronic CoreValve® System (MCS) which consists of a porcine pericardial bioprosthetic valve mounted and sutured in a self-expanding Nitinol frame. The bioprosthesis is housed in a collapsed position for percutaneous delivery via a catheter-based technique, and implanted within the diseased aortic valve. At the discretion of the participating physician (in accordance with the local standard of care), the procedure is performed utilizing local anesthesia (with or without conscious sedation) or under general anesthesia (with or without hemodynamic support or cardiac assistance).

The primary access site for the Medtronic CoreValve® System is the artery. The transfemoral approach has been reported in more than 15 published outcomes articles as of September 2010 representing more than 2500 procedures. In addition, the subclavian/axillary or direct aortic approaches have also been used as alternative access sites. The subclavian/axillary approach has been reported in nine published outcomes articles as of September 2010 representing more
than 100 procedures, and may represent up to 10% of implants at some implanting centers.xviii

The purpose of this protocol is to evaluate the safety and efficacy of the Medtronic CoreValve® System in the treatment of symptomatic severe aortic stenosis in subjects who have a predicted high risk for aortic valve surgery. High risk surgical subjects will be randomized to receive either transcatheter aortic valve implant (TAVI) with the Medtronic CoreValve® System (MCS) or SAVR in a 1:1 ratio.

The primary endpoint is all cause mortality at 12 months. The assumption for 12 month mortality for the SAVR arm is an estimate based on 12-month mortality as reported in the surgical literature for high risk AVR (table below). The subjects enrolled in this study are expected to have a higher mortality than observed in the surgical literature, as subjects enrolled in the High Risk Surgical Cohort must have an expected perioperative mortality of 15% (based on Investigator-estimated mortality or STS score >10). The complete references to the studies used to estimate the rates for the BAV and AVR comparator arms can be found in Section 16.

Table 1. All-cause mortality rates of high risk population from published data.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Mortality at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elayda et al.xix</td>
<td>1993</td>
<td>77</td>
<td>16%</td>
</tr>
<tr>
<td>Sundt et al.xx</td>
<td>2000</td>
<td>133</td>
<td>20%</td>
</tr>
<tr>
<td>Chiappini et al.xxi</td>
<td>2004</td>
<td>71</td>
<td>10%</td>
</tr>
<tr>
<td>Collart et al.xxii</td>
<td>2005</td>
<td>215</td>
<td>16%</td>
</tr>
<tr>
<td>Varadarajan et al.xxii</td>
<td>2006</td>
<td>80</td>
<td>13%</td>
</tr>
<tr>
<td>Melby et al.xxiv</td>
<td>2007</td>
<td>105</td>
<td>18%</td>
</tr>
</tbody>
</table>

Currently, the average patient undergoing surgery is older and has a greater number of comorbidities than the previously studied population. Given that the expected High Risk Surgical population will be older and at higher risk for surgery, it is estimated that the 12-month all-cause mortality rate among high risk SAVR subjects in the current study will be 20%.

Sundt et al.xx, Collart et al.xxii, and Melby et al.xxiv reported MACCE rates at 30 days. From these studies, the MACCE (defined as a composite of all cause death, MI (Q-wave and non-Q-wave), emergent cardiac surgery, stroke, and reintervention) rate ranged from 15% to 31% with meta-analytic average of 20.1% (95% CI 16.5-23.8%). Thus, for the current study it is assumed that the expected MACCE rate at 30 days will be 20%.

### 2.2 Medtronic CoreValve® System and Intended Use

The Medtronic CoreValve® System is intended for use in subjects with severe symptomatic Aortic Stenosis (AS), necessitating aortic valve replacement whose...
predicted risk of operative mortality is ≥15% (and predicted operative mortality or serious, irreversible morbidity risk of < 50%) at 30 days.

2.3 Primary Objective

The primary objective is to demonstrate that the safety and effectiveness of the Medtronic CoreValve® System (MCS), as measured by all cause mortality rates at 12 months, is non-inferior to surgical aortic valve replacement (SAVR) in the treatment of symptomatic severe aortic stenosis in subjects who have a predicted high risk for aortic valve surgery.
3. TRIAL PROTOCOL

3.1 Ethics & Regulatory Compliance

3.1.1 Applicable Regulations
This trial will be conducted in compliance with the protocol, the Sponsor’s standard operating procedures and/or guidelines, the United States Food and Drug Administration (FDA) and local regulations where applicable, the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki.

3.1.2 Institutional Review Board (IRB)
The trial will be conducted in accordance with 21 CFR 56 Institutional Review Boards. The trial protocol and consent must be approved by the responsible Institutional Review Board (IRB) at each investigational site. Trial activities must not commence prior to receipt of documentation of IRB approval by the site and Medtronic. The Investigator and trial staff must comply with the requirements of their IRB.

3.1.3 Ethical Conduct of the Trial
The trial will be conducted in accordance with the design and specific provisions of this protocol, in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice (GCP) and the applicable regulatory requirements.

3.1.4 Subject Information and Consent
All subjects must provide written informed consent in accordance with the site’s IRB, using an IRB-approved informed consent form. Trial-specific procedures beyond standard of care must not be performed until a signed informed consent has been obtained. The Investigator/designee, who has been trained on the protocol, will explain the nature and scope of the trial, potential risks and benefits of participation, and answer questions for the patient. If the patient agrees to participate, the informed consent form must be signed and personally dated by the patient or legally authorized representative. The person obtaining informed consent must also sign the informed consent form prior to any trial-related procedures. Any additional persons required by the site’s IRB to sign the informed consent form must also comply. The consent process should be documented in the patient’s medical record. All subjects are to be fully informed and trial conduct must be in accordance with the World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. Subject confidentiality will be maintained throughout the clinical trial in a way that assures that data can always be tracked back to the source data. For this purpose, a unique subject identification code will be used that allows identification of all data reported for each subject.
Data relating to the trial might be made available to third parties (for example in case of an audit performed by regulatory authorities), provided the data are treated as confidential and that the subject’s privacy is guaranteed. “Protected Health Information” will be maintained in compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

3.2 Trial Administration

3.2.1 Steering Committee

A Steering Committee will provide oversight of the Medtronic CoreValve® U.S. Pivotal Trial as well as issues relating to study enrollment and quality performance at individual sites. The Steering Committee will consist of, at a minimum, the following individuals:

- **Medtronic Membership:**
  - Committee Chairperson
  - Clinical & Medical Leadership
  - Facilitator

- **Non-Medtronic Membership:**
  - National Principal Investigators (Interventional Cardiologist and Cardiac Surgeon)
  - Selected Clinical Site Investigators
    - Cardiac Surgeon
    - Interventional Cardiologist

The functions of the Steering Committee include, but are not limited to the following:

- Provide oversight and direction for the trial
- Review of trial enrollment and trial progress
- Support site investigators in resolving any clinical or procedural issues that may impact patient well-being or integrity of the study
- Participate in investigator meetings with case review, protocol insights, etc.
- Review of Data Safety Monitoring Board (DSMB) recommendations
- Assist with publication efforts

The Steering Committee will establish a charter that outlines their roles and responsibilities and describes the planned frequency of meetings. The Steering Committee charter will be approved by Medtronic and the Steering Committee members.

3.2.2 Screening Committee

The Medtronic CoreValve® U.S. Pivotal Trial Screening Committee will ensure appropriate and consistent patient selection across all sites for the Medtronic CoreValve® U.S. Pivotal Trial. The Screening Committee will consist of
Medtronic CoreValve® U.S. Pivotal Trial investigators (interventional cardiologists and cardiac surgeons) and Medtronic CoreValve® proctors. Final decisions on patient eligibility will be made by two cardiac surgeons and one interventional cardiologist on the Screening Committee. Prior to the onset of the trial, the Screening Committee will establish a charter that outlines their roles and responsibilities and describes the Screening Committee process. The Screening Committee charter will be approved by Medtronic and the Screening Committee members.

3.2.3 Training and Education Committee
The Medtronic CoreValve® U.S. Pivotal Trial Training and Education Committee will review recommendations made by Medtronic field support and Medtronic CoreValve® proctors for transition of sites from the roll-in phase to the randomization phase of enrollment. The Committee will also review recommendations made by the Data Safety Monitoring Board (DSMB) after their scheduled reviews. It is the responsibility of the Training and Education Committee to make recommendations relative to the augmentation of physician training at a site level, as well as across the trial as a whole. The Training and Education Committee will consist of experienced Medtronic CoreValve® implanters and Medtronic CoreValve® U.S. Pivotal Trial investigators. Prior to the onset of the trial, the Training and Education Committee will establish a charter that outlines their roles and responsibilities and describes the planned frequency of meetings. The Training and Education Committee charter will be approved by Medtronic and the Training and Education Committee members.

3.2.4 Publication Committee
The Medtronic CoreValve® U.S. Pivotal Trial Publication Committee will review and approve publication ideas and facilitate submissions, including abstracts and manuscripts. The Publication Committee will consist of Medtronic CoreValve® U.S. Pivotal Trial investigators (interventional cardiologists and cardiac surgeons) and Medtronic representatives. The Publication Committee will establish a plan that outlines their roles and responsibilities and describes the planned frequency of meetings. The Publication Committee plan will be approved by Medtronic and the Publication Committee members.

3.3 Methodology

3.3.1 Purpose
To evaluate the safety and efficacy of the Medtronic CoreValve® System in the treatment of symptomatic severe aortic stenosis in subjects who have a predicted high risk for aortic valve surgery. The total trial duration is expected to be approximately seven years.
3.3.2 Patient Population
Subjects with symptomatic severe aortic stenosis (AS), necessitating aortic valve replacement whose predicted risk of operative mortality is $\geq 15\%$ (and predicted operative mortality or serious, irreversible morbidity risk of $< 50\%$) at 30 days.

3.3.3 Design
Subjects will be randomized on a 1:1 basis to either transcatheter aortic valve implant (TAVI) with the Medtronic CoreValve® System (MCS) or to surgical aortic valve replacement (SAVR).

3.3.4 Investigational Sites
The trial will be conducted at up to 45 investigational sites in the United States.

3.3.5 Number of Subjects
Roll-in cases: 3 per implanting site (inclusive of both High Risk Surgical and Extreme Risk patient populations and separate from evaluable sample size)
Proctored cases: minimum of 5 per site (inclusive of the 3 roll-in cases)
Sample size: 790 (395 MCS TAVI: 395 Surgical Aortic Valve Replacement (SAVR))
and up to 40 additional subjects enrolled with approximately 20 subjects randomized to TAVI and receiving a 23mm valve
Non-ilio-femoral will be limited to no more than 30% (249) of the 830 randomized subjects

3.3.6 Inclusion/Exclusion Criteria
To participate in this trial, the subject must meet ALL of the following inclusion criteria:
1. Subject must have co-morbidities such that one cardiologist and two cardiac surgeons agree predicted risk of operative mortality is $\geq 15\%$ (and predicted operative mortality or serious, irreversible morbidity risk of $< 50\%$) at 30 days.
2. Subject has senile degenerative aortic valve stenosis with:
   - mean gradient $> 40\text{ mmHg}$, or jet velocity greater than 4.0 m/sec by either resting or dobutamine stress echocardiogram, or simultaneous pressure recordings at cardiac catheterization (either resting or dobutamine stress), AND
   - an initial aortic valve area of $\leq 0.8\text{ cm}^2$ (or aortic valve area index $\leq 0.5\text{ cm}^2/m^2$) by resting echocardiogram or simultaneous pressure recordings at cardiac catheterization
3. Subject is symptomatic from his/her aortic valve stenosis, as demonstrated by New York Heart Association (NYHA) Functional Class II or greater.
4. The subject or the subject's legal representative has been informed of the nature of the trial, agrees to its provisions and has provided written informed consent as approved by the IRB of the respective clinical site.

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

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

**Clinical**

1. Evidence of an acute myocardial infarction ≤ 30 days before the intended treatment.

2. Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to the index procedure including bare metal stents. Additionally, any drug eluting stents placed within 6 months prior to the index procedure.

3. Blood dyscrasias as defined: leukopenia (WBC < 1000mm$^3$), thrombocytopenia (platelet count <50,000 cells/mm$^3$), history of bleeding diathesis or coagulopathy.

4. Untreated clinically significant coronary artery disease requiring revascularization.

5. Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support.


7. Severe ventricular dysfunction with left ventricular ejection fraction (LVEF) < 20% as measured by resting echocardiogram.

8. Recent (within 6 months) cerebrovascular accident (CVA) or transient ischemic attack (TIA).

9. End stage renal disease requiring chronic dialysis or creatinine clearance < 20 cc/min.

10. Active Gastrointestinal (GI) bleeding within the past 3 months.

11. A known hypersensitivity or contraindication to any of the following which cannot be adequately pre-medicated:
   - aspirin
   - heparin (HIT/HITTS)
   - nitinol (titanium or nickel)
   - ticlopidine and clopidogrel
   - contrast media

12. Ongoing sepsis, including active endocarditis.

13. Subject refuses a blood transfusion.

14. Life expectancy < 12 months due to associated non-cardiac co-morbid conditions.

15. Other medical, social, or psychological conditions that in the opinion of an Investigator precludes the subject from appropriate consent.
16. Severe dementia (resulting in either inability to provide informed consent for the trial/procedure, prevents independent lifestyle outside of a chronic care facility, or will fundamentally complicate rehabilitation from the procedure or compliance with follow-up visits).
17. Currently participating in an investigational drug or another device trial.
18. Symptomatic carotid or vertebral artery disease.
19. Subject has been offered surgical aortic valve replacement but declined.

**Anatomical**
20. Native aortic annulus size < 18 mm or > 29 mm per the baseline diagnostic imaging.
21. Pre-existing prosthetic heart valve in any position.
22. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation (3-4+)).
23. Moderate to severe (3-4+) mitral regurgitation or (4+) tricuspid regurgitation.
24. Moderate to severe mitral stenosis.
25. Hypertrophic obstructive cardiomyopathy.
26. New or untreated echocardiographic evidence of intracardiac mass, thrombus or vegetation.
27. Severe basal septal hypertrophy with an outflow gradient.
28. Aortic root angulation (angle between plane of aortic valve annulus and horizontal plane/vertebrae) > 70° (for femoral and left subclavian/axillary access) and > 30° (for right subclavian/axillary access).
29. Ascending aorta that exceeds the maximum diameter for any given native aortic annulus size (see table below)

<table>
<thead>
<tr>
<th>Aortic Annulus Diameter</th>
<th>Ascending Aorta Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 mm – 20 mm</td>
<td>&gt;34 mm</td>
</tr>
<tr>
<td>20 mm – 23 mm</td>
<td>&gt;40 mm</td>
</tr>
<tr>
<td>23 mm – 27 mm</td>
<td>&gt;&gt;43 mm</td>
</tr>
<tr>
<td>27 mm – 29 mm</td>
<td>&gt;43 mm</td>
</tr>
</tbody>
</table>

30. Congenital bicuspid or unicuspid valve verified by echocardiography.
31. Sinus of valsalva anatomy that would prevent adequate coronary perfusion.

**Vascular**
32. Transarterial access not able to accommodate an 18Fr sheath.

3.3.7 *Informed Consent*
Prior to enrolling in the trial, patients should be fully informed of the details of trial participation as required by applicable regulations, the site’s Institutional Review Board (IRB) and by Medtronic, Inc. Informed consent must be obtained from each patient or legally authorized representative prior to conducting any protocol-
induced activities beyond standard of care, by using the informed consent form (ICF) approved by that site’s IRB and by Medtronic, Inc. The consent form must be signed and dated by the patient or legal representative and by the person obtaining the consent. Any additional persons required by the site’s IRB to sign the informed consent form must also comply.

Prior to the patient or legal representative signing the ICF, the Investigator or authorized designee will fully explain to the patient or legal representative 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 patient or legal representative to read and review the consent form and to ask questions.

Signing the ICF serves to document the written and verbal information that the Investigator or authorized delegate provides to the patient or legal representative, the patient or legal representative’s understanding of the information, and their agreement to participate. The Investigator or authorized delegate must document in the patient’s medical records that the patient was consented and the date on which the consent was obtained. The original signed consent form will be retained in the patient’s trial records. A copy of the informed consent will be provided to the patient or legal representative and a copy placed in the patient’s medical record.
3.3.8 Enrollment Flowchart for randomization to MCS TAVI vs. SAVR

Figure 1: Enrollment Flowchart

Subjects with Symptomatic Aortic Stenosis

Obtain Informed Consent

Physician Screening Assessment

Pass

No

Subject Not Enrolled

Screening Committee Review

Pass

Ilio-femoral Access?

No

Non-Ilio-femoral Access?

Yes

Subject Enrolled, Randomized 1:1

Subject Enrolled, Randomized 1:1

Subject Not Enrolled

MCS TAVI Ilio-femoral

MCS TAVI Non-Ilio-femoral

Total N: 395 SAVR 395 MCS TAVI

SAVR

3.3.9
**Trial Training**

Protocol-specific training and education of all site staff with roles in this trial will take place during the site initiation visit, and throughout the trial as needed. The sponsor will maintain documentation of attendance at each of these training opportunities. Training will include the specifics of trial conduct, product-specific information, and adverse event reporting. A Medtronic representative may be present at each site’s MCS TAVI procedures.

Training for the implanting investigators includes but is not limited to the following:

- **On-line training**, including
  - Pathophysiology and Natural History of Aortic Stenosis
  - General Product Description
  - Medtronic CoreValve® U.S. Pivotal Trial Inclusion/Exclusion Criteria

- **Face-to-face didactic training**, including
  - Aortic Anatomy and Current Procedures
  - Medtronic CoreValve® Technology Review
  - Procedure Steps
  - Patient selection
  - Implant procedure – Pre-Procedure, Anesthesia and Post-Procedure Patient Care
  - Device Preparation & Loading
  - Complication Management
  - Clinical Data Overview

- **Case observations**

- **Case proctoring**
  - A minimum of 5 procedures will be proctored by a Medtronic-trained physician.

- **Training for the full team conducted on-site** will include the following:
  - Product Use
  - Procedure Steps
  - Device Preparation & Loading
  - Good Clinical Practice

### 3.4 Trial Procedures

#### 3.4.1 Screening Procedures

Prior to subject participation in this trial, the Investigator must obtain written IRB approval for the trial protocol, informed consent form, and Health Insurance Portability and Accountability Act (HIPAA) Authorization. The approved consent form should clearly reflect the IRB approval date. The Patient Address Form (PAF) and Medical Billing Release Form should also be completed at this time.
All potential subjects for trial entry must be screened for eligibility. Prior to any trial-specific tests or procedures, written informed consent must be obtained from the subject.

Failure to obtain a signed and hand dated informed consent prior to the procedure constitutes a protocol violation, which is reportable to the IRB and the Food and Drug Administration (FDA).

The following tests and procedures must be performed prior to randomization to verify eligibility. The recommended timeframe for these tests and procedures is approximately 30 days prior to submission to the Screening Committee, unless otherwise specified:

- Clinical assessments including: vital signs and all major systems findings, weight, height and body surface area (BSA); BSA will be calculated from height and weight by use of the formula by Dubois and Dubois (BSA = 0.007184 × weight [kg]^{0.425} × height [m]^{0.725}), Grip Strength Test, Gait Test, and Mini Mental Status Exam (MMSE-2E).

- NYHA classification

- STS Risk Score Assessment

- Routine laboratory tests (most recent) including complete blood count (CBC), creatinine, cardiac enzymes CK (and CK-MB if CK is elevated ≥ 2X the laboratory upper limit of normal), international normalized ratio (INR), Partial Thromboplastin Time (PTT), liver panel and albumin.

- Subject demographics, medical history, risk factors targeted to cardiovascular disease

- 12-lead Electrocardiogram

- Cardiovascular imaging studies:
  - Comprehensive transthoracic 2D echocardiogram (TTE). The TTE must be performed within 45 days prior to submission to the Screening Committee. (Note: if patient recently underwent BAV, a TTE should be obtained post-BAV; within 45 days prior to submission to the Screening Committee). Echocardiograms will be performed according to the Echocardiography Procedures found in Appendix 17.8. All echocardiograms for enrolled subjects will be independently analyzed by the Echocardiographic Core Lab.

  - Screening Computed Tomography (CT) angiograms (e.g. CT-torso) with complete visualization of both iliacs, femorals and aorta (and subclavian/axillaries, if applicable), up to and including the aortic annulus. CT angiograms will be performed according to the CT Angiography Acquisition Guidelines found in Appendix 17.20. If the CT angiogram was conducted in the last 365 days and subject has not had a peripheral vascular intervention since the time of the image, a more recent exam is not required as long as visualization of both iliacs and femorals (and subclavian/axillaries, if
applicable) to the aorta can be viewed. However, if the subject had a peripheral vascular intervention within the 365 day window, angiography obtained at the completion of the procedure may be used as an alternative to a repeat CT scan provided it has been obtained within 90 days of submission to the Screening Committee.

- Selective coronary arteriography to assess the presence and severity of coronary artery disease which should include angiograms of both coronary arteries and all bypass grafts (if applicable).

If the coronary arteriogram has been performed within the last 365 days and the subject qualifies for the study (no significant coronary artery disease), a more recent exam is not required. However, if the subject had evidence of significant coronary artery disease and/or received a coronary intervention within the 365 day window, angiography obtained at the completion of the procedure may be used as an alternative provided it has been obtained within 90 days of submission to the Screening Committee.

- Modified Rankin Scale (for subjects with history of stroke only)
- Logistic EuroScore

Two cardiac surgeons and one interventional cardiologist at each participating site must evaluate each patient for inclusion into the appropriate cohort (High Risk Surgical vs. Extreme Risk) and are required to sign off on the Screening Worksheet to be submitted to the Screening Committee. In addition, each patient must be examined in-person by at least one of the cardiac surgeons to evaluate the risk and determine eligibility for the study. The final eligibility for each subject will be confirmed by the Screening Committee. Additional assessments may be performed to evaluate risk and vascular access, including (but not limited to) pulmonary function test and BNP labwork.

3.4.2 Screening Committee Procedures

The Medtronic CoreValve® U.S. Pivotal Trial Screening Committee will review screening information to make the final determination regarding eligibility of the prospective subject to be enrolled in the Medtronic CoreValve® U.S. Pivotal Trial.

The following information should be submitted to the Screening Committee:

- Completed Patient Screening Worksheet including, but not limited to:
  - Demographics
  - Clinical Assessments including: Vital Signs, Grip Strength Test, Gait Test, and Mini Mental Status Exam (MMSE-2E)
  - Surgical Risk Assessment
  - Case Planning
  - Medical History and Co-Morbidities
Anatomical Measurements

DICOM-compatible images and cines of all screening exams:

- Comprehensive transthoracic 2D echocardiogram (TTE). The TTE must be performed within 45 days prior to submission to the Screening Committee. (Note: if patient recently underwent BAV, a TTE should be obtained post-BAV; within 45 days prior to submission to the Screening Committee). Echocardiograms will be performed according to the Echocardiography Procedures found in Appendix 17.8.

- Screening CT angiography (e.g. CT-torso) with complete visualization of both iliacs, femorals and aorta (and subclavian/axillaries, if applicable), up to and including the aortic annulus. CT angiograms will be performed according to the CT Angiography Acquisition Guidelines found in Appendix 17.20.

- Selective coronary arteriography to assess the presence and severity of coronary artery disease which should include angiograms of both coronary arteries and all bypass grafts (if applicable).

STS calculation print out

3.4.3 Roll-in Cases

The first three successfully enrolled patients at each implanting site inclusive of both High Risk Surgical and Extreme Risk patient populations will be considered “roll-in” subjects, will not be randomized, and will automatically be assigned to MCS TAVI. A maximum of three roll-in subjects is allowed per site. The purpose of the roll-in subjects is to provide the investigators the time for training and familiarization with the protocol and devices. The Medtronic CoreValve® U.S. Pivotal Trial Training and Education Committee will review recommendations made by Medtronic field support, Medtronic CoreValve Proctors and the Steering Committee for transition of sites from the roll-in phase to the randomization phase of enrollment after the first three subjects have been treated.

A successful roll-in patient, which counts towards the limit of three roll-in patients, is defined as the patient leaving the procedure room with one CoreValve device in the correct position and not requiring emergency surgery. An unsuccessful roll-in patient, which does not count towards the limit of three roll-in patients, is defined as any patient taken to the procedure room for the purpose of CoreValve implantation, but does not leave the procedure room with one CoreValve device in the correct position or requires emergency surgery.

A site must have three successful roll-in patients before they can be evaluated to move into the randomization phase. The Training and Education Committee will review and document their decisions based on the technique of the investigators, as well as the frequency, severity and nature of events in the roll-in subjects.
Subjects enrolled as roll-in subjects will be followed for safety following the same schedule as subjects who are randomized to MCS TAVI. However, the results for the roll-in population will be analyzed separately from the Pivotal trial subjects.

3.4.4 Enrollment and Randomization

Prior to randomization of a subject, the following must occur:

- Confirm patient signed informed consent.
- Confirm patient meets all of the inclusion and none of the exclusion criteria, (with the exception of a percutaneous coronary or peripheral intervention and evidence of an acute myocardial infarction which must not occur within 30 days prior to the index procedure) including approval by the Screening Committee.

Due to the inclusion/exclusion criteria, not all subjects that consent to the trial will be enrolled. All sites will be required to maintain a record of patients screened for the trial meeting general inclusion criteria who have signed the approved informed consent document. For subjects that do not meet trial criteria, the reason for not continuing in the trial must be documented on the screening log in IXRS. Randomization will occur only if the patient meets all inclusion criteria and does not meet any exclusion criteria and has been assessed by the Screening Committee as being an appropriate candidate for enrollment in the Medtronic CoreValve® U.S. Pivotal Trial.

Subjects will be considered enrolled into the trial at the time of randomization. Enrollments shall not exceed 20% (158) of randomized subjects at any individual site. Subjects must have their MCS TAVI or SAVR procedure no later than 30 days post-randomization. Any events or hospitalizations occurring prior to these index procedures will not be counted as part of the primary endpoint. If a subject remains hospitalized beyond 30 days after device placement, this counts as an aortic valve disease hospitalization secondary endpoint occurring on day 31.

Trial randomization will not be blinded. Once randomization is complete and a treatment arm is assigned, crossover from SAVR to TAVI treatment is not permitted. The sponsor will maintain strict device accountability to ensure that only those subjects randomized to the MCS TAVI treatment arm receive the Medtronic CoreValve® PAV.

Distribution of the subjects within the trial groups will be controlled at the implanting sites by means of central randomization using interactive voice/web randomization service (IXRS). The randomization scheme will be securely stored at the IXRS provider (Appendix 17.11).

Randomization with an assignment to the treatment arm or control arm (MCS TAVI or SAVR) will be executed in a 1:1 ratio. Stratified randomization by investigational site and by intended access site (ilio-femoral or non-ilio-femoral) will be used to ensure subjects will be allocated to each comparison group proportionately. Non-ilio-femoral will be limited to no more than 30% (264) of the 880 randomized subjects.
Baseline

Baseline assessments must occur within 14 days after enrollment and include:

- Brief physical examination including vital signs and all major systems findings
- NYHA classification
- 12-lead Electrocardiogram
- Routine laboratory tests including complete blood count (CBC), creatinine, B-type natriuretic peptide (BNP), plasma-free hemoglobin, Cardiac Enzymes CK (and CK-MB if CK is elevated ≥ 2X the laboratory upper limit of normal), international normalized ratio (INR), Partial Thromboplastin Time (PTT), liver panel and albumin
- For patients with an existing permanent pacemaker or defibrillator only: Perform a full interrogation and an assessment of AV conduction (Refer to the Pacing Guidelines in Appendix 17.14). Print a copy of the interrogation. It is recommended to save the interrogation via standard center practice (i.e. diskette, CD, flash drive). Retain the printed and saved copies of the interrogation in the subject's file for source verification.
- NIH Stroke Scale
- A six minute walk test per the American Thoracic Society Guidelines (detailed instructions can be found in Appendix 17.15), will be performed unless the subject is exempt due to any of the following conditions: postural hypotension, postural arrhythmia, resting systolic pressure less than 95 mmHg, non-ambulatory due to arthritis, neuromuscular disease or Peripheral Vascular Disease, Chronic Obstructive Pulmonary Disease with O₂ desaturation upon ambulation or oxygen dependent, or unstable angina. Subjects with any of these conditions will not undergo the test, but the reasons for not performing the test must be documented on the six minute walk test case report form.
- Quality of Life Questionnaires (Kansas City Cardiomyopathy Questionnaire (KCCQ), SF-12, and EuroQoL)
- Assessment of concomitant medications
- Documentation of all adverse events/serious adverse events from enrollment to discharge including all unanticipated adverse device effects (UADE), technical observations, reinterventions or repeat admission to the catheterization suite and deaths.
  - Any patient with evidence of a neurological event should have a neurology consult and subsequently an imaging study if deemed necessary by the neurologist.
- Document any changes to subject condition that affect inclusion/exclusion criteria
3.4.5.1 **MCS TAVI**
The following procedures are recommended for MCS TAVI subjects. The Instructions For Use (IFU) and Medtronic CoreValve® Proctors may also be consulted for additional guidance. Refer to Table 2: Schedule of Assessments for data collection requirements. Items indicated below in bold are required for CRF completion.

**Pre-Procedure**
- If the patient is currently on warfarin therapy prior to the procedure it is recommended to
  - Discontinue warfarin 3 days prior to the procedure
  - Confirm that the INR < 1.8 prior to the procedure
  - aspirin (81-325 mg) or clopidogrel (75 mg) daily or ticlopidine if clopidogrel is contraindicated) for 3 days prior to the procedure.
- If the patient is currently not on warfarin therapy prior to the procedure
  - aspirin (81-325 mg) on the day of the procedure and clopidogrel, 300 mg
- Consider adjunctive proton pump inhibitors, H₂ antagonists or antacids
- **Routine laboratory tests including complete blood count (CBC), BNP, plasma free hemoglobin, international normalized ratio (INR), Partial Thromboplastin Time (PTT), liver panel and albumin.**
- Cardiac enzymes CK (and CK-MB if CK is elevated ≥ 2X the laboratory upper limit of normal) obtained within 48 hours of the procedure.
- Perform 12-lead Electrocardiogram
- **Check serum creatinine and creatinine clearance.**
  - If the GFR < 60 cc/min, consider:
    - Fluid hydration on the day prior to the procedure
    - Discontinuation of NSAIDs and ACE inhibitors

**MCS TAVI Procedure**

Subject must meet all inclusion/exclusion criteria at the time of procedure

- **Joint Participation**
  - The heart team’s interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of transcathether aortic valve replacement (TAVR).
- **Medications**
  One hour prior to the procedure, prophylactic antibiotic therapy of the Investigator’s choice should be initiated:
  - Cefuroxime 750mg IV 1 hour pre-procedure, then 6 hours and 12 hours post-procedure
  - If allergic to Penicillin, prescribe Vancomycin 1g IV,
Consider holding anti-hypertensives

### Anesthesia and Procedural Set Up

- Establish a central venous line.
- Administer general anesthesia or conscious sedation per hospital protocol.
- Prior to beginning the Medtronic CoreValve® System implant, place a temporary 4-5 Fr. balloon-tip pacing wire in a stable location within the right ventricular (a screw-tip wire may be used for more secure placement for subjects at high-risk for dislodgement, if necessary)
- Whenever possible, use the upper torso venous system (e.g., jugular, subclavian) for temporary pacing wire access.
- Use fluoroscopy to guide wire placement and stability
- Confirm sensing and capture
- Program the backup pacing rate to minimize ventricular pacing (e.g. 30-40 bpm). If heart block develops, adjust the rate accordingly
- Record ECG and angiogram (Peri-procedural angiographic cine film in DICOM format) during the procedure

### Vascular Access

- The primary access artery will be used to introduce the CoreValve device and the balloon catheter; the secondary access artery will be used to introduce the reference pigtail.
- Insert a 6-Fr introducer sheath into the secondary access artery.
- Insert 18 Fr introducer sheath into the primary access artery using hospital protocol (either percutaneously or surgical cut down)
- Administer anticoagulant therapy according to hospital protocol. If heparin is administered as an anticoagulant, check activated clotting time (ACT) at five minutes and monitor every 30-60 minutes after initial bolus of heparin
- Maintain ACT ≥ 250 seconds
- Anticoagulant may be administered at any time prior to this point, but avoid delaying beyond this point

### Crossing the native valve

- Advance the graduated pigtail catheter to the ascending aorta and position the distal tip in the noncoronary cusp of the native aortic valve
- Identify the ideal annular viewing plane using contrast injections at various angiographic angles, preferably in the left anterior oblique (LAO) projection
- Insert an angiographic catheter over a standard, J-tip guidewire into the primary access sheath and advance to the ascending aorta
- Exchange the J-tip guidewire for a 0.035-in (0.889-mm) straight-tip guidewire. Advance the straight-tip guidewire across the native aortic valve into the left ventricle
After crossing the native aortic valve with the guidewire, advance the angiographic catheter into the left ventricle.

- Exchange the straight-tip guidewires for an exchange-length J-tip guidewire.
- Exchange the angiographic catheter for a 6 Fr pigtail catheter.
- Remove the guidewire and connect the catheter to the transducer. Using both catheters, record the aortic pressure gradient.
- Using a right anterior oblique (RAO) projection, advance previously pigtail-shaped, 0.035-in (0.889-mm) high-support guidewire through the pigtail catheter and position in the apex of the left ventricle.
- Remove the pigtail catheter while maintaining guidewire position in the left ventricle.

**Rapid Pacing and Pre-dilatation of the Implant site**

- Insert the valvuloplasty balloon through the 18 Fr introducer sheath and advance it to the ascending aorta.
- Perform a rapid pacing test. A successful test is defined as 1-to-1 pacing capture with an immediate drop in pressure and elimination of the systolic-diastolic waveform.
- Reposition the angiographic equipment to the ideal viewing plane as previously described. Position the valvuloplasty balloon across the native valve, while maintaining strict fluoroscopic surveillance of the distal tip of the guidewire in the left ventricle (LV).
- Perform BAV per hospital protocol and remove the valvuloplasty balloon while maintaining guidewire position across the native aortic valve.
- Balloon sizing directed to 1:1 sizing of the minimal annular diameter by CTA or echocardiogram with maximum 25 mm balloon.
- Perform full balloon expansion.

**Medtronic CoreValve® Implantation**

- Insert the device over the 0.035-in (0.889-mm) guidewire and advance it, while maintaining strict fluoroscopic surveillance of the guidewire in the LV.
- When crossing the aortic arch, control the guidewire preventing it from moving forward.
- Advance the device through the native valve. Perform an angiogram to confirm that the graduated pigtail catheter is in position within the noncoronary cusp of the aortic root, preferably in the shallow LAO projection.
- Use Fluoroscopy to identify the appropriate landmarks.
- Place the bioprosthesis within the aortic annulus (4 mm - 6 mm below the annulus). The annulus is defined as the angiographic floor of the aortic root.
- After attaining optimal catheter position, slowly turn the micro knob and begin to deploy the bioprosthesis. As the inflow aspect of the bioprosthesis starts to flare outward, monitor bioprosthesis position under fluoroscopy.
Caution: During implantation, if resistance to deployment is encountered (for example, the micro knob starts clicking or is tight or stuck), apply mild upward pressure to the macro slider while turning the micro knob. If the bioprosthesis still does not deploy, remove it from the patient and use another system.

Perform an angiogram. Once annular contact is made, the bioprosthesis should not be advanced into a lower position.

Continue deploying rapidly to the 2/3 deployment point; stop turning the micro knob.

Perform an angiogram to assess the location of the bioprosthesis. Optimal placement of the bioprosthesis is within the aortic annulus (4 mm - 6 mm below the annulus).

If the bioprosthesis is positioned low, carefully pull the DCS to reposition the bioprosthesis.

Evaluate the valve position and valve function using hemodynamic, aortography, and possible echocardiography.

When satisfactory position is achieved, continue to turn the micro knob until both frame loops disengage.

Use orthogonal views under fluoroscopy to confirm that the frame loops have detached from the catheter tabs. If a frame loop is still attached to a catheter tab, under fluoroscopy, advance the catheter slightly and, if necessary, gently rotate the handle clockwise (<180°) and counterclockwise (<180°) to disengage the loop from the catheter tab.

Withdraw the DCS carefully to the aorta avoiding contact with the inflow portion of the frame.

**Post Deployment**

Withdraw the DCS to the aorta, while maintaining guidewire position.

Close the DCS capsule and remove the DCS through the 18 Fr introducer sheath.

Advance a 6-Fr pigtail catheter over the guidewire into the left ventricle.

Remove the guidewire and connect the pigtail catheter to the transducer.

Using both pigtail catheters, record aortic pressure gradient.

Withdraw 6-Fr pigtail.

Perform postimplant aortogram with the reference pigtail to assure coronary patency and assess aortic regurgitations.

Remove the 18-Fr introducer sheath and complete the puncture site closure per hospital protocol.

Perform contrast angiography of the primary vessels to verify the absence of any vascular complications with the reference pigtail.

Remove the reference pigtail catheter over a standard guidewire.

Remove the 6 Fr introducer and close the access site per hospital protocol.
Ballooning as needed during the implant procedure is standard practice and should not be considered a reintervention.

Immediate Post-Procedure

The procedure is considered complete after final angiography has been performed, and the introducer sheath has been removed from the subject. Thereafter, if an introducer sheath is re-introduced, this is considered a repeat intervention, which must be documented on the reintervention eCRF.

- Anticoagulants should be discontinued per hospital standard.
- Activated clotting time (ACT) should be monitored per hospital standards but recommendation is >250 seconds.
- **Cardiac Enzymes**: CK within 8-12 hours post procedure and at any time when a clinical ischemic event is suspected. CK-MB is required if CK is elevated ≥2X the laboratory upper limit of normal. If a clinical event is confirmed, a total of 3 draws of cardiac enzymes within the first 24 hours (drawn every 8 hours) following the clinical event should be obtained.
- 12-lead Electrocardiogram (performed within 48 hours post MCS TAVI)
- NIHSS should be administered within 24 hours post-procedure
- Modified Rankin Scale (for patients with a suspected or new neurological event only)
  - For subjects with a stroke, assessment to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-stroke.
- An echocardiogram must be done 24-48 hours post-procedure to assess device success.
- It is recommended that subjects are treated for a minimum of three months with dual anti-platelet medication.
  - If the patient is on warfarin therapy post-procedure:
    - it is recommended that subjects are prescribed either daily aspirin (>81 mg) or daily clopidogrel (75 mg) (or ticlopidine, if clopidogrel is contraindicated) for at least three months following the procedure.
  - If the patient will not be on warfarin therapy post-procedure:
    - it is recommended that subjects are prescribed daily aspirin (≥81 mg) and daily clopidogrel (75 mg) (or ticlopidine, if clopidogrel is contraindicated) for at least three months following the procedure.
- Assessment of concomitant medications must be performed
- For patients with permanent pacemakers or defibrillators only: Perform a full interrogation and an assessment of AV conduction within 48 hours post procedure (Refer to the Pacing Guidelines in Appendix 17.14). Print a copy of the interrogation. It is
recommended to save the interrogation via standard center practice (i.e. diskette, CD, flash drive). Retain the printed and saved copies of the interrogation in the subject's file for source verification.

- Documentation of all adverse events/serious adverse events from enrollment to discharge including all unanticipated adverse device effects (UADE), technical observations, reinterventions or repeat admissions to the catheterization suite and deaths.
  - Any patient with evidence of a neurological event should have a neurology consult and subsequently an imaging study if deemed necessary by the neurologist.

**Post-Procedure Pacing guidelines**

- All patients should stay on telemetry until discharge
- Maintain temporary pacing until at least 48 hours post-implant in CV-ICU unless patient has a pre-existing permanent pacemaker or defibrillator
- After 48 hours, obtain Electrocardiogram (ECG) and assess patient rhythm and conduction
- Based on assessment, and with the consult of an electrophysiologist as needed, take one of the following actions:
  - Discontinue temporary pacing
  - Continue temporary pacing for another 24 hours (longer if needed) to make further assessments
  - Place a permanent pacemaker according to ACC/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities (Class I or IIb for Acquired Atrioventricular Block in Adults or Permanent Pacing in Chronic Bifascicular Block)
  - **Prior to the permanent pacemaker implantation, document the reason for the placement of the permanent pacemaker via a 12-lead ECG.**
    - For complete heart block, review patient medications.
    - Consider withholding some medications to assess for patient's intrinsic rate and conduction.
    - If heart block persists off medications, a permanent pacemaker should be considered.
    - If a permanent pacemaker is required, a dual chamber system is recommended to optimize patient hemodynamics.
    - If a permanent pacemaker is implanted, perform a device interrogation and an assessment of AV conduction post insertion and prior to hospital discharge as well as at every follow-up visit to evaluate device utilization (Refer to the Pacing Guidelines in Appendix 17.14).
Assessments done at discharge
Prior to hospital discharge (or no later than 7 days post-MCS TAVI, whichever occurs first) the following tests and procedures must be performed and data collected:

- Brief physical examination including vital signs and all major systems findings
- Routine laboratory tests including CBC, creatinine, BNP, hemoglobin and plasma-free hemoglobin.
- 12-lead Electrocardiogram
- Comprehensive transthoracic 2D echocardiogram (TTE). The TTE should be performed as close to discharge (or no later than 7 days, whichever is sooner) as possible. Echocardiograms will be performed according to the Echocardiography Procedures found in Appendix 17.8. All echocardiograms for enrolled subjects will be independently analyzed by the Echocardiographic Core Lab.
- NIH Stroke Scale
  - Any patient with evidence of a neurological event should have a neurology consult and an imaging study if deemed necessary.
- Modified Rankin Scale (for subjects with a suspected or new neurological event only)
  - Assessment must be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-stroke.
- Concomitant Medications Assessment
  - All medications administered during this trial will be recorded in the subject’s medical record.
  - Use of relevant medications (diuretics, aspirin, anticoagulants, ACE-I, ARB, beta-blockers, statins and anti-platelets) must be reported on the eCRF through at least the 12 month follow-up assessment.
- Documentation of all adverse events/serious adverse events from enrollment to discharge including all unanticipated adverse device effects (UADE), technical observations, reinterventions or repeat admissions to the catheterization suite and deaths.
  - Any patient with evidence of a neurological event should have a neurology consult and subsequently an imaging study if deemed necessary by the neurologist.
- For patients with permanent pacemakers or defibrillators only: Perform a full interrogation and an assessment of AV conduction (Refer to the Pacing Guidelines in Appendix 17.14). Print a copy of the interrogation. It is recommended to save the interrogation via standard center practice (i.e. diskette, CD, flash drive). Retain the printed and saved copies of the interrogation in the subject's file for source verification.
3.4.5.2 Surgical Aortic Valve Replacement

Subjects randomized to SAVR should be treated according to the surgeon and hospital’s standard practices. Subject must meet inclusion/exclusion criteria at the time of procedure. The SAVR procedure must be an isolated procedure (no concomitant procedures). The surgeon or co-surgeon performing the SAVR must be a trial investigator for the site.

All medications administered during this trial will be recorded in the subject’s medical record. Use of relevant medications (diuretics, aspirin, anticoagulants, ACE-I, ARB, beta-blockers, statins, and anti-platelets) must be reported on the eCRF through at least the 12-month follow up assessment.

Immediate Post-Procedure

The procedure is considered complete at the time of skin closure. Immediately post-procedure the following tests and procedures must be performed and data collected:

- Cardiac Enzymes: CK within 8-12 hours post procedure and at any time when a clinical ischemic event is suspected. CK-MB is required if CK is elevated >2X the laboratory upper limit of normal. If a clinical event is confirmed, a total of 3 draws of cardiac enzymes within the first 24 hours (drawn every 8 hours) following the clinical event should be obtained.
- 12-lead Electrocardiogram (performed within 48 hours of SAVR)
- NIHSS should be administered within 24 hours post-procedure
- Modified Rankin Scale (for patients with a suspected or new neurological event only)
  - For subjects with a stroke, assessment to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-stroke.
- Comprehensive transthoracic 2D echocardiogram (TTE). The TTE will be performed according to the Echocardiography Procedure found in Appendix 17.8. All echocardiograms for enrolled subjects will be independently analyzed by the Echocardiographic Core Lab. A TTE should be performed 24-48 hours post-procedure to assess device success.
- Assessment of concomitant medications must be performed.
- For patients with permanent pacemakers or defibrillators only: Perform a full interrogation and an assessment of AV conduction within 48 hours post procedure (Refer to the Pacing Guidelines in Appendix 17.14). Print a copy of the interrogation. It is recommended to save the interrogation via standard center practice (i.e. diskette, CD, flash drive). Retain the printed and saved copies of the interrogation in the subject’s file for source verification.
- Documentation of all adverse events/serious adverse events from enrollment to discharge including all unanticipated adverse device effects (UADE), technical observations, reinterventions or repeat admissions to the catheterization suite and deaths.
Any patient with evidence of a neurological event should have a neurology consult and subsequently an imaging study if deemed necessary by the neurologist.

Assessments done at discharge

Prior to hospital discharge (or no later than 7 days post-procedure, whichever occurs first) the following tests and procedures must be performed and data collected:

- Brief physical examination including vital signs and all major systems findings
- Routine laboratory tests including CBC, creatinine, BNP, hemoglobin, and plasma-free hemoglobin
- 12-lead Electrocardiogram
- Comprehensive transthoracic 2D echocardiogram (TTE) The TTE will be performed according to the Echocardiography Procedure found in Appendix 17.8. All echocardiograms for enrolled subjects will be independently analyzed by the Echocardiographic Core Lab. The TTE should be performed as close to discharge (or 7 days, whichever is sooner) as possible.
- NIHSS
  - NIHSS also to be done within 24 hours of any aortic reintervention
    - Any patient with evidence of a neurological event should have a neurology consult and an imaging study if deemed necessary.
- Modified Rankin Scale (for subjects with a suspected or new neurological event only)
  - Assessment must be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-stroke
- Concomitant Medications Assessment
  - All medications administered during this trial will be recorded in the subject’s medical record.
- Use of relevant medications (diuretics, aspirin, anticoagulants, ACE-I, ARB, beta-blockers, statins, and anti-platelets) must be reported on the eCRF through at least the 12 month follow-up assessment.
- Documentation of all adverse events/serious adverse events from enrollment to discharge including all unanticipated adverse device effects (UADE), technical observations, reinterventions or repeat admissions to the catheterization suite and deaths.
  - Any patient with evidence of a neurological event should have a neurology consult and subsequently an imaging study if deemed necessary by the neurologist.
For patients with permanent pacemakers or defibrillators only: Perform a full interrogation and an assessment of AV conduction (Refer to the Pacing Guidelines in Appendix 17.14). Print a copy of the interrogation. It is recommended to save the interrogation via standard center practice (i.e. diskette, CD, flash drive). Retain the printed and saved copies of the interrogation in the subject's file for source verification.

3.4.6 Follow-up Evaluations

All trial subjects will undergo follow-up evaluations at the following time points post implant (MCS TAVI or SAVR): 30 days (± 7 days), 6 months (180 ± 14 days), 12 months (365 to 410 days), and annually at 2 years (720 days ± 60 days), 3 years (1080 ± 60 days), 4 years (1440 days ± 60 days) and 5 years (1800 ± 60 days). All of these visits will require the subject to return to the clinic. The following assessments are required at the 30 day, 6 month and 12 month clinic visits.

- Brief physical examination including vital signs and all major systems findings
- NYHA classification
- 12-lead Electrocardiogram
- Rotational x-ray (12-month visit only and for MCS TAVI patients only)
- Comprehensive transthoracic 2D echocardiogram (TTE). The TTE will be performed according to the Echocardiography Procedure found in Appendix 17.8. All echocardiograms for enrolled subjects will be independently analyzed by the Echocardiographic Core Lab.
- BNP, hemoglobin, and plasma free hemoglobin
- NIH Stroke Scale
  - NIHSS also to be done within 24 hours of any aortic reintervention
- Modified Rankin Scale (for subjects with a suspected or new neurological event only)
  - Assessment must be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-stroke
- A six minute walk test per the American Thoracic Society Guidelines (detailed instructions can be found in Appendix 17.15), will be performed unless the subject is exempt due to any of the following conditions: postural hypotension, postural arrhythmia, resting systolic pressure less than 95 mmHg, non-ambulatory due to arthritis, neuromuscular disease or Peripheral Vascular Disease, Chronic Obstructive Pulmonary Disease with O₂ desaturation upon ambulation or oxygen dependent, or unstable angina. Subjects with any of these conditions will not undergo the test, but the reasons for not performing the test must be documented on the six minute walk test case report form. The six minute walk test is not required at the 6-month visit interval.
• Quality of Life Questionnaires (Kansas City Cardiomyopathy Questionnaire (KCCQ), SF-12, and EuroQoL)
• Assessment of concomitant medications
• Documentation of all adverse events/serious adverse events including all unanticipated adverse device effects (UADE), technical observations, reinterventions or repeat admission to the catheterization suite and deaths.
  o Any patient with evidence of a neurological event should have a neurology consult and subsequently an imaging study if deemed necessary by the neurologist.
• For patients with permanent pacemakers or defibrillators only (existing or new): Perform a full interrogation and an assessment of AV conduction (Refer to the Pacing Guidelines, Appendix 17.14). Print a copy of the interrogation. It is recommended to save the interrogation via standard center practice (i.e. diskette, CD, flash drive). Retain the printed and saved copies of the interrogation in the subject's file for source verification.

The following assessments are required at the annual clinic visits at 2, 3, 4 and 5 years.
• Brief physical examination including vital signs and all major systems findings
• NYHA classification
• 12-lead Electrocardiogram
• Rotational x-ray (for MCS TAVI only)
• Comprehensive transthoracic 2D echocardiogram (TTE). The TTE will be performed according to the Echocardiography Procedure found in Appendix 17.8. All echocardiograms for enrolled subjects will be independently analyzed by the Echocardiographic Core Lab.
• BNP, hemoglobin, and plasma free hemoglobin
• NIH Stroke Scale
  o NIHSS also to be done within 24 hours of any aortic reintervention
• Modified Rankin Scale (for subjects with a suspected or new neurological event only)
  o Assessment must be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-stroke
• Quality of Life Questionnaires (Kansas City Cardiomyopathy Questionnaire (KCCQ), SF-12, and EuroQoL)
• Documentation of serious adverse events, major adverse events, cardiovascular events, device-related events, including device-related technical observations, unanticipated adverse device effects (UADE), all strokes (CVAs) and deaths. Data related to pre-existing adverse events should be reconciled and resolved.
o Any patient with evidence of a neurological event should have a neurology consult and an imaging study if deemed necessary.

- For patients with permanent pacemakers or defibrillators only (existing or new): Perform a full interrogation and an assessment of AV conduction (Refer to the Pacing Guidelines, Appendix 17.14). Print a copy of the interrogation. It is recommended to save the interrogation via standard center practice (i.e. diskette, CD, flash drive). Retain the printed and saved copies of the interrogation in the subject’s file for source verification.

3.4.7 Data Collection

All scheduled testing and procedures to be conducted during the screening, index procedure and follow-up assessments are summarized in Table 2.
<table>
<thead>
<tr>
<th>Testing</th>
<th>Screening</th>
<th>Baseline (&lt;14 days after enrollment)</th>
<th>Implant Procedure/Valve Surgery</th>
<th>Immediate Post-Procedural</th>
<th>Discharge (or at 7 days post-procedure whichever occurs first)</th>
<th>1 month (±7 Days)</th>
<th>6 month (±14 Days)</th>
<th>Months 24, 36, 48 &amp; 60 (±60 Days)</th>
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<tr>
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<td>Grip Strength Test, Gait Test, and Mini Mental Exam</td>
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<td>Routine Laboratory Tests including Complete Blood Count, Creatinine, &amp; Creatinine Clearance</td>
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<td>X</td>
<td>X&lt;sup&gt;4&lt;/sup&gt;</td>
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<td>Rotational X-ray</td>
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<td>Transthoracic Echocardiogram (TTE)</td>
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<td>Computed Tomography (CT) Angiogram&lt;sup&gt;10&lt;/sup&gt;</td>
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<td>(X)&lt;sup&gt;11&lt;/sup&gt;</td>
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<td>6 Minute Walk Test</td>
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<td>Quality of Life Questionnaires</td>
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<td>Concomitant Medications</td>
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<td>X&lt;sup&gt;13&lt;/sup&gt;</td>
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<td>Testing</td>
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<td>6 months (± 14 Days)</td>
<td>1 year (± 30 Days)</td>
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</table>

(X) MCS TAVI subjects only (SAVR subjects will not have these assessments)

1 Document any changes to subject condition that affect inclusion/exclusion criteria
2 Subject must meet all inclusion/exclusion criteria at the time of procedure
3 Results should be sent to the Screening Committee for confirmation of eligibility.
4 Laboratory test results must be performed pre-procedure for subjects randomized to the MCS TAVI or SAVR. CK to be obtained within 48 hours of procedure.
5 CK obtained 8-12 hours post-procedure and at any time when a clinical ischemic event is suspected.
6 CK-MB is required if CK is elevated (≥ 2X the laboratory upper limit of normal). If a clinical event is confirmed, a total of 3 draws of cardiac enzymes within the first 24 hours (drawn every 8 hours) following the clinical event should be obtained.
7 Liver panel to include: SGPT (ALT), SGOT (AST), Total Bilirubin, Alkaline Phosphatase.
8 Electrocardiogram within 48 hours of procedure.
9 For patients with permanent pacemakers or defibrillators only.
10 TTE should be done 24-48 hours post-procedure to assess device success.
11 All subjects should have screening thoracic and abdominal CT angiograms with complete visualization of both iliacs, femorals and aorta (and subclavian/axillaries, if applicable), up to and including the aortic annulus.
12 Peri-procedural angiographic cine film in DICOM format for CoreValve patients only
13 NIHSS also to be done within 24 hours of any aortic reintervention.
14 NIHSS to be done within 24 hours of the procedure.
15 For subjects with a stroke, Modified Rankin assessments to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-stroke.
16 Modified Rankin to be performed at screening for patients with a previous history of stroke only.
17 SAE, MAE, cardiovascular events, device-related events, including device-related technical observations, UADEs, all strokes (CVAs) and death reports.

This trial contains a health economics review that will be done to compare the in-hospital and 12 month follow-up medical care resource utilization and cost for patients in each of the treatment groups. As part of this trial, patients will be asked to sign a Medical Billing Release Form. This form will be used by the Health Economics and Technology Assessment Group of the Mid America Heart Institute (MAHI) to collect hospital bills from the patient accounting department at any hospital to which patients are admitted, from the time of enrollment in the Medtronic CoreValve® U.S. Pivotal Trial through the study follow-up period. Resource utilization data should be collected by the site along with clinical data using case report forms. This information will be kept strictly confidential and be used solely to assess the medical expenses which occur as a direct result of participating in the Medtronic CoreValve® U.S. Pivotal Trial (Refer to Appendix 17.13 for additional information).
3.4.8 Unscheduled Follow-up Assessments
If a subject returns to the institution between their scheduled follow-up visits the visit will be treated as an unscheduled visit and the assessments completed at this visit will be done at the discretion of the investigator. eCRFs are provided for unscheduled visits.

3.4.9 Investigational Product Handling and Accountability
The Investigator shall maintain adequate records of the receipt and disposition of all investigational devices. At the trial closeout visit, the Investigator must return to the Sponsor any unused devices and a copy of the completed device inventory. The Investigator’s copy of the device reconciliation records must document any unused devices that have been returned to the Sponsor as well as all product usage including opened but unimplanted devices.

In the event of a device malfunction of the Medtronic CoreValve® System (MCS) prior to implant or in the event that a Medtronic CoreValve® PAV is explanted after implant (due to reintervention or autopsy), the PAV and/or affected MCS components should be returned to Medtronic to the following:

Medtronic, Inc.
Attn: Explant Lab [PCR#]
1851 E. Deere Avenue
Santa Ana, CA  92705-5720

Additional details surrounding the device return process are contained within the Medtronic explant kit and in Appendix 17.12.

3.4.10 Protocol Deviations
A protocol deviation is defined as an event where the clinical investigator or site personnel did not conduct the trial according to the protocol or the Investigator agreement. Deviations will be reported regardless of whether medically justifiable, pre-approved by Medtronic, or taken to protect the patient in an emergency.

A protocol deviation form is to be completed for each trial protocol deviation, including, but not limited to:

- Failure to obtain informed consent
- Incorrect version of consent provided to patient
- Failure to obtain IRB protocol review and approval before starting the trial
- Enrollment of patient during an IRB approval lapse
- Clinical investigator exceeding enrollment limits specified by sponsor
- Patient did not meet inclusion/exclusion criteria
- Incorrectly performed testing
- Protocol-required testing and/or measurements not done or performed outside of window
• Source data permanently missing
• UADE not reported in the required timeframe

FDA regulations [21 CFR 812.140] require that the Investigator maintain accurate, complete, and current records, including documents showing the dates of and reasons for each deviation from the protocol. Relevant information for each deviation will be documented on a deviation form completed by site personnel and reviewed by the Investigator.

Federal regulations [21 CFR 812.150] require Investigators to obtain prior approval from the sponsor before initiating changes in or deviations from the protocol, except when necessary to protect the life or physical well being of a patient in an emergency.

Prior approval by the sponsor is expected in those situations in which the Investigator anticipates, contemplates or makes a conscious decision to depart from procedures specified in the protocol. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, but is still considered a deviation (e.g. a trial subject who fails to attend a scheduled follow-up visit, a trial subject too ill to perform a protocol-required test). To obtain approval, the Investigator must call or email and discuss the potential deviation with the Medtronic trial manager or designee prior to initiating any changes.

FDA regulations require the Investigator to notify the sponsor and the reviewing IRB within 5 working days of the following deviations [21 CFR 812.150]:
- a deviation from protocol to protect the life or physical well being of a patient in an emergency
- failure to obtain an informed consent.

Investigators or an authorized designee must notify Medtronic as soon as possible by calling the trial manager or designee and completing the protocol deviation form.

The Investigator is required to adhere to local IRB procedures for reporting deviations.

The DSMB may review protocol deviations to ensure compliance and overall study integrity.

3.4.11 Subject Withdrawal or Discontinuation

All subjects will be encouraged to remain in the trial through the last follow-up visit at month 60. Subjects who discontinue participation prematurely after randomization will be included in the analysis of results (as appropriate) but they will not be replaced in the enrollment of total trial subjects. If a trial subject is discontinued from the trial early, a Study Exit eCRF must be completed describing the reason for discontinuation. The trial site and Sponsor 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 three attempts to make contact via telephone and if contact via phone is not successful, a certified letter from the Principal Investigator must be sent to
the subject’s last known address. Should both telephone and mail efforts to contact the subjects be unsuccessful, the subject’s primary physician should be contacted. 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 in the trial eCRFs.

3.4.12 Early Termination or Discontinuation of Trial
Possible reasons for early trial termination include:

- Unanticipated Adverse Device Effects (UADE) present an unreasonable risk to patients.
- Recommendation from DSMB.

If the trial is terminated early, the Sponsor will provide a written statement to the Investigators to enable notification of the IRBs. The Sponsor will also inform the FDA. If the trial enrollment is terminated early, the follow-up visits will continue for all enrolled subjects.

3.5 Adverse Events

3.5.1 Definitions
The definitions presented in this section allow for a clear understanding of adverse event data collection and subsequent analysis.

3.5.1.1 Adverse Event
An adverse event (AE) is any undesirable experience (sign, symptom, illness, or other medical event) occurring to the subject, and that appears or worsens during the clinical trial, whether or not associated with the investigational products or related procedures.

The following events are expected to occur with any surgical implant and therefore should not be reported as AEs, unless they occur outside of the stated timeframe:

Table 3. Unavoidable AEs

<table>
<thead>
<tr>
<th>Description of the Event</th>
<th>Timeframe (hours) from the Surgical Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthesia-related nausea and/or vomiting</td>
<td>24</td>
</tr>
<tr>
<td>Low-grade fever (&lt;100°F or &lt;37.8°C)</td>
<td>48</td>
</tr>
<tr>
<td>Back pain related to laying on the procedure table</td>
<td>72</td>
</tr>
<tr>
<td>Incisional pain (pain at access site)</td>
<td>72</td>
</tr>
<tr>
<td>Sleep problems or insomnia</td>
<td>72</td>
</tr>
<tr>
<td>Mild to moderate bruising or ecchymosis</td>
<td>168</td>
</tr>
</tbody>
</table>
3.5.1.2 Serious Adverse Event

A serious adverse event (SAE) is an event that meets any of the following criteria:

- Results in subject death
- Is life threatening* (i.e., the subject was at risk of death at the time of the event)
- Results in inpatient hospitalization
- Results in prolonged existing hospitalization
- Results in persistent or significant disability**/incapacity
- Results in congenital anomaly/birth defect
- Results in permanent impairment of a body function or permanent damage to a body structure
- Necessitated medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

* A life-threatening adverse event is any adverse event that places the subject, in the opinion of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

** The definition of disability is a substantial disruption of a person’s ability to conduct normal life functions.

3.5.1.3 Major Adverse Cardiovascular and Cerebrovascular Events

Major adverse cardiovascular and cerebrovascular events (MACCE) is defined as a composite of:

- All-cause death
- Myocardial infarction (MI)
- All stroke, and
- Reintervention (defined as any cardiac surgery or percutaneous reintervention catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve)

3.5.1.4 Major Adverse Event

Major adverse event (MAE) includes:

- MACCE
- Acute kidney Injury
- Cardiac tamponade
- Prosthetic valve dysfunction
- Cardiogenic shock
- Valve endocarditis
- Life-threatening, disabling or major bleeding
- Major vascular complication
- Cardiac perforation
- Device migration/Valve embolism

3.5.1.5 Adverse Device Effect (ADE) or Device-Related Adverse Event
An ADE is an adverse event with a reasonable possibility that the device caused or contributed to the event. During this clinical investigation an event should be considered related to the device when it is the result of the Medtronic CoreValve® System (MCS):
- The percutaneous aortic valve (PAV)
- The delivery catheter system (DCS)
- The compression loading system (CLS)
- The implant procedure
An event should be considered not related to the device when it is the result of:
- A pre-existing medical condition
- A new illness, injury or condition
- Medication

3.5.1.6 Unanticipated Adverse Device Effect (UADE)
An unanticipated adverse device effect or UADE is defined as “any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol or application (including a supplementary plan or application), or any other unanticipated serious problem associated with the device that relates to the rights, safety, or welfare of subjects” [21 CFR 812.3 (s)].
Those known adverse events related to the device, procedure or therapy are listed in Section 3.5.2.3 and in the Risk/Benefit Analysis section of this document (Section 4).

3.5.1.7 Technical Observation
A technical observation is a defect, malfunction, or failure of any part of the Medtronic CoreValve® System. This may pertain to the device or system not functioning according to its design intent. Each technical observation (whether or not associated with any untoward medical occurrence in a subject) will be reported on the Adverse Event (AE) eCRF and tabulated as an AE.

3.5.2 Reporting
Investigators are required to keep records on “all relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated)” [21 CFR 812.140]. Adverse event collection will begin from the point of study enrollment to study closure. All new or worsening (from baseline)
adverse events and technical observations will be captured on the AE eCRF through the 12-month follow-up visit. Once a subject has completed their 12-month scheduled follow-up visit, serious adverse events, major adverse events, cardiovascular events, device-related adverse events, including device related technical observations, unanticipated adverse device effects (UADE), all strokes (CVAs) and deaths will be required to be reported. It is the responsibility of the Investigator to assess the subject for adverse events and capture the required adverse event information on the AE eCRF.

Medtronic representatives or their designees will conduct monitoring visits to review source documentation and verify the complete and accurate capturing of adverse events.

The Investigator must also notify the responsible IRB regarding new and significant safety information and any event identified by Medtronic that require expedited FDA reporting as serious, unexpected, and related to the investigational device. It is the responsibility of the investigator to ensure site specific IRB safety reporting requirements are met.

Medtronic Clinical will ensure all device-related adverse events and all procedure-related SAEs are processed according to internal policies and procedures. When necessary, Medtronic Field Assurance will respond to sites in writing with the findings related to the product experiences.

The general procedure for investigators reporting any adverse event is as follows:

- If an adverse event occurs, complete all sections of the Adverse Event eCRF.
- Each unique event/diagnosis must be documented separately.
- Documented pre-existing conditions are not considered to be reportable AEs unless there is a change in the nature or severity of the condition.
- The Adverse Event eCRF must be reviewed by the Investigator

Reporting guidelines related to specific types of adverse events are outlined below.

### 3.5.2.1 Serious Adverse Events (SAEs)

Medtronic recommends that the Investigator notify the sponsor within 3 working days of first learning of any SAE using the electronic data capture (eCRF) system. If necessary, the Investigator may be requested to provide copies of source documentation regarding the event (e.g., physician/nurse notes or summaries).

Medtronic will conduct an evaluation of the event and if it is determined by Medtronic to be a UADE, it will be reported as described in the following sections.

### 3.5.2.2 Unanticipated Adverse Device Effects

Investigators must report any (potential) unanticipated adverse device effects to Medtronic and their IRB as soon as possible but no later than within 10 working days after the Investigator first learns of the event [21 CFR 812.150]. UADEs should be reported immediately via telephone as well as on an eCRF. The
Investigator should consider the device labeling and the Risk/Benefit Analysis section of this document (Section 4) when determining whether an event is unanticipated or not.

If an event is determined by Medtronic to be a UADE, Medtronic will report the event to all investigators to enable reporting to their respective IRBs. Medtronic will provide this notification within 10 working days after Medtronic first receives notice of the effect. [21 CFR 812.150]

If Medtronic and the DSMB determine that the event presents an unreasonable risk to the participating subjects, Medtronic must terminate all investigations or parts of investigations presenting the risk in the clinical trial 5 working days after making that determination and not later than 15 working days after Medtronic first receives notice of the effect. [21 CFR 812.46] Follow-up visits for enrolled subjects will continue according the schedule of assessments.

### 3.5.2.3 All Other Adverse Events

Medtronic recommends that the Investigator notify the sponsor within 10 working days of first learning of any other AE using the electronic data capture (eCRF) system. If necessary, the Investigator may be requested to provide copies of source documentation regarding the event (e.g., physician/nurse notes or summaries).

### 3.5.2.4 Anticipated Adverse Events

Potential risks associated with MCS TAVI may include, but are not limited to, the following:

- Death
- Acute myocardial infarction
- Stroke
- Urgent need for surgery
  - Coronary artery bypass
  - Heart valve replacement
  - Valve explant
- Urgent need for balloon valvuloplasty (note that BAV during implantation is expected)
- Urgent need for Percutaneous Coronary Intervention (PCI)
- Cardiogenic shock
- Perforation of the myocardium or vessel
- Cardiac Tamponade
- Ascending aorta trauma
- Myocardial ischemia
- Acute coronary artery occlusion
- Disturbances in the electrical system of the heart that may result in the permanent placement of a device (pacemaker)
  - Atrio-ventricular node block
- Bundle branch block
- Asystole
- Ventricular arrhythmias
- Valve or distal embolization
- Thrombosis (including valve thrombosis)
- Hemorrhage requiring transfusion
- Arteriovenous fistula
- Vessel dissection or spasm
- Valve migration
- Prosthetic valve dysfunction including but not limited to:
  - Fracture
  - Bending (out-of-round configuration) of the valve frame
  - Under-expansion of the valve frame
  - Calcification
  - Pannus
  - Wear, tear, prolapse, or retraction in the valve leaflet
  - Poor valve coaptation
  - Suture breaks or disruption
  - Leak
  - Mal-sizing (prosthesis-patient mismatch)
  - Malposition (either too high or too low)/malplacement
  - Regurgitation
  - Stenosis
- Mitral valve regurgitation
- Hypotension or hypertension
- Acute renal injury
- Allergic reaction to antiplatelet agents or contrast medium
- Infection (including endocarditis)
- Bowel ischemia
- Vascular access site or access related complications, including but not limited to:
  - pain
  - bleeding
  - hematoma
  - pseudoaneurysm
  - irreversible nerve injury
  - compartment syndrome
  - stenosis
3.5.2.5 Deaths
The Investigator should notify Medtronic and his/her IRB within 3 working days of learning of a subject’s death, whether or not the death is related to the investigational device. The Investigator should also attempt to determine, as conclusively as possible, whether such deaths are related to the Medtronic CoreValve® System. When an autopsy is conducted, a copy of the report should be provided to Medtronic. Medtronic will evaluate the event and if device-related and unexpected, the event will be reported as a UADE.

Any subject death will be reported on the Study Exit eCRF and accompanied by an Adverse Event eCRF identifying the cause of death.

3.5.3 Clinical Events Committee (CEC)
An independent Clinical Events Committee (CEC) will review and adjudicate, at a minimum, all deaths and endpoint related adverse events. The CEC will consist of interventional cardiologists, cardiologists and cardiovascular surgeons, including a chairperson, who are not participants in the trial.

The purpose of the CEC is to conduct a medical review and classify/adjudicate, at a minimum, all deaths and/or clinical endpoints collected in the trial according to definitions and processes outlined in the Medtronic CoreValve® U.S. Pivotal Trial protocol and the CEC charter, which will be developed and approved by Medtronic and the CEC members.

Events will be reviewed and adjudicated by a minimum of three CEC members, who will meet at regular intervals, via teleconference or in person, as deemed necessary. All other events will be reviewed and adjudicated by qualified internal Medtronic safety individual(s) to ensure they should not be adjudicated by the full CEC and that the events are appropriately classified by the investigator.

Prior to the onset of the trial, the CEC will establish explicit rules outlining the minimum amount of data required and the algorithm followed in order to classify/adjudicate a trial endpoint related clinical event. CEC decisions will be documented in meeting minutes, which will be maintained in the trial file.

3.5.4 Data Safety Monitoring Board (DSMB)
An independent, unblinded DSMB will be established and will be comprised of at least 3 experts, including a chairperson. The DSMB will have a minimum of one cardiac surgeon, one interventional cardiologist and one statistician, and will be independent of Medtronic and the trial investigators. Investigators participating in the trial may participate in the meetings to offer clarification surrounding events, but will not have voting privileges. Medtronic personnel may facilitate the DSMB meeting but will not have voting privileges. The DSMB will meet (via teleconference or in person) prior to the first subject enrollment to establish procedures for DSMB review, chairman appointment and guidelines for trial recommendations. The full DSMB will meet on a periodic basis to perform a comprehensive data review, including at a minimum, all adverse events and deaths, and will meet more frequently when needed. Primary and safety-related secondary endpoints may also be reviewed at these meetings. Meetings will consist of both open and closed sessions.
The DSMB will also perform a supplemental review of, at a minimum, all serious adverse events and deaths and any other data requested by the DSMB on a more frequent periodic basis to ensure patient safety. DSMB members will review the report, and when necessary provide recommendations about the conduct of the study and/or request a full DSMB meeting.

A DSMB charter will be developed and approved by Medtronic and the DSMB members. The committee will outline the criteria for both the full DSMB meeting and supplemental DSMB reviews within the DSMB charter.

Following each full DSMB meeting, the board will report to Medtronic in writing and may recommend changes in the conduct of the trial. These DSMB recommendations may include recommendations on trial status such as continuing the trial without modifications, continuing the trial with modifications, stopping the enrollment in the trial or a specific trial arm, or recommendations about trial conduct including recommendations around enrollment or protocol deviations.

In the case of UADEs, if Medtronic and the DSMB determine that the event presents an unreasonable risk to the participating subjects, Medtronic must terminate the clinical trial 5 working days after making that determination and not later than 15 working days after Medtronic first receives notice of the effect. [21 CFR 812.46]. 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. Additional details about the DSMB can be found in the DSMB charter.

3.6 Statistical Methods and Analysis

The statistical analyses will be performed by Medtronic employed statisticians and independently verified by the staff of the Biostatistics Department at the Harvard Clinical Research Institute and/or Saint Luke’s Mid America Heart Institute. Subjects will be analyzed using an "as treated" approach as the primary analysis. In addition, all randomized subjects will also be analyzed following the intent-to-treat (ITT) approach as an adjunctive analysis. For the primary analysis, "as treated" will be defined as when the patient 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. Using this definition, study subjects will be analyzed according to their first attempted procedure (TAVI or SAVR).

The 23mm valve was not available until late in the study; therefore if approximately 20 23mm CoreValve implants have not occurred at the time of approximately 790 randomized subjects, the 23mm subjects will not be included in the primary analysis. Therefore, up to 40 additional subjects will be randomized with about 20 23mm CoreValve implants. When 1 year data are available for the 23mm valve, the primary and secondary endpoint data will be summarized with descriptive statistics. If appropriate, the 23mm valve subjects will be pooled with the original 790 subjects in the primary analysis dataset and the primary and secondary endpoints will be recalculated. The primary endpoint
and the 6 secondary endpoints that include hypothesis testing will be analyzed without adjustments for multiple testing. The hierarchical test procedure described in section 3.6.7 Relevant Statistical Analysis Considerations will be followed for the 6 statistical tests defined in the section (secondary endpoints #5, #8 - 2 test, #9 - 2 tests, and powered secondary endpoint).

3.6.1 Description of Baseline Variables
Baseline demographic and clinical variables will be summarized for each of the treatment groups for the intent-to-treat, as treated, and per protocol populations. All continuous variables will be summarized as means, medians, standard deviations and interquartile ranges and compared between treatment groups using a two-sample t-test or the non-parametric Wilcoxon rank-sum test. Categorical variables will be summarized as frequencies and percentages and compared between treatment groups using Pearson’s $\chi^2$ test or Fisher’s exact test, as appropriate. Ordinal variables will be compared using Cochran-Mantel-Haenszel test with row mean scores.

3.6.2 Missing Data
Every effort will be undertaken to minimize missing data. Since all-cause mortality is the primary endpoint for this trial, a minimal amount of missing data is anticipated. However, if outcome data are missing, Kaplan-Meier rates at 12 months and their standard errors will be used in the calculation of the test statistic. To assess the potential impact of these missing data, a sensitivity analysis will be conducted which will include a complete case, a best-case (assume missing MCS TAVI subjects are alive and SAVR subjects have died), a worst-case (assume missing MCS TAVI subjects have died and SAVR subjects are alive), and a tipping point analysis.

3.6.3 Reports
Medtronic is responsible for the reports cited in Table 4. These reports are subject to regulatory retention and inspection requirements. In addition to the reports listed in Table 4, FDA or the reviewing IRB may request reports pertaining to any aspect of the clinical trial.

3.6.4 Primary Endpoint
The primary endpoint for the trial is all-cause mortality at 12 months.

3.6.5 Primary Hypothesis and Sample Size Determination

3.6.5.1 Primary Hypothesis
Primary Hypothesis: TAVI with the Medtronic CoreValve® System is non-inferior to surgical aortic valve replacement (SAVR) in 12 month all-cause mortality:

$H_0$: $\pi_{MCS\ TAVI} \geq \pi_{SAVR} + 7.5\%$

$H_A$: $\pi_{MCS\ TAVI} < \pi_{SAVR} + 7.5\%$
In the above expression $\pi_{\text{MCS TAVI}}$ and $\pi_{\text{SAVR}}$ denote binary rates of all-cause mortality during a fixed follow-up of 12 months. The one-sided Farrington and Manning test\textsuperscript{xxv} for non-inferiority of two binomial proportions will be carried out to assess statistical significance.

Powered Secondary Hypothesis: TAVI with the Medtronic CoreValve\textsuperscript{®} System is \textbf{superior} to SAVR in binary rate of MACCE at 30 days or hospital discharge, whichever is longer:

$H_0$: $\pi_{\text{MCS TAVI}} = \pi_{\text{SAVR}}$

$H_A$: $\pi_{\text{MCS TAVI}} < \pi_{\text{SAVR}}$

This one-sided test will be carried out at the 0.025 level using the pooled z-test without correction for continuity.

### 3.6.5.2 Sample Size Determination

**Primary Hypothesis**

Assumptions:

1:1 treatment allocation ratio  
One-sided alpha = 0.05  
$\pi_{\text{SAVR}} = 20.0\%$  
$\pi_{\text{MCS TAVI}} = 20.0\%$  
Power = >80\%

Assuming 1:1 treatment allocation ratio between study device and surgical valve replacement and assuming the proportion of all-cause mortality at 12 months equal to 20\% for both arms and a non-inferiority margin of 7.5\%, Power Analysis and Sample Size (PASS) software calculates that a total of $355$ subjects in each arm is required to attain 80\% power in a test of non-inferiority of the study device at the 0.05 level of significance. Accounting for a 10\% drop-out rate or loss to follow-up in each treatment arm, a total of $395 + 395 = 790$ subjects is required to have a minimum of 355 subjects in each arm.

**Powered Secondary Hypothesis**

Assumptions:

1:1 treatment allocation ratio  
One-sided alpha = 0.025  
$\pi_{\text{SAVR}} = 20.0\%$  
$\pi_{\text{MCS TAVI}} = 12.1\%$
For the secondary superiority hypothesis, assuming 1:1 treatment allocation ratio between study device and surgical valve replacement and assuming the proportion of MACCE at 30 days or hospital discharge, whichever is longer, equal to 20% in the surgical valve replacement arm and equal to 12.1% in the study device arm (39.5% relative treatment effect), PASS software calculates that 355 evaluable subjects per arm would yield 81.9% power for a one-sided test at the 0.025 level of significance.

3.6.6 Secondary Endpoints
The secondary endpoints are as follows:
The following secondary endpoints will be compared between MCS TAVI and SAVR subject cohorts:

1. MACCE-free survival at 30 days, 6 months, 12 months and annually thereafter up to 5 years.
   MACCE-free survival estimates will be provided for the randomized groups at 30 days, 6 months, 12 months and annually through five years. All subjects will be included in the analysis.
   The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.

2. The occurrence of individual MACCE components at 30 days, 6 months, 12 months and annually thereafter up to 5 years.
   MACCE components will be summarized and MACCE component event-free rates will be provided at 30 days, 6 months, 12 months and annually through 5 years. All subjects will be included in the analysis.
   The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.

3. MAE at 30 days, 6 months, 12 months and annually thereafter up to 5 years.
   MAE events will be summarized and MAE event-free rates will be provided at 30 days, 6 months, 12 months, and annually through five years. All subjects will be included in the analysis.
   The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.

4. Conduction disturbance requiring permanent pacemaker implantation at 30 days, 6 months, 12 months and annually thereafter up to 5 years.
   The incidence of conduction disturbance requiring permanent pacemaker implantation will be provided at 30 days, 6 months, 12 months and annually through five years, separately for new onset and pre-existing conduction disturbance. All subjects will be included in the analysis.
   The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.

5. Change in NYHA class from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years.
For each subject with paired data, the number of classes changed from baseline (-2, -1, 0, 1, 2, or 3) will be calculated at 30 days, 6 months, 12 months and annually through five years. The endpoint will be evaluated using a two-sample t-test or Wilcoxon rank-sum test as appropriate.

6. Change in distance walked during 6-minute walk test (6MWT) from baseline to 30 days and baseline to 12 months
All subjects who are able to perform the six-minute walk evaluation; and those subjects who are unable to perform the walk evaluation due to heart failure symptoms at the time of the follow-up visit will be included in the analysis.
The six-minute walk evaluation will be evaluated at 30 days and at 12 months using a two-sample t-test or Wilcoxon rank-sum test as appropriate.

7. Ratio of days alive out of hospital versus total days alive assessed at 12 months follow-up.
The proportion of post randomization days alive out of hospital against total days alive will be compared at twelve months. The numerator will be the number of days alive out of hospital, and the denominator will be the number of days alive as of the follow-up visit date. All hospitalizations will be included in this analysis, including hospitalization for device implant. All subjects will be included in the analysis.
The endpoint will be evaluated using continuous data analyses such as a two-sample t-test or Wilcoxon rank-sum test.

8. Quality of Life (QoL) change from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years.
The Kansas City Cardiomyopathy Questionnaire (KCCQ), SF-12, and EuroQoL will be assessed at baseline, 30 days, 6 months, 12 months and annually through five years. All subjects completing the questionnaires will be evaluated and the reasons for missing data will be provided.
The changes in QoL scores will be evaluated using a two-sample t-test or Wilcoxon rank-sum test as appropriate.

9. Echocardiographic assessment of prosthetic valve performance at discharge, 30 days, 6 months, 12 months, and annually thereafter up to 5 years using the following measures:
- transvalvular mean gradient
- effective orifice area
- degree of prosthetic aortic valve regurgitation (transvalvular and paravalvular)
The four echocardiographic measurements will be evaluated at discharge, 30 days, 6 months, 12 months and annually through five years. All subjects undergoing echocardiography procedures will be evaluated.
All measures will be evaluated using a two-sample t-test or the Wilcoxon rank-sum test for continuous variables, and the Mantel-Haenszel test for categorical variables, as appropriate.

10. Aortic valve disease related hospitalizations
The number of subjects re-hospitalized after the initial index procedure will be compared at 30 days, 6 months, 12 months and annually through five years. All subjects will be included in the analysis.
Hospitalization-free rates will be provided at 30-days, 6 months, 12 months and annually through five years. All subjects will be included in the analysis. The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.

11. Cardiovascular deaths and valve-related deaths
The number of cardiovascular deaths and valve-related deaths at 30 days, 6 months, 12 months, and annually through five years will be reported. All subjects will be included in the analysis.
The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.

12. Strokes
The number of strokes (of any severity) and TIAs at 30 days, 6 months, 12 months and annually through five years will be reported. All subjects will be included in the analysis. The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.

13. Index procedure related MAEs
Index procedure-related MAE events will be summarized and event rates will be provided at 30 days. The numerator will be the number of procedure-related MAE events experienced by the end of the follow-up visit, and the denominator will be the number of subjects evaluated at the follow-up visit plus the number of subjects not evaluated but who experienced a procedure-related MAE event prior to the end of the follow-up visit window.
The endpoint is descriptive and no statistical hypothesis test will be performed.

14. Length of index procedure hospital stay
The length of TAVI or SAVR hospital stay will be summarized for all subjects.
Descriptive statistics will be provided. The endpoint is descriptive and no statistical hypothesis test will be performed.
The following secondary endpoints will be assessed for the MCS TAVI cohort subjects only:

15. Device success defined as follows:
- successful vascular access, delivery and deployment of the device, and successful retrieval of the delivery system,
- correct position of the device in the proper anatomical location (placement in the annulus with no impedance on device function),
- Intended performance of the prosthetic valve\(^1\) (aortic valve area > 1.2 cm\(^2\) for 26, 29 and 31mm valves, ≥ 0.9 cm\(^2\) for 23mm valve(by echocardiography using the continuity equation) and mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/sec, without moderate or severe prosthetic valve AR)

- Only one valve implanted in the proper anatomical location

\(^1\) assessed acutely in a resting state, either within 24-48 hours after the index procedure or before hospital discharge

Device success, as defined above, will be calculated for all subjects undergoing the TAVI procedure.
The endpoint is descriptive and no statistical hypothesis test will be performed.

16. Procedural success, defined as device success and absence of in-hospital MACCE.
Procedure success, as defined above, will be calculated for all subjects undergoing the TAVI procedure.
The endpoint is descriptive and no statistical hypothesis test will be performed.

17. Evidence of prosthetic valve dysfunction at 30 days, 6 months, 12 months and annually thereafter up to 5 years.
The number of subjects with evidence of prosthetic valve dysfunction will be evaluated at 30 days, 6 months, 12 months and annually through five years. All subjects will be included in the analysis.
A Kaplan-Meier survival analysis will be performed. The endpoint is descriptive and no statistical hypothesis test will be performed.

3.6.7 Relevant Statistical Analysis Considerations
All statistical tests and/or confidence intervals, as appropriate, will be performed at \(\alpha=0.05\) (2-sided), except when specified otherwise. All reported p-values greater than or equal to 0.001 will be rounded to three decimal places. P-values less than 0.001 will be displayed as “<0.001.”

Provided the 12-month mortality primary objective is met with a significant p-value, to keep the overall (familywise) Type I error rate at 0.05, a hierarchical test procedure will be applied to the 30-day (or hospital discharge, whichever is longer) MACCE powered secondary hypothesis and five of the secondary objective hypothesis tests. The goal of this hierarchical procedure is to make statistically valid claims of significance in the device labeling.

In this hierarchical test procedure, each objective is examined in the pre-specified order. The hierarchical testing order will be:

1. Change in transvalvular mean gradient from baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #9. The one-sided two-sample t-test will be used to test non-inferiority at a level of 0.05 the hypotheses:

\[ H_0: \mu_{MCS\ TAVI} \leq \mu_{SAVR} - 15 \]
\[ H_A: \mu_{\text{MCS TAVI}} > \mu_{\text{SAVR}} -15 \]

In the above expression \(\mu_{\text{MCS TAVI}}\) and \(\mu_{\text{SAVR}}\) denote the mean improvements in mean gradient from baseline to 12 months measured in mmHg.

2. Change in effective orifice area baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #9. The one-sided two-sample t-test will be used to test non-inferiority at a level 0.05 the hypotheses:

\[ H_0: \mu_{\text{MCS TAVI}} \leq \mu_{\text{SAVR}} -0.375 \]
\[ H_A: \mu_{\text{MCS TAVI}} > \mu_{\text{SAVR}} -0.375 \]

In the above expression \(\mu_{\text{MCS TAVI}}\) and \(\mu_{\text{SAVR}}\) denote the mean improvements in effective orifice area from baseline to 12 months measured in cm².

3. Change in NYHA classification from baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #5. The one-sided two-sample t-test will be used to test non-inferiority at a level 0.05 the hypotheses:

\[ H_0: \mu_{\text{MCS TAVI}} \leq \mu_{\text{SAVR}} -0.375 \]
\[ H_A: \mu_{\text{MCS TAVI}} > \mu_{\text{SAVR}} -0.375 \]

In the above expression \(\mu_{\text{MCS TAVI}}\) and \(\mu_{\text{SAVR}}\) denote the mean number of classification improvements in NYHA from baseline to 12 months.

4. Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score from baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #8. The one-sided two-sample t-test will be used to test non-inferiority at a level 0.05 the hypotheses:

\[ H_0: \mu_{\text{MCS TAVI}} \leq \mu_{\text{SAVR}} -5 \]
\[ H_A: \mu_{\text{MCS TAVI}} > \mu_{\text{SAVR}} -5 \]

In the above expression \(\mu_{\text{MCS TAVI}}\) and \(\mu_{\text{SAVR}}\) denote the mean improvements in the KCCQ score from baseline to 12 months.

5. Powered Secondary Hypothesis: TAVI with the Medtronic CoreValve® System is superior to SAVR in binary rate of MACCE at 30 days or hospital discharge, whichever is longer. This one-sided test will be carried out at the 0.025 level using the pooled z-test without correction for continuity to test the hypotheses:

\[ H_0: \pi_{\text{MCS TAVI}} = \pi_{\text{SAVR}} \]
\[ H_A: \pi_{\text{MCS TAVI}} < \pi_{\text{SAVR}} \]

In the above expression \(\pi_{\text{MCS TAVI}}\) and \(\pi_{\text{SAVR}}\) denote the binary rate of MACCE at 30 days or hospital discharge.
6. Change in SF-12 Physical Summary Scale from baseline to 30 days: TAVI vs. SAVR from secondary objective #8. The two-sided two-sample t-test will be used to test at a level 0.05 the hypotheses:

\[ H_0: \mu_{MCS\ TAVI} = \mu_{SAVR} \]
\[ H_A: \mu_{MCS\ TAVI} \neq \mu_{SAVR} \]

In the above expression \( \mu_{MCS\ TAVI} \) and \( \mu_{SAVR} \) denote the mean improvements in the SF-12 Physical Summary Scale from baseline to 30 days.

As the trial confirmation is not dependent on the secondary endpoints, multiplicity adjustments will not be made in the analyses of the secondary endpoints. Summary data from other secondary objectives, such as device success and procedural success from secondary objectives #15 and #16, respectively, may be provided in the device labeling. However, no claims of statistical significance or other statistical inference will be made.

A poolability analysis among investigational centers, access site (ilio-femoral or non-ilio-femoral), and primary baseline demographics will be performed for the primary endpoint and will be described in the Statistical Analysis Plan. In particular, the primary endpoint and key secondary endpoints such as MACCE- and MAE-free survival will be examined for differences in outcome between genders and between access sites. Additionally, tests for these outcomes will be performed to evaluate potential interactions between treatment and gender and between treatment and access site.

3.7 Data and Quality Management

3.7.1 Electronic Data Capture
Medtronic will use the Oracle Clinical Remote Data Capture database system for data collection.

3.7.2 Data Collection
Required data will be recorded on electronic case report forms (eCRFs) by authorized site personnel as indicated on the Delegation of Authority Log. 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.

The sponsor and/or assigned designee will be responsible for the processing and quality control of the data. All trial-related documents must be retained for a period of at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational device. 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 the Sponsor and the investigator. Should the investigator wish to assign the trial records to another party or move them to another location, advance written notice should be given to the Sponsor.

3.7.3 Core Laboratories Procedures

Data from the core lab will be entered by the core lab and stored in the Oracle Clinical Remote Data Capture system as described in the Medtronic CoreValve® U.S. Pivotal Trial Data Management Plan.

3.7.4 Source Documents

Source documentation is defined as the first time the data appear and may include all clinical records, hospital records, surgery reports, autopsy reports, and any other material that contains original information used for trial data collection or adverse event reporting. No eCRFs may serve as source documents.

Source documentation may vary from site to site.

The source documents must be retained by the investigational site for a period of 2 years after trial conclusion and made available for monitoring or auditing by the sponsor’s representative or representatives of the FDA and other applicable regulatory agencies. The Investigator must ensure the availability of source documents from which the information on the eCRFs was derived.

3.8 Records and Reports

3.8.1 Responsibilities of the Sponsor

The Sponsor must maintain the following records:

- All essential correspondence related to the clinical trial
- Signed Investigator Agreement
- Curriculum vitae for each Investigator
- Records of device shipment and disposition (shipping receipts, material destruct records, etc.)
- Adverse event information
- Complaint documentation
- All data forms, prepared and signed by the Investigators and received source documentation and core lab reports
- Protocol and report of prior investigations
- Site monitoring reports
- Financial disclosure information

The Sponsor is responsible for the preparation of, the accuracy of the data contained in, the review of and the submission of the reports listed in Table 4.
Table 4. Sponsor Reporting Responsibilities

<table>
<thead>
<tr>
<th>Report</th>
<th>Submit to</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unanticipated Adverse Device Effects (UADE)</td>
<td>IRB, Investigators, FDA</td>
<td>Medtronic will report on any confirmed unanticipated adverse device effect evaluation within 10 working days after first receiving notice of the effect. (21 CFR 812.150)</td>
</tr>
<tr>
<td>Withdrawal of IRB approval</td>
<td>IRB, Investigators, FDA</td>
<td>Notification, when appropriate, will be made within 5 working days after Medtronic receives notice of withdrawal of IRB approval.</td>
</tr>
<tr>
<td>Withdrawal of FDA approval</td>
<td>IRB, Investigators</td>
<td>Notification will be made within 5 working days after Medtronic receives notice of withdrawal of FDA approval.</td>
</tr>
<tr>
<td>Current Investigator List</td>
<td>FDA</td>
<td>Medtronic will submit a current list of the names and addresses of all participating Investigators at six-month intervals, beginning six months after FDA approval of IDE.</td>
</tr>
<tr>
<td>Progress Report</td>
<td>IRB, Investigators, FDA</td>
<td>A progress report will be submitted at least yearly.</td>
</tr>
<tr>
<td>Recall and Device Disposition</td>
<td>IRB, Investigators, FDA</td>
<td>Notification will be made within 30 working days of Medtronic’s request that an Investigator return, repair or otherwise dispose of any devices. Such notification will state why the request was made.</td>
</tr>
<tr>
<td>Final Report</td>
<td>IRB, Investigators, FDA</td>
<td>Notification will be made within 30 working days of the completion or termination of the investigation. A final report will be submitted within six months after trial completion or termination.</td>
</tr>
<tr>
<td>Failure to obtain Informed Consent</td>
<td>FDA</td>
<td>Notification will be made within 5 working days after Medtronic’s receipt of such notification indicating Informed Consent was not obtained.</td>
</tr>
<tr>
<td>Emergency Deviations from Investigational Plan</td>
<td>FDA</td>
<td>Notification will be made within 5 working days after Medtronic learns of an emergency deviation from the Investigational Plan where the deviation was made to protect the life or physical well being of a subject.</td>
</tr>
</tbody>
</table>

Version 12.0  Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients) Page 64 of 94 22-August-2012
3.8.2 Responsibilities of the Investigator

The Investigator is responsible for the preparation, review, signature, and retention of the records listed below:

- All essential correspondence that pertains to the investigation
- Device use/disposition records
- Records of each subject’s case history and exposure to the device. Case histories include the CRFs and supporting data (source documentation), including, for example:
  - Signed and dated consent forms
  - Medical records, including, for example, progress notes of the physicians, the subject’s hospital chart(s) and the nurses’ notes
  - All adverse event information
  - A record of the exposure of each subject to the investigational device (e.g., date of implant procedure and follow-up assessment dates)
  - Documentation of any deviation from the protocol, including the date and the rationale for such deviation
- Signed Investigator Agreement and curriculum vitae
- The protocol and any amendments

The Investigator may withdraw from responsibility to maintain records by transferring custody to another person, who will accept responsibility for record and report maintenance.

The Investigator is responsible for the preparation, review, signature, and submission of the reports listed below in Table 5. These are also subject to inspection by government agencies and must be retained as specified above.

<table>
<thead>
<tr>
<th>Report</th>
<th>Submitted to</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unanticipated Adverse Device Effects (UADE)</td>
<td>Sponsor, IRB</td>
<td>UADEs should be reported immediately via telephone as well as on an eCRF. UADEs must be submitted as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect. (21 CFR 812.150)</td>
</tr>
<tr>
<td>Serious Adverse Events and Deaths</td>
<td>Sponsor</td>
<td>Medtronic requests that the Investigator’s report on all serious adverse events and deaths be submitted within 3 working days after the Investigator first learns of the event.</td>
</tr>
<tr>
<td>Withdrawal of IRB approval</td>
<td>Sponsor</td>
<td>The Investigator must report a withdrawal of the reviewing IRB, approval within 5 working days.</td>
</tr>
<tr>
<td>Progress Report</td>
<td>Sponsor, IRB</td>
<td>The Investigator must submit a progress report on an annual basis if the trial lasts longer than one year.</td>
</tr>
</tbody>
</table>
4. RISK / BENEFIT ANALYSIS

4.1 Potential Risks and Discomforts

There are risks for participants in this trial. However, it should be noted that most of the risks of trial participation are not materially different than those entailed by an individual who undergoes the same treatment outside of the context of this trial.

Known adverse events that may result from TAVI include but may not be limited to:

- Death
- Acute myocardial infarction
- Stroke
- Urgent need for surgery
  - Coronary artery bypass
  - Heart valve replacement
  - Valve explant
- Urgent need for balloon valvuloplasty (note that BAV during implantation is expected)
- Urgent need for Percutaneous Coronary Intervention (PCI)
- Cardiogenic shock
- Perforation of the myocardium or vessel
- Cardiac Tamponade
- Ascending aorta trauma
- Myocardial ischemia
- Acute coronary artery occlusion
- Disturbances in the electrical system of the heart that may result in the permanent placement of a device (pacemaker)
  - Atrio-ventricular node block
  - Bundle branch block
  - Asystole
- Ventricular arrhythmias
- Valve or distal embolization
- Thrombosis (including valve thrombosis)
- Hemorrhage requiring transfusion
- Arteriovenous fistula
- Vessel dissection or spasm
- Valve migration
- Prosthetic valve dysfunction including but not limited to:
  - Fracture
  - Bending (out-of-round configuration) of the valve frame
  - Under-expansion of the valve frame
  - Calcification
  - Pannus
  - Wear, tear, prolapse or retraction in the valve leaflet
  - Poor valve coaptation
  - Suture breaks or disruption
  - Leak
  - Mal-sizing (prosthesis-patient mismatch)
  - Malposition (either too high or too low)/malplacement
  - Regurgitation
  - Stenosis
- Mitral valve regurgitation
- Hypotension or hypertension
- Acute renal injury
- Allergic reaction to antiplatelet agents or contrast medium
- Infection (including endocarditis)
- Bowel ischemia
- Vascular access site or access related complications, including but not limited to:
  - pain
- bleeding
- hematoma
- pseudoaneurysm
- irreversible nerve injury
- compartment syndrome
- stenosis

There have been no voluntary or involuntary regulatory recalls of the Medtronic CoreValve® System in the United States to date. The original 18Fr Delivery Catheter System has been improved with the addition of the AccuTrak™ stability layer which has been added to aid in accuracy in the deployment of the Medtronic CoreValve® PAV. The 31mm and 23 mm valve sizes were added to increase the treatable annulus range. A new Delivery Catheter System (DCS-C4-18FR-23MM) will be used to deploy 23mm Percutaneous Aortic Valve (PAV). There are no other design changes anticipated for the Medtronic CoreValve® System during the clinical trial.

4.2 Methods to Minimize Risks

The investigational plan is specifically designed to manage and minimize risks through careful subject selection, thorough training of investigators, adherence to the pre-determined time points to assess subject clinical status and regular clinical monitoring visits by Sponsor appointed monitoring personnel.

In addition, an independent Data Safety Monitoring Board will monitor safety of the subjects throughout the trial.

4.3 Potential Benefits

The targeted trial population (generally elderly patients of both genders) has been shown to have high mortality if the severe aortic stenosis is left untreated. This population also has high risk for mortality and morbidity if treated surgically or are managed medically. The less invasive investigational treatment of transcatheter aortic valve implantation has shown in research to reduce mortality and morbidity.
5. DESCRIPTION OF MEDTRONIC COREVALVE® SYSTEM

5.1 Investigational Product Description

The Medtronic CoreValve® System (MCS) consists of 3 components: the Percutaneous Aortic Valve Bioprosthesis (PAV) in Figure 2 below, the Delivery Catheter System (DCS) in Figure 3, and the Compression Loading System (CLS) in Figure 4.

Percutaneous Aortic Valve Bioprosthesis

Figure 2: Percutaneous Aortic Valve (PAV)

The PAV is manufactured by suturing valve leaflets and a skirt, made from a single layer of porcine pericardium, into a tri-leaflet configuration. The PAV is designed to replace the native aortic heart valve without open heart surgery and without concomitant surgical removal of the failed native valve.

The self-expanding multi-level frame is made of Nitinol and is radiopaque.

The PAV is available for a range of aortic annulus and ascending aortic diameters as shown in Table 6 below.

<table>
<thead>
<tr>
<th>Model</th>
<th>Size (mm)</th>
<th>Aortic Annulus Diameter (range in mm)</th>
<th>Ascending Aortic Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCS-P3-2334</td>
<td>23</td>
<td>18–20</td>
<td>≤34</td>
</tr>
<tr>
<td>MCS-P3-640</td>
<td>26</td>
<td>20-23</td>
<td>≤40</td>
</tr>
<tr>
<td>MCS-P3-943</td>
<td>29</td>
<td>23-27</td>
<td>≤43</td>
</tr>
<tr>
<td>MCS-P3-3143</td>
<td>31</td>
<td>26-29</td>
<td>≤43</td>
</tr>
</tbody>
</table>
Delivery Catheter System

The AccuTrak™ DCS (DCS-C4-18FR) is compatible with a 0.889-mm (0.035-in) guidewire. The working length of the AccuTrak™ DCS is 112.5 cm. It incorporates a protective deployment sheath that houses and deploys the PAV. The AccuTrak™ DCS-C4-18FR can be used to house and deliver the 26mm, 29mm, and 31mm sizes of the PAV. The outer diameter of the DCS is 12Fr, the stability layer is 15Fr and the outer diameter of the valve capsule is 18 Fr.

Figure 3: Delivery Catheter System (DCS)

A new Delivery Catheter System (DCS-C4-18FR-23MM) will be used to deploy 23mm Percutaneous Aortic Valve (PAV). The DCS-C4-18FR-23MM has a shortened Capsule and Plunger (5mm) for delivery of the 23mm PAV but the working length of the new AccuTrak™ DCS is 112.5 cm similar to DCS-C4-18Fr used to deploy other PAV sizes.

Design Changes for Delivery Catheter System (DCS) specific to 23mm
The AccuTrak™ DCS features an integrated handle designed to provide the user with accurate and controlled deployment. After the DCS is placed in the vicinity of the aortic annulus, the user retracts the deployment sheath, thereby deploying the PAV to the desired location. In use, the deployment sheath can be partially pulled back to evaluate the PAV location prior to fully releasing the PAV. In this way, the user can make slight adjustments to the PAV location if needed prior to release.

Compression Loading System (Model CLS-3000-18 FR)

Figure 4: Compression Loading System (CLS)

The CLS (Model CLS-3000-18FR) compresses the PAV into the DCS. The CLS is comprised of the following elements:

- inflow cone
- inflow tube (straight tube)
- outflow cap
- outflow cone
- outflow tube (tube with flared ends)

Medtronic may incorporate additional devices into this clinical study providing they receive regulatory approval and the scientific soundness of the study is not adversely affected.

5.2 Medtronic CoreValve® Ordering, Storage, and Disposition

Devices will be ordered through Medtronic.

As stated in the Instructions for Use (IFU), the PAV should be stored at 15°C to 25°C (59°F to 77°F). Avoid exposing the PAV to extreme fluctuations of temperature. Avoid freezing the PAV. Appropriate inventory control should be maintained so that PAVs with earlier Use By dates are implanted preferentially. Store the delivery system and compression loading system in a cool, dry environment.

All implanting sites will maintain device logs to document the disposition of all components of the Medtronic CoreValve® System.
6. MONITORING AND AUDITING

6.1 Monitoring
The investigational site will be monitored to ensure compliance with the trial protocol, adherence to applicable regulations, and accuracy of trial data. A monitoring visit will be conducted primarily to ensure the safety and wellbeing of the subjects is preserved. Monitoring visits will also be used to verify that trial data submitted on case report forms are complete and accurate with respect to the subject records and to verify device accountability. Site personnel will complete eCRFs following each subject visit. Trial data submitted will be reviewed against patient charts and other sources containing original records of patient data. Source document verification will occur in accordance to the CoreValve Monitoring Plan.

The responsible individual for this trial is included on the title page of the CIP.

The progress of the trial will be monitored by:

- On-site review, as deemed appropriate by the sponsor
- Telephone communications between the site personnel (e.g., Investigator, Trial Coordinator) and trial monitors
- Review of eCRFs and the associated clinical records
- Review of regulatory documents

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

6.2 Auditing
Medtronic may conduct audits at participating clinical sites. The purpose of an audit is to verify the performance of the monitoring process and the trial conduct, independently of the personnel directly involved in the trial. Regulatory bodies, such as the Food and Drug Administration, may also perform inspections at participating sites. The investigator and/or institution shall permit Medtronic and regulatory bodies direct access to source data and documents.

7. LABELING
Instructions for Use and additional labeling are attached in Appendix 17.1.

8. CONSENT MATERIALS
The template consents for the trial are attached in Appendix 17.2.

9. IRB INFORMATION
IRB information is attached in Appendix 17.3.
10. OTHER INSTITUTIONS
Information regarding other institutions involved in this trial is located in Appendices 17.4, 17.8, 17.9, 17.10, 17.11, 17.12, and 17.13.

11. ADDITIONAL RECORDS AND REPORTS
Information regarding additional Records and Reports can be found in Appendix 17.5.

12. REPORT OF PRIOR INVESTIGATIONS
The Report of Prior Investigations is attached in Appendix 17.18.

13. PUBLICATION POLICY
Medtronic, as the Sponsor of this trial, recognizing the seminal importance of this investigation, is committed to the widespread dissemination of all primary and secondary endpoint results. A publication plan will be implemented and followed. At the conclusion of the trial, a multisite abstract reporting the primary results will be prepared by the National Principal Investigators (in collaboration with others including but not limited to the Steering Committee, directors of the core laboratories, CEC, and Lead Investigators from high enrolling sites) and presented at an annual scientific meeting (e.g., Transcatheter Cardiovascular Therapeutics, EuroPCR, the American Heart Association, or the American College of Cardiology). 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 both the preparation and publication of the multisite results, and then only with written permission from Medtronic.

Following analysis and presentation of the primary endpoint results, active participation of all committee members, Investigators from high enrolling sites, 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 Steering Committee.

A separate publication plan will provide detailed information about the publication committee, authorship, publication proposals, and requests for data.
### 14. **AMENDMENTS TO THE CLINICAL INVESTIGATIONAL PLAN**

All amendments to the CIP shall be agreed between the sponsor and the clinical investigator(s). Amendments will be recorded with a justification for the amendments in the log below:

<table>
<thead>
<tr>
<th>Version</th>
<th>Description of change</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>Original version submitted to FDA</td>
</tr>
<tr>
<td>August 26, 2010</td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>Address FDA conditional Approval Letter (October 13, 2010), administrative edits as required</td>
</tr>
<tr>
<td>November 2, 2010</td>
<td></td>
</tr>
<tr>
<td>3.0</td>
<td>Allow for non-ilio-femoral access, administrative edits as required (this version was not implemented or distributed to sites)</td>
</tr>
<tr>
<td>December 13, 2010</td>
<td></td>
</tr>
<tr>
<td>4.0</td>
<td>Address FDA conditional Approval Letter (January 14, 2011), administrative edits as required</td>
</tr>
<tr>
<td>February 1, 2011</td>
<td></td>
</tr>
<tr>
<td>5.0</td>
<td>Allow for additional sites, statistical analysis clarification and administrative edits as required (this version was not implemented or distributed to sites)</td>
</tr>
<tr>
<td>May 26, 2011</td>
<td></td>
</tr>
<tr>
<td>6.0</td>
<td>Address FDA questions received via email (June 22, 2011). Administrative edits as required</td>
</tr>
<tr>
<td>July 11, 2011</td>
<td></td>
</tr>
<tr>
<td>7.0</td>
<td>Increase proportion of non-ilio-femoral sample size</td>
</tr>
<tr>
<td>October 1, 2011</td>
<td></td>
</tr>
<tr>
<td>8.0</td>
<td>Allow for additional valve size, clarifications and administrative edits</td>
</tr>
<tr>
<td>October 10, 2011</td>
<td></td>
</tr>
<tr>
<td>9.0</td>
<td>Allow for additional valve size, clarifications and administrative edits (this version was not implemented or distributed to sites)</td>
</tr>
<tr>
<td>December 5, 2011</td>
<td></td>
</tr>
<tr>
<td>10.0</td>
<td>Address FDA questions received via email (January 3, 2012). Administrative edits as required</td>
</tr>
<tr>
<td>January 25, 2012</td>
<td></td>
</tr>
<tr>
<td>11.0</td>
<td>Increase sample size, CMS reimbursement language and administrative edits.</td>
</tr>
<tr>
<td>July 30, 2012</td>
<td></td>
</tr>
<tr>
<td>12.0</td>
<td>Change sample size back to original sample size of 790 subjects.</td>
</tr>
</tbody>
</table>
## 15. ABBREVIATIONS AND DEFINITIONS

### 15.1 List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D</td>
<td>Two dimensional</td>
</tr>
<tr>
<td>3D</td>
<td>Three dimensional</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ACT</td>
<td>Active Clotting Time</td>
</tr>
<tr>
<td>ADE</td>
<td>Adverse Device Effect</td>
</tr>
<tr>
<td>AR</td>
<td>Aortic regurgitation</td>
</tr>
<tr>
<td>AS</td>
<td>Aortic stenosis</td>
</tr>
<tr>
<td>AVR</td>
<td>Aortic valve replacement</td>
</tr>
<tr>
<td>BAV</td>
<td>Balloon Aortic Valvuloplasty</td>
</tr>
<tr>
<td>BSA</td>
<td>Body Surface Area</td>
</tr>
<tr>
<td>BNP</td>
<td>B-type Natriuretic Peptide</td>
</tr>
<tr>
<td>CEC</td>
<td>Clinical Events Committee</td>
</tr>
<tr>
<td>CIP</td>
<td>Clinical Investigational Plan</td>
</tr>
<tr>
<td>CLS</td>
<td>Compression loading system</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CVA</td>
<td>Cerebrovascular accident</td>
</tr>
<tr>
<td>DCS</td>
<td>Delivery catheter system</td>
</tr>
<tr>
<td>DSMB</td>
<td>Data Safety Monitoring Board</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case report form</td>
</tr>
<tr>
<td>EuroSCORE</td>
<td>European System for Cardiac Operative Risk Evaluation</td>
</tr>
<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration</td>
</tr>
<tr>
<td>GCP</td>
<td>Good clinical practice</td>
</tr>
<tr>
<td>HIPAA</td>
<td>Health Insurance Portability and Accountability Act</td>
</tr>
<tr>
<td>HIT/HITTS</td>
<td>Heparin-Induced Thrombocytopenia / Heparin-Induced Thrombocytopenia and Thrombosis</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>IFU</td>
<td>Instructions for use</td>
</tr>
<tr>
<td>ITT</td>
<td>Intent-to-treat</td>
</tr>
<tr>
<td>IXRS</td>
<td>Interactive Voice/Web Response System</td>
</tr>
<tr>
<td>LBBB</td>
<td>Left Bundle Branch Block</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left ventricular ejection fraction</td>
</tr>
<tr>
<td>LVOT</td>
<td>Left ventricular outflow tract</td>
</tr>
<tr>
<td>MACCE</td>
<td>Major adverse cardiovascular and cerebrovascular event</td>
</tr>
<tr>
<td>MAE</td>
<td>Major Adverse Event</td>
</tr>
<tr>
<td>MCS</td>
<td>Medtronic CoreValve® System</td>
</tr>
<tr>
<td>MI</td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>NYHA</td>
<td>New York Heart Association</td>
</tr>
<tr>
<td>PAV</td>
<td>Percutaneous aortic valve</td>
</tr>
<tr>
<td>PCI</td>
<td>Percutaneous Coronary Intervention</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of Life</td>
</tr>
<tr>
<td>RBBB</td>
<td>Right Bundle Branch Block</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SAVR</td>
<td>Surgical Aortic Valve Replacement</td>
</tr>
<tr>
<td>STS</td>
<td>Society of Thoracic Surgeons</td>
</tr>
<tr>
<td>TAVI</td>
<td>Transcatheter aortic valve implant</td>
</tr>
<tr>
<td>TAVR</td>
<td>Transcatheter aortic valve replacement</td>
</tr>
<tr>
<td>TEE</td>
<td>Transesophageal echocardiography</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient Ischemic Attack</td>
</tr>
<tr>
<td>TTE</td>
<td>Transthoracic echocardiography</td>
</tr>
<tr>
<td>UADE</td>
<td>Unanticipated adverse device effect</td>
</tr>
</tbody>
</table>
15.2 Definition of Terms

ACUTE KIDNEY INJURY


<table>
<thead>
<tr>
<th>Acute Kidney Injury: Modified RIFLE Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stages</td>
</tr>
<tr>
<td>Change in Serum Creatinine (up to 72 hours) compared to Baseline</td>
</tr>
<tr>
<td>Stage 1</td>
</tr>
<tr>
<td>Increase in serum creatinine to 150-200% (1.5-2.0 x increase compared with baseline) or increase of ≥ 0.3 mg/dl (≥26.4 μmol/L)</td>
</tr>
<tr>
<td>Stage 2*</td>
</tr>
<tr>
<td>Increase in serum creatinine to 200-300% (&gt; 2-3 x increase compared with baseline)</td>
</tr>
<tr>
<td>Stage 3**</td>
</tr>
<tr>
<td>Increase in serum creatinine to ≥300% (&gt; 3 x increase compared with baseline) or serum creatinine of ≥ 4.0 mg/d (≥354 μmol/L) with an acute increase of at least 0.5 mg/dl (44 μmol/L)</td>
</tr>
<tr>
<td>* Stage 2 and 3 acute renal injuries will be considered to be serious adverse events.</td>
</tr>
<tr>
<td>** Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria</td>
</tr>
</tbody>
</table>

ACUTE VESSEL OCCLUSION

The state of complete luminal obstruction with no antegrade blood flow.

ADVERSE EVENT (AE)

An adverse event is any undesirable experience (sign, symptom, illness, or other medical event) occurring to the subject, and that appears or worsens during the clinical trial, whether or not associated with the investigational products or related procedures.

AORTIC DISSECTION

Intimal tear resulting in blood splitting the aortic media and producing a false lumen that can progress in an antegrade or retrograde direction. Aortic dissection is further classified using Stanford classification (Types A and B depending on whether ascending or descending aorta involved) or DeBakey classification (Types I, II and III) as shown below.

- Major Aortic Dissection: Type A and Types I and II.
  - Major aortic dissections will be considered to be serious adverse events.
- Minor Aortic Dissection: Type B and Type III
**AORTIC REGURGITATION (AR)**

Aortic valve incompetence resulting in backward flow of blood.

Aortic Valve Regurgitation will be defined based on the definition published in the European Heart Journal; January 6, 2011, titled "Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium".

<table>
<thead>
<tr>
<th>Prosthetic Aortic Valve Regurgitation Criteria (Central and Paravalvular)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>Valve Structure and Motion Mechanical or bioprosthetic</td>
</tr>
<tr>
<td>Structural parameters Left ventricular size</td>
</tr>
<tr>
<td>Doppler parameters (qualitative or semiquantitative)</td>
</tr>
<tr>
<td>Jet width in central jets (% LVO diameter): color*</td>
</tr>
<tr>
<td>Jet density: CW Doppler</td>
</tr>
<tr>
<td>LV outflow vs. pulmonary flow: PW Doppler</td>
</tr>
<tr>
<td>Diastolic flow reversal in the ascending aorta: PW Doppler</td>
</tr>
<tr>
<td>Circumferential extent of paraprosthetic AR (%)***</td>
</tr>
<tr>
<td>Doppler parameters (quantitative)</td>
</tr>
<tr>
<td>Regurgitant fraction (%)</td>
</tr>
</tbody>
</table>

*Parameter applicable to central jets and is less accurate in eccentric jets

** Influenced by left ventricular compliance

*** For paravalvular aortic regurgitation

AR=aortic regurgitation; CW= continuous wave; LVO= left ventricular outflow; PW= pulsed wave

Moderate or severe aortic regurgitation (AR) will be considered a serious adverse event.

**AORTIC STENOSIS (AS)**

A narrowing, stiffening or stricture of the aortic valve.

ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease (published in the August 1, 2006, issues of Journal of the American College of Cardiology and Circulation)

<table>
<thead>
<tr>
<th>Aortic Stenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicator</td>
</tr>
<tr>
<td>Jet velocity (m/s)</td>
</tr>
<tr>
<td>Mean gradient (mmHg)</td>
</tr>
<tr>
<td>Valve area (cm²)</td>
</tr>
<tr>
<td>Valve area index (cm²/m²)</td>
</tr>
</tbody>
</table>

Moderate or severe AS will be considered a serious adverse event.

**ARRHYTHMIA**

Any variation from the normal rhythm of the heart beat, including sinus arrhythmia, premature beat, heart block, atrial fibrillation, atrial flutter and tachycardia.

- Major Arrhythmias: Complete heart block, ventricular tachycardia and ventricular fibrillation
• Serious Arrhythmias: Any arrhythmia requiring surgical or invasive intervention or DC cardioversion

BLEEDING EVENT

Bleeding event will be defined based on the definition published in the European Heart Journal; January 6, 2011, titled “Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium”.

<table>
<thead>
<tr>
<th>Life-threatening or Disabling Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fatal bleeding OR</td>
</tr>
<tr>
<td>• Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome OR</td>
</tr>
<tr>
<td>• Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery OR</td>
</tr>
<tr>
<td>• Overt source of bleeding with drop in hemoglobin of ≥5 g/dL or whole blood or packed red blood cells (RBC) transfusion ≥4 units*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Major Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0g/dL or requiring transfusion of 2-3 units of whole blood/RBC AND</td>
</tr>
<tr>
<td>• Does not meet criteria of life-threatening or disabling bleeding</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Any bleeding worthy of clinical mention (e.g. access site hematoma) that does not qualify as life-threatening, disabling or major</td>
</tr>
</tbody>
</table>

* Given one unit of packed RBC typically will raise blood hemoglobin concentration by 1 g/dL, an estimated decrease in hemoglobin will be calculated.

Life-threatening and Major bleeding events are considered to be serious.

BUNDLE BRANCH BLOCK


Left Bundle Branch Block (LBBB)

• QRS duration 120 ms or longer
• Delayed onset of intrinsicsoid deflection in I, V5, and V6 ≥60 ms
• Broad and notched or slurred R waves in I, aVL, V5, and V6
• rS or QS complexes in right precordial leads
• ST-segment and T waves in opposite polarity to the major QRS deflection

Right Bundle Branch Block (RBBB)

• QRS duration ≥120 ms
• rsR= or rSR= complexes in V1 and V2
• Delayed onset of intrinsicsoid deflection in V1 and V2 ≥50 ms
• Broad, slurred S wave in I, V5,

Any new or worsening LBBB or RBBB that requires the placement of a permanent pacemaker and/or other surgical or invasive intervention will be considered to be serious.
CARDIAC TAMponade
Clinical syndrome caused by the accumulation of fluid in the pericardial space, resulting in reduced ventricular filling and subsequent hemodynamic compromise.

CARDIOGENIC SHOCK
Patient was, at the time of procedure, in a clinical state of hyperfusion sustained for greater than 30 minutes, according to either of the following criteria:
1. Systolic BP < 80 and/or Cardiac Index < 1.8 despite maximal treatment;
2. IV inotropes and/or IABP necessary to maintain Systolic BP > 80 and/or CI > 1.8

CEREBRAL INFARCTION
Evidence of brain cell death from imaging studies or pathological examination. If there are clinical symptoms, then it is a stroke, otherwise it is an asymptomatic cerebral infarction.

CHRONIC RENAL INSUFFICIENCY
Kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m² for or ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine test or imaging studies.

CONDUCTION DISTURBANCE REQUIRING PERMANENT PACEMAKER IMPLANTATION
ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease (published in the August 1, 2006, issues of Journal of the American College of Cardiology and Circulation)
Any disturbance in the cardiac electrical conduction system that meets the American College of Cardiology (ACC)/American Heart Association (AHA)/ Heart Rhythm Society (HRS) Class I or Ila Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities for Acquired Atrioventricular Block in Adults or Permanent Pacing in Chronic Bifascicular Block.

DEATH
A serious adverse event that is classified by the following:
All-cause death: All deaths from any cause after a valve intervention. This includes all cardiovascular and non-cardiovascular deaths.

Cardiovascular Death:
(Cardiovascular death will be defined based on the definition published in the European Heart Journal; January 6, 2011, titled "Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium". Any one of the following criteria:

- Any death due to proximate cardiac cause (e.g. MI, cardiac tamponade, worsening heart failure)
- Unwitnessed death and death of unknown cause
- All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure
- Death caused by non-coronary vascular conditions such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease

Note: All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in subjects with coexisting potentially fatal non-cardiac disease (e.g., cancer, infection) should be classified as cardiac.

Non-cardiovascular death: Any death not covered by the above definitions, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.
Valve-related death:
- Any death caused by prosthetic valve dysfunction, valve thrombosis, embolism, bleeding event, or implanted valve endocarditis;
- Death related to reintervention on the operated valve

DEVICE MIGRATION/VALVE EMBOLISM
Obvious spontaneous movement of the Medtronic CoreValve® PAV from its documented original implant position, after access site closure, as confirmed by X-ray, echocardiography, CT scan or direct assessment during open heart surgery or autopsy.

DEVICE MALPLACEMENT/MALPOSITION
Placement of the Medtronic CoreValve® PAV in a non-therapeutic location, either inadvertently, or possibly intentionally due to unintended problems during the Medtronic CoreValve® System (MCS) delivery or procedure that necessitates placement in the non-therapeutic location. This does include movement during retrieval of the delivery catheter following BAV post implantation.

DEVICE RELATED
Events that occur as the direct result of the Medtronic CoreValve® System (MCS) as it relates to delivery, placement, efficacy or durability; these may involve the implanted device or the delivery system components.

DEVICE RELATED COMPLICATIONS
Complications associated with the device as it relates to delivery, placement, efficacy or durability; these may involve the implanted device or the delivery system.

DEVICE SUCCESS
Device success is defined as follows:
- successful vascular access, delivery and deployment of the device, and successful retrieval of the delivery system,
- correct position of the device in the proper anatomical location (placement in the annulus with no impedance on device function),
- Intended performance of the prosthetic valve¹ (aortic valve area > 1.2 cm² for 26, 29 and 31mm valves, ≥ 0.9 cm² for 23mm valve (by echocardiography using the continuity equation) and mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/sec, without moderate or severe prosthetic valve AR)
- Only one valve implanted in the proper anatomical location

¹ assessed acutely in a resting state, either within 24-48 hours after the index procedure or before hospital discharge

EMBOLISM
Free flowing blood clot or lesion material that is located in the systemic or pulmonary circulation that occurs in the absence of infection after the immediate perioperative period. Embolism may be manifested by a neurological event or a noncerebral embolic event.

ENCEPHALOPATHY
Episodes of confusion, agitation and/or combativeness; alterations and fluctuations in levels of consciousness; acute problems with cognition, including memory and changes in perception including hallucinations.
ENDOCARDITIS

Implanted valve endocarditis: Any infection involving an implanted valve. The diagnosis of operated valvular endocarditis is based on one of the following criteria:

- re-operation with evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriologic studies;
- autopsy findings of abscess, pus, or vegetation involving a replaced valve; or
- in the absence of reoperation or autopsy, meeting of the Duke Criteria for endocarditis.

Infective endocarditis is diagnosed based on Duke criteria and necessitates 2 major criteria, or 1 major and 3 minor criteria, or 5 minor criteria

Major criteria 1: Positive blood culture for infective endocarditis

Typical microorganism consistent with infective endocarditis from 2 separate blood cultures, as noted below:

- Viridans streptococci, Streptococcus bovis, or HACEK group (Haemophilus. Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrdoens, Kingella or
- Community-acquired Staphylococcus aureus or enterococci, in the absence of a primary focus

-OR-

Microorganisms consistent with infective endocarditis from persistently positive blood cultures defined as:

- Two positive cultures of blood samples drawn >12 hours apart, or
- All of 3 or a majority of 4 separate cultures of blood (with first and last sample drawn 1 hour apart)

Major criteria 2: Evidence of endocardial involvement

Positive echocardiogram for infective endocarditis defined as:

- oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation, or
- abscess, or
- new partial dehiscence of prosthetic valve

-OR-

New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)

Minor criteria 1: Predisposition: predisposing heart condition or intravenous drug use

Minor criteria 2: Fever: temperature > 38.0° C (100.4° F)

Minor criteria 3: Vascular phenomena: major arterial emboli, septic pulmonary inaracts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions

Minor criteria 4: Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth spots, and rheumatoid factor

Minor criteria 5: 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 infective endocarditis

Minor criteria 6: Echocardiographic findings: consistent with infective endocarditis but do not meet a major criterion as noted above

EXPLANT

Removal of the investigational valve implant for any reason, including post-mortem.

HEMOLYSIS

A plasma free hemoglobin value > 40 mg/dL is considered to be hemolysis and a reportable adverse event.

- Major hemolysis: A plasma free hemoglobin value > 40 mg/dL that requires intervention (i.e. iron replacement, blood transfusion, folic acid administration, corticosteroids, Intravenous immunoglobulin G (IVIG) and/or surgery). Major hemolysis events will be considered to be serious adverse events.
**Minor hemolysis:** A plasma free hemoglobin value > 40 mg/dL that does not require intervention.

### HOSPITALIZATION FOR SIGNS AND SYMPTOMS RELATED TO AORTIC VALVE DISEASE

Aortic valve disease hospitalizations are defined as a non-elective hospital admission for signs and symptoms related to aortic valve disease (as described below) that results in at least a two-night stay (i.e., where the admission date and the discharge date differ by at least two calendar days). For the purpose of the protocol, overnight stays at nursing home facilities or extended care facilities do not meet the protocol definition of hospitalization. This does include the administration or augmentation of intravenous heart failure therapy (e.g., inotropes, diuretics, and/or vasodilators).

Patients with signs and symptoms related to aortic valve disease (as described below) who are hospitalized for less than two days or who are treated and released from the emergency department or an outpatient clinic (including treatment for intravenous heart failure therapy (e.g., inotropes, diuretics, and/or vasodilators)), will not be counted as aortic valve disease hospitalizations.

Aortic valve disease will be evaluated using documented evidence of the following signs and symptoms. An independent Clinical Events Committee (CEC) will review all available source documentation for any hospitalizations identified as possibly related to aortic valve disease. The CEC adjudication will be used for final analysis.

<table>
<thead>
<tr>
<th>Signs and Symptoms of Aortic Valve Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sign/Symptom</strong></td>
</tr>
<tr>
<td><strong>Aortic Valve Dysfunction</strong></td>
</tr>
<tr>
<td>Shortness of breath/dyspnea</td>
</tr>
<tr>
<td>Exercise intolerance</td>
</tr>
<tr>
<td>Dizziness/syncope</td>
</tr>
<tr>
<td>Chest pain</td>
</tr>
<tr>
<td><strong>Worsening Heart Failure</strong></td>
</tr>
<tr>
<td><strong>Volume Overload</strong></td>
</tr>
<tr>
<td>Orthopnea</td>
</tr>
<tr>
<td>Paroxysmal nocturnal dyspnea</td>
</tr>
<tr>
<td>Jugular venous distension</td>
</tr>
<tr>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>Peripheral edema</td>
</tr>
<tr>
<td>Pulmonary rales</td>
</tr>
<tr>
<td>Abdominal-jugular reflux</td>
</tr>
</tbody>
</table>
the flat hand over the abdomen.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiographic evidence of pulmonary edema</td>
<td>NA</td>
</tr>
<tr>
<td>Elevated B-type natriuretic peptide level</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Hypoperfusion</strong></td>
<td></td>
</tr>
<tr>
<td>Narrow pulse pressure</td>
<td>Pulse pressure &lt; 30 mmHg</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Systolic BP &lt; 90 systolic</td>
</tr>
<tr>
<td>Renal or hepatic dysfunction</td>
<td>• Rise in baseline creatinine by 25%</td>
</tr>
<tr>
<td></td>
<td>• Increase in LFT (SGOT, SGPT) &gt; 2 times normal</td>
</tr>
<tr>
<td>Low serum sodium concentration</td>
<td>Serum sodium &lt; 130 mEq/dL</td>
</tr>
</tbody>
</table>

**INFECTION**
Elevated body temperature (fever), and White Blood Count (WBC) > 12,000/ml, and Significant leftward shift on Differential.

**INTRACRANIAL HEMORRHAGE**
Collection of blood between the brain and skull. Subcategorized as epidural, subdural and subarachnoid bleeds.

**MAJOR ADVERSE CARDIOVASCULAR AND CEREBROVASCULAR EVENTS (MACCE)**
Defined as a composite rate of
- all-cause death
- myocardial infarction (MI)
- all stroke, and
- reintervention (defined as any cardiac surgery or percutaneous reintervention catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve)

**MAJOR ADVERSE EVENT (MAE)**
Major Adverse events include the following:
- MACCE
- Acute kidney Injury
- Cardiac tamponade
- Prosthetic valve dysfunction
- Cardiogenic shock
- Valve endocarditis
- Life-threatening, disabling or major bleeding
- Major vascular complication
- Cardiac Perforation
- Device Migration/Valve embolism

**MITRAL STENOSIS**
A narrowing, stiffening or stricture of the mitral valve.

ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease (published in the August 1, 2006, issues of Journal of the American College of Cardiology and Circulation)
Mitral Stenosis

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Gradient (mmHg)</td>
<td>Less than 5</td>
<td>5-10</td>
<td>Greater than 10</td>
</tr>
<tr>
<td>Pulmonary artery systolic pressure (mmHg)</td>
<td>Less than 30</td>
<td>30-50</td>
<td>Greater than 50</td>
</tr>
<tr>
<td>Valve area (cm²)</td>
<td>Greater than 1.5</td>
<td>1.0-1.5</td>
<td>Less than 1.0</td>
</tr>
</tbody>
</table>

Moderate or severe MS will be considered a serious adverse event.

**MYOCARDIAL INFARCTION (MI)**

Myocardial infarction will be defined based on the definition published in the European Heart Journal; January 6, 2011, titled “Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium”.

<table>
<thead>
<tr>
<th>Peri-Procedural MI (≤ 72 hours after the index procedure)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. New ischemic symptoms (e.g. chest pain or shortness of breath), or new ischemic signs (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, or imaging evidence of new loss of viable myocardium or new wall motion abnormality)</td>
<td></td>
</tr>
<tr>
<td>2. Elevated cardiac biomarkers (preferably CK-MB) within 72 hours after the index procedure, consisting of two or more post-procedure samples that are ≥ 6-8 hours apart with a 20% increase in the second sample and a peak value exceeding 10x the 99th percentile upper reference limit (URL) or a peak value exceeding 5x the 99th percentile URL with new pathological Q waves in at least 2 contiguous leads.</td>
<td></td>
</tr>
</tbody>
</table>
MYOCARDIAL INFARCTION (MI) - continued

### Spontaneous MI

(> 72 hours after the index procedure)

Any one of the following criteria:

1. Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with evidence of myocardial ischemia with at least one of the following:
   - ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]);
   - New pathological Q waves in at least 2 contiguous leads;
   - Imaging evidence of new loss of viable myocardium or new wall motion abnormality
2. Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
3. Pathological findings of an acute myocardial infarction.

All myocardial infarctions will be considered serious adverse events.

NEUROLOGICAL EVENT

Any central, new neurological deficit, whether temporary or permanent and whether focal or global, that occurs after the subject emerges from anesthesia.

NEW YORK HEART ASSOCIATION CLASSIFICATION (NYHA)

Classification system for defining cardiac disease and related functional limitations into four broad categorizations:

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

PARAVALVULAR AORTIC REGURGITATION

Leakage due to a separation of the prosthetic valve from the annulus. Diagnosis of paravalvular leak may be obtained from echocardiogram; however definitive diagnosis is obtained at reoperation, explant, or autopsy.

All moderate or severe paravalvular leaks will be classified as Serious Adverse Events.

(Refer to the definition of Aortic Regurgitation for additional paravalvular leak severity criteria)
PATIENT PROSTHESIS MISMATCH (PPM)


- Severe PPM will be defined as an EOA ≤ 0.65 cm2/m2 BSA
- Moderate PPM defined as a patient with an EOA ≤ 0.85 cm2/m2 BSA

PERMANENT PACEMAKER IMPLANTATION

Implantation of permanent pacemaker after the index procedure due to occurrence of conduction disturbances.

- **Procedure-related**: Permanent Pacemaker is implanted in subjects with new onset conduction disturbances or worsening of existing conduction disturbances
- **Not related to procedure**: Permanent Pacemaker is implanted in subjects with known conduction disturbances that did not advance after the index procedure.

PROCEDURE RELATED COMPLICATIONS

Complications associated with any part of the vascular access procedure, associated treatments or necessary secondary interventions that do not necessarily involve the device. This includes morbidity associated with either pre-medication, or anesthesia, or other adjunct to the surgical procedure. Other technical errors including inappropriate patient selection, inappropriate operator techniques, measurements, or judgment that do not involve the device itself are also included.

PROCEDURAL SUCCESS

Defined as device success without occurrence of in-hospital MACCE.

PROCEDURE-RELATED EVENTS

Events occurring during or as a direct result of the index procedure. Events that occur before extubation and before access site closure are classified as procedural.

PROSTHETIC VALVE DYSFUNCTION

Prosthetic Valve Dysfunction will be defined based on the definition published in the European Heart Journal; January 6, 2011, titled "Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium". Failure modes of prosthetic valve dysfunction include, but are not limited to, the following:

- **Aortic Stenosis**
  - Stent creep
  - Pannus
  - Calcification
  - Support structure deformation (out-of-round configuration), under-expansion, fracture, or trauma (cardi-pulmonary resuscitation, blunt chest trauma)
  - Mal-sizing (prosthesis-patient mismatch(PPM))
  - Endocarditis
  - Prosthetic valve thrombosis
  - Native leaflet prolapse impeding prosthetic leaflet motion

- **Aortic Regurgitation**
  - Pannus
  - Calcification
  - Support structure deformation (out-of-round configuration), under-expansion, fracture, or trauma (cardi-pulmonary resuscitation, blunt chest trauma)
  - Endocarditis
  - Prosthetic valve thrombosis
- Mal-position (too high, too low)/malplacement
- Acute mal-coaptation
- Leaflet wear, tear/perforation, prolapse or retraction
- Suture breakage or disruption
- Native leaflet prolapse impeding prosthetic leaflet motion

Prosthetic valve dysfunction will be considered serious when it meets the definition of a serious adverse event (SAE).

**REINTERVENTION**
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.

**RESPIRATORY INSUFFICIENCY**
Post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) ratio [FEV1/FVC] less than 70%.
Post-bronchodilator FEV1 less than 80% predicted, with or without chronic symptoms (i.e., cough or sputum production).

**RESPIRATORY FAILURE**
The need for ventilatory support for > 72 hours associated with an inability to wean from the respirator for any reason.

**RIGHT VENTRICULAR INSUFFICIENCY**
Defined as sequelae of right ventricular failure including the following:
- Significantly decreased right ventricular systolic and/or diastolic function
- Tricuspid valvular regurgitation secondary to elevated pressure

Clinical symptoms to include:
- Hepatic congestion
- Ascites
- Anasarca
- Presence of “hepato-jugular reflux”
- Edema

**SERIOUS ADVERSE EVENT (SAE)**
A serious adverse event (SAE) is an event that meets any of the following criteria:
- Results in subject death
- Is life threatening* (i.e., the subject was at risk of death at the time of the event)
- Results in inpatient hospitalization
- Results in prolonged existing hospitalization
- Results in persistent or significant disability**/incapacity
- Results in congenital anomaly/birth defect
- Results in permanent impairment of a body function or permanent damage to a body structure
- Necessitated medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure
*A life-threatening adverse event is any adverse event that places the subject, in the opinion of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

**The definition of disability is a substantial disruption of a person’s ability to conduct normal life functions.

STROKE (CVA)

Stroke and TIA will be defined based on the definition published in the European Heart Journal; January 6, 2011, titled "Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium".

### Stroke Diagnostic Criteria

- Rapid onset of a focal or global neurological deficit with at least one of the following:
  - change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke
- Duration of a focal or global neurological deficit ≥ 24 hours; OR < 24 hours, if therapeutic intervention(s) were performed (e.g. thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; OR the neurologic deficit results in death
- No other readily identifiable non-stroke cause for the clinical presentations (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences)*
- Confirmation of the diagnosis by at least one of the following:
  - Neurology or neurosurgical specialist
  - Neuroimaging procedure (MR or CT scan or cerebral angiography)
  - Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)

### Stroke Definitions

- Transient Ischemic Attack
  - New focal neurologic deficit with rapid symptom resolution (usually 1-2 hours), always within 24 hours
  - Neuroimaging without tissue injury
- Stroke: (diagnosis as above, preferably with positive neuroimaging study)+
  - Minor (non-clinically important disability) - modified Rankin score < 2 at 30 and 90 days
  - Major (clinically important disability) - modified Rankin score ≥ 2 at 30 and 90 days

*Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies

+ Major and Minor stroke will be adjudicated and analyzed using the MRS at 90 days only.
## Modified Rankin Scale

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

Clinically important disabilities (major strokes) will be considered to be serious adverse events. Strokes will be further categorized to the following:

- Ischemic stroke is defined as an acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.
- Hemorrhagic stroke is defined as an acute symptomatic episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.
- Undetermined stroke is defined as a stroke with insufficient information to allow categorization as A or B.

### TECHNICAL OBSERVATION

A defect, malfunction, or failure of any part of the Medtronic CoreValve® System. This may pertain to the device or system not functioning according to its design intent.

### TRANSIENT ISCHEMIC ATTACK (TIA)

(Refer to the definition of TIA under stroke above.)

- New focal neurologic deficit with rapid symptom resolution (usually 1-2 hours), always within 24 hours
- Neuroimaging without tissue injury

### VALVE THROMBOSIS

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. 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 also be counted as valve thrombosis.
VASCULAR COMPLICATIONS

Vascular Complications will be defined based on the definition published in the European Heart Journal; January 6, 2011, titled "Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium".

<table>
<thead>
<tr>
<th>Vascular Access Site and Access Related Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Vascular Complications</strong></td>
</tr>
<tr>
<td>1. Any thoracic aortic dissection</td>
</tr>
<tr>
<td>2. Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, or compartment syndrome) leading to either death, need for significant blood transfusions (≥ 4 units), unplanned percutaneous or surgical intervention, or irreversible end-organ damage (e.g. hypogastric artery occlusion causing visceral ischemia or spinal artery injury causing neurologic impairment)</td>
</tr>
<tr>
<td>3. Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage</td>
</tr>
<tr>
<td>4. Failure of percutaneous access site closure leading to either death, need for significant blood transfusions (≥ 4 units), unplanned percutaneous or surgical intervention, or irreversible end-organ damage.</td>
</tr>
</tbody>
</table>

| **Minor Vascular Complications**                      |
| 1. Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula or pseudoaneuysms requiring compression or thrombin injection therapy, or hematomas requiring transfusion of ≥ 2 but < 4 units) not requiring unplanned percutaneous or surgical intervention and not resulting in irreversible end-organ damage |
| 2. Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage |
| 3. Failure of percutaneous access site closure that did not result in an interventional or surgical correction and is not associated with death, need for significant blood transfusions (≥4 units), or irreversible end-organ damage. |

Major vascular complications will be considered to be serious adverse events.
16. BIBLIOGRAPHY / LITERATURE REVIEW


<table>
<thead>
<tr>
<th>#</th>
<th>Protocol Section</th>
<th>Prior Version</th>
<th>Proposed change</th>
<th>Reason for the change</th>
<th>Justification</th>
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</thead>
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<td>1</td>
<td>Title Page Footer</td>
<td>Version 1.0 August 26, 2010</td>
<td>Version 2.0 November 2, 2010</td>
<td>Reflect protocol version</td>
<td>Version control</td>
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<tr>
<td>2</td>
<td>Page 2</td>
<td>Mailstop 82</td>
<td>Mailstop 66</td>
<td>Clinical group moved to a new area of the building</td>
<td>Updated Address</td>
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<tr>
<td>3</td>
<td>Table of Contents- List of Appendices</td>
<td>17.6 Sample Case Report Forms (CRFs)</td>
<td>17.6 Sample Electronic Case Report Forms (eCRFs)</td>
<td>Clarification that the CRF are in electronic format.</td>
<td>Does not change the meaning of the protocol.</td>
</tr>
<tr>
<td>5</td>
<td>Table of Contents- List of Appendices</td>
<td>17.9 Medtronic CoreValve® Frailty Index</td>
<td>17.9 Medtronic CoreValve® Clinical Assessment Guidelines</td>
<td>Changed to address FDA’s October 13, 2010 Conditional Approval letter Q5a.</td>
<td>Updated to comply with FDA conditions of approval.</td>
</tr>
<tr>
<td>6</td>
<td>Synopsis – Secondary Endpoints</td>
<td>Repeat Hospitalization</td>
<td>Aortic valve disease hospitalization</td>
<td>Inadvertent omission. Definition was updated based on G100012 February 16, 2010 Deficiency Letter Q12.</td>
<td>Updated to comply with FDA request.</td>
</tr>
<tr>
<td>7</td>
<td>Synopsis – Secondary Endpoints</td>
<td>1. Device success defined as follows:</td>
<td>The following secondary endpoints will be assessed for the MCS TAVI cohort subjects only:</td>
<td>Clarification that device success applies only to the investigational device.</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>8</td>
<td>Synopsis – Sample Size</td>
<td>790 (395 MCS TAVI &amp; 395 Surgical Aortic Valve Replacement (SAVR)</td>
<td>790 (395 MCS TAVI &amp; 395 SAVR)</td>
<td>Definition of SAVR is defined elsewhere.</td>
<td>Does not change the meaning of the protocol.</td>
</tr>
<tr>
<td>9</td>
<td>Exclusion Criteria</td>
<td>27. Severe basal septal hypertrophy with outflow gradient.</td>
<td>27. Severe basal septal hypertrophy with an outflow gradient.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>2.1 Background</td>
<td>Aortic stenosis (AS) causes left ventricular outflow obstruction in adults, with severe AS defined as a combination of echocardiographic parameters: an aortic jet velocity &gt;4 m/s, a mean gradient &gt;40 mmHg, and a valve area &lt;1.0 cm², according to the ACC/AHA guidelines for the management of valvular heart disease.</td>
<td>Aortic stenosis (AS) causes left ventricular outflow obstruction in adults, with severe AS defined as a combination of echocardiographic parameters: an aortic jet velocity &gt;4 m/s, a mean gradient &gt;40 mmHg, and a valve area &lt;1.0 cm², according to the ACC/AHA guidelines for the management of valvular heart disease.</td>
<td>Adjusted endnote numbering.</td>
<td>Does not change the meaning of the protocol.</td>
</tr>
<tr>
<td>#</td>
<td>Protocol Section</td>
<td>Prior Version</td>
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<td>Reason for the change</td>
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<tr>
<td>11</td>
<td>3.3.9</td>
<td>On-line training, including Good Clinical Practice</td>
<td>Training for the full team conducted on-site will include the following: Good Clinical Practice</td>
<td>Moved the requirement for GCP training from online training to full team training</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>12</td>
<td>3.3.9</td>
<td>On-line training, including Pre- and post-patient procedural care</td>
<td>Deleted Pre- and post-patient procedural care</td>
<td>Not requiring these online modules</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>13</td>
<td>3.4.1 Screening</td>
<td>Physical examination including: vital signs and all major systems findings, weight, height and body surface area (BSA); BSA will be calculated from height and weight by use of the formula by Dubois and Dubois ([BSA = 0.007184 x weight [kg]^{0.425} x height [m]^{0.725}], Medtronic CoreValve® Frailty Index.</td>
<td>Clinical assessments including: vital signs and all major systems findings, weight, height and body surface area (BSA); BSA will be calculated from height and weight by use of the formula by Dubois and Dubois ([BSA = 0.007184 x weight [kg]^{0.425} x height [m]^{0.725}], Grip Strength Test, &quot;Timed up and go&quot; (TUG) Test, and Mini Mental Status Exam (MMSE-2E).</td>
<td>Changed to address FDA’s October 13, 2010 Conditional Approval letter Q.5a and Q.5c.</td>
<td>Updated to comply with FDA conditions of approval.</td>
</tr>
<tr>
<td>14</td>
<td>3.4.1 Screening</td>
<td>Routine laboratory tests (most recent) including complete blood count (CBC), platelet count, cardiac enzymes (CK and CK-MB), international normalized ratio (INR), Partial Thromboplastin Time (PTT), liver panel and albumin.</td>
<td>Routine laboratory tests (most recent) including complete blood count (CBC), creatinine, cardiac enzymes (CK and CK-MB), international normalized ratio (INR), Partial Thromboplastin Time (PTT), liver panel and albumin.</td>
<td>Platelet count was removed because it is included in the CBC, and the wording was, therefore, redundant. Creatinine test was added to assess acute kidney injury based on the VARC definition.</td>
<td>All laboratory tests were updated to align with revised Table of Assessments (Table 2) based on the FDA conditions of approval (5a).</td>
</tr>
<tr>
<td>15</td>
<td>3.4.1 Screening</td>
<td>Screening Thoracic and Abdominal Computed Tomography (CT) angiograms (e.g. CT-torso) with complete visualization of both iliacs, femorals and aorta, up to and including the aortic annulus. In the situation where subjects have compromised renal function that precludes contrast media, Magnetic Resonance (MR) imaging may be used as an alternative. CT angiograms will be performed according to the CT Angiography Acquisition Guidelines found in Appendix 17.20.</td>
<td>Screening Computed Tomography (CT) angiograms (e.g. CT-torso) with complete visualization of both iliacs, femorals and aorta, up to and including the aortic annulus. In the situation where subjects have compromised renal function that precludes contrast media, Magnetic Resonance (MR) imaging may be used as an alternative. CT angiograms will be performed according to the CT Angiography Acquisition Guidelines found in Appendix 17.20.</td>
<td>Allowed flexibility of individual site preference on type of CT as long as visualization requirements are met.</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>16</td>
<td>3.4.1 Screening</td>
<td>NA</td>
<td>Logistic EuroScore</td>
<td>Collection of additional risk data</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>17</td>
<td>3.4.1 Screening</td>
<td>For patients with an existing permanent pacemaker or defibrillator only: Perform a full interrogation. Save the</td>
<td>For patients with an existing permanent pacemaker or defibrillator only: Perform a full interrogation and an</td>
<td>Clarification of interrogation</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>#</td>
<td>Protocol Section</td>
<td>Prior Version</td>
<td>Proposed change</td>
<td>Reason for the change</td>
<td>Justification</td>
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<td></td>
<td></td>
<td>data on a diskette and retain the diskette in the subject’s file for source verification</td>
<td>assessment of AV conduction. Save the data on a diskette and retain the diskette in the subject’s file for source verification</td>
<td>requirements to match the data collected on the CRFs. Clarification to ensure that AV conduction and/or ventricular pacing is assessed as this is not always standard of care with just an interrogation. It will be important to compare dependence on ventricular pacing at each time point during the study and the only way to accurately do this is to ensure that AV conduction testing is completed and not just a simple full interrogation.</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Section 3.4.4 Enrollment and Randomization (Previously 3.4.1 Screening Procedures)</td>
<td>(Previously 3.4.1 Screening Procedures)</td>
<td>Now Section 3.4.4 Enrollment and Randomization</td>
<td>The Screening Assessment was split into two different Assessments: Screen (pre-randomization) Baseline (within 14 days of randomization)</td>
<td>No content change. Either repeated or moved to a separate form.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B-type Natriuretic Peptide (BNP), hemoglobin, and plasma free hemoglobin</td>
<td></td>
<td>The BNP, NIHSS and six minute walk test were removed from the original screening form because they are now collected at baseline. NOTE: some assessments are performed at both time points.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>National Institutes of Health Stroke Scale (NIHSS)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>A six minute walk test per the American Thoracic Society Guidelines (detailed instructions can be found in Appendix 17.15), will be performed unless the subject is exempt due to any of the following conditions: postural hypotension, postural arrhythmia, resting systolic pressure less than 95 mmHg, non-ambulatory due to arthritis, neuromuscular disease or Peripheral Vascular Disease (PVD), Chronic Obstructive Pulmonary Disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-lead Electrocardiogram</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Routine laboratory tests including complete blood count (CBC), creatinine, B-type natriuretic peptide (BNP), plasma-free hemoglobin, Cardiac Enzymes (CK and CK-MB), international normalized ratio (INR), Partial Thromboplastin Time (PTT), liver panel and albumin (for patients whose procedures occur within 14 days of enrollment, labs do not need to be repeated).</td>
<td></td>
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</tr>
</tbody>
</table>

Original Version: HR Version 1.0
Update Version: HR Version 2.0
### Comprehensive Table of Changes Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients)

<table>
<thead>
<tr>
<th>#</th>
<th>Protocol Section</th>
<th>Prior Version</th>
<th>Proposed change</th>
<th>Reason for the change</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td>3.4.1 Screening Procedures</td>
<td>NA</td>
<td>For patients with an existing permanent pacemaker or defibrillator only: Perform a full interrogation and an assessment of AV conduction. Save the data on a diskette and retain the diskette in the subject’s file for source verification.</td>
<td>Refer to Section XXX, below.</td>
<td>Updated to comply with FDA conditions of</td>
</tr>
</tbody>
</table>
### Comprehensive Table of Changes Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients)

<table>
<thead>
<tr>
<th>#</th>
<th>Protocol Section</th>
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<th>Reason for the change</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>3.4.2 Screening Committee Procedures</td>
<td>The Medtronic CoreValve® U.S. Pivotal Trial Screening Committee will review baseline information to make the final determination regarding eligibility of the prospective subject to be enrolled in the Medtronic CoreValve® U.S. Pivotal Trial</td>
<td>Inclusion into the appropriate cohort (High Risk Surgical vs. Extreme Risk) and are required to sign off on the Screening Worksheet to be submitted to the Screening Committee. In addition, each patient must be examined in-person by at least one of the cardiac surgeons to evaluate the risk and determine eligibility for the study.</td>
<td>2010 Conditional Approval letter Q5b.</td>
<td>No content change. Either repeated or moved to a separate form.</td>
</tr>
</tbody>
</table>

| 21 | 3.4.2 Screening Committee Procedures | The following information should be submitted to the Screening Committee:  
- Completed Patient Screening Worksheet including, but not limited to:  
  - Demographics  
  - Physical Measurements & Vital Signs  
  - Surgical Risk Assessment  
  - Case Planning  
  - Medtronic CoreValve(R) Frailty Index  
  - Medical History and Co-Morbidities  
  - Anatomical Measurements | Updated to address FDA’s October 13, 2010 Conditional Approval letter Q5a and Q5c | No content change. Either repeated or moved to a separate form. |

| 22 | 3.4.2 Screening Committee Procedures | Screening CT angiography e.g. CT-torso with complete visualization of both iliacs, femorals and aorta, up to and including the aortic annulus. CT angiograms will be performed according to the CT Angiography Acquisition Guidelines found in Appendix 17.20. | Updated to address FDA’s October 13, 2010 Conditional Approval letter Q5a and Q5c | No content change. Either repeated or moved to a separate form. |

| 23 | 3.4.4 Enrollment and Randomization | Obtain signed informed consent. | Confirm patient signed informed consent. | Minor wording clarification | No impact on overall protocol requirements. |

| 24 | 3.4.5.1 MCS TAVI Pre-Procedure | If the patient is currently on warfarin therapy prior to the procedure  
- Discontinue warfarin 3 days prior to the procedure | If the patient is currently on warfarin therapy prior to the procedure  
- Discontinue warfarin 3 days prior to the procedure | Minor wording clarification | No impact on overall protocol requirements. |
## Comprehensive Table of Changes Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients)

<table>
<thead>
<tr>
<th>#</th>
<th>Protocol Section</th>
<th>Prior Version</th>
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<th>Reason for the change</th>
<th>Justification</th>
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</thead>
<tbody>
<tr>
<td>25</td>
<td>3.4.5.1 MCS TAVI Pre-Procedure</td>
<td>Routine laboratory tests including complete blood count (CBC), platelet count, international normalized ratio (INR), Partial Thromboplastin Time (PTT), liver panel and albumin.</td>
<td>Routine laboratory tests including complete blood count (CBC), BNP, plasma free hemoglobin, international normalized ratio (INR), Partial Thromboplastin Time (PTT), liver panel and albumin.</td>
<td>Platelet count is included in CBD. Added to pre-procedure to be consistent with tests collected baseline because the baseline labs can used as the pre-procedure labs if Baseline is within 14 days.</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>26</td>
<td>3.4.5.1 MCS TAVI Procedure</td>
<td>Anesthesia and Procedural Set Up</td>
<td>Anesthesia and Procedural Set Up</td>
<td>Clarification of where to place the 4-5 Fr. Balloon-tip pacing wire and when a screw-tip wire may be needed.</td>
<td>No impact on overall protocol requirements.</td>
</tr>
</tbody>
</table>

Original Version: HR Version 1.0
Update Version: HR Version 2.0
## Comprehensive Table of Changes Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients)

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<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>27</td>
<td>3.4.5.1 MCS TAVI, Immediate Post-Procedure</td>
<td>NIHSS should be administered within 24 hours post-procedure. Modified Rankin Scale for subjects with a stroke to be performed at 30 days and 3 months post-stroke.</td>
<td>NIHSS should be administered within 24 hours post-procedure. For subjects with a neurological event, additional NIHSS exams to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-event. Modified Rankin Scale. For subjects with a stroke, assessment to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-stroke.</td>
<td>Added clarification for performing pacing.</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>28</td>
<td>3.4.5.1 MCS TAVI, Immediate Post-Procedure</td>
<td>If the patient will not be on warfarin therapy post-procedure: it is recommended that subjects are prescribed daily aspirin (81 to 325 mg) or daily clopidogrel (75 mg) (or ticlopidine, if clopidogrel is contraindicated) for at least three months following the procedure.</td>
<td>If the patient will not be on warfarin therapy post-procedure: it is recommended that subjects are prescribed daily aspirin (81 to 325 mg) and daily clopidogrel (75 mg) (or ticlopidine, if clopidogrel is contraindicated) for at least three months following the procedure.</td>
<td>Inadvertent error. Recommended that patient be given both an anticoagulant and an antiplatelet. This is consistent with standard US hospital practice.</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>29</td>
<td>3.4.5.1 MCS TAVI, Immediate Post-Procedure</td>
<td>NA</td>
<td>Assessment of concomitant medications</td>
<td>Inadvertent omission. Updated to reflect information currently collected in the CRF.</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>30</td>
<td>3.4.5.1 MCS TAVI, Post-Procedure Pacing Guidelines</td>
<td>Place a permanent pacemaker according to ACC/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities.</td>
<td>Place a permanent pacemaker according to ACC/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities (Class I or IIb for Acquired Atrioventricular Block in Adults or Permanent Pacing in Chronic Bifascicular Block). Prior to the permanent pacemaker implantation, a 12-lead ECG documenting the reason for the placement of the permanent pacemaker is recommended.</td>
<td>Additional clarification for placement of a permanent pacemaker. Clarified the definition of a conduction disturbance requiring permanent pacing to aid in endpoint adjudication based on the ACC/AHA/HRS Guidelines.</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>#</td>
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<td>Reason for the change</td>
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<tr>
<td>31</td>
<td>3.4.5.1 MCS TAVI, Immediate Post-Procedure</td>
<td>If a permanent pacemaker is implanted, perform a device interrogation post insertion and prior to hospital discharge as well as at every follow-up visit to evaluate device utilization.</td>
<td>If a permanent pacemaker is implanted, perform a device interrogation and an assessment of AV conduction post insertion and prior to hospital discharge as well as at every follow-up visit to evaluate device utilization.</td>
<td>Minor wording clarification. Consistent with information collected on CRFs and reinforce the importance of obtaining both a full interrogation and an assessment of AV conduction which may or may not be standard procedure when conducting a full interrogation. Refer also to Item 17.</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>32</td>
<td>3.4.5.1 MCS TAVI, Assessments done at discharge</td>
<td>Routine laboratory tests including CBC, platelet count, BNP, hemoglobin and plasma-free hemoglobin. 12-lead Electrocardiogram</td>
<td>Routine laboratory tests including CBC, creatinine, BNP, hemoglobin and plasma-free hemoglobin. 12-lead Electrocardiogram</td>
<td>Same as above to assess acute kidney injury based on the VARC definition.</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>33</td>
<td>3.4.5.1 MCS TAVI, Assessments done at discharge</td>
<td>NIH Stroke Scale  - NIHSS also to be done within 24 hours of any reintervention  - Any patient with evidence of a neurological event should have a neurology consult and an imaging study if deemed necessary. Modified Rankin Scale (for subjects with a stroke only – to be performed at 30 days and 3 months post-stroke.)</td>
<td>NIH Stroke Scale  - For subjects with a neurological event, to be performed at 7 days, 30 days and 3 months post-event. NIHSS also to be done within 24 hours of any aortic reintervention  - Any patient with evidence of a neurological event should have a neurology consult and an imaging study if deemed necessary. Modified Rankin Scale  - For subjects with a stroke, assessment to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-stroke.</td>
<td>Added clarification of follow-up assessment for patients with a neurological event. This complies with VARC definition for stroke and when the assessment should be performed. Updated to be consistent with contents of Table 2. Schedule of Assessments.</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>34</td>
<td>3.4.5.1 MCS TAVI, Assessments done at discharge</td>
<td>NIH Stroke Scale  - NIHSS also to be done within 24 hours of any reintervention  - Any patient with evidence of a neurological</td>
<td>NIH Stroke Scale  - For subjects with a neurological event, to be performed at 7 days, 30 days and 3 months post-event. NIHSS also to be done</td>
<td>Same as above</td>
<td></td>
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<tr>
<td>35</td>
<td>3.4.5.1 MCS TAVI, Assessments done at discharge</td>
<td>event should have a neurology consult and an imaging study if deemed necessary. Modified Rankin Scale (for subjects with a stroke only – to be performed at 30 days and 3 months post-stroke.)</td>
<td>NIHSS should be administered within 24 post-procedure. For subjects with a neurological event, additional NIHSS exams to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-event. Modified Rankin Scale</td>
<td>Please refer to item # 17 and 31 above.</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>36</td>
<td>3.4.5.2 Surgical Aortic Valve Replacement – Immediate Post-Procedure</td>
<td>NIHSS should be administered within 24 post-procedure</td>
<td>NIHSS should be administered within 24 post-procedure. For subjects with a neurological event, additional NIHSS exams to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-event. Modified Rankin Scale</td>
<td>Same as above.</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>37</td>
<td>3.4.5.2 Surgical Aortic Valve Replacement – Assessments done at discharge</td>
<td>Routine laboratory tests including CBC, platelet count, BNP, hemoglobin and plasma-free hemoglobin. 12-lead Electrocardiogram</td>
<td>Routine laboratory tests including CBC, creatinine, BNP, hemoglobin and plasma-free hemoglobin. 12-lead Electrocardiogram</td>
<td>Same as above to assess acute kidney injury based on the VARC definition.</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>38</td>
<td>3.4.5.2 Surgical Aortic Valve Replacement – Assessments done at discharge</td>
<td>NIH Stroke Scale (NIHSS should also be done within 24 hours of any aortic reintervention) Any patient with evidence of a neurological event should have a neurology consult and an imaging study if deemed necessary. Modified Rankin Scale (for subjects with a stroke only – to be performed at 30 days and 3 months post-stroke.)</td>
<td>NIHSS For subjects with a neurological event, additional NIHSS exams to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-event. Modified Rankin Scale</td>
<td>Same as above.</td>
<td>No impact on overall protocol requirements.</td>
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<tr>
<td>39</td>
<td>3.4.5.2 Surgical Aortic Valve Replacement – Assessments done at discharge</td>
<td>For patients with permanent pacemakers or defibrillators only: Perform a full interrogation. Save the data on a diskette and retain the diskette in the subject’s file for source verification</td>
<td>For patients with permanent pacemakers or defibrillators only: Perform a full interrogation and an assessment of AV conduction. Save the data on a diskette and retain the diskette in the subject’s file for source verification</td>
<td>Please refer to item # 17 and 31 above.</td>
<td>No impact on overall protocol requirements.</td>
</tr>
</tbody>
</table>
| 40  | 3.4.6 Follow-up Evaluations (30 day, 6 month and 12 month) | NIH Stroke Scale (NIHSS should also be done within 24 hours of any aortic reintervention) Modified Rankin Scale (for subjects with a stroke only – to be performed at 30 days and 3 months post-stroke.) | NIHSS  
- For subjects with a neurological event, additional NIHSS exams to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-event.  
- NIHSS should also be done within 24 hours of aortic reintervention  
Modified Rankin Scale  
For subjects with a stroke, assessment to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-stroke. | Both 30 day, 6 month and 12 month  
And  
2, 3, 4 and 5 years. | No impact on overall protocol requirements. |
| 41  | 3.4.6 Follow-up Evaluations (30 day, 6 month and 12 month) | For patients with permanent pacemakers or defibrillators only (existing or new): Perform a full interrogation at the beginning of each follow-up visit. Save the data on a diskette and retain the diskette in the subject’s file for source verification | For patients with permanent pacemakers or defibrillators only (existing or new): Perform a full interrogation and an assessment of AV conduction at the beginning of each follow-up visit. Save the data on a diskette and retain the diskette in the subject’s file for source verification | Please refer to item # 17 and 31 above. | No impact on overall protocol requirements. |
| 42  | 3.4.6 Follow-up Evaluations (annual clinic visits at 2, 3, 4 and 5 years) | NA | NIH Stroke Scale  
- For subjects with a neurological event, additional NIHSS exams to be to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-event.  
- NIHSS also to be done within 24 hours of any aortic reintervention  
Modified Rankin Scale  
- For subjects with a stroke, assessment to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-stroke. | Please refer to items 27 and 33 above. | No impact on overall protocol requirements. |
| 43  | 3.4.6 Follow-up Evaluations (annual clinic) | Documentation of serious adverse events, major adverse events, device-related events, including device-related | Documentation of serious adverse events, major adverse events, cardiovascular events, device-related events, | Changed to address FDA’s October 13, 2010 Conditional Approval | Updated to comply with FDA conditions of approval. |
### Comprehensive Table of Changes Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients)

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<tr>
<td>44</td>
<td>3.4.6 Follow-up Evaluations (annual clinic visits at 2, 3, 4 and 5 years)</td>
<td>technical observations, unanticipated adverse device effects (UADE), all strokes (CVAs) and deaths. Data related to pre-existing adverse events should be reconciled and resolved.</td>
<td>including device-related technical observations, unanticipated adverse device effects (UADE), all strokes (CVAs) and deaths. Data related to pre-existing adverse events should be reconciled and resolved.</td>
<td>letter 5e.</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>3.4.7 Data Collection Table 2. Schedule of Assessments</td>
<td>Screening Assessment:  - The BNP, NIHSS and six minute walk test  - Medtronic CoreValve Frailty Index (Baseline)  - Routine Laboratory Tests including Complete Blood Count, &amp; Platelet Count  - Pacemaker/defibrillator interrogation</td>
<td>Screening Assessment:  - These were moved to the Baseline assessment  - Baseline Assessment (added): Demographics and Medical History were moved above Clinical Assessment.  - Grip Strength Test, 15-foot “up and go” (TUG) Test, and Mini Mental Exam  - Logistic EuroScore (Baseline)  - Routine Laboratory Tests including Complete Blood Count, &amp; Creatinine  - Revised order of tests in table  - Pacemaker/defibrillator interrogation and an assessment of AV conduction</td>
<td>The Screening Assessment was split into two different Assessments:  - Screening (pre-randomization)  - Baseline (within 14 days of randomization)  Refer to Item 16.</td>
<td>No content change. Either repeated or moved to a separate form.</td>
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Original Version: HR Version 1.0
Update Version: HR Version 2.0
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<tr>
<td>46</td>
<td>3.4.7 Data Collection Table 2. Schedule of Assessments - Footnotes</td>
<td>For any patient that has a stroke, Modified Rankin scale must be performed at 30 days (±7 days) and 3 months (±7 days) post-stroke.</td>
<td>For subjects with a stroke, Modified Rankin assessments to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-stroke</td>
<td>Minor working clarification.</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>47</td>
<td>3.4.7 Data Collection Table 2. Schedule of Assessments</td>
<td>CoreValve Frailty Index</td>
<td>Grip Strength Test, 15-foot “up and go” (TUG) Test, and Mini Mental Exam</td>
<td>Changed to address FDA’s October 13, 2010 Conditional Approval letter Q5a.</td>
<td>Updated to comply with FDA conditions of approval.</td>
</tr>
<tr>
<td>48</td>
<td>3.4.7 Data Collection Table 2. Schedule of Assessments</td>
<td>Routine Laboratory Tests including Complete Blood Count, &amp; Platelet Count</td>
<td>Routine Laboratory Tests including Complete Blood Count, &amp; Creatinine</td>
<td>Removed individual items which are inclusive of CBC added Creatinine</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>3.4.7 Data Collection Table 2. Schedule of Assessments</td>
<td>NA</td>
<td>Liver panel to include: SGPT (ALT), SGOT (AST), Total Bilirubin, Alkaline Phosphatase</td>
<td>To specifically call out the tests to be performed for a Liver Panel.</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>3.4.7 Data Collection Table 2. Schedule of Assessments</td>
<td>NA</td>
<td>Liver panel to include: SGPT (ALT), SGOT (AST), Total Bilirubin, Alkaline Phosphatase</td>
<td>To specifically call out the tests to be performed for a Liver Panel. NOTE: Footnote ordering changed from prior revision.</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>51</td>
<td>3.4.7 Data Collection Table 2. Schedule of Assessments - Footnotes</td>
<td>NA</td>
<td>Rotational X-ray to be performed annually after 1 year for MCS TAVI subjects only</td>
<td>To clarify that the tests specific to MCS TAVI</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>52</td>
<td>3.4.7 Data Collection Table 2. Schedule of</td>
<td>NIHSS to be done within 24 hours of any reintervention</td>
<td>In addition to the protocol required assessment, For subjects with a neurological event, additional NIHSS exams to be performed at 7 days or discharge (whichever occurs first), 30 days and 90 days post-</td>
<td>Please refer to Items 27 and 33 above.</td>
<td>No impact on overall protocol requirements.</td>
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</table>
### Comprehensive Table of Changes Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients)

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<tbody>
<tr>
<td>53</td>
<td>Assessments - Footnotes</td>
<td>3.4.9</td>
<td>The Investigator shall maintain adequate records of the receipt and disposition of all investigational devices. At the trial closeout visit, the Investigator must return to the Sponsor any unused devices and a copy of the completed device inventory. The Investigator’s copy of the device reconciliation records must document any unused devices that have been returned to the Sponsor as well as all product usage including opened but unimplanted devices.</td>
<td>The Investigator shall maintain adequate records of the receipt and disposition of all investigational devices. At the trial closeout visit, the Investigator must return to the Sponsor any unused devices and a copy of the completed device inventory. The Investigator’s copy of the device reconciliation records must document any unused devices that have been returned to the Sponsor as well as all product usage including opened but unimplanted devices.</td>
<td>Added reference to MCS System, not just the PAV. Reordered wording of section for ease of reading.</td>
</tr>
<tr>
<td>54</td>
<td>Investigational Product Handling and Accountability</td>
<td>NA</td>
<td>This trial contains a health economics review that will be done to compare the in-hospital and 12 month follow-up medical care resource utilization and cost for patients in each of the treatment groups. As part of this trial, patients will be asked to sign a Medical Billing Release Form. This form will be used by the Health Economics and Technology Assessment Group of the Mid America Heart Institute (MAHI) to collect hospital bills from the patient accounting department at any hospital to which patients are admitted, from the time of enrollment in the Medtronic CoreValve® U.S. Pivotal Trial through the study follow-up period. Resource utilization data should be collected by the site along with clinical data using case report forms.</td>
<td>This trial contains a health economics review that will be done to compare the in-hospital and 12 month follow-up medical care resource utilization and cost for patients in each of the treatment groups. As part of this trial, patients will be asked to sign a Medical Billing Release Form. This form will be used by the Health Economics and Technology Assessment Group of the Mid America Heart Institute (MAHI) to collect hospital bills from the patient accounting department at any hospital to which patients are admitted, from the time of enrollment in the Medtronic CoreValve® U.S. Pivotal Trial through the study follow-up period. Resource utilization data should be collected by the site along with clinical data using case report forms.</td>
<td>Previously protocol didn’t mention health economics, but it was in the Informed Consent, so added to body of protocol. Consistent with data collected on CRF and IC, but not specifically called out.</td>
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<tr>
<td>55</td>
<td>The Investigator shall maintain adequate records of the receipt and disposition of all investigational devices. At the trial closeout visit, the Investigator must return to the Sponsor any unused devices and a copy of the completed device inventory. The Investigator’s copy of the device reconciliation records must document any unused devices that have been returned to the Sponsor as well as all product usage including opened but unimplanted devices. In the event that a Medtronic CoreValve® PAV is explanted (due to reintervention or autopsy), the Medtronic CoreValve® PAV should be returned per the Explanted Device/Pathology Core Lab Protocol in Appendix 17.12. In the event of a device malfunction of the Medtronic CoreValve® System (MCS) prior to implant, affect MCS components should be returned to: Explant Laboratory Medtronic, Inc. SS-84 1851 E. Deere Avenue Santa Ana, CA 92705-5720 Additional details surrounding the device return process are contained within the Medtronic explant kit.</td>
<td>The Investigator shall maintain adequate records of the receipt and disposition of all investigational devices. At the trial closeout visit, the Investigator must return to the Sponsor any unused devices and a copy of the completed device inventory. The Investigator’s copy of the device reconciliation records must document any unused devices that have been returned to the Sponsor as well as all product usage including opened but unimplanted devices. In the event of a device malfunction of the Medtronic CoreValve® System (MCS) prior to implant or in the event that a Medtronic CoreValve® PAV is explanted after implant (due to reintervention or autopsy), the PAV and/or affected MCS components should be returned to Medtronic to the following: Medtronic, Inc. Attn: Explant Lab [PCR#] 1851 E. Deere Avenue Santa Ana, CA 92705-5720 Additional details surrounding the device return process are contained within the Medtronic explant kit and in Appendix 17.12</td>
<td>Revised wording order for clarification</td>
<td>No impact on overall protocol requirements.</td>
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<tr>
<td>56</td>
<td>Major adverse cardiovascular and cerebrovascular events (MACCE) is defined as a composite of:  - all-cause death  - myocardial infarction (MI)  - major stroke, and Reintervention (defined as any cardiac surgery or percutaneous reintervention catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve</td>
<td>• All-cause death  • Myocardial infarction (MI)  • Major stroke, and Reintervention (defined as any cardiac surgery or percutaneous reintervention catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve</td>
<td>Capitalization</td>
<td>No impact on overall protocol requirements.</td>
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<td>57</td>
<td>3.5.1.4</td>
<td>Embolism</td>
<td>• Valve embolism</td>
<td>Clarified that the definition of a MAE is specific to valve embolisms only.</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>58</td>
<td>3.5.1.4</td>
<td>Not included in previous version</td>
<td>• Cardiac Perforation</td>
<td>Cardiac Perforation was inadvertently deleted from the definition of a MAE. This has been in previous protocol version and was added back in to be consistent with industry definition of MAE.</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>59</td>
<td>3.5.2</td>
<td></td>
<td>Once a subject has completed their 12-month scheduled follow-up visit, serious adverse events, major adverse events, device-related adverse events, including device related technical observations, unanticipated adverse device effects (UADE), all strokes (CVAs) and deaths will be required to be reported.</td>
<td>Clarification to satisfy FDA condition of approval question 5(e).</td>
<td>Updated to comply with FDA conditions of approval.</td>
</tr>
<tr>
<td>60</td>
<td>3.5.2</td>
<td></td>
<td>The Investigator must also notify the responsible IRB regarding new and significant safety information and any event identified by Medtronic that require expedited FDA reporting as serious, unexpected, and related to the investigational device.</td>
<td>Reinforce investigators responsibilities concerning IRB reporting which may be different than 21 CFR requirements</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>61</td>
<td>3.5.2.1</td>
<td>Medtronic requests that the Investigator notify the sponsor within 3 working days of learning of any SAE using the electronic data capture (eCRF) system.</td>
<td>Medtronic requests that the Investigator notify the sponsor within 3 working days of first learning of any SAE using the electronic data capture (eCRF) system.</td>
<td>Clarification on timing</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>62</td>
<td>3.5.2.3</td>
<td>Embolism</td>
<td>• Valve or distal embolization</td>
<td>Although the definition of a MAE is specific to valve embolisms, the known risks to the subjects are inclusive of both valve and distal embolizations. Clarified to be inclusive of all embolizations</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>63</td>
<td>3.5.2.3</td>
<td>Thrombosis</td>
<td>• Thrombosis (including valve thrombosis)</td>
<td>Clarification that the known risks for the</td>
<td>No impact on overall protocol requirements.</td>
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## Comprehensive Table of Changes Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients)

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</table>
| 64 | 3.5.2.3          | • Prosthetic valve dysfunction including but not limited to:  
|    |                  | o Fracture  
|    |                  | o Bending of the valve frame  
|    |                  | o Under-expansion of the valve frame  
|    |                  | o Calcification  
|    |                  | o Wear or tear in the valve leaf  
|    |                  | o Poor valve coaptation  
|    |                  | o Suture breaks or disruption  
|    |                  | o Leak  
|    |                  | o Malposition (either too high or too low)  
|    |                  | o Regurgitation  
|    |                  | | | clinical trial include any thrombosis which is inclusive of valve thrombosis.  
|    |                  | | | Clarification to be consistent with the VARC definition and add more clarity around definition of bending per FDA question  
|    |                  | | | No impact on overall protocol requirements.  
| 65 | Infection        | Infection (including endocarditis)    | Clarification that infections is inclusive of endocarditis  
|    |                  | | | No impact on overall protocol requirements.  
| 66 | Complications at the area where the doctor opened the skin, including  
|    |                  | o pain  
|    |                  | o bleeding  
|    |                  | o hematoma  
|    |                  | o pseudoaneurysm  
|    |                  | | | Vascular access site or access related complications, including but not limited to:  
|    |                  | o pain  
|    |                  | o bleeding  
|    |                  | o hematoma  
|    |                  | o pseudoaneurysm  
|    |                  | o irreversible nerve injury  
|    |                  | o compartment syndrome  
|    |                  | o stenosis  
|    |                  | | | Added clarification to align with the VARC definition for vascular complication  
|    |                  | | | No impact on overall protocol requirements.  

Original Version: HR Version 1.0  
Update Version: HR Version 2.0
### Comprehensive Table of Changes Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients)

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<tr>
<td>67</td>
<td>3.5.2.4</td>
<td>Any subject death will be reported on the eCRF and accompanied by an adverse event identifying the cause of death.</td>
<td>Any subject death will be reported on the Study Exit eCRF and accompanied by an Adverse Event eCRF identifying the cause of death.</td>
<td>Clarification that deaths will be captured on the Study Exit eCRF and in addition, an AE eCRF is required.</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>68</td>
<td>3.5.4</td>
<td>The DSMB will meet (via teleconference or in person) prior to subject enrollment to establish procedures for DSMB review, chairman appointment and guidelines for trial recommendation.</td>
<td>The DSMB will meet (via teleconference or in person) prior to the first subject enrollment to establish procedures for DSMB review, chairman appointment and guidelines for trial recommendations.</td>
<td>Added clarification around DSMB meeting timing.</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>69</td>
<td>3.5.4</td>
<td>The DSMB will also perform a supplemental review of, at a minimum, serious adverse events and deaths and any other data requested by the DSMB on a more frequent periodic basis to ensure patient safety. DSMB members would review the report, and when necessary provide recommendations about the conduct of the study and/or request a full DSMB meeting.</td>
<td>The DSMB will also perform a supplemental review of, at a minimum, all serious adverse events and deaths and any other data requested by the DSMB on a more frequent periodic basis to ensure patient safety. DSMB members will review the report, and when necessary provide recommendations about the conduct of the study and/or request a full DSMB meeting.</td>
<td>Added clarification around DSMB supplemental report expectations</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>70</td>
<td>3.5.4</td>
<td>A DSMB charter will be developed and approved by Medtronic. The committee will outline the criteria for both the full DSMB meeting and supplemental DSMB reviews.</td>
<td>A DSMB charter will be developed and approved by Medtronic and the DSMB members. The committee will outline the criteria for both the full DSMB meeting and supplemental DSMB reviews within the DSMB charter.</td>
<td>Added clarification the DSMB charter will be approved by both Medtronic and the DSMB members via the DSMB chairman.</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>71</td>
<td>3.5.4</td>
<td>In the case of UADEs, if Medtronic and the DSMB determine that the event presents an unreasonable risk to the participating subjects, Medtronic must terminate the clinical trial 5 working days after making that determination and not later than 15 working days after Medtronic first receives notice of the effect. [21 CFR 812.46].</td>
<td>In the case of UADEs, if Medtronic and the DSMB determine that the event presents an unreasonable risk to the participating subjects, Medtronic must terminate the clinical trial 5 working days after making that determination and not later than 15 working days after Medtronic first receives notice of the effect. [21 CFR 812.46]. All clinical sites will be notified of this action.</td>
<td>Clarification that in the event there is an unreasonable risk to the safety of the subjects in the study, the trial will be terminated and all centers will be notified immediately.</td>
<td>21 CFR 812.46</td>
</tr>
<tr>
<td>72</td>
<td>3.6</td>
<td>The statistical analyses will be performed by Medtronic employed statisticians and independently verified by the staff of the Biostatistics Department at the Harvard Clinical Research Institute. All randomized subjects will be analyzed following the intent-to-treat (ITT) approach.</td>
<td>The statistical analyses will be performed by Medtronic employed statisticians and independently verified by the staff of the Biostatistics Department at the Harvard Clinical Research Institute. Subjects will be analyzed using an &quot;as treated&quot; approach as the primary analysis. In addition, all randomized subjects will also be analyzed following the intent-to-treat (ITT) approach as an adjunctive analysis. For the primary analysis, &quot;as treated&quot; will be defined in the FDA question</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Original Version: HR Version 1.0
Update Version: HR Version 2.0
## Comprehensive Table of Changes Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients)

<table>
<thead>
<tr>
<th>#</th>
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<th>Justification</th>
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<tbody>
<tr>
<td>75</td>
<td>3.6.2</td>
<td>Every effort will be undertaken to minimize missing data. In time-to-event outcomes drop-outs 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 for continuous or categorical outcomes. The number of subjects included in each analysis will be reported so that the reader can assess the potential impact of missing data. For the primary endpoint, a sensitivity analysis will be conducted to assess the impact of censored data and will include a worst-case analysis.</td>
<td>Following manner: the start of the procedure (the procedure has been attempted). Using this definition, study subjects will be analyzed according to their first attempted procedure (TAVI or SAVR).</td>
<td>Every effort will be undertaken to minimize missing data. Since all cause mortality is the primary endpoint for this trial, a minimal amount of missing data is anticipated. However, if outcome data are missing, only subjects whose status is known will be included in the binomial proportions in the calculation of the Farrington and Manning test statistic. To assess the potential impact of these missing data, a sensitivity analysis will be conducted which will include a best-case (assume missing MCS TAVI subjects are alive and SAVR subjects have died) and a worst-case (assume missing MCS TAVI subjects have died and SAVR subjects are alive) analysis.</td>
<td></td>
</tr>
<tr>
<td>74</td>
<td>3.6.3</td>
<td>Powered Secondary Hypothesis: TAVI with the Medtronic CoreValve® System is superior to SAVR in binary rate of mortality at 30 days.</td>
<td>Powered Secondary Hypothesis: TAVI with the Medtronic CoreValve® System is superior to SAVR in binary rate of MACCE at 30 days or hospital discharge, whichever is longer.</td>
<td>FDA question</td>
<td></td>
</tr>
<tr>
<td>75</td>
<td>3.6.5.2</td>
<td>For the secondary superiority hypothesis, assuming 1:1 treatment allocation ratio between study device and surgical valve replacement and assuming the proportion of MACCE at 30 days or hospital discharge, whichever is longer, equal to 20% in the surgical valve replacement arm and equal to 12.1% in the study device arm (39.5% relative treatment effect), 355 evaluable subjects per arm would yield 81.9% power for a one-sided test at the 0.025 level of significance.</td>
<td>FDA question</td>
<td></td>
<td></td>
</tr>
<tr>
<td>76</td>
<td>3.6.6</td>
<td>10. Repeat hospitalizations The number of subjects re-hospitalized after the initial index procedure will be compared at 30 days, 6 months, 12 months and annually through five years. All subjects will be included in the analysis. Hospitalization-free rates will be provided at 30-days, 6 months, 12 months and annually through five years. All subjects will be included</td>
<td>10. Aortic valve disease related hospitalizations The number of subjects re-hospitalized after the initial index procedure will be compared at 30 days, 6 months, 12 months and annually through five years. All subjects will be included in the analysis. Hospitalization-free rates will be provided at 30-days, 6 months, 12 months and annually through five years. All subjects will be included</td>
<td>See above</td>
<td></td>
</tr>
</tbody>
</table>

Original Version: HR Version 1.0  
Update Version: HR Version 2.0
## Comprehensive Table of Changes Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients)

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<tr>
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</thead>
<tbody>
<tr>
<td>77</td>
<td>3.6.6</td>
<td></td>
<td>in the analysis. The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.</td>
<td>in the analysis. The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.</td>
<td>See above</td>
</tr>
<tr>
<td>78</td>
<td>3.6.6</td>
<td>DEVICE SUCCESS</td>
<td>The following secondary endpoints will be assessed for the MCS TAVI cohort subjects only:</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>1. Device success defined as follows:</td>
<td>To satisfy the FDA conditional of approval question #2 and to be in compliance with the VARC definition of AR.</td>
<td>Updated to comply with FDA conditions of approval.</td>
</tr>
<tr>
<td></td>
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<td>• successful vascular access, delivery and deployment of the device, and successful retrieval of the delivery system,</td>
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<tr>
<td></td>
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<td></td>
<td>• correct position of the device in the proper anatomical location (placement in the annulus with no impedance on device function),</td>
<td></td>
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<td></td>
<td>• successful device function assessed acutely in a resting state, either within 24-48 hours after the index procedure or before hospital discharge, where successful device function is defined as follows:</td>
<td></td>
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<td></td>
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<td>o absence of device migration (device within aortic annular region) assessed qualitatively by echocardiography</td>
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<td></td>
<td>o less than moderate (2+) aortic regurgitation by echocardiography</td>
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<td>o effective orifice area &gt; 1.2 cm² by echocardiography using the continuity equation.</td>
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<td></td>
<td>o Only one valve implanted in the proper anatomical location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>79</td>
<td>3.6.7</td>
<td></td>
<td>Provided the 12-month mortality primary objective and the 30-day (or hospital discharge, whichever is longer) MACCE powered secondary hypothesis are met with significant p-values, to keep the overall (familywise) Type I error rate at 0.05, a hierarchical test procedure will be applied to five of the secondary objective</td>
<td>See above</td>
<td></td>
</tr>
</tbody>
</table>
Comprehensive Table of Changes Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients)

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</thead>
<tbody>
<tr>
<td>80</td>
<td>Table 4 The Investigator’s report on any unanticipated adverse effect must be submitted as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect.</td>
<td>UADEs should be reported immediately via telephone as well as on an eCRF and meet the following: the Investigator’s report on any unanticipated adverse effect must be submitted as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect.</td>
<td>Clarification that Medtronic recommends a telephone call immediately upon notification of a UADE to ensure regulatory timelines are met</td>
<td>- No impact on overall protocol requirements.</td>
<td></td>
</tr>
<tr>
<td>81</td>
<td></td>
<td></td>
<td><strong>Death</strong></td>
<td><strong>Death</strong></td>
<td>Please refer to items 62-66 above</td>
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</tr>
<tr>
<td>1</td>
<td>Thrombosis</td>
<td></td>
<td>Valve or distal embolization</td>
<td></td>
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<tr>
<td>2</td>
<td>Hemorrhage requiring transfusion</td>
<td></td>
<td>Thrombosis (including valve thrombosis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Arterovenous fistula</td>
<td></td>
<td>Hemorrhage requiring transfusion</td>
<td></td>
<td></td>
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<tr>
<td>4</td>
<td>Vessel dissection or spasm</td>
<td></td>
<td>Arterovenous fistula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Valve migration</td>
<td></td>
<td>Vessel dissection or spasm</td>
<td></td>
<td></td>
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<tr>
<td>6</td>
<td>Prosthetic valve dysfunction including but not limited to:</td>
<td></td>
<td>Valve migration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Fracture</td>
<td></td>
<td>Prosthetic valve dysfunction including but not limited to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Bending of the valve frame</td>
<td></td>
<td>Fracture</td>
<td></td>
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</tr>
<tr>
<td>9</td>
<td>Under-expansion of the valve frame</td>
<td></td>
<td>Bending (out-of-round configuration) of the valve frame</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Calcification</td>
<td></td>
<td>Under-expansion of the valve frame</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Wear or tear in the valve leaf</td>
<td></td>
<td>Calcification</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Poor valve coaptation</td>
<td></td>
<td>Pannus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Suture breaks or disruption</td>
<td></td>
<td>Wear, tear, prolapse or retraction in the valve leaf</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Leak</td>
<td></td>
<td>Poor valve coaptation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Mal-sizing</td>
<td></td>
<td>Leak</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Malposition (either too high or too low)</td>
<td></td>
<td>Mal-sizing (prosthesis-patient mismatch)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Regurgitation</td>
<td></td>
<td>Malposition (either too high or too low)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Stenosis</td>
<td></td>
<td>Regurgitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Mitral valve regurgitation</td>
<td></td>
<td>Stenosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Hypotension or hypertension</td>
<td></td>
<td>Mitral valve regurgitation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>Acute renal injury</td>
<td></td>
<td>Hypotension or hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Allergic reaction to antiplatelet agents or contrast medium</td>
<td></td>
<td>Acute renal injury</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Infection</td>
<td></td>
<td>Allergic reaction to antiplatelet agents or contrast medium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Bowel ischemia</td>
<td></td>
<td>Infection (including endocarditis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Complications at the area where the doctor opened the skin, including</td>
<td></td>
<td>Bowel ischemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>pain</td>
<td></td>
<td>Vascular access site or access related complications, including but not limited to:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>bleeding</td>
<td></td>
<td>pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>hematoma</td>
<td></td>
<td>bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>pseudoaneurysm</td>
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Comprehensive Table of Changes Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients)

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</thead>
<tbody>
<tr>
<td>82</td>
<td>15.2 Definition of terms</td>
<td>AORTIC REGURGITATION (AR)</td>
<td>Aortic valve incompetence resulting in backward flow of blood. Further information can be found in the Echocardiography Procedures in Appendix 17.8. Moderate or severe aortic regurgitation (AR) via echo assessment and a grade ⩾ 2 using angiographic assessment, will be considered a serious adverse event.</td>
<td>Changed to be consistent with the VARC definition of AR to ensure standardization of TAVI definitions and to satisfy FDA response.</td>
<td>Updated to comply with FDA conditions of approval.</td>
</tr>
</tbody>
</table>

AORTIC REGURGITATION (AR)
Aortic valve incompetence resulting in backward flow of blood.

Aortic Valve Regurgitation will be defined according to the definition proposed by the Valve Academic Research Consortium (VARC) Consensus Report for Transcatheter Aortic Valve Implantation (TAVI); 2010-06-15.

**Prosthetic Aortic Valve R**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Valve Structure and Motion</th>
<th>Structural parameters</th>
<th>Doppler parameters (qualitative or semiquantitative)</th>
<th>Doppler parameters (quantitative)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mechanical or bioprothetic</td>
<td>Left ventricular size</td>
<td>Jet width in central jets (% LVO diameter): color*</td>
<td>Regurgitant volume (mL/beat)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Jet density: CW Doppler</td>
<td>Regurgitant fraction (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Jet deceleration rate (PHT, ms): CW Doppler**</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>LV outflow vs. pulmonary flow: PW Doppler</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>LV outflow reversal in the descending aorta: PW Doppler</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Circumferential extent of paraprosthetic AR (%)</td>
<td></td>
</tr>
</tbody>
</table>

*Parameter applicable to central jets and is less accurate in eccentric jets
**Influenced by left ventricular compliance
AR=aortic regurgitation; CW= continuous wave; LVO= left ventricular outflow; PW= pulsed wave

Moderate or severe aortic regurgitation (AR) will be...
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<tr>
<td>83</td>
<td>15.2 Definition of terms</td>
<td>ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease (published in the August 1, 2006, issues of Journal of the American College of Cardiology and Circulation)</td>
<td>Aortic Valve Regurgitation will be defined according to the definition proposed by the Valve Academic Research Consortium (VARC)</td>
<td>Changed to be consistent with the VARC definition of AR to ensure standardization of TAVI definitions and to satisfy FDA response.</td>
<td>Updated to comply with FDA conditions of approval.</td>
</tr>
<tr>
<td>84</td>
<td>15.2 Definition of terms</td>
<td>An insufficient forward cardiac output to maintain adequate perfusion of vital organs to meet ongoing demands for oxygenation and metabolism. Cardiogenic shock is due to either inadequate left ventricular pump function (such as in congestive heart failure) or inadequate left ventricular filling (such as in cardiac tamponade). Cardiogenic shock is defined as sustained hypotension (&gt;30 minutes) with evidence of tissue hypoperfusion including oliguria (&lt;30 mL/h), cool extremities, cyanosis and altered mental status.</td>
<td>CARDIOGENIC SHOCK Patient was, at the time of procedure, in a clinical state of hyperfusion sustained for greater than 30 minutes, according to either of the following criteria: 1. Systolic BP &lt; 80 and/or Cardiac Index &lt; 1.8 despite maximal treatment; 2. IV inotropes and/or IABP necessary to maintain Systolic BP &gt; 80 and/or CI &gt; 1.8</td>
<td>Redefined to be consistent with STS definition of cardiogenic shock</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>85</td>
<td>15.2 Definition of terms</td>
<td>Definition not defined in prior version</td>
<td>CONDUCTION DISTURBANCE REQUIRING PERMANENT PACEMAKER IMPLANTATION ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease (published in the August 1, 2006, issues of Journal of the American College of Cardiology and Circulation) Any disturbance in the cardiac electrical conduction system that meets the American College of Cardiology (ACC)/American Heart Association (AHA)/ Heart Rhythm Society (HRS) Class I or IIa Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities for Acquired Atrioventricular Block in Adults or Permanent PACING in Chronic Bifascicular Block.</td>
<td>Clarified the definition of a conduction disturbance requiring permanent pacing to aid in endpoint adjudication based on the ACC/AHA/HRS Guidelines</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>86</td>
<td>15.2 Definition of terms</td>
<td>DEVICE FAILURE • Inability to successfully deliver and place the device in stable position • Failure to retrieve the delivery catheter • More than one Medtronic CoreValve® PAV is implanted</td>
<td>DEVICE FAILURE • Inability to successfully deliver and place the device in stable position • Failure to retrieve the delivery catheter • More than one Medtronic CoreValve® PAV is implanted</td>
<td>See above in stats section (ensure consistency with the Device Success definition as requested by FDA and to be in compliance with VARC definition of AR)</td>
<td>No impact on overall protocol requirements.</td>
</tr>
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### Comprehensive Table of Changes Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients)

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<tr>
<td>87</td>
<td>15.2 Definition of terms</td>
<td><strong>DEVICE MALPLACEMENT</strong> Placement of the Medtronic CoreValve® PAV in a non-therapeutic location, either inadvertently, or possibly intentionally due to unintended problems during the Medtronic CoreValve® System (MCS) delivery that necessitates placement in the non-therapeutic location.</td>
<td><strong>DEVICE MALPLACEMENT</strong> Placement of the Medtronic CoreValve® PAV in a non-therapeutic location, either inadvertently, or possibly intentionally due to unintended problems during the Medtronic CoreValve® System (MCS) delivery or procedure that necessitates placement in the non-therapeutic location.</td>
<td>Clarified definition</td>
<td>No impact on overall protocol requirements.</td>
</tr>
<tr>
<td>88</td>
<td>15.2 Definition of terms</td>
<td><strong>DEVICE SUCCESS</strong> Device success is defined as follows:</td>
<td><strong>DEVICE SUCCESS</strong> Device success is defined as follows:</td>
<td>See above in stats section</td>
<td>Updated to comply with FDA conditions of approval.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• successful delivery and placement of the device, and successful retrieval of the delivery system,</td>
<td>• successful vascular access, delivery and deployment of the device, and successful retrieval of the delivery system,</td>
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<td></td>
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<td>• correct position of the device within the aortic annular region (placement in the annulus with no impedance on device function),</td>
<td>• correct position of the device in the proper anatomical location (placement in the annulus with no impedance on device function),</td>
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<tr>
<td></td>
<td></td>
<td>• successful device function assessed acutely in a resting state, either within 24-48 hours after the index procedure or before hospital discharge, where successful device function is defined as follows:</td>
<td>• Intended performance of the prosthetic valve (aortic valve area &gt; 1.2 cm² (by echocardiography using the continuity equation) and mean aortic valve gradient &lt; 20 mmHg or peak velocity &lt; 3 m/sec, without moderate or severe prosthetic valve AR)</td>
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<tr>
<td>89</td>
<td>15.2 Definition of terms</td>
<td>HOSPITALIZATION FOR SIGNS AND SYMPTOMS RELATED TO AORTIC VALVE DISEASE</td>
<td>Jugular valve distention: With the patient is positioned under 45°, and the filling level of the jugular vein determined. An abnormal response is more than 3 centimetres above the sternal angle.</td>
<td>Correction of spelling error</td>
<td>No impact on overall protocol requirements</td>
</tr>
</tbody>
</table>
| 90 | 15.2 Definition of terms | MAJOR ADVERSE EVENT (MAE) | • MACCE  
• Acute kidney injury  
• Cardiac tamponade  
• Prosthetic valve dysfunction  
• Cardiogenic shock  
• Valve endocarditis  
• Embolism  
• Life-threatening, disabling or major bleeding  
• Major vascular complication | Cardiac Perforation was inadvertently deleted from the definition of a MAE. This has been in previous protocol version and was added back in to be consistent with industry definition of MAE. | No impact on overall protocol requirements. |
| 90 | 15.2 Definition of Terms- Mitral Stenosis | Not in previous version | MITRAL STENOSIS  
Moderate or severe AS will be considered a serious adverse event | Correct typographical error. Should say MS, not AS. This was added for clarification and to be consistent with the AS definition of an SAE. | No impact on overall protocol requirements. |
| 91 | 15.2 Definition | Primary paravalvular leak | Primary paravalvular leak | Consistent with FDA | Updated to comply with |
## Comprehensive Table of Changes Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients)

<table>
<thead>
<tr>
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</table>
|    |                            | Defined as any evidence of leakage of blood around the prosthesis between the device and the native annulus. Primary paravalvular leaks will be stratified by the following:  
  - **All leaks**: evidence of moderate to severe paravalvular regurgitation by echocardiography  
  - **Minor leaks**: A paravalvular leak with graded ≥2+ aortic regurgitation and does not require surgical intervention  
  - **Major leaks**: A paravalvular leak with graded ≥2+ aortic regurgitation or requires surgical intervention  
  Paravalvular leaks will be classified as Serious Adverse Events.                                                                 | request to use assessment of moderate to severe rather than 2+ to classify and assess AS, including paravalvular leaks. | FDA conditions of approval.                                                                 |
| 92 | 15.2 Definition of Terms – Paravalvular Leak | Cl rically important disabilities will be considered to be serious adverse events | Clinically important disabilities (major strokes) will be considered to be serious adverse events | Clarification. Consistent with an earlier FDA response | No impact on overall protocol requirements. |
| 93 | 15.2 Definition of Terms – Technical Observation | Not in glossary of terms in previous versions. | TECHNICAL OBSERVATION  
A defect, malfunction, or failure of any part of the Medtronic CoreValve® System. This may pertain to the device or system not functioning according to its design intent. Technical observations may or may not be related to an adverse event in a subject. | Has always been in the body of the protocol but was inadvertently left out of the glossary terms so was added for consistency and accuracy. | No impact on overall protocol requirements. |
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<tbody>
<tr>
<td>1</td>
<td>Section 3.4.1 Cardiovascular imaging studies: Section 3.4.1 Page 26 Section 3.4.2 Page 27</td>
<td>1. Screening Computed Tomography (CT) angiograms (e.g. CT-torso) with complete visualization of both iliacs, femorals and aorta, up to and including the aortic annulus. In the situation where subjects have compromised renal function that precludes contrast media, Magnetic Resonance (MR) imaging may be used as an alternative. CT angiograms will be performed according to the CT Angiography Acquisition Guidelines found in Appendix 17.20. 2. If the CT angiogram was conducted in the last 365 days and subject has not had a peripheral vascular intervention since the time of the image, a more recent exam is not required as long as visualization of both iliacs and femorals to the aorta can be viewed. However, if the subject had a peripheral vascular intervention, the exam must be more recent (within 90 days of being sent to the Screening Committee). 3. Screening CT angiography (e.g. CT-torso) with complete visualization of both iliacs, femorals and aorta, up to and including the aortic annulus. CT angiograms will be performed according to the CT Angiography Acquisition Guidelines found in Appendix 17.20.</td>
<td>1. Screening Computed Tomography (CT) angiograms (e.g. CT-torso) with complete visualization of both iliacs, femorals and aorta (and subclavian/axillaries, if applicable), up to and including the aortic annulus. In the situation where subjects have compromised renal function that precludes contrast media, Magnetic Resonance (MR) imaging may be used as an alternative. CT angiograms will be performed according to the CT Angiography Acquisition Guidelines found in Appendix 17.20. 2. If the CT angiogram was conducted in the last 365 days and subject has not had a peripheral vascular intervention since the time of the image, a more recent exam is not required as long as visualization of both iliacs and femorals (and subclavian/axillaries, if applicable) to the aorta can be viewed. However, if the subject had a peripheral vascular intervention, the exam must be more recent (within 90 days of being sent to the Screening Committee). 3. Screening CT angiography (e.g. CT-torso) with complete visualization of both iliacs, femorals and aorta (and subclavian/axillaries, if applicable), up to and including the aortic annulus. CT angiograms will be performed according to the CT Angiography Acquisition Guidelines found in Appendix 17.20.</td>
<td>Additional information specific to addition of non-ilio-femoral subjects.</td>
<td>Updated per November 30, 2010 teleconference with FDA regarding inclusion of non-ilio-femoral subjects enrolled in trial.</td>
</tr>
<tr>
<td>2</td>
<td>Section 3.4.1 Cardiovascular imaging studies</td>
<td>For patients with an existing permanent pacemaker or defibrillator only: Perform a full interrogation and an assessment of AV conduction. Save the data on a diskette and retain the diskette in the subject's file for source verification.</td>
<td>Deleted</td>
<td>Interrogation of the pacemaker is carried out at baseline</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>3</td>
<td>Section 3.4.1 Screening Procedures</td>
<td>“Timed up and go” (TUG) Test</td>
<td>Replaced with Gait Test</td>
<td>Clarifications based on investigator feedback.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>4</td>
<td>Section 3.4.4 Baseline</td>
<td>For patients with an existing permanent pacemaker or defibrillator only: Perform a full interrogation and an assessment of AV conduction. Save the data on a diskette and retain the diskette in the subject's file for source verification.</td>
<td>For patients with an existing permanent pacemaker or defibrillator only: Perform a full interrogation and an assessment of AV conduction (Refer to the Pacing Guidelines in Appendix 17.14). Print a copy of the interrogation and save the data on a diskette. Retain the printed copy of the interrogation and the diskette in the subject's file for source verification.</td>
<td>Clarifications based on investigator feedback.</td>
<td>No change to overall meaning of the protocol.</td>
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<tr>
<td>5</td>
<td>Section 3.4.4 Baseline</td>
<td>Documentation of all adverse events, technical observations, and deaths, including all unanticipated adverse device effects (UADE), reinterventions or repeat admission to the catheterization suite.</td>
<td>Documentation of all adverse events/serious adverse events from enrollment to discharge including all unanticipated adverse device effects (UADE), technical observations, reinterventions or repeat admission to the catheterization suite and deaths.</td>
<td>Clarifications based on investigator feedback.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>6</td>
<td>Section 3.4.5 Set the back up pacing rate at a minimum of 30 bpm</td>
<td></td>
<td>Program the backup pacing rate to minimize ventricular pacing (e.g. 30-40 bpm).</td>
<td>Updated for consistency and clarity.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>7</td>
<td>Section 3.4.5.1 Vascular Access</td>
<td>Added</td>
<td>• The primary access artery will be used to introduce the CoreValve device and the balloon catheter; the secondary access artery will be used to introduce the reference pigtail. • Insert a 6-Fr introducer sheath into the secondary access artery.</td>
<td>Update to reflect specific to addition of non-ilio-femoral subjects.</td>
<td>Updated to reflect updated IFU in response to November 30, 2010 teleconference with FDA regarding inclusion of non-ilio-femoral subjects.</td>
</tr>
<tr>
<td>8</td>
<td>Section 3.4.5.1 Vascular Access</td>
<td>• Exchange the J-tip guidewire for a 0.035-in (0.889-mm) straight-tip guidewire. Advance the straight-tip guidewire across the aortic valve into the left ventricle.</td>
<td>• Exchange the J-tip guidewire for a 0.035-in (0.889-mm) straight-tip guidewire. Advance the straight-tip guidewire across the native aortic valve into the left ventricle.</td>
<td>Clarifications based on investigator feedback.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>9</td>
<td>Section 3.4.5.1 Vascular Access</td>
<td>• Perform full balloon expansion (high pressure)</td>
<td>• Perform full balloon expansion</td>
<td>Clarifications based on investigator feedback.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>10</td>
<td>Section 3.4.5.1 Vascular Access</td>
<td>• Insert 18 Fr Sheath using hospital protocol (either percutaneously or surgical cut down)</td>
<td>• Insert 18 Fr introducer sheath into the primary access artery using hospital protocol (either percutaneously or surgical cut down)</td>
<td>Updated for consistency and clarity.</td>
<td>Updated to reflect updated IFU in response to November 12 and 30, 2010 teleconferences with FDA regarding inclusion of non-ilio-femoral subjects.</td>
</tr>
<tr>
<td>11</td>
<td>Section 3.4.5.1 Rapid Pacing and Predilatation of the Implant site</td>
<td>• Perform a rapid pacing test. A successful test is defined as 1-to-1 pacing capture with an immediate drop in pressure and reduction of the systolic-diastolic waveform and reduction of peak systolic pressures &lt; 60 mmHg, usually 180-200 bpm.</td>
<td>• Perform a rapid pacing test. A successful test is defined as 1-to-1 pacing capture with an immediate drop in pressure and elimination of the systolic-diastolic waveform.</td>
<td>Updated for consistency and clarity.</td>
<td>Updated to reflect updated IFU in response to November 12 and 30, 2010 teleconferences with FDA regarding inclusion of non-ilio-femoral subjects.</td>
</tr>
<tr>
<td>12</td>
<td>Section 3.4.5.1 Medtronic CoreValve® Implantation</td>
<td>• Insert the device over the 0.035-in (0.889-mm) guidewire and advance it to the descending aorta, while maintaining strict fluoroscopic surveillance of the guidewire in the LV.</td>
<td>• Insert the device over the 0.035-in (0.889-mm) guidewire and advance it, while maintaining strict fluoroscopic surveillance of the guidewire in the LV.</td>
<td>Updated for consistency and clarity.</td>
<td>Updated to reflect updated IFU in response to November 12 and 30, 2010 teleconferences with FDA regarding inclusion of non-ilio-femoral subjects.</td>
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<tr>
<td>13</td>
<td>Section 3.4.5.1</td>
<td>Medtronic CoreValve® Implantation</td>
<td>• Advance the device through the native valve. Perform an angiogram to confirm</td>
<td>• Advance the device through the native valve. Perform an angiogram to confirm the</td>
<td>Updated to reflect updated IFU in response to November 12 and 30, 2010 teleconferences with FDA regarding inclusion of non-iliofemoral subjects.</td>
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<td></td>
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<td></td>
<td>that the <strong>graduated</strong> pigtail catheter is in position within the noncoronary</td>
<td><strong>graduated</strong> pigtail catheter is in position within the noncoronary cusp of the</td>
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<td></td>
<td>cusp of the aortic root, preferably in the shallow LAO projection</td>
<td>aortic root, preferably in the shallow LAO projection</td>
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<tr>
<td></td>
<td>Section 3.4.5.1</td>
<td>Medtronic CoreValve® Implantation</td>
<td>• Place the bioprosthesis within the aortic annulus (<strong>less that</strong> 6 mm below</td>
<td>• Place the bioprosthesis within the aortic annulus (4 mm - 6 mm below the annulus).</td>
<td>Updated for consistency and clarity.</td>
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<td></td>
<td></td>
<td></td>
<td>the annulus). The annulus is defined as the angiographic floor of the <strong>cusp</strong>.</td>
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<td></td>
</tr>
<tr>
<td>14</td>
<td>Section 3.4.5.1</td>
<td>Medtronic CoreValve® Implantation</td>
<td>• Perform an angiogram to assess the location of the bioprosthesis. Optimal</td>
<td>• Perform an angiogram to assess the location of the bioprosthesis. Optimal</td>
<td>Updated to reflect updated IFU in response to November 12 and 30, 2010 teleconferences with FDA regarding inclusion of non-iliofemoral subjects.</td>
</tr>
<tr>
<td></td>
<td>Post Deployment</td>
<td></td>
<td>placement of the bioprosthesis is within the aortic annulus (<strong>approximately</strong> 6 mm below the annulus).</td>
<td>placement of the bioprosthesis is within the aortic annulus (4 mm - 6 mm below the annulus).</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Section 3.4.5.1</td>
<td>Medtronic CoreValve® Implantation</td>
<td>• Withdraw the DCS carefully into the <strong>ascending</strong> aorta avoiding contact with</td>
<td>• Withdraw the DCS carefully <strong>to</strong> the aorta avoiding contact with the inflow portion of the frame</td>
<td>Updated to reflect updated IFU in response to November 12 and 30, 2010 teleconferences with FDA regarding inclusion of non-iliofemoral subjects.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>the inflow portion of the frame</td>
<td>• Withdraw the DCS <strong>to</strong> the aorta, while maintaining guidewire position.</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Section 3.4.5.1</td>
<td>Medtronic CoreValve® Implantation</td>
<td>• Perform contrast angiography of the primary iliac and femoral vessels to verify</td>
<td>• Perform contrast angiography of the primary vessels to verify the absence of any</td>
<td>Updated to reflect updated IFU in response to November 12 and 30, 2010 teleconferences with FDA regarding inclusion of non-iliofemoral subjects.</td>
</tr>
<tr>
<td></td>
<td>Post Deployment</td>
<td></td>
<td>the absence of any vascular complications with the <strong>5-Fr</strong> reference pigtail.</td>
<td>vascular complications with the reference pigtail</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Section 3.4.5.1</td>
<td>Post Deployment</td>
<td><strong>Deleted</strong></td>
<td></td>
<td>Updated for consistency and clarity.</td>
</tr>
<tr>
<td>18</td>
<td>Section 3.4.5.1</td>
<td>Post Deployment</td>
<td>Perform contrast angiography of the primary iliac and femoral vessels to verify</td>
<td>Perform contrast angiography of the primary vessels to verify the absence of any</td>
<td>Updated to reflect updated IFU in response to November 12 and 30, 2010 teleconferences with FDA regarding inclusion of non-iliofemoral subjects.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>the absence of any vascular complications with the <strong>5-Fr</strong> reference pigtail.</td>
<td>vascular complications with the reference pigtail</td>
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## Comprehensive Protocol Table of Changes (High Risk Study)

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<tr>
<td>19</td>
<td>Section 3.4.5.1 Post Deployment</td>
<td>• Perform postimplant aortogram with the 5-Fr reference pigtail to assure coronary patency and assess aortic regurgitations.</td>
<td>• Perform postimplant aortogram with the reference pigtail to assure coronary patency and assess aortic regurgitations.</td>
<td>Updated for consistency and clarity.</td>
<td>Updated to reflect updated IFU in response to November 12 and 30, 2010 teleconferences with FDA regarding inclusion of non-iliofemoral subjects.</td>
</tr>
<tr>
<td>20</td>
<td>Section 3.4.5.1 Post Deployment</td>
<td>• Remove the 18-Fr introducer sheath and complete the access site closure per hospital protocol.</td>
<td>• Remove the 18-Fr introducer sheath and complete the puncture site closure per hospital protocol.</td>
<td>Updated for consistency and clarity.</td>
<td>Updated to reflect updated IFU in response to November 12 and 30, 2010 teleconferences with FDA regarding inclusion of non-iliofemoral subjects.</td>
</tr>
<tr>
<td>21</td>
<td>Section 3.4.5.1 Post Deployment</td>
<td>• Remove the 5-Fr reference pigtail catheter over a standard guidewire.</td>
<td>• Remove the reference pigtail catheter over a standard guidewire.</td>
<td>Updated for consistency and clarity.</td>
<td>Updated to reflect updated IFU in response to November 12 and 30, 2010 teleconferences with FDA regarding inclusion of non-iliofemoral subjects.</td>
</tr>
<tr>
<td>22</td>
<td>Section 3.4.5.1 Immediate Post-Procedure Cardiac Enzymes (CK and CK-MB) Note: CK within 8-12 hours post procedure and at any time when a clinical ischemic event is suspected. CK-MB is required if CK is elevated ≥2X the laboratory upper limit of normal. If a clinical event is confirmed, a total of 3 sets of cardiac enzymes within the first 24 hours (drawn every 8 hours) following the clinical event should be obtained.</td>
<td>• Cardiac Enzymes: CK within 8-12 hours post procedure and at any time when a clinical ischemic event is suspected. CK-MB is required if CK is elevated ≥2X the laboratory upper limit of normal. If a clinical event is confirmed, a total of 3 draws of cardiac enzymes within the first 24 hours (drawn every 8 hours) following the clinical event should be obtained.</td>
<td></td>
<td>Updated for consistency and clarity.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>23</td>
<td>Section 3.4.5.1 Immediate Post-Procedure Assessments done at discharge</td>
<td>• Documentation of all adverse events/serious adverse events from enrollment to discharge including all unanticipated adverse device effects (UADE), reinterventions or repeat admissions to the catheterization suite.</td>
<td>• Documentation of all adverse events/serious adverse events from enrollment to discharge including all unanticipated adverse device effects (UADE), technical observations, reinterventions or repeat admissions to the catheterization suite and deaths. • Any patient with evidence of a neurological event should have a neurology consult and subsequently an imaging study if deemed necessary by the neurologist.</td>
<td>Updated for consistency and clarity.</td>
<td>Clarifications based on investigator feedback.</td>
</tr>
<tr>
<td>24</td>
<td>Section 3.4.5.1 Post-Procedure Pacing guidelines</td>
<td>• Prior to the permanent pacemaker implantation, a 12-lead ECG documenting the reason for the placement of the permanent pacemaker is recommended.</td>
<td>• Prior to the permanent pacemaker implantation, document the reason for the placement of the permanent pacemaker via a 12-lead ECG.</td>
<td>Updated for consistency and clarity.</td>
<td>Updated to reflect updated IFU in response to November 12 and 30, 2010 teleconferences with FDA regarding inclusion of non-iliofemoral subjects.</td>
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</tr>
<tr>
<td>25</td>
<td>Section 3.4.5.1. Post-Procedure Pacing guidelines</td>
<td>• If a permanent pacemaker is implanted, perform a device interrogation and an assessment of AV conduction post insertion and prior to hospital discharge as well as at every follow-up visit to evaluate device utilization.</td>
<td>• If a permanent pacemaker is implanted, perform a device interrogation and an assessment of AV conduction post insertion and prior to hospital discharge as well as at every follow-up visit to evaluate device utilization (Refer to the Pacing Guidelines in Appendix 17.14).</td>
<td>Clarifications based on investigator feedback.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>26</td>
<td>Section 3.4.5.1 Assessments done at discharge Section 3.4.5.2 Assessments done at discharge</td>
<td>• Perform a full interrogation and an assessment of AV conduction. Save the data on a diskette and retain the diskette in the subject's file for source verification.</td>
<td>• Perform a full interrogation and an assessment of AV conduction (Refer to the Pacing Guidelines in Appendix 17.14). Print a copy of the interrogation and save the data on a diskette. Retain the printed copy of the interrogation and the diskette in the subject's file for source verification.</td>
<td>Clarifications based on investigator feedback.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>27</td>
<td>Section 3.4.8 Follow-up Evaluations</td>
<td>All trial subjects will undergo follow-up evaluations at the following time points post implant (MCS TAVI or SAVR): 30 days (± 7 days), 6 months (180 ± 14 days), 12 months (360 ± 45 days), and annually at 2 years (720 days ± 60 days), 3 years (1080 ± 60 days), 4 years (1440 days ± 60 days) and 5 years (1800 ± 60 days). All of these visits will require the subject to return to the clinic.</td>
<td>All trial subjects will undergo follow-up evaluations at the following time points post implant (MCS TAVI or SAVR): 30 days (± 7 days), 6 months (180 ± 14 days), 12 months (365 to 410 days), and annually at 2 years (720 days ± 60 days), 3 years (1080 ± 60 days), 4 years (1440 days ± 60 days) and 5 years (1800 ± 60 days). All of these visits will require the subject to return to the clinic.</td>
<td>Updated visit window. To ensure subjects are followed at least 365 days for primary analysis.</td>
<td>No change to overall protocol meaning.</td>
</tr>
<tr>
<td>28</td>
<td>Section 3.4.8 Follow-up Evaluations</td>
<td>• Documentation of all adverse events, technical observations and deaths, including all unanticipated adverse device effects (UADE), reinterventions or repeat admission to the catheterization suite.</td>
<td>• Documentation of all adverse events/serious adverse events including all unanticipated adverse device effects (UADE), technical observations, reinterventions or repeat admissions to the catheterization suite and deaths.</td>
<td>Clarifications based on investigator feedback.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>29</td>
<td>Section 3.4.8 Follow-up Evaluations</td>
<td>• For patients with permanent pacemakers or defibrillators only (existing or new): Perform a full interrogation and an assessment of AV conduction at the beginning of each follow-up visit. Save the data on a diskette and retain the diskette in the subject's file for source verification.</td>
<td>• For patients with permanent pacemakers or defibrillators only (existing or new): Perform a full interrogation and an assessment of AV conduction (Refer to the Pacing Guidelines, Appendix 17.14). Print a copy of the interrogation and save the data on a diskette. Retain the printed copy of the interrogation and the diskette in the subject's file for source.</td>
<td>Clarifications based on investigator feedback.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>30</td>
<td>Table 2. Schedule of Assessments</td>
<td>Month 12 (368 days) (± 45 Days)</td>
<td>Month 12 (365 to 410 days)</td>
<td>Updated visit window. To ensure subjects are followed at least 365 days for primary analysis.</td>
<td>No change to overall protocol meaning.</td>
</tr>
<tr>
<td>31</td>
<td>Table 2. Schedule of Assessments</td>
<td>Grip Strength Test, 15-foot “up and go” (TUG) Test, and Mini Mental Exam</td>
<td>Grip Strength Test, Gait Test, and Mini Mental Exam</td>
<td>Consistency with wording in protocol.</td>
<td>No change to overall meaning of the protocol.</td>
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<tr>
<td>32</td>
<td>Table 2. Schedule of Assessments</td>
<td>B-type Natriuretic Peptide, Plasma Free Hemoglobin</td>
<td>B-type Natriuretic Peptide, Hemoglobin, Plasma Free Hemoglobin</td>
<td>Inadvertent omission. Consistency with wording in protocol.</td>
<td>No change to overall protocol meaning.</td>
</tr>
<tr>
<td>33</td>
<td>Table 2. Schedule of Assessments</td>
<td>In the row, Pacemaker/defibrillator interrogation and an assessment of AV conduction ¹</td>
<td>Removed the “X” from Screening column</td>
<td>Inadvertent omission. Consistency with wording in protocol.</td>
<td>No change to overall protocol meaning.</td>
</tr>
<tr>
<td>34</td>
<td>Table 2. Schedule of Assessments</td>
<td>• ¹Laboratory test results must be performed pre-procedure for subjects randomized to the MCS TAVI or SAVR. ²CK to be obtained within 48 hours of procedure. ³CK 8-12 hours post procedure and at any time when a clinical ischemic event is suspected. CK-MB is required if CK is elevated (≥ 2X the laboratory upper limit of normal). If a clinical event is confirmed, a total of 3 sets of cardiac enzymes within the first 24 hours.</td>
<td>• ²Laboratory test results must be performed pre-procedure for subjects randomized to the MCS TAVI or SAVR. CK to be obtained within 48 hours of procedure. ³CK 8-12 hours post procedure and at any time when a clinical ischemic event is suspected. CK-MB is required if CK is elevated (≥ 2X the laboratory upper limit of normal). If a clinical event is confirmed, a total of 3 draws of cardiac enzymes within the first 24 hours.</td>
<td>Clarifications based on investigator feedback.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>35</td>
<td>Table 2. Schedule of Assessments</td>
<td>¹³ SAE, MAE, device-related events, including device-related technical observations, UADEs, all strokes (CVAs) and death reports.</td>
<td>¹³ SAE, MAE, cardiovascular events, device-related events, including device-related technical observations, UADEs, all strokes (CVAs) and death reports.</td>
<td>Updated for consistency and clarity.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>36</td>
<td>Table 2. Schedule of Assessments</td>
<td>Rotational X-ray to be performed annually after 1 year for MCS TAVI subjects only</td>
<td>Deleted, Footnotes adjusted throughout per deleted footnote</td>
<td>Deleted as this footnote was redundant.</td>
<td>This footnote is same the (X) MCS TAVI subjects only (SAVR subjects will not have these assessments) which is included as a note below the table.</td>
</tr>
<tr>
<td>37</td>
<td>Table 2. Schedule of Assessments</td>
<td>⁷All subjects should have screening thoracic and abdominal CT angiograms with complete visualization of both iliacs, femorals and aorta up to and including the aortic annulus. (MRI may be used as an alternative in situations where subjects have compromised renal function).</td>
<td>⁸All subjects should have screening thoracic and abdominal CT angiograms with complete visualization of both iliacs, femorals and aorta (and subclavian/axillaries as applicable), up to and including the aortic annulus. (MRI may be used as an alternative in situations where subjects have compromised renal function).</td>
<td>Updated for consistency and clarity.</td>
<td>Updated per November 12 and 30, 2010 teleconferences with FDA regarding inclusion of non-ilio-femoral subjects enrolled in trial.</td>
</tr>
<tr>
<td>38</td>
<td>Section 3.5.1.1 Adverse Event</td>
<td>Added Table Title</td>
<td>Table 3. Unavoidable AEs</td>
<td>Administrative change.</td>
<td>No change to overall protocol meaning.</td>
</tr>
<tr>
<td>39</td>
<td>Section 3.5.1.3 Major Adverse Cardiovascular and Cerebrovascular Events</td>
<td>Major stroke</td>
<td>All stroke</td>
<td>Clarification</td>
<td>Updated in response to conditions of approval from FDA.</td>
</tr>
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</table>
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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>40</td>
<td>Section 3.5.1.4</td>
<td>Major Adverse Event</td>
<td>Added</td>
<td>Device migration</td>
<td>Clarification</td>
</tr>
<tr>
<td>41</td>
<td>Section 3.5.1.7</td>
<td>Technical Observation</td>
<td>Technical observations may or may not be related to an adverse event in a subject. Technical observations (whether or not associated with any untoward medical occurrence in a subject) will be reported on the Adverse Event (AE) eCRF.</td>
<td>Each technical observation (whether or not associated with any untoward medical occurrence in a subject) will be reported on the Adverse Event (AE) eCRF and tabulated as an AE.</td>
<td>Clarification</td>
</tr>
<tr>
<td>42</td>
<td>Section 3.5.2</td>
<td>Reporting</td>
<td>Investigators are required to keep records on &quot;all relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated)&quot; [21 CFR 812.140]. All new or worsening (from baseline) adverse events and technical observations will be captured on the AE eCRF. It is the responsibility of the Investigator to assess the subject for adverse events and capture the required adverse event information on the AE eCRF. Once a subject has completed their 12-month scheduled follow-up visit, serious adverse events, major adverse events, cardiovascular events, device-related adverse events, including device-related technical observations, unanticipated adverse device effects (UADE), all strokes (CVAs) and deaths will be required to be reported.</td>
<td>Investigators are required to keep records on &quot;all relevant observations, including records concerning adverse device effects (whether anticipated or unanticipated)&quot; [21 CFR 812.140]. Adverse event collection will occur from the point of study enrollment to study closure. All new or worsening (from baseline) adverse events and technical observations will be captured on the AE eCRF through the 12-month follow-up visit. Once a subject has completed their 12-month scheduled follow-up visit, serious adverse events, major adverse events, cardiovascular events, device-related adverse events, including device-related technical observations, unanticipated adverse device effects (UADE), all strokes (CVAs) and deaths will be required to be reported. It is the responsibility of the Investigator to assess the subject for adverse events and capture the required adverse event information on the AE eCRF.</td>
<td>Clarifications based on investigator feedback.</td>
</tr>
<tr>
<td>43</td>
<td>Section 3.5.2.3</td>
<td>All Other Adverse Events</td>
<td>Added</td>
<td>Medtronic requests that the Investigator notify the sponsor within 10 working days of first learning of any other AE using the electronic data capture (eCRF) system. If necessary, the Investigator may be requested to provide copies of source documentation regarding the event (e.g., physician/nurse notes or summaries).</td>
<td>Clarifications based on investigator feedback.</td>
</tr>
<tr>
<td>44</td>
<td>Section 3.6</td>
<td>Statistical Methods and Analysis</td>
<td>The statistical analyses will be performed by Medtronic employed statisticians and independently verified by the staff of the Biostatistics Department at the Harvard Clinical Research Institute.</td>
<td>The statistical analyses will be performed by Medtronic employed statisticians and independently verified by the staff of the Biostatistics Department at the Harvard Clinical Research Institute and/or Saint Luke's Mid America Heart Institute.</td>
<td>Inadvertent omission.</td>
</tr>
<tr>
<td>45</td>
<td>Section 3.6.7</td>
<td>Relevant Statistical Analysis Considerations</td>
<td>Corrected 0.0001, see bolded text</td>
<td>All statistical tests and/or confidence intervals, as appropriate, will be performed at α=0.05 (2-sided), except when specified otherwise. All reported p-values greater than or equal to 0.001 will be rounded to three decimal places. P-values less than 0.001 will be displayed as “&lt;0.001.”</td>
<td>Typographical error</td>
</tr>
</tbody>
</table>
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<tr>
<td>46</td>
<td>Section 3.8.2 Table 5</td>
<td>UADEs should be reported immediately via telephone as well as on an eCRF and meet the following: the Investigator’s report on any unanticipated adverse effect must be submitted as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect.</td>
<td>UADEs should be reported immediately via telephone as well as on an eCRF. UADEs must be submitted as soon as possible, but in no event later than 10 working days after the Investigator first learns of the effect. (21 CFR 812.150)</td>
<td>Updated for consistency and clarity; add reference to CRF</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>47</td>
<td>Section 5.1 Investigational Product Description</td>
<td>Figure 4 &amp; 5, Table 6 Deleted</td>
<td>Updated for consistency in IFU</td>
<td>No change to overall meaning of the protocol.</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>Section 15.2 Definition of Terms</td>
<td>DEATH A serious adverse event that is classified by the following: All-cause death: All deaths from any cause after a valve intervention or randomization to optimal medical management. This includes all cardiovascular and non-cardiovascular deaths.</td>
<td>DEATH A serious adverse event that is classified by the following: All-cause death: All deaths from any cause after a valve intervention. This includes all cardiovascular and non-cardiovascular deaths.</td>
<td>Definition updated to be consistent with the updated Extreme Risk Protocol</td>
<td>Updated per November 12 and 30, 2010 teleconferences with FDA regarding removal of OMM arm.</td>
</tr>
<tr>
<td>49</td>
<td>Section 15.2 Definition of Terms</td>
<td>DEVICE FAILURE • Inability to successfully deliver and place the device in stable position • Failure to retrieve the delivery catheter • More than one Medtronic CoreValve® PAV is implanted • Unsuccessful device function as assessed acutely (within 24-48 hours post-implantation or prior to hospital discharge), where unsuccessful device function is defined as follows: o Device migration assessed qualitatively by echocardiography o Moderate or severe prosthetic valve AR o Effective orifice area ≤ 1.2 cm² by echocardiography using the continuity equation</td>
<td>Deleted</td>
<td>This definition was removed to avoid confusion. Device Success is defined and if the event does not meet this criterion, it is defaulted to device failure.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>50</td>
<td>Section 15.2 Definition of Terms</td>
<td>HEMOLYSIS Two plasma free hemoglobin values &gt; 40 mg/dL with the two readings taken within a single forty-eight (48) hour period. If the second plasma free hemoglobin assessment is not performed within 48 hours following an initial determination of &gt; 40 mg/dL, this would qualify as an adverse event. • Major hemolysis: Red cell destruction as evidenced by a positive finding of unrobilinogen in the urine that requires intervention (e.g. iron supplements, transfusion, invasive intervention). Major hemolysis events will be considered to be serious adverse events. • Minor hemolysis: Red cell destruction as evidenced by a positive finding of unrobilinogen in the urine that does not require intervention.</td>
<td>HEMOLYSIS A plasma free hemoglobin value &gt; 40 mg/dL is considered to be hemolysis and a reportable adverse event. • Major hemolysis: A plasma free hemoglobin value &gt; 40 mg/dL that requires intervention (i.e. iron replacement, blood transfusion, folic acid administration, corticosteroids, Intravenous immunoglobulin G (IVIG) and/or surgery). Major hemolysis events will be considered to be serious adverse events. • Minor hemolysis: A plasma free hemoglobin value &gt; 40 mg/dL that does not require intervention.</td>
<td>Updated definition to remove unrobilinogen as not applicable to this patient population.</td>
<td>Physician feedback and noted that definition should not require unrobilinogen.</td>
</tr>
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<tr>
<td>51</td>
<td>Section 15.2 Definition of Terms</td>
<td>MAJOR ADVERSE CARDIOVASCULAR AND CEREBROVASCULAR EVENTS (MACCE) Major stroke</td>
<td>MAJOR ADVERSE CARDIOVASCULAR AND CEREBROVASCULAR EVENTS (MACCE) All stroke</td>
<td>Clarification</td>
<td>Updated in response to conditions of approval from FDA.</td>
</tr>
<tr>
<td>52</td>
<td>Section 15.2 Definition of Terms</td>
<td>Added</td>
<td>MAJOR ADVERSE EVENT (MAE) Device Migration</td>
<td>Clarification</td>
<td>Updated in response to conditions of approval from FDA.</td>
</tr>
<tr>
<td>53</td>
<td>Section 15.2 Definition of Terms</td>
<td>PARAVALVULAR LEAK (as measured by echocardiogram) Leakage due to a separation of the prosthetic valve from the annulus. Any evidence of leakage of blood around the device. Diagnosis of paravalvular leak may be obtained from echocardiogram; however definitive diagnosis is obtained at reoperation, explant, or autopsy. Primary paravalvular leak Defined as any evidence of leakage of blood around the prosthesis between the device and the native annulus. Primary paravalvular leaks will be stratified by the following: • All leaks: evidence of moderate to severe paravalvular regurgitation by echocardiography • Minor leaks: A paravalvular leak with moderate to severe aortic regurgitation and does not require surgical intervention • Major leaks: A paravalvular leak with moderate to severe aortic regurgitation or requires surgical intervention All moderate or severe paravalvular leaks will be classified as Serious Adverse Events. (Refer to the definition of Aortic Regurgitation for additional paravalvular leak severity criteria)</td>
<td>PARAVALVULAR AORTIC REGURGITATION Leakage due to a separation of the prosthetic valve from the annulus. Diagnosis of paravalvular leak may be obtained from echocardiogram; however definitive diagnosis is obtained at reoperation, explant, or autopsy. All moderate or severe paravalvular leaks will be classified as Serious Adverse Events. (Refer to the definition of Aortic Regurgitation for additional paravalvular leak severity criteria)</td>
<td>Clarification</td>
<td>Updated in response to conditions of approval from FDA.</td>
</tr>
<tr>
<td>54</td>
<td>Section 15.2 Definition of Terms</td>
<td>PROSTHETIC VALVE DYSFUNCTION o Mal-position (too high, too low)</td>
<td>PROSTHETIC VALVE DYSFUNCTION o Mal-position (too high, too low)/malplacement</td>
<td>Clarification</td>
<td>Updated in response to conditions of approval from FDA.</td>
</tr>
<tr>
<td>55</td>
<td>Section 15.2 Definition of Terms</td>
<td>TECHNICAL OBSERVATION A defect, malfunction, or failure of any part of the Medtronic CoreValve® System. This may pertain to the device or system not functioning according to its design intent. Technical observations may or may not be related to an adverse event in a subject.</td>
<td>TECHNICAL OBSERVATION A defect, malfunction, or failure of any part of the Medtronic CoreValve® System. This may pertain to the device or system not functioning according to its design intent.</td>
<td>Clarification</td>
<td>Updated in response to conditions of approval from FDA.</td>
</tr>
<tr>
<td>56</td>
<td>ALL</td>
<td>N/A</td>
<td>Formatting and typographical updates throughout the protocols to reflect re-numbering of sections, footnotes, endnotes etc., or minor typographical errors where appropriate</td>
<td>Formatting changes only</td>
<td>No change to overall content of the protocol.</td>
</tr>
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</table>
| 57 | 2.1 Background | Aortic valve disease hospitalizations are defined as a non-elective hospital admission for signs and symptoms related to aortic valve disease (as described below) that results in at least a two-night stay (i.e., where the admission date and the discharge date differ by at least two calendar days). For the purpose of the protocol, overnight stays at nursing home facilities or extended care facilities do not meet the protocol definition of hospitalization. This does include the administration or augmentation of intravenous heart failure therapy (e.g., inotropes, diuretics, and/or vasodilators). Patients with signs and symptoms related to aortic valve disease who are hospitalized for less than two days or who are treated and released from the emergency department or an outpatient clinic (including treatment for intravenous heart failure therapy (e.g., inotropes, diuretics, and/or vasodilators)), will not be counted as aortic valve disease hospitalizations. Aortic valve disease will be evaluated using documented evidence of the following signs and symptoms. An independent Clinical Events Committee (CEC) will review all available source documentation for all hospitalizations to determine if they are aortic valve disease hospitalizations. The CEC adjudication will be used for final analysis. Signs and symptoms of aortic valve disease include, but are not limited to, the following: **Signs and Symptoms of Aortic Valve Disease Table**  

<p>|    |                |                | Deleted          | The endpoint was updated based on the performance goal. Therefore, aortic valve disease and previous background is no applicable to background/co-primary endpoint justification. | Updated per November 23, 2010 Briefing document and November 12 and 30, 2010 teleconferences with FDA regarding removal of OMM arm. Protocol no longer has co-primary endpoints but rather one primary endpoint as described. |</p>
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<td>58</td>
<td>Title Page Footer</td>
<td>Version 2.0</td>
<td>Version 4.0</td>
<td>Reflect Protocol Version</td>
<td>Revision Control</td>
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<tr>
<td>59</td>
<td>Synopsis: Secondary Endpoints</td>
<td>10. Aortic valve disease hospitalization</td>
<td>10. Aortic valve disease hospitalization at 30 days, 6 months, 12 months and annually thereafter up to 5 years.</td>
<td>Inadvertent omission. Clarification of timepoints at which hospitalization (secondary endpoint) will be analyzed.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>60</td>
<td>Synopsis: Secondary Endpoints</td>
<td>11. Cardiovascular deaths and valve-related deaths</td>
<td>11. Cardiovascular deaths and valve-related deaths at 30 days, 6 months, 12 months and annually thereafter up to 5 years.</td>
<td>Inadvertent omission. Clarification of timepoints secondary endpoint will be analyzed.</td>
<td>No change to overall meaning of the protocol.</td>
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<tr>
<td>61</td>
<td>Synopsis: Exclusion Criteria</td>
<td>28. Aortic root angulation &gt; 7°.</td>
<td>28. Aortic root angulation (angle between plane of aortic valve annulus and horizontal plane/vertebrae) &gt; 7° (for femoral and left subclavian/axillary access) and &gt; 30° (for right subclavian/axillary access).</td>
<td>Additional exclusion specific to subclavian subjects.</td>
<td>Updated per November 30, 2010 teleconference with FDA regarding inclusion of non-ilio-femoral subjects enrolled in trial.</td>
</tr>
<tr>
<td>62</td>
<td>Section 2.1 Page 14/15</td>
<td>Added</td>
<td>The primary access site for the Medtronic CoreValve system is the transfemoral artery. The transfemoral approach has been reported in more than 15 published outcomes articles as of September 2010 representing more than 2500 procedures. In addition, the subclavian/axillary or direct aortic approaches have also been used as alternative access sites. The subclavian/axillary approach has been reported in nine published outcomes articles as of September 2010 representing more than 100 procedures, and may represent up to 10% of implants at some implanting centers. xix</td>
<td>Additional information specific to addition of non-ilio-femoral subjects.</td>
<td>Updated per November 30, 2010 teleconference with FDA regarding inclusion of non-ilio-femoral subjects enrolled in trial.</td>
</tr>
<tr>
<td>63</td>
<td>Section 2.1 Table 1</td>
<td>Title changed: Table 1. Mortality rates of high risk population from published data.</td>
<td>Table 1. All-cause mortality rates of high risk population from published data.</td>
<td>Inadvertent omission. Clarification that endpoint is all-cause mortality.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>64</td>
<td>Section 2.1 Page 15</td>
<td>Given that the expected High Risk Surgical population will be older and at higher risk for surgery, it is estimated that the 12-month mortality rate among high risk SAVR subjects in the current study will be 20%.</td>
<td>Given that the expected High Risk Surgical population will be older and at higher risk for surgery, it is estimated that the 12-month all-cause mortality rate among high risk SAVR subjects in the current study will be 20%.</td>
<td>Inadvertent omission. Clarification that endpoint is all-cause mortality.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>65</td>
<td>Section 3 Section 3.6 Exclusion Criteria</td>
<td>28. Aortic root angulation &gt; 7°.</td>
<td>28. Aortic root angulation (angle between plane of aortic valve annulus and horizontal plane/vertebrae) &gt; 7° (for femoral and left subclavian/axillary access) and &gt; 30° (for right subclavian/axillary access).</td>
<td>Additional exclusion specific to subclavian subjects.</td>
<td>Updated per November 30, 2010 teleconference with FDA regarding inclusion of non-ilio-femoral subjects enrolled in trial.</td>
</tr>
<tr>
<td>66</td>
<td>Section 3.3.8 Enrollment Flowchart</td>
<td>Updated</td>
<td>See Page 23 of protocol. Added Questions on access and the enrollment into MCS TAVI ilio-femoral and non-ilio-femoral access groups.</td>
<td>Additional information specific to addition of non-ilio-femoral subjects.</td>
<td>Updated per November 30, 2010 teleconference with FDA regarding inclusion of non-ilio-femoral subjects enrolled in trial.</td>
</tr>
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<td>Reason for the change</td>
<td>Justification</td>
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<tr>
<td>67</td>
<td>Section 3.4.4</td>
<td>Randomization with an assignment to the treatment arm or control arm (MCS TAVI or SAVR) will be executed in a 1:1 ratio. Stratified randomization by implanting site will be used to ensure subjects at each site will be allocated to each comparison group proportionately.</td>
<td>Randomization with an assignment to the treatment arm or control arm (MCS TAVI or SAVR) will be executed in a 1:1 ratio. Stratified randomization by investigational site and by intended access site (ilio-femoral or non-ilio-femoral) will be used to ensure subjects will be allocated to each comparison group proportionately.</td>
<td>Additional information specific to addition of non-ilio-femoral subjects.</td>
<td>Updated per November 30, 2010 teleconference with FDA regarding inclusion of non-ilio-femoral subjects enrolled in trial.</td>
</tr>
<tr>
<td>68</td>
<td>Section 3.4.4</td>
<td>Subjects will be considered enrolled into the trial at the time of randomization. Subjects must have their MCS TAVI or SAVR procedure no later than 30 days post-randomization.</td>
<td>Subjects will be considered enrolled into the trial at the time of randomization. Subjects must have their MCS TAVI or SAVR procedure no later than 30 days post-randomization. Any events or hospitalizations occurring prior to these index procedures will not be counted as part of the primary endpoint. If a subject remains hospitalized beyond 30 days after device placement, this counts as an aortic valve disease hospitalization secondary endpoint occurring on day 31.</td>
<td>Inadvertent omission. This language was previously included in Extreme Risk protocol but left out of the High Risk Protocol, updated for consistency.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>69</td>
<td>Section 3.4.4</td>
<td>Added</td>
<td>Enrollments shall not exceed 20% (158) of randomized subjects at any individual site. Non-ilio-femoral will be limited to no more than 20% (158) of the 790 randomized subjects.</td>
<td></td>
<td>Updated to ensure accurate statistical analysis without bias from any individual site with high enrollment. Updated per conditions of approval from FDA regarding inclusion of non-ilio-femoral subjects enrolled in trial.</td>
</tr>
<tr>
<td>70</td>
<td>Section 3.4.5.2</td>
<td>Surgical Aortic Valve Replacement</td>
<td>The procedure is considered complete at the time of skin closure.</td>
<td>Clarification</td>
<td>Updated in response to conditions of approval from FDA.</td>
</tr>
<tr>
<td>71</td>
<td>Section 3.6</td>
<td>Statistical Methods and Analysis</td>
<td>For the primary analysis, &quot;as treated&quot; will be defined in the following manner: the start of the procedure (the procedure has been attempted). Using this definition, study subjects will be analyzed according to their first attempted procedure (TAVI or SAVR).</td>
<td>Clarification of &quot;as treated&quot; definition</td>
<td>Updated in response to conditions of approval from FDA.</td>
</tr>
<tr>
<td>72</td>
<td>Section 3.6.1</td>
<td>Description of Baseline Variables</td>
<td>Baseline demographic and clinical variables will be summarized for all the intent-to-treat and per protocol populations.</td>
<td>Clarification</td>
<td>Updated in response to conditions of approval from FDA.</td>
</tr>
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<tbody>
<tr>
<td>73</td>
<td>Section 3.6.2 Missing Data</td>
<td>Every effort will be undertaken to minimize missing data. Since all-cause mortality is the primary endpoint for this trial, a minimal amount of missing data is anticipated. However, if outcome data are missing, only subjects whose status is known will be included in the binomial proportions in the calculation of the Farrington and Manning test statistic. To assess the potential impact of these missing data, a sensitivity analysis will be conducted which will include a best-case (assumed missing MCS TAVI subjects are alive and SAVR subjects have died) and a worst-case (assumed missing MCS TAVI subjects have died and SAVR subjects are alive) analysis.</td>
<td>Every effort will be undertaken to minimize missing data. Since all-cause mortality is the primary endpoint for this trial, a minimal amount of missing data is anticipated. However, if outcome data are missing, Kaplan-Meier rates at 12 months will replace the binomial proportions in the calculation of the Farrington and Manning test statistic. To assess the potential impact of these missing data, a sensitivity analysis will be conducted which will include a complete case, a best-case (assumed missing MCS TAVI subjects are alive and SAVR subjects have died), a worst-case (assumed missing MCS TAVI subjects have died and SAVR subjects are alive), and a tipping point analysis.</td>
<td>Clarification</td>
<td>Updated in response to conditions of approval from FDA.</td>
</tr>
<tr>
<td>74</td>
<td>Section 3.6.5.1 Primary Hypothesis</td>
<td>Primary Hypothesis: TAVI with the Medtronic CoreValve® System is non-inferior to surgical aortic valve replacement (SAVR) in 12 month mortality.</td>
<td>Primary Hypothesis: TAVI with the Medtronic CoreValve® System is non-inferior to surgical aortic valve replacement (SAVR) in 12 month mortality.</td>
<td>Clarified for consistency.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>75</td>
<td>Section 3.6.5.2 Sample Size Determination</td>
<td>Evaluable sample size: 710 (355 MCS TAVI : 355 SAVR)</td>
<td>Deleted</td>
<td>Verbiage deleted for clarity. Removed as the focus should be on the total sample size to be enrolled vs. evaluable subjects for the endpoints.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>76</td>
<td>Section 3.6.5.2 Sample Size Determination</td>
<td>Assuming 1:1 treatment allocation ratio between study device and surgical valve replacement and assuming the proportion of all-cause mortality at 12 months equal to 20% for both arms and a non-inferiority margin of 7.5%, a total of 355 subjects in each arm is required to attain 80% power in a test of non-inferiority of the study device at the 0.05 level of significance.</td>
<td>Assuming 1:1 treatment allocation ratio between study device and surgical valve replacement and assuming the proportion of all-cause mortality at 12 months equal to 20% for both arms and a non-inferiority margin of 7.5%, Power Analysis and Sample Size (PASS) software calculates that a total of 355 subjects in each arm is required to attain 80% power in a test of non-inferiority of the study device at the 0.05 level of significance.</td>
<td>Inadvertent omission. Clarification of software used to calculate sample size.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>77</td>
<td>Section 3.6.5.2 Sample Size Determination</td>
<td>For the secondary superiority hypothesis, assuming 1:1 treatment allocation ratio between study device and surgical valve replacement and assuming the proportion of MACCE at 30 days or hospital discharge, whichever is longer, equal to 20% in the surgical valve replacement arm and equal to 12.1% in the study device arm (39.5% relative treatment effect), 355 evaluable subjects per arm would yield 81.9% power for a one-sided test at the 0.025 level of significance.</td>
<td>For the secondary superiority hypothesis, assuming 1:1 treatment allocation ratio between study device and surgical valve replacement and assuming the proportion of MACCE at 30 days or hospital discharge, whichever is longer, equal to 20% in the surgical valve replacement arm and equal to 12.1% in the study device arm (39.5% relative treatment effect), PASS software calculates that 355 evaluable subjects per arm would yield 81.9% power for a one-sided test at the 0.025 level of significance.</td>
<td>Inadvertent omission. Clarification of software used to calculate sample size.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>78</td>
<td>Section 3.6.6 Secondary Endpoints</td>
<td>Under #1- The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.</td>
<td>The endpoint will be evaluated using Kaplan-Meier survival analysis and the log-rank test.</td>
<td>Typographical error</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>#</td>
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<tr>
<td>79</td>
<td>Section 3.6.7 Relevant Statistical Analysis Considerations</td>
<td>Provided the 12-month mortality primary objective and the 30-day (or hospital discharge, whichever is longer) MACCE powered secondary hypothesis are met with significant p-values, to keep the overall (familywise) Type I error rate at 0.05, a hierarchical test procedure will be applied to five of the secondary objective hypothesis tests.</td>
<td>Provided the 12-month mortality primary objective is met with a significant p-value, to keep the overall (familywise) Type I error rate at 0.05, a hierarchical test procedure will be applied to the 30-day (or hospital discharge, whichever is longer) MACCE powered secondary hypothesis and five of the secondary objective hypothesis tests.</td>
<td>Clarification</td>
<td>Updated in response to conditions of approval from FDA.</td>
</tr>
<tr>
<td>80</td>
<td>Section 3.6.7 Relevant Statistical Analysis Considerations</td>
<td>Added</td>
<td>5. Powered Secondary Hypothesis: TAVI with the Medtronic CoreValve® System is superior to SAVR in binary rate of MACCE at 30 days or hospital discharge, whichever is longer. This one-sided test will be carried out at the 0.025 level using the pooled z-test without correction for continuity to test the hypotheses: $H_0: &lt;MCS_{TAVI} = &lt;SAVR$ $H_1: &lt;MCS_{TAVI} &lt; &lt;SAVR$ In the above expression $&lt;MCS_{TAVI}$ and $&lt;SAVR$ denote the binary rate of MACCE at 30 days or hospital discharge.</td>
<td>Clarification</td>
<td>Updated in response to conditions of approval from FDA.</td>
</tr>
<tr>
<td>81</td>
<td>Section 3.6.7 Relevant Statistical Analysis Considerations</td>
<td>A poolability analysis between investigational centers and primary baseline demographics will be performed for the primary endpoint and will be described in the Statistical Analysis Plan.</td>
<td>A poolability analysis among investigational centers, access site (ilio-femoral or non-ilio-femoral), and primary baseline demographics will be performed for the primary endpoint and will be described in the Statistical Analysis Plan. In particular, the primary endpoint and key secondary endpoints such as MACCE- and MAE-free survival will be examined for differences in outcome between genders and between access sites. Additionally, tests for these outcomes will be performed to evaluate potential interactions between treatment and gender and between treatment and access site.</td>
<td>Updated for consistency and clarity.</td>
<td>Updated to reflect updated IFU in response to November 12 and 30, 2010 teleconferences with FDA regarding inclusion of non-ilio-femoral subjects.</td>
</tr>
<tr>
<td>82</td>
<td>Section 3.8.1 Table 4</td>
<td>Added</td>
<td>Medtronic will report on any confirmed unanticipated adverse device-effect evaluation within 10 working days after first receiving notice of the effect. (21 CFR 812.150)</td>
<td>Updated for consistency and clarity, added reference to CRF</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>83</td>
<td>Section 14 Amendments to the Clinical Investigational Plan</td>
<td>Added</td>
<td>• August 26, 2010 - Original Version submitted to FDA • November 2, 2010 - Address FDA conditions, administrative edits as required • 3.0 December 13, 2010 - Allow for non-ilio-femoral access, administrative edits as required (this version was not implemented or distributed to sites) • 4.0 February 1, 2011 - Address FDA feedback, administrative edits as required</td>
<td>Inadvertent omission. Documentation of versions and associated changes</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
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</tr>
<tr>
<td>1</td>
<td>Section 1 Synopsis: Trial Sites</td>
<td>The trial will be conducted at up to 40 sites in the United States.</td>
<td>The trial will be conducted at up to 45 sites in the United States.</td>
<td>Reflects Medtronic’s request for 5 additional sites</td>
<td>Refer to Section 5.0 of this submission.</td>
</tr>
<tr>
<td></td>
<td>Section 3.3.4 Investigational Sites</td>
<td></td>
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<tr>
<td>2</td>
<td>Section 1 Synopsis: Inclusion Criteria</td>
<td>2. Subject has senile degenerative aortic valve stenosis with mean gradient &gt; 40 mmHg or jet velocity greater than 4.0 m/s, or an initial aortic valve area of ≤ 0.8 cm² (or aortic valve area index ≤ 0.5 cm²/m²) by resting echocardiogram.</td>
<td>2. Subject has senile degenerative aortic valve stenosis with mean gradient &gt; 40 mmHg or jet velocity greater than 4.0 m/s, and an initial aortic valve area of ≤ 0.8 cm² (or aortic valve area index ≤ 0.5 cm²/m²) by echocardiogram or simultaneous pressure recordings at cardiac catheterization – at rest or with dobutamine stress echocardiogram.</td>
<td>Clarifications based on investigator and Steering Committee feedback.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td></td>
<td>Section 3.3.6 Inclusion/Exclusion Criteria</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Section 1 Synopsis: Exclusion Criteria</td>
<td>Added</td>
<td>30. For patients with native coronary artery dependent circulation:</td>
<td>Clarifications based on investigator and Steering Committee feedback. Reflects current practice of the Screening committee; Sinus of Valsalva dimensions (and potential coronary occlusion) are considered as part of patient screening.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td></td>
<td>Section 3.3.6 Inclusion/Exclusion Criteria</td>
<td></td>
<td>• Sinus of valsalva width &lt; 29 mm unless the aortic annulus is 20-23 mm, in which case the sinus of valsalva width &lt; 27 mm, OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Section 3.2 Trial Administration Operations Committee</td>
<td>Steering Committee</td>
<td>Clarified use of terms for consistency across documents</td>
<td>No change to overall meaning of the protocol.</td>
<td></td>
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<tr>
<td></td>
<td>Section 13 Publication Policy</td>
<td></td>
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</tbody>
</table>
| 5 | Section 3.2.1 Steering Committee | Non-Medtronic Membership:  
- National Principal Investigators (Interventional Cardiologist and Cardiac Surgeon)  
- Consulting Specialties  
- Medtronic CoreValve® Proctor  
- Heart Failure physician  
- Neurologist  
- Electrophysiologist  
- Interventional Cardiologist  
- Quality of Life Specialist | Non-Medtronic Membership:  
- National Principal Investigators (Interventional Cardiologist and Cardiac Surgeon) | The purpose of the Steering Committee is to oversee the conduct of the study; although other specialists are regularly consulted, they are not members of the CoreValve IDE Steering Committee. | No change to overall meaning of the protocol. |
| 6 | Section 3.2.1 Steering Committee | Prior to the onset of the trial, the Operations Committee will establish a charter that outlines their roles and responsibilities and describes the planned frequency of meetings. | The Steering Committee will establish a charter that outlines their roles and responsibilities and describes the planned frequency of meetings. | Minor wording clarification | No change to overall meaning of the protocol. |
| 7 | Section 3.2.4 Publication Committee | Prior to the onset of the trial, the Publication Committee will establish a plan that outlines their roles and responsibilities and describes the planned frequency of meetings. | The Publication Committee will establish a plan that outlines their roles and responsibilities and describes the planned frequency of meetings. | Clarification of timing | No change to overall meaning of the protocol. |
| 8 | Section 3.4.1 Screening Procedures | Added | The Patient Address Form (PAF) and Medical Billing Release Form should also be completed at this time. | Added for clarity of meaning | No change to overall meaning of the protocol. |
## Comprehensive Protocol Table of Changes (High Risk Study)

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<tbody>
<tr>
<td>9</td>
<td>Section 3.4.1 Screening Procedures</td>
<td>In the situation where subjects have compromised renal function that precludes contrast media, Magnetic Resonance (MR) imaging may be used as an alternative.</td>
<td>Removed</td>
<td>Clarifications based on investigator and Screening Committee feedback; MRI is not an acceptable alternative to CT imaging. To date, no centers have used MRI as an alternative</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>13</td>
<td>Section 3.4.1 Screening Procedures</td>
<td>However, if the subject had a peripheral vascular intervention, the exam must be more recent (within 90 days of being sent to the Screening Committee)</td>
<td>However, if the subject had a peripheral vascular intervention, the exam must be performed no more than 90 days prior to submission to the Screening Committee and must also be post intervention. Imaging obtained at the completion of the intervention may be used.</td>
<td>Clarification of examination timing.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>14</td>
<td>Section 3.4.1 Screening Procedures</td>
<td>However, if the subject had evidence of significant coronary artery disease and/or received a coronary intervention, the exam must be repeated within 90 days of being sent to the Screening Committee.</td>
<td>However, if the subject had evidence of significant coronary artery disease and/or received a coronary intervention, the exam must be performed no more than 90 days prior to submission to the Screening Committee and must also be post intervention. Imaging obtained at the completion of the intervention may be used.</td>
<td>Clarification</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>15</td>
<td>Section 3.4.1 Screening Procedures</td>
<td>NA</td>
<td>Additional assessments may be performed to evaluate risk, including (but not limited to) pulmonary function test and BNP labwork.</td>
<td>Clarification</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
</tbody>
</table>
| 16 | Section 3.4.2 Screening Committee Procedures | NA | The following information should be submitted to the Screening Committee...  
- STS calculation print out | Inadvertent omission; STS Risk assessment is listed as a required screening test, but it is not specifically called out as part of the information to be sent to the Screening Committee | No change to overall meaning of the protocol. |
| 17 | Section 3.4.3 Roll-in Cases | The first three successfully screened patients at each implanting site inclusive of both the High Risk Surgical and Extreme Risk patient populations will be considered “roll-in” subjects and will | The first three successfully enrolled patients at each implanting site inclusive of both the High Risk Surgical and Extreme Risk patient populations will be considered “roll-in” subjects and will | Clarification; not all patients who are screened will be enrolled in the | No change to overall meaning of the protocol. |

Original Version: HR Version 4.0  
Update Version: HR Version 5.0
<table>
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<tbody>
<tr>
<td>automatically be assigned to MCS TAVI.</td>
<td>automatically be assigned to MCS TAVI.</td>
<td>study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18 Section 3.4.3 Roll-in Cases</td>
<td>The Medtronic CoreValve® U.S. Pivotal Trial Training and Education Committee will review recommendations made by Medtronic field support and Medtronic CoreValve® Proctors for transition of sites from the roll-in phase to the pivotal phase of enrollment.</td>
<td>The Medtronic CoreValve® U.S. Pivotal Trial Training and Education Committee will review recommendations made by Medtronic field support, Medtronic CoreValve® Proctors and the Steering Committee for transition of sites from the roll-in phase to the pivotal phase of enrollment after the first three subjects have been treated. A patient will be considered a treated roll-in patient once the Medtronic CoreValve® Delivery Catheter System is introduced into the patient. A site must have three treated roll-in patients before they can be evaluated to move into the pivotal phase.</td>
<td>Clarification of when a patient is considered a roll-in patient</td>
<td>Consistent with Briefing Document #19, and agreed to by FDA via email on April 27, 2011 (refer Appendix 1 of this submission).</td>
</tr>
<tr>
<td>19 Section 3.4.4 Enrollment</td>
<td>• Confirm patient meets all of the inclusion and none of the exclusion criteria, including approval by the Screening Committee.</td>
<td>Prior to enrollment of a subject, the following must occur: • Confirm patient meets all of the inclusion and none of the exclusion criteria, (with the exception of a percutaneous coronary or peripheral intervention and evidence of an acute myocardial infarction which must not occur within 30 days prior to the index procedure) including approval by the Screening Committee.</td>
<td>Clarifications based on investigator and Screening Committee feedback; consistent with clarifications to inclusion/exclusion criteria.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>20 Section 3.4.4 Enrollment</td>
<td>For subjects that do not meet trial criteria, the reason for not continuing in the trial must be documented on the screening log.</td>
<td>For subjects that do not meet trial criteria, the reason for not continuing in the trial must be documented on the screening log in IXRS.</td>
<td>Added for clarity of meaning</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>21 Section 3.4.4 Enrollment</td>
<td>Baseline assessments should occur within 14 days of enrollment and include:</td>
<td>Baseline assessments must occur within 14 days after enrollment and include:</td>
<td>Clarification to emphasize requirement and timing of assessments.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>22 Section 3.4.4 Enrollment</td>
<td>• Confirm inclusion/exclusion criteria</td>
<td>• Document any changes to subject condition that affect inclusion/exclusion criteria</td>
<td>Clarification to ensure that any changes in patient condition which affect inclusion/exclusion criteria are documented.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>23 Section 3.4.4 Enrollment</td>
<td>(for patients whose procedures occur within 14 days of enrollment, labs do not need to be repeated).</td>
<td>Removed</td>
<td>Removed redundancy of meaning to introductory sentence</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>24 Section 3.4.4 Enrollment</td>
<td>• NIH Stroke Scale o For subjects with a neurological event, additional NIHSS exams to be performed at 7</td>
<td>• NIH Stroke Scale o In addition, for subjects with a neurological event, additional NIHSS exams to be</td>
<td>Minor wording clarification</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
</tbody>
</table>
### Comprehensive Protocol Table of Changes (High Risk Study)

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<tbody>
<tr>
<td>25</td>
<td>Section 3.4.1 MCS TAVI</td>
<td>Added</td>
<td>Refer to Table 2: Schedule of Assessments for data collection requirements. Items indicated below in bold are required for CRF completion.</td>
<td>Added for clarity of meaning.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>26</td>
<td>Section 3.4.1 MCS TAVI</td>
<td>If the patient is currently on warfarin therapy prior to the procedure</td>
<td>If the patient is currently on warfarin therapy prior to the procedure it is recommended to:</td>
<td>Minor wording clarification</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
</tbody>
</table>
| 27 | Section 3.4.1 MCS TAVI | Unbolded text | The following pre procedure text was bolded:  
- Routine laboratory tests including complete blood count (CBC), BNP, plasma free hemoglobin, international normalized ratio (INR), Partial Thromboplastin Time (PTT), liver panel, and albumin.  
- Cardiac enzymes (CK and CK-MB) obtained within 48 hours of the procedure.  
- Check serum creatinine and creatinine clearance. | To indicate that the bolded text is required assessments for CRF completion. Clarity for sites | No change to overall meaning of the protocol. |
| 28 | Section 3.4.1 MCS TAVI | Added | Subject must meet all inclusion/exclusion criteria at the time of procedure | Added clarification to ensure that patient condition has not changed | No change to overall meaning of the protocol. |
| 29 | Section 3.4.1 MCS TAVI | Unbolded text | The following pre MCS TAVI Procedure text was bolded:  
- Record ECG and angiogram (Peri-procedural angiographic cine film in DICOM format) during the procedure | To indicate that the bolded text is required assessments for CRF completion. Clarity for sites | No change to overall meaning of the protocol. |
| 30 | Section 3.4.1 MCS TAVI | Unbolded text | The following pre Immediate Post Procedure text was bolded:  
- Cardiac Enzymes: CK within 8-12 hours post procedure and at any time when a clinical ischemic event is suspected. CK-MB is required if CK is elevated ≥2X the laboratory upper limit of normal. If a clinical event is confirmed, a total of 3 draws of cardiac enzymes within the first 24 hours (drawn every 8 hours) following the clinical event should be obtained.  
- 12-lead Electrocardiogram (performed within 48 hours) | To indicate that the bolded text is required assessments for CRF completion. Clarity for sites | No change to overall meaning of the protocol. |
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</table>
| 1 | | | hours post MCS TAVI)  
- 31NIHSS should be administered within 24 hours post-procedure  
  - In addition, for subjects with a neurological event, additional NIHSS exams to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-event.  
- Modified Rankin Scale (for patients with a suspected or new neurological event only)  
  - For subjects with a stroke, assessment to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-stroke.  
- An echocardiogram must be done 24-48 hours post-procedure to assess device success.  
- Assessment of concomitant medications must be performed  
- For patients with permanent pacemakers or defibrillators only: Perform a full interrogation and an assessment of AV conduction within 48 hours post procedure (Refer to the Pacing Guidelines in Appendix 17.14). Print a copy of the interrogation and save the data on a diskette. Retain the printed copy of the interrogation and the diskette in the subject's file for source verification  
- Documentation of all adverse events/serious adverse events from enrollment to discharge including all unanticipated adverse device effects (UADE), technical observations, reinterventions or repeat admissions to the catheterization suite and deaths.  
  - Any patient with evidence of a neurological event should have a neurology consult and subsequently an imaging study if deemed necessary by the neurologist. | | |
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<tbody>
<tr>
<td>32</td>
<td>Section 3.4.1 MCS TAVI</td>
<td>12-lead Electrocardiogram (performed within 48 hours of MCS TAVI)</td>
<td>12-lead Electrocardiogram (performed within 48 hours post MCS TAVI)</td>
<td>Minor wording clarification</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>33</td>
<td>Section 3.4.1 MCS TAVI</td>
<td>Modified Rankin Scale</td>
<td>Modified Rankin Scale (for patients with a suspected or new neurological event only)</td>
<td>Clarify this is required only for patients with a neurological event</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>34</td>
<td>Section 3.4.1 MCS TAVI</td>
<td>An echocardiogram should be done 24-48 hours post-procedure to assess device success</td>
<td>An echocardiogram must be done 24-48 hours post-procedure to assess device success</td>
<td>Clarification to emphasize requirements</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
</tbody>
</table>
| 35 | Section 3.4.1 MCS TAVI | o If the patient is on warfarin therapy post-procedure: - it is recommended that subjects are prescribed either daily aspirin (81 to 325 mg) or daily clopidogrel (75 mg) (or ticlopidine, if clopidogrel is contraindicated) for at least three months following the procedure.  
   o If the patient will not be on warfarin therapy post-procedure: - it is recommended that subjects are prescribed daily aspirin (81 to 325 mg) and daily clopidogrel (75 mg) (or ticlopidine, if clopidogrel is contraindicated) for at least three months following the procedure. | o If the patient is on warfarin therapy post-procedure: - it is recommended that subjects are prescribed either daily aspirin (81 mg) or daily clopidogrel (75 mg) (or ticlopidine, if clopidogrel is contraindicated) for at least three months following the procedure.  
   o If the patient will not be on warfarin therapy post-procedure: - it is recommended that subjects are prescribed daily aspirin (≥ 81 mg) and daily clopidogrel (75 mg) (or ticlopidine, if clopidogrel is contraindicated) for at least three months following the procedure. | Clarifications based on investigator and feedback to minimize unnecessary bleeding. | No change to overall meaning of the protocol. |
| 36 | Section 3.4.1 MCS TAVI | Assesment of concomitant medications | Assessment of concomitant medications must be performed | Clarification to emphasize requirement | No change to overall meaning of the protocol. |
| 37 | Section 3.4.1 MCS TAVI | Added | For patients with permanent pacemakers or defibrillators only: Perform a full interrogation and an assessment of AV conduction within 48 hours post procedure (Refer to the Pacing Guidelines in Appendix 17.14). Print a copy of the interrogation and save the data on a diskette. Retain the printed copy of the interrogation and the diskette in the subject’s file for source verification | Previously omitted; added to clarify requirements for pacemaker interrogation | No change to overall meaning of the protocol. |
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</tr>
</thead>
</table>
| 38 | Section 3.4.1 MCS TAVI | Unbolded text | The following pre Immediate Post Procedure Pacing Guidelines text was bolded:  
  o After 48 hours, obtain Electrocardiogram (ECG) and assess patient rhythm and conduction  
  o Prior to the permanent pacemaker implantation, document the reason for the placement of the permanent pacemaker via a 12-lead ECG. | To indicate that the bolded text is required assessments for CRF completion. Clarity for sites | No change to overall meaning of the protocol. |
| 39 | Section 3.4.1 MCS TAVI | Maintain temporary pacing until at least 48 hours post-implant in CV-ICU | Maintain temporary pacing until at least 48 hours post-implant in CV-ICU unless patient has a pre-existing permanent pacemaker or defibrillator | Minor wording clarification | No change to overall meaning of the protocol. |
| 40 | 3.4.1 MCS TAVI | Unbolded text | The following pre Assessments Done at Discharge text was bolded:  
  o Brief physical examination including vital signs and all major systems findings  
  o Routine laboratory tests including CBC, creatinine, BNP, hemoglobin and plasma-free hemoglobin.  
  o 12-lead Electrocardiogram  
  o Comprehensive transthoracic 2D echocardiogram (TTE). The TTE should be performed as close to discharge (or no later than 7 days, whichever is sooner) as possible. Echocardiograms will be performed according to the Echocardiography Procedures found in Appendix 17.8. All echocardiograms for enrolled subjects will be independently analyzed by the Echocardiographic Core Lab.  
  o NIH Stroke Scale  
    - In addition, for subjects with a neurological event, additional NIHSS exams to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-event. NIHSS also to be done within 24 hours of any aortic reintervention  
    - Any patient with evidence of a neurological event should have a neurology consult and an imaging study if deemed necessary. | To indicate that the bolded text are required assessments for CRF completion. Clarity for sites | No change to overall meaning of the protocol. |
## Comprehensive Protocol Table of Changes (High Risk Study)

<table>
<thead>
<tr>
<th>#</th>
<th>Protocol Section</th>
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<th>Reason for the change</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>41</td>
<td>3.4.1 MCS TAVI Assessments Done at Discharge</td>
<td>Prior to hospital discharge (or within 7 days post-MCS TAVI, whichever occurs first)</td>
<td>Prior to hospital discharge (or no later than 7 days post-MCS TAVI, whichever occurs first)</td>
<td>Minor wording clarification</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>42</td>
<td>3.4.1 MCS TAVI Assessments Done at Discharge</td>
<td>TTE should be performed as close to discharge (or 7 days, whichever is sooner)</td>
<td>TTE should be performed as close to discharge (or no later than 7 days, whichever is sooner)</td>
<td>Minor wording clarification</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
</tbody>
</table>
## Comprehensive Protocol Table of Changes (High Risk Study)

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<thead>
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<tbody>
<tr>
<td>43</td>
<td>Section 3.4.1</td>
<td>NIH Stroke Scale</td>
<td>• NIH Stroke Scale</td>
<td>Minor wording clarification</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td></td>
<td>MCS TAVI</td>
<td>o For subjects with a neurological event, additional NIHSS exams to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-event.</td>
<td>o In addition, for subjects with a neurological event, additional NIHSS exams to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-event.</td>
<td></td>
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</tr>
<tr>
<td>44</td>
<td>Section 3.4.1</td>
<td>Modified Rankin Scale</td>
<td>• Modified Rankin Scale (for patients with a suspected or new neurological event only)</td>
<td>Clarification of meaning</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td></td>
<td>MCS TAVI</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>45</td>
<td>Section 3.4.6</td>
<td>NIH Stroke Scale</td>
<td>• NIH Stroke Scale</td>
<td>Minor wording clarification</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td>o For subjects with a neurological event, additional NIHSS exams to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-event.</td>
<td>o In addition, for subjects with a neurological event, additional NIHSS exams to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-event.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>Section 3.4.6</td>
<td>Modified Rankin Scale</td>
<td>• Modified Rankin Scale (for patients with a suspected or new neurological event only)</td>
<td>Minor wording clarification</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td></td>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>Table 2: Schedule of Assessments</td>
<td>Baseline(within 14 days of enrollment)</td>
<td>Baseline(&lt; 14 days after enrollment)</td>
<td>Clarification of timing</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>48</td>
<td>Table 2: Schedule of Assessments</td>
<td>Routine Laboratory Tests including Complete Blood Count, Creatinine</td>
<td>Routine Laboratory Tests including Complete Blood Count, Creatinine, &amp; Creatinine Clearance</td>
<td>Clarification to include creatinine clearance</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>49</td>
<td>Table 2: Schedule of Assessments</td>
<td>Added Footnote to Baseline and Implant Evaluation</td>
<td>Document any changes to subject condition that affect inclusion/exclusion criteria</td>
<td>Added clarification to ensure that patient condition has not changed; changed numbering of footnotes</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>50</td>
<td>Table 2: Schedule of Assessments</td>
<td>Added Footnote to Baseline and Implant Evaluation</td>
<td>Subject must meet all inclusion/exclusion criteria at the time of procedure</td>
<td>Added clarification to ensure that patient condition has not changed</td>
<td>No change to overall meaning of the protocol.</td>
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<tr>
<td>51</td>
<td>Table 2: Schedule of Assessments</td>
<td>Added footnote to Implant Procedure/Valve Surgery</td>
<td>Peri-procedural angiographic cine film in DICOM format</td>
<td>Clarification of meaning</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>52</td>
<td>Section 3.5.1.2 Serious Adverse Events</td>
<td>Events that do not meet these criteria are considered non-serious</td>
<td>NA</td>
<td>Removed for because the statement is inaccurate.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>53</td>
<td>Section 3.5.1.4 Major Adverse Event</td>
<td>Removed: Valve Embolism</td>
<td>Device migration/Valve embolism</td>
<td>Clarifications based on CEC and proctor feedback.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>54</td>
<td>Section 3.5.2.1 Serious Adverse Events (SAEs)</td>
<td>Medtronic requests that the investigator notify the sponsor within 3 working days of first learning of any SAE using the electronic data capture (eCRF) system.</td>
<td>Medtronic recommends that the investigator notify the sponsor within 3 working days of first learning of any SAE using the electronic data capture (eCRF) system.</td>
<td>Minor wording clarification</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>55</td>
<td>Section 3.5.2.3 Other Adverse Events</td>
<td>Medtronic requests that the investigator notify the sponsor within 10 working days of first learning of any other AE using the electronic data capture (eCRF) system.</td>
<td>Medtronic recommends that the investigator notify the sponsor within 10 working days of first learning of any other AE using the electronic data capture (eCRF) system.</td>
<td>Minor wording clarification</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>56</td>
<td>Section 3.5.2.4 Anticipated Adverse Events</td>
<td>Malposition (either too high or too low)</td>
<td>Malposition (either too high or too low)/malplacement</td>
<td>Inadvertent omission</td>
<td>Updated to be consistent with Changes to Protocol Section 15.2 in response to FDA G100012/S003 Conditions of Approval Q1</td>
</tr>
<tr>
<td>57</td>
<td>Section 3.5.4 Data Safety Monitoring Board (DSMB)</td>
<td>All data presented at the meetings will be considered confidential and returned to the trial statistician at the closure of the DSMB meeting.</td>
<td>All data presented at the meetings will be considered confidential.</td>
<td>Data will be provided electronically to the DSMB and may not be returned to the sponsor.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>58</td>
<td>Section 3.6.6 Secondary Endpoints</td>
<td>9. The four echocardiographic measurements will be evaluated at discharge, 6 months, 12 months and annually through five years.</td>
<td>9. The four echocardiographic measurements will be evaluated at discharge, 30 days, 6 months, 12 months and annually through five years.</td>
<td>Inadvertently omitted</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>59</td>
<td>Section 4.1 Potential Risks and Discomforts</td>
<td>Malposition (either too high or too low)</td>
<td>Malposition (either too high or too low)/malplacement</td>
<td>Inadvertent omission</td>
<td>Updated to be consistent with Changes to Protocol Section 15.2 in response to FDA G100012/S003 Conditions of Approval Q1</td>
</tr>
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Original Version: HR Version 4.0
Update Version: HR Version 5.0
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<tbody>
<tr>
<td>60</td>
<td>Section 14 Amendments to the Investigational Plan</td>
<td>3.0 November 2, 2010 Address FDA conditions, administrative edits as required 5.0 February 1, 2011 Address FDA conditions, administrative edits as required</td>
<td>3.0 November 2, 2010 Address FDA conditional Approval Letter (October 13, 2010), administrative edits as required 5.0 February 1, 2011, Address FDA conditional Approval Letter (January 14, 2011), administrative edits as required</td>
<td>Clarification to reference which set of FDA conditions were addressed by the protocol changes</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>61</td>
<td>Section 15.2 Definition of Terms</td>
<td>Aortic Regurgitation Table Parameter – Severe Intermediate</td>
<td>Aortic Regurgitation Table Parameter – Severe Greatly increased</td>
<td>Modified to align with VARC definition</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>62</td>
<td>Section 15.2 Definition of Terms</td>
<td>Added</td>
<td>CEREBRAL INFARCTION Evidence of brain cell death from imaging studies or pathological examination. If there are clinical symptoms, then it is a stroke, otherwise it is an asymptomatic cerebral infarction.</td>
<td>Added per FDA request for Neuro Sub Study Version 2, May 12, 2011</td>
<td>Included in response to FDA's Current Thinking Regarding Neurological Assessments for Transcatheter Valve Trials, Q1b.</td>
</tr>
<tr>
<td>63</td>
<td>Section 15.2 Definition of Terms</td>
<td>DEVICE MIGRATION Obvious movement of the Medtronic CoreValve® PAV from its documented original implant position, after access site closure, as confirmed by X-ray, echocardiography, CT scan or direct assessment during open heart surgery or autopsy.</td>
<td>DEVICE MIGRATION/VALVE EMBOLISM Obvious spontaneous movement of the Medtronic CoreValve® PAV from its documented original implant position, after access site closure, as confirmed by X-ray, echocardiography, CT scan or direct assessment during open heart surgery or autopsy.</td>
<td>Clarifications based on CEC and proctor feedback (Refer also to line 67).</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>64</td>
<td>Section 15.2 Definition of Terms</td>
<td>DEVICE MALPLACEMENT Placement of the Medtronic CoreValve® PAV in a non-therapeutic location, either inadvertently, or possibly intentionally due to unintended problems during the Medtronic CoreValve® System (MCS) delivery or procedure that necessitates placement in the non-therapeutic location.</td>
<td>DEVICE MALPLACEMENT/MALPOSITION Placement of the Medtronic CoreValve® PAV in a non-therapeutic location, either inadvertently, or possibly intentionally due to unintended problems during the Medtronic CoreValve® System (MCS) delivery or procedure that necessitates placement in the non-therapeutic location. This does not include movement during retrieval of the delivery catheter or following BAC post implantation.</td>
<td>Clarifications based on CEC and proctor feedback.</td>
<td>No change to overall meaning of the protocol; Consistent with Changes to Protocol Section 15.2 in response to FDA G100012/S003 Conditions of Approval Q1</td>
</tr>
<tr>
<td>65</td>
<td>Section 15.2 Definition of Terms</td>
<td>Added</td>
<td>ENCEPHALOPATHY Guy M. McKhann, et al. Encephalopathy and Stroke After Coronary Artery Bypass Grafting: Incidence, Consequences, and Prediction. Arch Neurol 2002;59:1422-1428. Episodes of confusion, agitation and/or combative ness; alterations and fluctuations in levels of consciousness; acute problems with cognition, including memory and changes in perception including hallucinations</td>
<td>Added Per FDA request for the for Neuro Sub Study Version 2, May 12, 2011</td>
<td>In response to G100012/S009 Conditional Approval Letter April 8, 2010 Q11 and FDA’s Current Thinking Regarding Neurological Assessments for Transcatheter Valve Trials, Q1d.</td>
</tr>
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</tr>
<tr>
<td>66</td>
<td>Section 15.2 Definition of Terms</td>
<td>Added</td>
<td>INTRACRANIAL HEMMORRHAGE Collection of blood between the brain and skull. Subcategorized as epidural, subdural and subarachnoid bleeds.</td>
<td>Added per FDA request for Neuro Sub Study Version 2, May 12, 2011</td>
<td>Included in response to FDA's Current Thinking Regarding Neurological Assessments for Transcatheter Valve Trials, Q1e.</td>
</tr>
<tr>
<td>67</td>
<td>Section 15.2 Definition of Terms: Adverse Event</td>
<td>Removed</td>
<td>Valve Embolism</td>
<td>Removed for redundancy; &quot;Device migration&quot; was changed to &quot;Device Migration/Valve Embolism&quot;</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Device Migration</td>
<td>Device Migration/Valve embolism</td>
<td>Clarifications based on CEC and proctor feedback.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>68</td>
<td>Title Page Footer</td>
<td>Version 4.0 February 1, 2011</td>
<td>Version 5.0 May 26, 2011</td>
<td>Reflect Protocol Version</td>
<td>Revision Control</td>
</tr>
<tr>
<td>69</td>
<td>Section 1 Synopsis: Exclusion Criteria</td>
<td>2. Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to the index procedure with bare metal stents and 6 months with drug eluting stents.</td>
<td>2. Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to the index procedure including bare metal stents. Additionally, any drug eluting stents placed within 6 months prior to the index procedure.</td>
<td>Clarification of meaning</td>
<td>No change to overall meaning of the protocol</td>
</tr>
<tr>
<td></td>
<td>Section 3.3.6 Inclusion/Exclusion Criteria</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>70</td>
<td>Section 2.1 Background</td>
<td>Therefore, the assumption of 20% mortality at one year is likely conservative for this subject population</td>
<td>Removed</td>
<td>Not relevant background information for the current protocol design</td>
<td>No change to overall meaning of the protocol</td>
</tr>
</tbody>
</table>
## Comprehensive Protocol Table of Changes (High Risk Study)

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<tbody>
<tr>
<td>71</td>
<td>Section 3.4.5.2</td>
<td>Added</td>
<td>Subject must meet inclusion/exclusion criteria at the time of procedure.</td>
<td>Added clarification to ensure that patient condition has not changed</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>72</td>
<td>Section 3.4.5.2</td>
<td>NIH Stroke Scale</td>
<td>For subjects with a neurological event, additional NIHSS exams to be performed at 7 days or discharge (whichever occurs first), 30 days and 3 months post-event.</td>
<td>NIH Stroke Scale</td>
<td>Minor wording clarification</td>
</tr>
<tr>
<td>73</td>
<td>Section 3.4.5.2</td>
<td>Modified Rankin Scale</td>
<td>Modified Rankin Scale (for patients with a suspected or new neurological event only)</td>
<td>Clarify this is required only for patients with a neurological event</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>74</td>
<td>Section 3.6.2</td>
<td>However, if outcome data are missing, Kaplan-Meier rates at 12 months will replace the binomial proportions in the calculation of the Farrington and Manning test statistic.</td>
<td>However, if outcome data are missing, Kaplan-Meier rates at 12 months and their standard errors will be used in the calculation of the test statistic.</td>
<td>Updated due to Kaplan-Meier rates having different standard errors than sample proportions</td>
<td>Updated in response to G10012/S007 Conditional Approval Letter dated April 7, 2011 Q2.</td>
</tr>
<tr>
<td>75</td>
<td>Section 14</td>
<td>Added</td>
<td>5.0 May 26, 2011</td>
<td>Allow for additional sites, statistical analysis clarification and administrative edits as required</td>
<td>Documentation of versions and associated changes</td>
</tr>
<tr>
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<td>-------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1</td>
<td>1. Synopsis</td>
<td>2. Subject has senile degenerative aortic valve stenosis with mean gradient &gt; 40 mmHg or jet velocity greater than 4.0 m/s, and an initial aortic valve area of ≤ 0.8 cm² (or aortic valve area index ≤ 0.5 cm²/m²) by echocardiogram or simultaneous pressure recordings at cardiac catheterization – at rest or with dobutamine stress echocardiogram.</td>
<td>2. Subject has senile degenerative aortic valve stenosis with:</td>
<td>Changed format for readability. Inclusion criteria did not change.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• mean gradient &gt; 40 mmHg or jet velocity greater than 4.0 m/s by either resting or dobutamine stress echocardiogram, or simultaneous pressure recordings at cardiac catheterization (either resting or dobutamine stress), AND</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• an initial aortic valve area of ≤ 0.8 cm² (or aortic valve area index ≤ 0.5 cm²/m²) by resting echocardiogram or simultaneous pressure recordings at cardiac catheterization.</td>
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</tr>
<tr>
<td>2</td>
<td>3.4.1 Screening Procedures</td>
<td>Additional assessments may be performed to evaluate risk, including (but not limited to) pulmonary function test and BNP lab work.</td>
<td>Additional assessments may be performed to evaluate risk and \textit{vascular access}, including (but not limited to) pulmonary function test and BNP lab work.</td>
<td>Clarification to reflect standard practice of the Screening Committee. The purpose of the Screening Committee (§3.4.2) is to determine patient eligibility. Vascular access is an exclusion criteria: Vascular – Transarterial access not able to accommodate 18Fr sheath.</td>
<td>No change to overall meaning of the protocol, or practice of the Screening Committee.</td>
</tr>
<tr>
<td>3</td>
<td>3.4.4 Enrollment and Randomization</td>
<td>• For patients with an existing permanent pacemaker or defibrillator only: Perform a full interrogation and an assessment of AV conduction (Refer to the Pacing Guidelines in Appendix 17.14). Print a copy of the interrogation and save the data on a diskette. Retain the printed copy of the interrogation and the diskette in the subject’s file for source verification.</td>
<td>• For patients with an existing permanent pacemaker or defibrillator only: Perform a full interrogation and an assessment of AV conduction (Refer to the Pacing Guidelines in Appendix 17.14). Print a copy of the interrogation. It is recommended to save the interrogation via standard center practice (i.e. diskette, CD, flash drive). Retain the printed and saved copies of the interrogation in the subject’s file for source verification.</td>
<td>Minor clarification to reflect standard hospital paper and electronic formats of saving pacemaker interrogation data. (Now includes CD and flash drives).</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>4</td>
<td>3.4.4 Enrollment and Randomization</td>
<td>• NIH Stroke Scale</td>
<td>• NIH Stroke Scale</td>
<td>Modified to align with final VARC definition. The final version does not include NIHSS assessment.</td>
<td>In response to FDA questions in June 22, 2011 email (G100012/S-13).</td>
</tr>
</tbody>
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<td>3</td>
<td>System TAVI event.</td>
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<td>4</td>
<td>3.4.6 Follow-Up Evaluations</td>
<td></td>
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</tr>
<tr>
<td>5</td>
<td>Table 2: Schedule of Assessments</td>
<td></td>
<td></td>
<td></td>
<td>In response to FDA questions in June 22, 2011 email (G100012/S-13).</td>
</tr>
<tr>
<td>6</td>
<td>15.2 Definition of Terms – Acute Kidney injury, Aortic Regurgitation, Bleeding event, Death, Myocardial Infarction, Prosthetic Valve Dysfunction, Stroke, Vascular complications</td>
<td>will be defined according to the definition proposed by the Valve Academic Research Consortium (VARC) Consensus Report for Transcatheter Aortic Valve Implantation (TAVI); 2010-06-15</td>
<td>will be defined based on the definition published in the European Heart Journal; January 6, 2011, titled &quot;Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium&quot;.</td>
<td>Reference updated to align with final VARC definition.</td>
<td>In response to FDA questions in June 22, 2011 email (G100012/S-13).</td>
</tr>
<tr>
<td>7</td>
<td>Stage 2* Increase in serum creatinine to 200-300% (&gt; 2-3 x increase compared with baseline)</td>
<td></td>
<td>Stage 2* Increase in serum creatinine to 200-300% (&gt; 2-3 x increase compared with baseline) or increase between &gt;0.3 mg/dL (&gt;26.4 μmol/L) and &lt;4.0 mg/dL (&lt;354 μmol/L)</td>
<td>FDA noted that MDT was using the draft VARC definition for stroke, and recommended updates to the final definition. This definition was also updated to align with final VARC definition.</td>
<td>In response to FDA questions in June 22, 2011 email (G100012/S-13).</td>
</tr>
<tr>
<td>8</td>
<td>Valve, Moderate: Usually normal Valve, Severe: Usually normal Doppler parameters: Circumferential extent of paraprosthetic AR (%)*** For paravalvular aortic regurgitation</td>
<td></td>
<td>Valve, Moderate: Usually abnormal Valve, Severe: Usually abnormal Doppler parameters: Circumferential extent of paraprosthetic AR (%)***</td>
<td>FDA noted that MDT was using the draft VARC definition for stroke, and recommended updates to the final definition. This definition was also updated to align with final VARC definition.</td>
<td>In response to FDA questions in June 22, 2011 email (G100012/S-13).</td>
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<tr>
<td>9</td>
<td>15.2 Definition of Terms – Mitral Stenosis</td>
<td>Moderate or severe AS will be considered a serious adverse event.</td>
<td>Moderate or severe MS will be considered a serious adverse event.</td>
<td>Typographical error</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>10</td>
<td>15.2 Definition of Terms – Myocardial Infarction</td>
<td>Peri Procedural MI 1. (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes – either elevation &gt;1 mm or depression &gt;1 mm in two or more contiguous leads, hemodynamic instability, or imaging evidence of new loss of viable myocardium or new wall motion abnormality). 2. Elevated cardiac biomarkers evidence, (preferably CK-MB) within 72 hours after the index procedure, consisting of two or more post-procedure samples that are 6-8 hours apart with a 20% increase in the second sample and a peak value exceeding 10x the 99th percentile upper reference limit (URL) or a peak value exceeding 5x the 99th percentile URL and with new pathological Q waves in at least 2 contiguous leads.</td>
<td>Peri Procedural MI 1. (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, or imaging evidence of new loss of viable myocardium or new wall motion abnormality). 2. Elevated cardiac biomarkers evidence, (preferably CK-MB) within 72 hours after the index procedure, consisting of two or more post-procedure samples that are 6-8 hours apart with a 20% increase in the second sample and a peak value exceeding 10x the 99th percentile upper reference limit (URL) or a peak value exceeding 5x the 99th percentile URL with new pathological Q waves in at least 2 contiguous leads.</td>
<td>FDA noted that MDT was using the draft VARC definition for stroke, and recommended updates to the final definition. This definition was also updated to align with final VARC definition.</td>
<td>In response to FDA questions in June 22, 2011 email (G100012/S-13).</td>
</tr>
<tr>
<td>11</td>
<td>15.2 Definition of Terms – Stroke</td>
<td>• Stroke: (diagnosis as above, preferably with positive neuroimaging study)+  o Minor (non-clinically important disability) - modified Rankin score &lt; 2 at 7 days or prior to discharge AND NIHSS score ≥ 3 (above baseline) at 7 days or prior to discharge and at 30-day assessment  Major (clinically important disability) - modified Rankin score ≥ 2 at 7 days or prior to discharge AND NIHSS score ≥ 3 (above baseline) at 7 days or prior to discharge and at 30-day assessment</td>
<td>• Stroke: (diagnosis as above, preferably with positive neuroimaging study)+  o Minor (non-clinically important disability) - modified Rankin score &lt; 2 at 30 and 90 days  Major (clinically important disability) - modified Rankin score ≥ 2 at 30 and 90 days</td>
<td>Modified to align with final VARC definition, as requested by FDA.</td>
<td>In response to FDA questions in June 22, 2011 email (G100012/S-13) and July 12, 2010 teleconference.</td>
</tr>
<tr>
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<td>Reason for the change</td>
<td>Justification</td>
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<tr>
<td>13</td>
<td>Section 14 Amendments to</td>
<td>5.0 May 26, 2011 Allow for</td>
<td>5.0 May 26, 2011 Allow for</td>
<td>Documentation of versions</td>
<td>No change to overall meaning of the protocol.</td>
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<tr>
<td></td>
<td>the Investigational Plan</td>
<td>additional sites, statistical</td>
<td>additional sites, statistical</td>
<td>and associated changes</td>
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<td>analysis clarification and</td>
<td>analysis clarification and</td>
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<td>6.0 July 11, 2011 Address FDA</td>
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<td>questions received via email</td>
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<td>(June 22, 2011). Administrative</td>
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<td>edits as required</td>
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</table>
# Comprehensive Protocol Table of Changes (High Risk Study)

## Changes to the High Risk Protocol

<table>
<thead>
<tr>
<th>#</th>
<th>Protocol Section</th>
<th>Prior Version</th>
<th>Proposed change</th>
<th>Reason for the change</th>
<th>Justification</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Title Page Footer</td>
<td>Version 6.0 July 11, 2011</td>
<td>Version 7.0 October 1, 2011</td>
<td>Reflect Protocol Version</td>
<td>Revision Control</td>
</tr>
<tr>
<td>2</td>
<td>Section 14 Amendments to the Investigational Plan</td>
<td>NA</td>
<td>Version 7.0 October 1, 2011</td>
<td>Increase maximum allowed proportion of non-ilio-femoral sample size</td>
<td>Documentation of versions and associated changes</td>
</tr>
<tr>
<td>3</td>
<td>Synopsis-Sample Size</td>
<td>790 (395 MCS TAVI &amp; 395 SAVR)</td>
<td>790 (395 MCS TAVI &amp; 395 SAVR) Non-ilio-femoral will be limited to no more than 30% (237) of the 790 randomized subjects.</td>
<td>Enrollment limit added to this section of the protocol. Limit increased to 30% protocols to reflect increased use of alternative access sites expected upon commercialization.</td>
<td>The High Risk Surgical protocol includes 790 patients randomized 1:1 between TAVI and SAVR and primary analysis includes all access sites. Therefore, there is no impact to statistical analysis plan.</td>
</tr>
<tr>
<td>4</td>
<td>3.3.5 Number of Subjects Sample Size</td>
<td>Non-ilio-femoral will be limited to no more than 20% (158) of the 790 randomized subjects</td>
<td>Non-ilio-femoral will be limited to no more than 30% (237) of the 790 randomized subjects</td>
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</tbody>
</table>

## Changes to the Informed Consents (Combined, High Risk Surgical, Roll-In Patients)

<table>
<thead>
<tr>
<th>#</th>
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<th>Reason for the change</th>
<th>Justification</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Title Page Footer</td>
<td>01-July-11</td>
<td>29-Sept-11</td>
<td>Reflect Protocol Version</td>
<td>Revision Control</td>
</tr>
<tr>
<td>2</td>
<td>Purpose of the Study</td>
<td>This study will involve up to 1497 subjects at up to 45 hospitals in the United States, and is anticipated to take approximately 7 years to complete</td>
<td>This study will involve approximately 1612 subjects at up to 45 hospitals in the United States, and is anticipated to take approximately 7 years to complete</td>
<td>Updated to reflect revised total of patients in the study. High Risk: 395 TAVI + 395 SAVR = 790 (no change) Extreme Risk: 487 (PG) + 200 NIF = 687 (increase by 100) Roll-Ins: 45 sites x 3 = 135</td>
<td>Updated to include additional number of Extreme Risk Patients in the NIF arm.</td>
</tr>
</tbody>
</table>

Original Version: HR Version 6.0
Update Version: HR Version 7.0
## Comprehensive Protocol Table of Changes (High Risk Study)

<table>
<thead>
<tr>
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<th>Justification</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>3.3.6 Inclusion/Exclusion Criteria</td>
<td>Blood dyscrasias as defined: leukopenia (WBC &lt; 1000/mm³), thrombocytopenia (platelet count &lt;50,000 cells/mm³), history of bleeding diathesis or coagulopathy, or hypercoagulable states.</td>
<td>Blood dyscrasias as defined: leukopenia (WBC &lt; 1000/mm³), thrombocytopenia (platelet count &lt;50,000 cells/mm³), history of bleeding diathesis or coagulopathy.</td>
<td>Current practice is to treat patients with hypercoaguable states with Warfarin. Patients can be managed with Warfarin following TAVR. Effectively treat patients with warfarin, does not align with current clinical practice.</td>
<td>Does not change the overall protocol.</td>
</tr>
<tr>
<td>2</td>
<td>3.3.6 Inclusion/Exclusion Criteria</td>
<td>GI bleeding within the past 3 months</td>
<td>Active GI bleeding within the past 3 months.</td>
<td>Minor wording clarification.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>3</td>
<td>3.3.6 Inclusion/Exclusion Criteria</td>
<td>Native aortic annulus size &lt; 20 mm or &gt; 27 mm per the baseline diagnostic imaging.</td>
<td>Native aortic annulus size &lt; 20 mm or &gt; 29 mm per the baseline diagnostic imaging.</td>
<td>Additional range added to allow for 31mm valve.</td>
<td>Addition of 31mm PAV.</td>
</tr>
<tr>
<td>4</td>
<td>3.3.6 Inclusion/Exclusion Criteria</td>
<td>Severe mitral (3-4+) or severe tricuspid regurgitation.</td>
<td>Moderate to severe (3-4+) or severe (4+) mitral or severe (4+) tricuspid regurgitation.</td>
<td>Additional wording clarification to delineate the difference between mitral and tricuspid regurgitation.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>5</td>
<td>3.3.6 Inclusion/Exclusion Criteria</td>
<td>For patients with native coronary artery dependent circulation: Sinus of Valsalva width &lt; 29 mm unless the aortic annulus is 20-23 mm, in which case the sinus of Valsalva width &lt; 27 mm, OR Height of the left or right coronary sinus of Valsalva (to the tubular aorta) &lt; 15mm</td>
<td>Sinus of Valsalva anatomy that would prevent adequate coronary perfusion</td>
<td>Reworded based on Screening Committee recommendation. There are three possible measurements that could be used to determine the Sinus of Valsalva measurements, causing confusion. The purpose of the evaluation is to determine that there is adequate coronary perfusion. Therefore, the wording was simplified to reflect the purpose for the measurement.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
</tbody>
</table>
# Comprehensive Protocol Table of Changes (High Risk Study)

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</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>3.4.1 Screening Procedures</td>
<td>If the CT angiogram was conducted in the last 365 days and subject has not had a peripheral vascular intervention since the time of the image, a more recent exam is not required as long as visualization of both iliacs and femorals (and subclavian/axillaries, if applicable) to the aorta can be viewed. However, if the subject had a peripheral vascular intervention, the exam must be performed no more than 90 days prior to submission to the Screening Committee and must also be post intervention. Imaging obtained at the completion of the intervention may be used.</td>
<td>If the CT angiogram was conducted in the last 365 days and subject has not had a peripheral vascular intervention since the time of the image, a more recent exam is not required as long as visualization of both iliacs and femorals (and subclavian/axillaries, if applicable) to the aorta can be viewed. However, if the subject had a peripheral vascular intervention within the 365 day CT window, angiography obtained at the completion of the procedure may be used as an alternative to a repeat CT scan provided it has been obtained within 90 days of submission to the Screening Committee.</td>
<td>Intended to reduce the risk to the patient of repeat imaging procedures.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>7</td>
<td>3.4.1 Screening Procedures</td>
<td>If the coronary arteriogram has been performed within the last 365 days and the subject qualifies for the study (no significant coronary artery disease), a more recent exam is not required. However, if the subject had evidence of significant coronary artery disease and/or received a coronary intervention, the exam must be performed no more than 90 days prior to submission to the Screening Committee and must also be post intervention. Imaging obtained at the completion of the intervention may be used.</td>
<td>If the coronary arteriogram has been performed within the last 365 days and the subject qualifies for the study (no significant coronary artery disease), a more recent exam is not required. However, if the subject had evidence of significant coronary artery disease and/or received a coronary intervention within the 365 day window, angiography obtained at the completion of the procedure may be used as an alternative provided it has been obtained within 90 days of submission to the Screening Committee.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>4.1 Potential Risks and Discomforts</td>
<td>There have been no voluntary or involuntary regulatory recalls of the Medtronic CoreValve® System to date. The original 18Fr Delivery Catheter System has been improved with the addition of the AccuTrak™ stability layer which has been added to aid in accuracy in the deployment of the Medtronic CoreValve® PAV. There are no design changes anticipated for the Medtronic CoreValve® System during the clinical trial.</td>
<td>There have been no voluntary or involuntary regulatory recalls of the Medtronic CoreValve® System in the United States to date. The original 18Fr Delivery Catheter System has been improved with the addition of the AccuTrak™ stability layer which has been added to aid in accuracy in the deployment of the Medtronic CoreValve® PAV. A 31mm valve size was added to increase the treatable annulus range. There are no other design changes anticipated for the Medtronic CoreValve® System during the clinical trial.</td>
<td>Updated for clarity and to include the addition of the 31mm PAV.</td>
<td></td>
</tr>
</tbody>
</table>

### Table 6

<table>
<thead>
<tr>
<th>Model</th>
<th>Size (mm)</th>
<th>Aortic Annulus Diameter (range in mm)</th>
<th>Ascending Aortic Diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCS-P3-640</td>
<td>26</td>
<td>20-23</td>
<td>≤40</td>
</tr>
<tr>
<td>MCS-P3-943</td>
<td>29</td>
<td>23-27</td>
<td>≤43</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model</th>
<th>Size (mm)</th>
<th>Aortic Annulus Diameter (range in mm)</th>
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<tbody>
<tr>
<td>MCS-P3-640</td>
<td>26</td>
<td>20-23</td>
<td>≤40</td>
</tr>
<tr>
<td>MCS-P3-943</td>
<td>29</td>
<td>23-27</td>
<td>≤43</td>
</tr>
<tr>
<td>MCS-P3-3743</td>
<td>31</td>
<td>25-29</td>
<td>≤43</td>
</tr>
</tbody>
</table>

Additional valve size and annulus range added to allow for 31mm valve. Addition of 31mm PAV.
<table>
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<th>#</th>
<th>Protocol Section</th>
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<th>Proposed change</th>
<th>Reason for the change</th>
<th>Justification</th>
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</thead>
<tbody>
<tr>
<td>10</td>
<td>5.1 Investigational Product Description Delivery Catheter System</td>
<td>The AccuTrak™ DCS (DCS-C4-18FR) is compatible with a 0.889-mm (0.035-in) guidewire. The working length of the AccuTrak™ DCS is 112.5 cm. It incorporates a protective deployment sheath that houses and deploys the PAV. The AccuTrak™ DCS can be used to house and deliver both the commercially available sizes of the PAV (26mm, and 29mm PAV). The outer diameter of the DCS is 12Fr, the stability layer is 15Fr and the outer diameter of the valve capsule is 18 Fr.</td>
<td>The AccuTrak™ DCS (DCS-C4-18FR) is compatible with a 0.889-mm (0.035-in) guidewire. The working length of the AccuTrak™ DCS is 112.5 cm. It incorporates a protective deployment sheath that houses and deploys the PAV. The AccuTrak™ DCS can be used to house and deliver all clinically available sizes of the PAV (26mm, 29mm, and 31mm PAV). The outer diameter of the DCS is 12Fr, the stability layer is 15Fr and the outer diameter of the valve capsule is 18 Fr.</td>
<td>Updated description to allow for 31mm valve.</td>
<td>Addition of 31mm PAV.</td>
</tr>
<tr>
<td>11</td>
<td>15.2 Definition of Terms</td>
<td>INTRACRANIAL HEMORRHAGE</td>
<td>INTRACRANIAL HEMORRHAGE</td>
<td>Correction of inadvertent spelling error.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>12</td>
<td>15.2 Definition of Terms HOSPITALIZATION FOR SIGNS AND SYMPTOMS RELATED TO AORTIC VALVE DISEASE</td>
<td>Aortic valve disease will be evaluated using documented evidence of the following signs and symptoms. An independent Clinical Events Committee (CEC) will review all available source documentation for all hospitalizations to determine if they are aortic valve disease hospitalizations. The CEC adjudication will be used for final analysis.</td>
<td>Aortic valve disease will be evaluated using documented evidence of the following signs and symptoms. An independent Clinical Events Committee (CEC) will review all available source documentation for any hospitalizations identified as possibly related to aortic valve disease. The CEC adjudication will be used for final analysis.</td>
<td>Minor wording clarification</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>14</td>
<td>Section 14 Amendments to the Investigational Plan</td>
<td>NA</td>
<td>8.0 October 10, 2011</td>
<td>Documentation of versions and associated changes</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>15</td>
<td>15.2 Definition of Terms DEVICE MALPLACEMENT/MALPOSITION</td>
<td>Placement of the Medtronic CoreValve® PAV in a non-therapeutic location, either inadvertently, or possibly intentionally due to unintended problems during the Medtronic CoreValve® System (MCS) delivery or procedure that necessitates placement in the non-therapeutic location. This does include movement during retrieval of the delivery catheter following BAV post implantation.</td>
<td>Placement of the Medtronic CoreValve® PAV in a non-therapeutic location, either inadvertently, or possibly intentionally due to unintended problems during the Medtronic CoreValve® System (MCS) delivery or procedure that necessitates placement in the non-therapeutic location. This does include movement during retrieval of the delivery catheter following BAV post implantation.</td>
<td>Correction of inadvertent spelling error.</td>
<td>No change to overall meaning of the protocol.</td>
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<tr>
<td>1</td>
<td>1. Synopsis</td>
<td>15. Device success defined as follows:</td>
<td>15. Device success defined as follows:</td>
<td>Modified Secondary Endpoint related to intended performance from smaller EOA of 23mm PAV (refer to G100012/S-031 Section 1.3).</td>
<td>Addition of 23 mm PAV</td>
</tr>
<tr>
<td></td>
<td>3.6.5</td>
<td>successful vascular access, delivery and deployment of the device, and successful retrieval of the delivery system, correct position of the device in the proper anatomical location (placement in the annulus with no impedance on device function), Intended performance of the prosthetic valve (aortic valve area &gt; 1.2 cm² (by echocardiography using the continuity equation) and mean aortic valve gradient &lt; 20 mmHg or peak velocity &lt; 3 m/sec, without moderate or severe prosthetic valve AR) Only one valve implanted in the proper anatomical location</td>
<td>only one valve implanted in the proper anatomical location</td>
<td>Additional range added to allow for 23mm valve. The 23mm has an aortic annulus diameter of 18-20mm.</td>
<td>Addition of 23mm PAV</td>
</tr>
<tr>
<td>2</td>
<td>1. Synopsis</td>
<td>#19 (ER) / #20 (HR) Native aortic annulus size &lt; 20 mm or &gt; 29 mm per the baseline diagnostic imaging.</td>
<td>#19 (ER) / #20 (HR) Native aortic annulus size &lt; 20 mm or &gt; 29 mm per the baseline diagnostic imaging.</td>
<td>Additional range added to allow for 23mm valve. The 23mm has an aortic annulus diameter of 18-20mm.</td>
<td>Addition of 23mm PAV</td>
</tr>
<tr>
<td></td>
<td>3.3.6</td>
<td>#25 (ER) / #26 (HR) Echocardiographic evidence of intracardiac mass, thrombus or vegetation.</td>
<td>#25 (ER) / #26 (HR) New or untreated Echocardiographic evidence of intracardiac mass, thrombus or vegetation</td>
<td>To clarify only untreated patients with documented intracardiac thrombus should be excluded from the protocol. Patients who have been adequately treated with anticoagulation therapy are deemed low risk for a thromboembolic event during or after the procedure and do not warrant exclusion. Additionally, all patients will receive anticoagulation therapy per protocol.</td>
<td>No change to overall meaning of the protocol</td>
</tr>
<tr>
<td>5</td>
<td>1. Synopsis</td>
<td>#28 (ER) / #29 (HR) Ascending aorta diameter &gt;43mm unless the</td>
<td>#28 (ER) / #29 (HR) Ascending aorta that exceeds the maximum diameter for any given native aortic annulus size (see table)</td>
<td>Additional criteria added to allow for 23mm</td>
<td>Addition of 23mm PAV</td>
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Original Version: HR Version 8.0
Update Version: HR Version 10.0
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Comprehensive Protocol Table of Changes (High Risk Study)

<table>
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<tr>
<td>3.3.6</td>
<td>Inclusion/Exclusion Criteria</td>
<td>aortic annulus is 20-23 mm in which case the ascending aorta diameter &gt;40 mm.</td>
<td>below): Aortic Annulus Diameter Ascending Aorta Diameter</td>
<td></td>
<td>no change to overall meaning of the protocol</td>
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<td>18 mm – 20 mm &gt; 34 mm</td>
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<td>20 mm – 23 mm &gt; 40 mm</td>
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<td>23 mm – 27 mm &gt;43 mm</td>
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<td>27 mm – 29 mm &gt; 43 mm</td>
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<tr>
<td>6</td>
<td>3.4.7 Data Collection Table 2 Schedule of Assessments</td>
<td></td>
<td>Computed Tomography (CT) X11</td>
<td></td>
<td>11 Peri-procedural angiographic cine film in DICOM format for CoreValve patients only</td>
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<tr>
<td>7</td>
<td>4.1 Risk Benefit Analysis Potential Risks and Discomforts</td>
<td>31mm valve size was added to increase the treatable annulus range. There are no other design changes anticipated for the Medtronic CoreValve® System during the clinical trial.</td>
<td>The 31 mm and 23 mm valve sizes were added to increase the treatable annulus range. A new Delivery Catheter System (DCS-C4-18FR-23MM) will be used to deploy 23mm Percutaneous Aortic Valve (PAV). There are no other design changes anticipated for the Medtronic CoreValve® System during the clinical trial.</td>
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<tr>
<td>8</td>
<td>5.1 Investigational Product Description Table 6</td>
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<td>9</td>
<td>5.1 Investigational Product Description Delivery Catheter System</td>
<td>The AccuTrak™ DCS can be used to house and deliver all clinically available sizes of the PAV (26mm, 29mm, and 31mm PAV). The outer diameter of the DCS is 12Fr, the stability layer is 15Fr and the outer diameter of the valve capsule is 18 Fr.</td>
<td>The AccuTrak™ DCS-C4-18FR can be used to house and deliver the 26mm, 29mm, and 31mm sizes of the PAV. The outer diameter of the DCS is 12Fr, the stability layer is 15Fr and the outer diameter of the valve capsule is 18 Fr. A new Delivery Catheter System (DCS-C4-18FR-23MM) will be used to deploy 23mm Percutaneous Aortic Valve (PAV). The DCS-C4-18FR-23MM has a shortened Capsule and Plunger (5mm) for delivery of the 23mm PAV but the working length of the new</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Original Version: HR Version 8.0
Update Version: HR Version 10.0
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<tr>
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<th>Justification</th>
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</thead>
<tbody>
<tr>
<td>10</td>
<td>Appendix 17.1 Instructions for Use</td>
<td>Includes PAV sizes 26, 29, and 31mm</td>
<td>Includes PAV sizes 23, 26, 29 and 31mm</td>
<td>Updated IFU for the 23mm PAV.</td>
<td>Addition of 23 mm PAV</td>
</tr>
<tr>
<td>11</td>
<td>Appendix 17.6 sample electronic Case Report Forms (eCRFs)</td>
<td>NA</td>
<td>The Inclusion/Exclusion Case report form was updated to include the new annulus range for the 23mm PAV. The CoreValve Procedure Form was updated to include the device success criteria specific to the 23mm PAV</td>
<td>Updated eCRFs for the 23mm PAV.</td>
<td>Addition of 23 mm PAV</td>
</tr>
<tr>
<td>12</td>
<td>Appendix 17.18 Investigator’s Brochure/Report of Prior Investigations</td>
<td>NA</td>
<td>Updates include: Device Description- Addition of 23mm PAV model to Table 1.0 Addition of DCS-18FR-23MM and Description Device Identification and traceability Addition of 23mm PAV model Addition of DCS-18FR-23MM</td>
<td>Updated IB for the 23mm PAV.</td>
<td>Addition of 23 mm PAV</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>Title Page Footer</td>
<td>Version 10.0 25-January-2012</td>
<td>Version 11.0 30-July-2012</td>
<td>Reflect Protocol Version</td>
<td>Revision Control</td>
</tr>
<tr>
<td>2</td>
<td>3.4.1 3.4.4 3.4.5</td>
<td>Routine laboratory tests (most recent) including complete blood count (CBC), creatinine, cardiac enzymes (CK and CK-MB), international normalized ratio (INR), Partial Thromboplastin Time (PTT), liver panel and albumin.</td>
<td>Routine laboratory tests (most recent) including complete blood count (CBC), creatinine, cardiac enzymes CK (and CK-MB if CK is elevated ≥ 2X the laboratory upper limit of normal), international normalized ratio (INR), Partial Thromboplastin Time (PTT), liver panel and albumin.</td>
<td>Clarification that CK-MB is only required if CK is elevated.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>3</td>
<td>3.4.3 Roll-in Cases</td>
<td>A patient will be considered a treated roll-in patient once the Medtronic CoreValve Delivery Catheter System is introduced into the patient. A site must have three treated roll-in patients before they can be evaluated to move to the randomization phase.</td>
<td>A successful roll-in patient, which counts towards the limit of three roll-in patients, is defined as the patient leaving the procedure room with one CoreValve device in the correct position and not requiring emergency surgery. An unsuccessful roll-in patient, which does not count towards the limit of three roll-in patients, is defined as any patient taken to the procedure room for the purpose of CoreValve implantation, but does not leave the procedure room with one CoreValve device in the correct position and not requiring emergency surgery. A site must have three successful roll-in patients before they can be evaluated to move into the randomization phase.</td>
<td>FDA proposed language change to define successful roll-in patients.</td>
<td>Meet FDA request.</td>
</tr>
<tr>
<td>4</td>
<td>3.4.5 MCS TAVI Procedure</td>
<td>NA</td>
<td>• Joint Participation  o The heart team’s interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of transcatheter aortic valve replacement (TAVR)</td>
<td>CMS National Coverage Decision was released since v.10.o of protocols</td>
<td>Meet CMS National Coverage Decision</td>
</tr>
<tr>
<td>5</td>
<td>3.4.5 Post-Procedure Pacing Guidelines</td>
<td>After 48 hours, obtain Electrocardiogram (ECG) and assess patient rhythm and conduction</td>
<td>After 48 hours, obtain Electrocardiogram (ECG) and assess patient rhythm and conduction</td>
<td>Correction of inadvertent error, text should not be bold.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>6</td>
<td>3.7.3 Core Laboratories Procedures</td>
<td>Data from the core lab will be transferred to Medtronic and stored in the Oracle Clinical Remote Data Capture system as described in the Medtronic CoreValve® U.S. Pivotal Trial Data Management Plan.</td>
<td>Data from the core lab will be entered by the core lab and stored in the Oracle Clinical Remote Data Capture system as described in the Medtronic CoreValve® U.S. Pivotal Trial Data Management Plan.</td>
<td>Clarification that the core labs will enter data directly.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>7</td>
<td>6.1 Monitoring</td>
<td>There will be 100% source document verification.</td>
<td>Source document verification will occur in accordance to the CoreValve Monitoring Plan.</td>
<td>Align protocol with revision to the monitoring plan.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>8</td>
<td>Section 15.1 List of Abbreviations</td>
<td>NA</td>
<td>TAVR Transcatheter aortic valve replacement</td>
<td>Added definition of abbreviation due to use of TAVR abbreviation in protocol.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>9</td>
<td>Section 15.2</td>
<td>Increase in serum creatinine to 200-300% (&gt; 2-3 x increase)</td>
<td>Increase in serum creatinine to 200-300% (&gt; 2-3 x increase)</td>
<td>Typographical error in the</td>
<td>Reflect current VARC</td>
</tr>
<tr>
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</tr>
<tr>
<td></td>
<td>Definition of Terms</td>
<td>Acute Kidney Injury – Stage 2 pushed to baseline) or increase between &gt;0.3 mg/dL (&lt;28.4 μmol/L) and &lt;4.0 mg/dL (&lt;354 μmol/L)</td>
<td>compared with baseline)</td>
<td>Vascular Academic Research Consortium (VARC) definition of Acute Kidney Injury (AKI)</td>
<td>definition</td>
</tr>
<tr>
<td>10</td>
<td>Appendix 17.3 Investigator site and IRB Information</td>
<td>NA</td>
<td>Added site and IRB information for Hartford Hospital and corrections to</td>
<td>45th site was activated on the study.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>11</td>
<td>Appendix 17.6 Sample Electronic Case Report Forms (eCRFs)</td>
<td>NA</td>
<td>Administrative edits</td>
<td>Updated to reflect current protocol</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>12</td>
<td>Appendix 17.18 Investigators’ Brochure/Report of Prior Investigations</td>
<td>NA</td>
<td>Administrative edits</td>
<td>Updated to reflect current published literature</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>13</td>
<td>1. Synopsis 3.3.5 Number of Subjects</td>
<td>Sample Size: 790 (395 MCS TAVI &amp; 395 SAVR)</td>
<td>Sample Size: 840 (420 MCS TAVI &amp; 420 SAVR) and up to 40 subjects enrolled with approximately 20 subjects randomized to TAVI and receiving a 23mm valve</td>
<td>Increased to ensure a minimum number of evaluable subjects and 15 patients with a 23 mm PAV implant</td>
<td>To allow enrollment of additional High Risk patients</td>
</tr>
<tr>
<td>14</td>
<td>3.3.6 Inclusion/Exclusion Criteria</td>
<td>23. Moderate to severe (3-4+) mitral regurgitation or (4+) tricuspid regurgitation associated with reduced right ventricular function or right heart failure.</td>
<td>23. Moderate to severe (3-4+) mitral regurgitation or (4+) tricuspid regurgitation.</td>
<td>Correction of inadvertent error.</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>15</td>
<td>3.3.8 Enrollment Flowchart</td>
<td>Total N: 395 SAVR 395 MCS TAVI</td>
<td>Total N: 420 SAVR 420 MCS TAVI</td>
<td>Increased to ensure a minimum number of evaluable subjects</td>
<td>To allow enrollment of additional High Risk patients</td>
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<td>-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>------------------------</td>
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</tbody>
</table>
| 16 | 3.4.5.2 Surgical Aortic Valve Replacement Immediate Post-Procedure | NA            | • Assessment of concomitant medications must be performed.  
• For patients with permanent pacemakers or defibrillators only: Perform a full interrogation and an assessment of AV conduction within 48 hours post procedure (Refer to the Pacing Guidelines in Appendix 17.14).  
Print a copy of the interrogation. It is recommended to save the interrogation via standard center practice (i.e. diskette, CD, flash drive). Retain the printed and saved copies of the interrogation in the subject's file for source verification.  
• Documentation of all adverse events/serious adverse events from enrollment to discharge including all unanticipated adverse device effects (UADE), technical observations, reinterventions or repeat admissions to the catheterization suite and deaths. | Correction of inadvertent error to insert missing text. | No change to overall meaning of the protocol. |
| 17 | 3.4.8 Follow-up Evaluations | • For patients with permanent pacemakers or defibrillators only (existing or new): Perform a full interrogation and an assessment of AV conduction (Refer to the Pacing Guidelines, Appendix 17.14).  
Print a copy of the interrogation. It is recommended to save the interrogation via standard center practice (i.e. diskette, CD, flash drive). Retain the printed and saved copies of the interrogation in the subject's file for source verification.  
The following assessments are required at the annual clinic visits at 2, 3, 4 and 5 years. | • For patients with permanent pacemakers or defibrillators only (existing or new): Perform a full interrogation and an assessment of AV conduction (Refer to the Pacing Guidelines, Appendix 17.14).  
Print a copy of the interrogation. It is recommended to save the interrogation via standard center practice (i.e. diskette, CD, flash drive). Retain the printed and saved copies of the interrogation in the subject's file for source verification.  
The following assessments are required at the annual clinic visits at 2, 3, 4 and 5 years. | Correction of inadvertent error, to add needed paragraph break. | No change to overall meaning of the protocol. |
| 18 | 3.6 Statistical Methods and Analysis | NA            | The 23mm valve was not available until late in the study; therefore if approximately 20 23mm CoreValve implants have not occurred at the time of approximately 840 randomized subjects, the 23mm subjects will not be included in the primary analysis.  
Therefore, up to 40 additional subjects will be randomized with about 20 23mm CoreValve implants. When 1 year data are available for the 23mm valve, the primary and secondary endpoint data will be summarized with descriptive statistics. If appropriate, the 23mm valve subjects will be pooled with the original 840 subjects in the primary analysis dataset and the primary and secondary endpoints will be recalculated. The primary endpoint | Increased to ensure a minimum of 15 patients with a 23 mm PAV implant | To allow for additional 23 mm PAV patients |
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<td>19</td>
<td>3.6.5.2 Sample Size Determination</td>
<td>Assuming 1:1 treatment allocation ratio between study device and surgical valve replacement and assuming the proportion of all-cause mortality at 12 months equal to 20% for both arms and a non-inferiority margin of 7.5%, Power Analysis and Sample Size (PASS) software calculates that a total of 355 subjects in each arm is required to attain 80% power in a test of non-inferiority of the study device at the 0.05 level of significance. Accounting for 10% loss to follow-up, a total of 395 x 395 = 790 subjects is required.</td>
<td>Assuming 1:1 treatment allocation ratio between study device and surgical valve replacement and assuming the proportion of all-cause mortality at 12 months equal to 20% for both arms and a non-inferiority margin of 7.5%, Power Analysis and Sample Size (PASS) software calculates that a total of 355 subjects in each arm is required to attain 80% power in a test of non-inferiority of the study device at the 0.05 level of significance. Accounting for a 15% drop-out rate or loss to follow-up in each treatment arm, a total of 420 x 420 = 840 subjects is required.</td>
<td>Increased to ensure a minimum number of evaluable subjects</td>
<td>To allow enrollment of additional High Risk patients</td>
</tr>
<tr>
<td>20</td>
<td>Section 14 Amendments to the Investigational Plan</td>
<td>NA</td>
<td>11.0 July 30, 2012 Increase sample size, CMS reimbursement language and administrative edits.</td>
<td>Documentation of versions and associated changes</td>
<td>No change to overall meaning of the protocol</td>
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<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1. Synopsis</td>
<td>Sample Size: 840 (420 MCS TAVI &amp; 420 SAVR) and up to 40 additional subjects enrolled with approximately 20 subjects randomized to TAVI and receiving a 23mm valve Non-ilio-femoral will be limited to no more than 30% (264) of the 880 randomized subjects.</td>
<td>Sample Size: 790 (395 MCS TAVI &amp; 395 SAVR) and up to 40 additional subjects enrolled with approximately 20 subjects randomized to TAVI and receiving a 23mm valve Non-ilio-femoral will be limited to no more than 30% (249) of the 830 randomized subjects.</td>
<td>Revert back to original sample size</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>2</td>
<td>3.3.8 Enrollment Flowchart</td>
<td>Total N: 420 SAVR 420 MCS TAVI</td>
<td>Total N: 395 SAVR 395 MCS TAVI</td>
<td>Revert back to original sample size</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>3</td>
<td>3.6 Statistical Methods and Analysis</td>
<td>The 23mm valve was not available until late in the study; therefore if approximately 20 23mm CoreValve implants have not occurred at the time of approximately 840 randomized subjects, the 23mm subjects will not be included in the primary analysis. Therefore, up to 40 additional subjects will be randomized with about 20 23mm CoreValve implants. When 1 year data are available for the 23mm valve, the primary and secondary endpoint data will be summarized with descriptive statistics. If appropriate, the 23mm valve subjects will be pooled with the original 840 subjects in the primary analysis dataset and the primary and secondary endpoints will be recalculated.</td>
<td>The 23mm valve was not available until late in the study; therefore if approximately 20 23mm CoreValve implants have not occurred at the time of approximately 790 randomized subjects, the 23mm subjects will not be included in the primary analysis. Therefore, up to 40 additional subjects will be randomized with about 20 23mm CoreValve implants. When 1 year data are available for the 23mm valve, the primary and secondary endpoint data will be summarized with descriptive statistics. If appropriate, the 23mm valve subjects will be pooled with the original 790 subjects in the primary analysis dataset and the primary and secondary endpoints will be recalculated.</td>
<td>Revert back to original sample size</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>4</td>
<td>3.6.5.2 Sample Size Determination</td>
<td>Accounting for a 15% drop-out rate or loss to follow-up in each treatment arm, a total of 420+420 = 840 subjects is required to have a minimum of 355 subjects in each arm.</td>
<td>Accounting for a 10% drop-out rate or loss to follow-up in each treatment arm, a total of 395+395 = 790 subjects is required to have a minimum of 355 subjects in each arm.</td>
<td>Revert back to original sample size</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
<tr>
<td>5</td>
<td>Section 14 Amendments to the Investigational Plan</td>
<td>NA</td>
<td>12.0 August 22, 2012 Change sample size back to original sample size of 790 subjects.</td>
<td>Documentation of versions and associated changes</td>
<td>No change to overall meaning of the protocol.</td>
</tr>
</tbody>
</table>
CardioVascular Structural Heart Clinical Department

Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients)

Statistical Analysis Plan

Version 1
Date: 03 MAR 2011

IDE No. G100012
CIP No. MCV-US-2009-01 (High Risk Surgical)

Prepared by:

Christopher Wiggenhorn, Ph.D.
Principal Statistician
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3.3.4.1 Hypothesis and/or Parameters to Be Estimated

3.3.4.2 Endpoint Definition

3.3.4.3 Data Collection and Analysis Methods

3.3.5 Secondary Objective #5 - NYHA

3.3.5.1 Hypothesis and/or Parameters to Be Estimated

3.3.5.2 Endpoint Definition

3.3.5.3 Data Collection and Analysis Methods

3.3.6 Secondary Objective #6 - Six-Minute Walk Test

3.3.6.1 Hypothesis and/or Parameters to Be Estimated

3.3.6.2 Endpoint Definition

3.3.6.3 Data Collection and Analysis Methods

3.3.7 Secondary Objective #7 - Ratio of Days Alive Out of Hospital Versus Total Days Alive

3.3.7.1 Hypothesis and/or Parameters to Be Estimated

3.3.7.2 Endpoint Definition

3.3.7.3 Data Collection and Analysis Methods

3.3.8 Secondary Objective #8 - Quality of Life

3.3.8.1 Hypothesis and/or Parameters to Be Estimated

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3.3.9 Secondary Objective #9 - Echocardiographic Assessment of Valve Performance

3.3.9.1 Hypothesis and/or Parameters to Be Estimated

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3.3.10 Secondary Objective #10 - Aortic Valve Disease-Related Hospitalizations

3.3.10.1 Hypothesis and/or Parameters to Be Estimated

3.3.10.2 Endpoint Definition

3.3.10.3 Data Collection and Analysis Methods

3.3.11 Secondary Objective #11 - Cardiovascular Deaths and Valve-Related Deaths

3.3.11.1 Hypothesis and/or Parameters to Be Estimated

3.3.11.2 Endpoint Definition

3.3.11.3 Data Collection and Analysis Methods

3.3.12 Secondary Objective #12 - Strokes and TIAs

3.3.12.1 Hypothesis and/or Parameters to Be Estimated

3.3.12.2 Endpoint Definition

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3.3.13 Secondary Objective #13 - Index Procedure-Related MAEs

3.3.13.1 Hypothesis and/or Parameters to Be Estimated

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3.3.14 Secondary Objective #14 - Length of Index Procedure Hospital Stay

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3.3.16.1 Hypothesis and/or Parameters to Be Estimated

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1 PURPOSE OF SAP

This Statistical Analysis Plan has been designed to document, before data are analyzed, the rationale for the study design, and the planned analyses that will be included in study reports. The design and analyses are consistent with the objectives of the Clinical Investigational Plan (CIP).

2 RATIONALE FOR STUDY DESIGN

The purpose of this study is to evaluate the safety and efficacy of the Medtronic CoreValve® System in the treatment of symptomatic severe aortic stenosis in subjects who have a predicted high risk for aortic valve surgery. High risk surgical subjects will be randomized to receive either transcatheter aortic valve implant (TAVI) with the Medtronic CoreValve® System (MCS) or surgical aortic valve replacement (SAVR) in a 1:1 ratio.

This statistical analysis plan is developed based on the Clinical Investigational Plan Version 4.0.

3 DESCRIPTION OF ANALYSIS

3.1 General Summaries

3.1.1 Description of Baseline Variables

Baseline demographic and clinical variables will be summarized for each of the treatment groups for the intent-to-treat, as treated, implanted, and per protocol populations. Refer to section 3.1.3.7 for definitions of these analysis sets. All continuous variables will be summarized with means, medians, standard deviations, interquartile ranges, minimums, and maximums and compared between treatment groups using a two-sample t-test or the non-parametric Wilcoxon rank-sum test. Categorical variables will be summarized with frequencies and percentages and compared between treatment groups using Pearson’s χ² test or Fisher’s exact test, as appropriate. Ordinal variables will be compared using Cochran-Mantel-Haenszel test with row mean scores.

Age will be calculated as the difference in days between the subject’s date of birth and the date of signing the informed consent, divided by 365.25.

3.1.2 Reports for which this Statistical Analysis Plan applies

This Statistical Analysis Plan applies to the study report for Pre-market Approval Application (PMA) to the Food and Drug Administration (FDA) and to the final report.
3.1.3 Special Considerations

3.1.3.1 Report Timing and Cutoff Dates

The PMA report will be generated after all enrolled subjects have completed their 12-month follow-up visit in-window or later (or, if early, have been followed for at least 365 days via a subsequent follow-up form), have died, or have exited from the study.

Cutoff dates will be applied to all site case report forms. A Visit Cutoff Date and a Received Cutoff Date will be used. The visit cutoff date will be the first date on which all enrolled subjects have been followed for 12 months, have died, or have exited from the study. The visit, assessment, and event dates will be used to determine which case report forms satisfy the visit cutoff date. The received cutoff date will be determined near the time of the database closure and will chosen to ensure that all known deaths, 12-month visits, and other forms of critical importance have been received while still allowing adequate time for data cleaning between the received cutoff date and the date of database closure. The "logints" log-in timestamp field will be used to determine which case report forms satisfy the received cutoff date.

Any forms which do not have a visit date directly on the form (e.g., the protocol deviation form) will use the visit date from the corresponding form for that entry. Forms with multiple dates (e.g., the protocol deviation form and the medication form) will apply cutoff dates to individual lines of data on the form.

The final report will be generated after all enrolled subjects have been followed for 5 years, have died, or have exited from the study. Because the intent is to report on all study data, it is not expected that cutoff dates will apply to the final report.

3.1.3.2 Missing Data

Unless specified in each objective, no statistical techniques will be used to impute missing data. If a subject’s data are missing for any reason, that subject will not be included in that portion of the analysis. The number of subjects included in each analysis will be reported so that the potential impact of missing data can be assessed. See sections 3.2.1.5 and 3.2.2.5 for the handling of missing data for the primary objective and powered secondary hypothesis, respectively.

In the case of partial dates, if only the month and year are known, the event or assessment will be analyzed as if it occurred on the 15th of that month. If only the year is known, the event or assessment will be analyzed as if it occurred on June 30th of that year. These resolutions of partial dates are subject to the restrictions that pre-procedure events and assessments must occur between the randomization date and the procedure date and post-procedure events and assessments must occur no earlier than the procedure date.

3.1.3.3 P-Values

All statistical tests and/or confidence intervals, as appropriate, will be performed at $\alpha = 0.05$ (2-sided), except when specified otherwise. All reported p-values greater
than or equal to 0.001 will be rounded to three decimal places. P-values less than 0.001 will be displayed as “<0.001.”

3.1.3.4 **Student’s t-Tests**

For analyses of continuous data, given the sample sizes, it is expected that, even if the underlying data are not normal, that the sampling distributions of the sample means will be sufficiently normal to permit use of paired and 2-sample t-tests. Only in unusual cases will these be replaced with the Wilcoxon signed-rank and rank-sum tests, respectively.

For any two-sample t-test performed, the t-statistic will be calculated based on equal variances if the test for equality of variances is nonsignificant (p > 0.05). Otherwise, the t-statistic based on unequal variances will be used to compare the two samples.

3.1.3.5 **Chi-Square Tests**

For analyses of categorical data, chi-square tests will be used unless there are expected cell counts of less than 5. In those cases, Fisher’s exact test will be used.

3.1.3.6 **Kaplan-Meier Analyses**

Secondary objectives #1-4, #10-12, and #17 call for a Kaplan-Meier analysis of event-free rates at 30 days, 6 months, 12 months and annually through five years. For these analyses, these times correspond to 30 days, 183 days, 365 days, 730 days, 1095 days, 1460 days, and 1825 days, respectively. At each time point with data, the product-limit estimate of the event-free rate, the number of subjects at risk, the number of subjects with events, and the Peto standard error of the estimate will be presented.

For subjects without an event, the date of censoring will be the latest date of all follow-up visits, assessments, and events (including death).

3.1.3.7 **Analysis Sets**

There are four different analysis sets that are defined for this study. The primary analysis will be the “as treated” analysis. Data from roll-in patients will be presented separately with descriptive statistics.

3.1.3.7.1 **Intent-to-Treat**

The intent-to-treat population consists of all randomized subjects. Subjects will be analyzed according to the randomization assignment and the stratified access site (ilio-femoral or non-ilio-femoral), regardless of whether a procedure is actually attempted, which device the subject actually receives, and which access site is actually used. This population excludes roll-in patients. Because not all subjects in this population will have a procedure, time zero begins at the date of randomization.

3.1.3.7.2 **As Treated**

The as treated population consists of all randomized patients 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 (TAVI or SAVR). TAVI subjects will be analyzed according to the access site on the procedure form, while SAVR subjects will be analyzed according to the stratified access site. This population excludes roll-in patients. Time zero begins at the date of attempted procedure.

3.1.3.7.3 Implanted
The implanted population consists of all as treated subjects who are actually implanted with either the CoreValve device or a surgical valve. To be considered implanted, an MCS TAVI subject’s device disposition form must show at least one device with a final disposition of “Implanted,” while an SAVR subject’s procedure form must indicate the valve manufacturer and model as well as the suture method. Time zero begins at the date of the procedure.

3.1.3.7.4 Per Protocol
Based on the ICH E9 Statistical Principles for Clinical Trials recommendations, the per protocol population should satisfy the following:

1. The completion of a certain prespecified minimal exposure to the treatment regimen
2. The availability of measurements of the primary variable(s)
3. The absence of any major protocol violations, including the violation of entry criteria

To meet these requirements, the per protocol population will consist of all implanted subjects who were implanted according to their randomization and access site stratification and who have at least 12 months (365 days) of follow-up or have experienced the primary endpoint (death) prior to 12 months. These subjects must satisfy all inclusion/exclusion criteria. Time zero begins at the date of the procedure.

3.1.3.8 Interim Analysis
No formal interim analysis is planned, and there are no plans for early termination of the study due to superiority or futility of the investigational therapy.

3.1.3.9 Data Safety Monitoring Board (DSMB)
An independent, unblinded DSMB will be established and will be comprised of at least 3 experts, including a chairperson. The DSMB will have a minimum of one cardiac surgeon, one interventional cardiologist and one statistician, and will be independent of Medtronic and the trial investigators. Investigators participating in the trial may participate in the meetings to offer clarification surrounding events, but will not have voting privileges. Medtronic personnel may facilitate the DSMB meeting but will not have voting privileges. The DSMB will meet (via teleconference or in person) prior to the first subject enrollment to establish procedures for DSMB review, chairman appointment, and guidelines for trial recommendations. The full DSMB will meet on a periodic basis to perform a comprehensive data review, including at a minimum all adverse events and deaths, and will meet more frequently when needed. Primary and safety-related
secondary endpoints may also be reviewed at these meetings. Meetings will consist of both open and closed sessions.

The DSMB will also perform a supplemental review of, at a minimum, all serious adverse events and deaths and any other data requested by the DSMB on a more frequent periodic basis to ensure patient safety. DSMB members will review the report, and when necessary, provide recommendations about the conduct of the study and/or request a full DSMB meeting.

A DSMB charter will be developed and approved by Medtronic and the DSMB members. The committee will outline the criteria for both the full DSMB meeting and supplemental DSMB reviews within the DSMB charter.

Following each full DSMB meeting, the board will report to Medtronic in writing and may recommend changes in the conduct of the trial. These DSMB recommendations may include recommendations on trial status such as continuing the trial without modifications, continuing the trial with modifications, stopping the enrollment in the trial or a specific trial arm, or recommendations about trial conduct including recommendations around enrollment or protocol deviations.

In the case of UADEs, if Medtronic and the DSMB determine that the event presents an unreasonable risk to the participating subjects, Medtronic must terminate the clinical trial 5 working days after making that determination and not later than 15 working days after Medtronic first receives notice of the effect [21 CFR 812.46]. 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.

Additional details about the DSMB can be found in the DSMB charter.

3.2 Primary Objective

3.2.1 Primary Objective

The primary objective is to demonstrate that the safety and effectiveness of the Medtronic CoreValve® System (MCS), as measured by all cause mortality rates at 12 months, is non-inferior to surgical aortic valve replacement (SAVR) in the treatment of symptomatic severe aortic stenosis in subjects who have a predicted high risk for aortic valve surgery.

3.2.1.1 Hypothesis and/or Parameters to Be Estimated

Primary Hypothesis: TAVI with the Medtronic CoreValve® System is non-inferior to surgical aortic valve replacement (SAVR) in 12 month all-cause mortality:

\[
H_0: \pi_{\text{MCS TAVI}} \geq \pi_{\text{SAVR}} + 7.5\%
\]

\[
H_A: \pi_{\text{MCS TAVI}} < \pi_{\text{SAVR}} + 7.5\%
\]

In the above expression, \(\pi_{\text{MCS TAVI}}\) and \(\pi_{\text{SAVR}}\) denote binary rates of all-cause mortality during a fixed follow-up of 12 months.
3.2.1.2 **Endpoint Definition**

The primary endpoint is the binary rate of all-cause mortality at 12 months. For each treatment group, the numerator will be the number of subjects who died at or before 12 months (365 days), and the denominator will be the number of subjects in the analysis cohort.

3.2.1.3 **Sample Size Methods and Assumptions**

**A. Sample Size Calculation and Methods**

The following are assumptions for the sample size estimate:

1:1 treatment allocation ratio

One-sided alpha = 0.05

\[ \pi_{SAVR} = 20.0\% \]

\[ \pi_{MCS\ TAVI} = 20.0\% \]

Power = >80%

Assuming 1:1 treatment allocation ratio between study device and surgical valve replacement and assuming the proportion of all-cause mortality at 12 months equal to 20% for both arms and a non-inferiority margin of 7.5%, Power Analysis and Sample Size (PASS) software calculates that a total of 355 subjects in each arm is required to attain 80% power in a Farrington and Manning test of non-inferiority of the study device at the 0.05 level of significance.
Accounting for 10% loss to follow-up, a total of $395 + 395 = 790$ subjects is required.

**B. Rationale for Choice of Hypothesis**

The assumption for 12 month mortality for the SAVR arm is an estimate based on 12-month mortality as reported in the surgical literature for high risk AVR (table below). The subjects enrolled in this study are expected to have a higher mortality than observed in the surgical literature, as subjects enrolled in the High Risk Surgical Cohort must have an expected perioperative mortality of 15% (based on Investigator-estimated mortality or STS score >10).
Table 1. All-cause mortality rates of high risk population from published data.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Mortality at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elayda et al.</td>
<td>1993</td>
<td>77</td>
<td>16%</td>
</tr>
<tr>
<td>Sundt et al.</td>
<td>2000</td>
<td>133</td>
<td>20%</td>
</tr>
<tr>
<td>Chiappini et al.</td>
<td>2004</td>
<td>71</td>
<td>10%</td>
</tr>
<tr>
<td>Collart et al.</td>
<td>2005</td>
<td>215</td>
<td>16%</td>
</tr>
<tr>
<td>Varadarajan et al.</td>
<td>2006</td>
<td>80</td>
<td>13%</td>
</tr>
<tr>
<td>Melby et al.</td>
<td>2007</td>
<td>105</td>
<td>18%</td>
</tr>
</tbody>
</table>

Currently, the average patient undergoing surgery is older and has a greater number of comorbidities than the previously studied population. Given that the expected High Risk Surgical population will be older and at higher risk for surgery, it is estimated that the 12-month all-cause mortality rate among high risk SAVR subjects in the current study will be 20%.

3.2.1.4 Data Collection and Analysis Methods

A. Data Collection and Analysis

Death data will be collected on a CEC adjudication form.

The one-sided Farrington and Manning\(^{ii}\) test for non-inferiority of two binomial proportions will be carried out to assess statistical significance at the 0.05 level. The test statistic will be calculated as:

\[
z = \frac{p_1 - p_2 - \delta_0}{\sqrt{\frac{\hat{p}_1 (1 - \hat{p}_1)}{n_1} + \frac{\hat{p}_2 (1 - \hat{p}_2)}{n_2}}}
\]

Where \( p_1 \) and \( p_2 \) are the usual sample proportions, \( n_1 \) and \( n_2 \) are the sizes of the analysis cohorts, and \( \delta_0 = 0.075 \). In the calculation of the standard error, \( \hat{p}_1 \) and \( \hat{p}_2 \) are the maximum likelihood estimators under the constraint that the difference equals \( \delta_0 \), where that solution is given by

\[
\begin{align*}
\hat{p}_1 &= 2u \cos(w) - b / 3a \\
\hat{p}_2 &= \hat{p}_1 + \delta_0
\end{align*}
\]

where
Assuming that non-inferiority is proven at the one-sided 0.05 level, a subsequent test for superiority will be performed using the above test statistic with $\delta_0 = 0$. Because this is a closed test procedure, no adjustment for multiplicity is needed.

Additionally, a 90% large sample confidence interval for the difference in proportions will be as:

$$(p_1 - p_2) \pm z_{0.025} \sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}}$$

B. Determination of Patients/Data for Analysis

This objective will be analyzed for the intent-to-treat, as treated, implanted and per protocol populations.

3.2.1.5 Missing Data

Every effort will be undertaken to minimize missing data. Since all-cause mortality is the primary endpoint for this trial, a minimal amount of missing data is anticipated. Subjects with any follow-up visits, assessments, or events on or after day 365 will be considered to have complete data for the purposes of this analysis, although only deaths occurring on or before 12 months (365 days) will count toward the primary endpoint. However, if outcome data are missing, Kaplan-Meier rates at 12 months will replace the binomial proportions in the calculation of the Farrington and Manning test statistic.

To assess the potential impact of any missing data, a sensitivity analysis will be conducted which will include a complete case (including only subjects whose status is known at 365 days), a best-case (assume missing MCS TAVI subjects are alive and SAVR subjects have died), a worst-case (assume missing MCS TAVI subjects have died and SAVR subjects are alive), and a tipping point analysis.

3.2.2 Powered Secondary Hypothesis

TAVI with the Medtronic CoreValve® System is superior to SAVR in binary rate of MACCE at 30 days or hospital discharge, whichever is longer.
3.2.2.1 **Hypothesis and/or Parameters to Be Estimated**

Powered Secondary Hypothesis: TAVI with the Medtronic CoreValve® System is superior to surgical aortic valve replacement (SAVR) in binary rate of MACCE at 30 days or hospital discharge, whichever is longer:

\[ H_0: \pi_{\text{MCS TAVI}} = \pi_{\text{SAVR}} \]
\[ H_A: \pi_{\text{MCS TAVI}} < \pi_{\text{SAVR}} \]

In the above expression \( \pi_{\text{MCS TAVI}} \) and \( \pi_{\text{SAVR}} \) denote binary rates of MACCE at 30 days or hospital discharge, whichever is longer.

3.2.2.2 **Endpoint Definition**

The endpoint is the binary rate of MACCE at 30 days or hospital discharge, whichever is longer. For each treatment group, the numerator will be the number of subjects with a MACCE at 30 days or hospital discharge, whichever is longer, and the denominator will be the number of subjects in the analysis cohort. Refer to section 3.3.1.2 for the MACCE endpoint definition.

3.2.2.3 **Sample Size Methods and Assumptions**

A. **Sample Size Calculation and Methods**

The following are assumptions for the sample size estimate:

1:1 treatment allocation ratio

One-sided alpha = 0.025

\( \pi_{\text{SAVR}} = 20.0\% \)

\( \pi_{\text{MCS TAVI}} = 12.1\% \)

Power = >80%

For the secondary superiority hypothesis, assuming 1:1 treatment allocation ratio between study device and surgical valve replacement and assuming the proportion of MACCE at 30 days or hospital discharge, whichever is longer, equal to 20% in the surgical valve replacement arm and equal to 12.1% in the study device arm (39.5% relative treatment effect), PASS software calculates that 355 evaluable subjects per arm would yield 81.9% power for a one-sided test at the 0.025 level of significance.
B. Rationale for Choice of Hypothesis

Sundt et al.\textsuperscript{iv}, Collart et al.\textsuperscript{vi}, and Melby et al.\textsuperscript{viii} reported MACCE rates at 30 days. From these studies, the MACCE (defined as a composite of all cause death, MI (Q-wave and non-Q-wave), emergent cardiac surgery, stroke, and reintervention) rate ranged from 15% to 31% with meta-analytic average of 20.1% (95% CI 16.5-23.8%). Thus, for the current study it is assumed that the expected MACCE rate at 30 days will be 20%.

3.2.2.4 Data Collection and Analysis Methods

A. Data Collection and Analysis

MACCE data will be collected on a CEC adjudication form.

The test statistic will be calculated using the pooled z-test without correction for continuity:

$$z = \frac{P_{MCSTAVI} - P_{SAFR}}{\sqrt{p(1-p)\left(\frac{1}{n_{MCSTAVI}} + \frac{1}{n_{SAFR}}\right)}}$$
where \( p \) is the pooled sample proportion:

\[
p = \frac{n_{\text{MCSTAVI}} p_{\text{MCSTAVI}} + n_{\text{SAVR}} p_{\text{SAVR}}}{n_{\text{MCSTAVI}} + n_{\text{SAVR}}}
\]

In the above expressions \( p_{\text{MCSTAVI}} \) and \( p_{\text{SAVR}} \) are the sample proportions of subjects having a MACCE by 30 days or discharge, whichever is longer, and \( n_{\text{MCSTAVI}} \) and \( n_{\text{SAVR}} \) are the numbers of subjects in each analysis cohort. The test is one-sided and the resulting \( p \)-value will be compared to 0.025.

**B. Determination of Patients/Data for Analysis**

This objective will be analyzed for the intent-to-treat, as treated, implanted and per protocol populations.

3.2.2.5 **Missing Data**

Every effort will be undertaken to minimize missing data. Because MACCE is a safety endpoint and because this endpoint is evaluated at 30 days, a minimal amount of missing data is anticipated for this secondary hypothesis. Subjects with any follow-up visits, assessments, or events on or after day 30 will be considered to have complete data for the purposes of this analysis. However, if outcome data are missing, Kaplan-Meier rates at 30 days will replace the binomial proportions in the calculations above. For subjects whose discharge date was after 30 days, any events prior to discharge will be treated as occurring on day 30.

To assess the potential impact of any missing data, a sensitivity analysis will be conducted which will include a complete case (including only subjects whose status is known at 30 days or discharge, whichever is longer), a best-case (assume missing MCS TAVI subjects are MACCE-free and SAVR subjects have a MACCE), a worst-case (assume missing MCS TAVI subjects have a MACCE and SAVR subjects are MACCE-free), and a tipping point analysis.

3.3 **Secondary Objectives**

3.3.1 **Secondary Objective #1 – MACCE**

MACCE-free survival at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

3.3.1.1 **Hypothesis and/or Parameters to Be Estimated**

The following hypotheses will be tested:

\[ H_0: S(t)_{\text{MCSTAVI}} = S(t)_{\text{SAVR}} \text{ for all } t \]
\[ H_A: S(t)_{\text{MCSTAVI}} \neq S(t)_{\text{SAVR}} \text{ for at least one } t \]

In the above expressions \( S(t)_{\text{MCSTAVI}} \) and \( S(t)_{\text{SAVR}} \) denote the MACCE-free survival functions for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

MACCE-free survival estimates for each treatment group will be provided at 30 days, 6 months, 12 months and annually through five years.
3.3.1.2 Endpoint Definition

MACCE is defined as a composite of:
- All-cause death
- Myocardial infarction (MI)
- All stroke
- Reintervention (defined as any cardiac surgery or percutaneous reintervention catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve)

MACCE components will be adjudicated by the Clinical Events Committee (CEC).

3.3.1.3 Data Collection and Analysis Methods

A. Data Collection and Analysis

Data will be collected on a CEC adjudication form. A Kaplan-Meier survival analysis will be performed for each treatment group, and the log-rank test will be used to compare the treatment groups.

B. Determination of Patients/Data for Analysis

This objective will be analyzed for the as treated population.

3.3.2 Secondary Objective #2 - Individual MACCE Components

The occurrence of individual MACCE components at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

3.3.2.1 Hypothesis and/or Parameters to Be Estimated

For each of individual MACCE components the following hypotheses will be tested:

\[ H_0: S(t)_{MCS\ TAVI} = S(t)_{SAVR} \text{ for all } t \]
\[ H_A: S(t)_{MCS\ TAVI} \neq S(t)_{SAVR} \text{ for at least one } t \]

In the above expressions, \( S(t)_{MCS\ TAVI} \) and \( S(t)_{SAVR} \) denote the MACCE-free survival functions for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

MACCE-free survival estimates of individual MACCE components for each treatment group will be provided at 30 days, 6 months, 12 months and annually through five years.

3.3.2.2 Endpoint Definition

The four individual components of MACCE are all-cause death, myocardial infarction (MI), stroke, and reintervention.

3.3.2.3 Data Collection and Analysis Methods

A. Data Collection and Analysis

Data will be collected on a CEC adjudication form. A Kaplan-Meier survival analysis will be performed for each of the four components for each of the treatment groups. The log-rank test will be used to compare the treatment groups for each component.

B. Determination of Patients/Data for Analysis

This objective will be analyzed for the as treated population.
3.3.3 Secondary Objective #3 – MAE

MAE at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

3.3.3.1 Hypothesis and/or Parameters to Be Estimated

The following hypotheses will be tested:

\[ H_0: S(t)_{\text{MCS TAVI}} = S(t)_{\text{SAVR}} \text{ for all } t \]
\[ H_A: S(t)_{\text{MCS TAVI}} \neq S(t)_{\text{SAVR}} \text{ for at least one } t \]

In the above expressions \( S(t)_{\text{MCS TAVI}} \) and \( S(t)_{\text{SAVR}} \) denote the MAE-free survival functions for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

MAE-free survival estimates for each treatment group will be provided at 30 days, 6 months, 12 months and annually through five years.

3.3.3.2 Endpoint Definition

Major adverse events (MAE) include:

- MACCE
- Acute kidney injury
- Cardiac tamponade
- Prosthetic valve dysfunction
- Cardiogenic shock
- Valve endocarditis
- Valve embolism
- Life-threatening, disabling or major bleeding
- Major vascular complication
- Cardiac perforation
- Device migration

MAE components will be adjudicated by the Clinical Events Committee (CEC).

3.3.3.3 Data Collection and Analysis Methods

A. Data Collection and Analysis

Data will be collected on a CEC adjudication form. A Kaplan-Meier survival analysis will be performed for each treatment group, and the log-rank test will be used to compare the treatment groups.

B. Determination of Patients/Data for Analysis

This objective will be analyzed for the as treated population.

3.3.4 Secondary Objective #4 - Conduction Disturbance Requiring Permanent Pacemaker Implantation

Conduction disturbance requiring permanent pacemaker implantation at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

3.3.4.1 Hypothesis and/or Parameters to Be Estimated

Separately for new onset and pre-existing conduction disturbance, the following hypotheses will be tested:
H0: S(t)_{MCS TAVI} = S(t)_{SAVR} for all t  
Ha: S(t)_{MCS TAVI} ≠ S(t)_{SAVR} for at least one t

In the above expressions S(t)_{MCS TAVI} and S(t)_{SAVR} denote the pacemaker implantation-free survival functions for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

Pacemaker implantation-free survival estimates for each treatment group will be provided at 30 days, 6 months, 12 months and annually through five years, separately for new onset and pre-existing conduction disturbance.

3.3.4.2 Endpoint Definition

Conduction disturbance requiring permanent pacemaker implantation is defined as any disturbance in the cardiac electrical conduction system that meets the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) Class I or Ila Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities for Acquired Atroventricular Block in Adults or Permanent Pacing in Chronic Bifascicular Block. This endpoint will be adjudicated by an EKG core lab.

3.3.4.3 Data Collection and Analysis Methods

A. Data Collection and Analysis

Data will be collected on an EKG core lab adjudication form. Separately for new onset and pre-existing conduction disturbance, a Kaplan-Meier survival analysis will be performed for each treatment group, and the log-rank test will be used to compare the treatment groups.

B. Determination of Patients/Data for Analysis

This objective will be analyzed for the as treated population.

3.3.5 Secondary Objective #5 – NYHA

Change in NYHA class from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

3.3.5.1 Hypothesis and/or Parameters to Be Estimated

The following hypotheses will be tested at 30 days, 6 months, 12 months and annually thereafter up to 5 years:

H0: \mu_{MCS TAVI} = \mu_{SAVR} 
Ha: \mu_{MCS TAVI} ≠ \mu_{SAVR}

In the above expressions \mu_{MCS TAVI} and \mu_{SAVR} denotes the mean change in NYHA classification from baseline, for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

The following hypotheses will also be tested at 30 days, 6 months, 12 months and annually thereafter up to 5 years:

H0: \mu_{MCS TAVI} = 0 
Ha: \mu_{MCS TAVI} ≠ 0 

and
H0: \( \mu_{SAVR} = 0 \)
HA: \( \mu_{SAVR} \neq 0 \)

Additionally, a test of non-inferiority at 12 months will be performed as part of a hierarchical test procedure. Refer to section 3.3.18 for more details.

### 3.3.5.2 Endpoint Definition

New York Heart Association (NYHA) class is a classification system for defining cardiac disease and related functional limitations into four broad categorizations:

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

For each subject with paired data, the number of classes changed from baseline (-2, -1, 0, 1, 2, or 3) will be calculated at 30 days, 6 months, 12 months and annually through five years.

### 3.3.5.3 Data Collection and Analysis Methods

#### A. Data Collection and Analysis

Data will be collected on follow-up visit forms. NYHA classifications will be summarized with frequencies and percentages at baseline, 30 days, 6 months, 12 months and annually through five years. Change in NYHA classification from baseline will be summarized both with frequencies and percentages and as continuous data at baseline, 30 days, 6 months, 12 months and annually through five years. For each treatment group, a paired t-test will be performed to evaluate change from baseline at 30 days, 6 months, 12 months and annually through five years. A two-sample t-test will be used to compare the change from baseline for the two groups at 30 days, 6 months, 12 months and annually through five years.

#### B. Determination of Patients/Data for Analysis

This objective will be analyzed for the as treated population.

### 3.3.6 Secondary Objective #6 - Six-Minute Walk Test

Change in distance walked during 6-minute walk test (6MWT) from baseline to 30 days and baseline to 12 months

#### 3.3.6.1 Hypothesis and/or Parameters to Be Estimated

The following hypotheses will be tested at 30 days and 12 months:
\[ H_0: \mu_{\text{MCS TAVI}} = \mu_{\text{SAVR}} \]
\[ H_A: \mu_{\text{MCS TAVI}} \neq \mu_{\text{SAVR}} \]

In the above expressions, \( \mu_{\text{MCS TAVI}} \) and \( \mu_{\text{SAVR}} \) denotes the mean change in 6-minute walk test distances from baseline, for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

The following hypotheses will also be tested at 30 days and 12 months:

\[ H_0: \mu_{\text{MCS TAVI}} = 0 \]
\[ H_A: \mu_{\text{MCS TAVI}} \neq 0 \]

and

\[ H_0: \mu_{\text{SAVR}} = 0 \]
\[ H_A: \mu_{\text{SAVR}} \neq 0 \]

### 3.3.6.2 Endpoint Definition

The 6-minute walk test distance is defined as the distance, in meters, that is walked in six minutes.

### 3.3.6.3 Data Collection and Analysis Methods

**A. Data Collection and Analysis**

Data will be collected on a separate six minute walk test form for each follow-up visit. Distance walked at each time point will be summarized as continuous data. For each treatment group, a paired t-test will be performed to evaluate change from baseline at 30 days and 12 months. A two-sample t-test will be used to compare the change from baseline for the two groups at 30 days and 12 months.

**B. Determination of Patients/Data for Analysis**

A six minute walk test per the American Thoracic Society Guidelines will be performed unless the subject is exempt due to any of the following conditions: postural hypotension, postural arrhythmia, resting systolic pressure less than 95 mmHg, non-ambulatory due to arthritis, neuromuscular disease or Peripheral Vascular Disease, Chronic Obstructive Pulmonary Disease with \( \text{O}_2 \) desaturation upon ambulation or oxygen dependent, or unstable angina. Subjects with any of these conditions will not undergo the test, but the reasons for not performing the test must be documented on the six minute walk test case report form. These subjects will be excluded from the analysis.

All subjects who are able to perform the six-minute walk evaluation; and those subjects who are unable to perform the walk evaluation due to heart failure symptoms at the time of the baseline or follow-up visit will be included in the analysis. Subjects who are unable to perform the walk evaluation due to heart failure symptoms at the time of the baseline or follow-up visit will be assigned a distance walked of zero meters.

This objective will be analyzed for the as treated population.
3.3.7 Secondary Objective #7 - Ratio of Days Alive Out of Hospital Versus Total Days Alive

Ratio of days alive out of hospital versus total days alive assessed at 12 months follow-up.

3.3.7.1 Hypothesis and/or Parameters to Be Estimated

The following hypotheses will be tested:

$$H_0: \mu_{\text{MCS TAVI}} = \mu_{\text{SAVR}}$$

$$H_A: \mu_{\text{MCS TAVI}} \neq \mu_{\text{SAVR}}$$

In the above expressions, $\mu_{\text{MCS TAVI}}$ and $\mu_{\text{SAVR}}$ denotes the mean proportion of days alive out of hospital at 12 months, for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

For each treatment group, the mean proportion of days alive out of hospital will be estimated at 12 months.

3.3.7.2 Endpoint Definition

For each subject, the proportion of post-enrollment days alive out of hospital against total days alive will be calculated at 12 months. The numerator will be the number of days alive out of hospital, and the denominator will be the number of post-enrollment days alive as of the last follow-up date (the latest date of all follow-up visits, assessments, and events (including death)) or 365, whichever is smaller. All hospitalizations will be included in this analysis, including hospitalization for device implant.

3.3.7.3 Data Collection and Analysis Methods

A. Data Collection and Analysis

The admission date for the index procedure will be captured on the procedure form, and the discharge date will be captured on the discharge form. All other hospitalization dates will be collected on the hospitalization case report form. The proportion of days alive out of hospital will be summarized as with continuous data. A two-sample t-test will be used to compare the mean proportion for the two groups.

B. Determination of Patients/Data for Analysis

This objective will be analyzed for the as treated population.

3.3.8 Secondary Objective #8 - Quality of Life

Quality of Life (QoL) change from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

3.3.8.1 Hypothesis and/or Parameters to Be Estimated

For each QoL assessment, and for each follow-up time, the null hypothesis that the mean paired difference is the same for both treatment groups will be tested against the two-sided alternative that the mean paired difference is different.
Additionally, for each treatment group, for each QoL assessment, and for each follow-up time, the null hypothesis that the mean paired difference is zero will be tested against the two-sided alternative that the mean is not zero.

Finally, a test for the change in SF-12 Physical Summary Scale from baseline to 30 days and a test of non-inferiority for the Kansas City Cardiomyopathy Questionnaire (KCCQ) score at 12 months will be performed as part of a hierarchical test procedure.Refer to section 3.3.18 for more details.

3.3.8.2 Endpoint Definition
The Kansas City Cardiomyopathy Questionnaire (KCCQ), SF 12, and EuroQoL will be assessed at baseline, 30 days, 6 months, 12 months and annually through five years.

3.3.8.3 Data Collection and Analysis Methods
A. Data Collection and Analysis
Data will be collected on QoL questionnaires and entered in a separate database by a QoL core lab. For each treatment group, the changes in QoL scores will be evaluated using a paired t-test or Wilcoxon signed-rank test as appropriate. A two-sample t-test or Wilcoxon rank-sum test, as appropriate, will be used to compare the changes from baseline for the two groups.

B. Determination of Patients/Data for Analysis
All subjects completing the questionnaires will be evaluated and the reasons for missing data will be provided.

This objective will be analyzed for the as treated population.

3.3.9 Secondary Objective #9 - Echocardiographic Assessment of Valve Performance
Echocardiographic assessment of valve performance at discharge, 30 days, 6 months, 12 months and annually thereafter up to 5 years using the following measures:

- transvalvular mean gradient
- effective orifice area
- degree of aortic valve regurgitation (transvalvular and paravalvular)

3.3.9.1 Hypothesis and/or Parameters to Be Estimated
For both of the endpoints of transvalvular mean gradient and effective orifice area, the following hypotheses will be tested at discharge, 30 days, 6 months, 12 months and annually thereafter up to 5 years:

\[ H_0: \mu_{\text{MCS TAVI}} = \mu_{\text{SAVR}} \]
\[ H_A: \mu_{\text{MCS TAVI}} \neq \mu_{\text{SAVR}} \]

In the above expressions, \( \mu_{\text{MCS TAVI}} \) and \( \mu_{\text{SAVR}} \) denotes the mean change from baseline, for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.
For both of the endpoints of transvalvular mean gradient and effective orifice area, the following hypotheses will also be tested at discharge, 30 days, 6 months, 12 months and annually thereafter up to 5 years:

\[ H_0: \mu_{\text{MCS TAVI}} = 0 \]
\[ H_A: \mu_{\text{MCS TAVI}} \neq 0 \]

and

\[ H_0: \mu_{\text{SAVR}} = 0 \]
\[ H_A: \mu_{\text{SAVR}} \neq 0 \]

For both of the endpoints of transvalvular and paravalvular degree of aortic valve regurgitation, at discharge, 30 days, 6 months, 12 months and annually thereafter up to 5 years:

\[ H_0: \mu_{\text{MCS TAVI}} = \mu_{\text{SAVR}} \]
\[ H_A: \mu_{\text{MCS TAVI}} \neq \mu_{\text{SAVR}} \]

In the above expressions \( \mu_{\text{MCS TAVI}} \) and \( \mu_{\text{SAVR}} \) now denote row mean scores for the ordinal regurgitation data, for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

Additionally, tests of non-inferiority for transvalvular mean gradient and effective orifice area at 12 months will be performed as part of a hierarchical test procedure. Refer to section 3.3.18 for more details.

### 3.3.9.2 Endpoint Definition

All echocardiograms will be analyzed by an echo core lab which will determine the values for these endpoints. Transvalvular mean gradient will be measured in mmHg. Effective orifice area will be measured in cm². Degree of aortic valve regurgitation (transvalvular and paravalvular) will be described as mild, moderate, or severe.

### 3.3.9.3 Data Collection and Analysis Methods

#### A. Data Collection and Analysis

Data will be entered in a separate database by an echo core lab. For each treatment group, transvalvular mean gradient and effective orifice area at each time point will be summarized as with continuous data. For each treatment group, a paired t-test will be used to evaluate change from baseline at discharge, 30 days, 6 months, 12 months and annually through five years. A two-sample t-test will be used to compare the change from baseline for the two groups at 30 days, 6 months, 12 months and annually through five years.

Degree of aortic valve regurgitation will be summarized with frequencies and percentages at each time point. The two treatment groups will be compared using the Cochran-Mantel-Haenszel test with row mean scores.

#### B. Determination of Patients/Data for Analysis

All subjects undergoing echocardiography procedures will be evaluated.

This objective will be analyzed for the as treated and implanted populations.
3.3.10 Secondary Objective #10 - Aortic Valve Disease-Related Hospitalizations

Aortic valve disease related hospitalizations: the number of subjects re-hospitalized after the initial index procedure will be compared at 30 days, 6 months, 12 months and annually through five years.

3.3.10.1 Hypothesis and/or Parameters to Be Estimated

The following hypotheses will be tested:

\[ H_0: S(t)_{MCS\ TAVI} = S(t)_{SAVR} \text{ for all } t \]
\[ H_A: S(t)_{MCS\ TAVI} \neq S(t)_{SAVR} \text{ for at least one } t \]

In the above expressions \( S(t)_{MCS\ TAVI} \) and \( S(t)_{SAVR} \) denote the hospitalization-free survival functions for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

Hospitalization-free survival estimates for each treatment group will be provided at 30 days, 6 months, 12 months and annually through five years.

3.3.10.2 Endpoint Definition

Aortic valve disease hospitalizations are defined as a non-elective hospital admission for signs and symptoms related to aortic valve disease (as described below) that results in at least a two-night stay (i.e., where the admission date and the discharge date differ by at least two calendar days). For the purpose of the protocol, overnight stays at nursing home facilities or extended care facilities do not meet the protocol definition of hospitalization. This does include the administration or augmentation of intravenous heart failure therapy (e.g., inotropes, diuretics, and/or vasodilators).

Subjects with signs and symptoms related to aortic valve disease (as described below) who are hospitalized for less than two days or who are treated and released from the emergency department or an outpatient clinic (including treatment for intravenous heart failure therapy (e.g., inotropes, diuretics, and/or vasodilators)), will not be counted as aortic valve disease hospitalizations.

Aortic valve disease will be evaluated using documented evidence of the following signs and symptoms. An independent Clinical Events Committee (CEC) will review all available source documentation for all hospitalizations to determine if they are aortic valve disease hospitalizations. The CEC adjudication will be used for final analysis.

<table>
<thead>
<tr>
<th>Signs and Symptoms of Aortic Valve Disease</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aortic Valve Dysfunction</strong></td>
<td></td>
</tr>
<tr>
<td>Shortness of breath/dyspnea</td>
<td>A feeling of difficult or labored breathing that is out of proportion to the patient’s level of physical activity</td>
</tr>
<tr>
<td>Exercise intolerance</td>
<td>A condition where the patient is unable to do physical exercise at the level or for the duration that would be expected of someone in his/her general physical condition, or experiences unusually severe post-exercise pain, fatigue, or other negative effects</td>
</tr>
</tbody>
</table>
| Dizziness/syncope                         | Lightheadedness or unsteadiness of gait or a partial or complete loss of consciousness with interruption of
<table>
<thead>
<tr>
<th>Awareness of oneself and one’s surroundings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain</td>
</tr>
<tr>
<td><strong>Worsening Heart Failure</strong></td>
</tr>
<tr>
<td><strong>Volume Overload</strong></td>
</tr>
<tr>
<td>Orthopnea</td>
</tr>
<tr>
<td>Paroxysmal nocturnal dyspnea</td>
</tr>
<tr>
<td>Jugular venous distension</td>
</tr>
<tr>
<td>Hepatomegaly</td>
</tr>
<tr>
<td>Peripheral edema</td>
</tr>
<tr>
<td>Pulmonary rales</td>
</tr>
<tr>
<td>Abdominal-jugular reflux</td>
</tr>
<tr>
<td>Radiographic evidence of pulmonary edema</td>
</tr>
<tr>
<td>Elevated B-type natriuretic peptide level</td>
</tr>
<tr>
<td><strong>Hypoperfusion</strong></td>
</tr>
<tr>
<td>Narrow pulse pressure</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Renal or hepatic dysfunction</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Low serum sodium concentration</td>
</tr>
</tbody>
</table>

### 3.3.10.3 Data Collection and Analysis Methods

**A. Data Collection and Analysis**

Data will be collected on a CEC adjudication form. A Kaplan-Meier survival analysis will be performed for each treatment group, and the log-rank test will be used to compare the treatment groups.

**B. Determination of Patients/Data for Analysis**

This objective will be analyzed for the as treated population.

### 3.3.11 Secondary Objective #11 - Cardiovascular Deaths and Valve-Related Deaths

Cardiovascular deaths and valve-related deaths: the number of cardiovascular deaths and valve-related deaths at 30 days, 6 months, 12 months and annually through five years will be reported.
3.3.11.1 Hypothesis and/or Parameters to Be Estimated

For each endpoint the following hypotheses will be tested:

\[ H_0: S(t)_{\text{MCS TAVI}} = S(t)_{\text{SAVR}} \text{ for all } t \]
\[ H_A: S(t)_{\text{MCS TAVI}} \neq S(t)_{\text{SAVR}} \text{ for at least one } t \]

In the above expressions \( S(t)_{\text{MCS TAVI}} \) and \( S(t)_{\text{SAVR}} \) denote the survival functions for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

For each endpoint, survival estimates for each treatment group will be provided at 30 days, 6 months, 12 months and annually through five years.

3.3.11.2 Endpoint Definition

Cardiovascular death will be defined, according to the definition proposed by the Valve Academic Research Consortium (VARC) Consensus Report for Transcatheter Aortic Valve Implantation (TAVI); 2010-06-15, as any one of the following:

- Any death due to proximate cardiac cause (e.g. MI, cardiac tamponade, worsening heart failure)
- Unwitnessed death and death of unknown cause
- All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure
- Death caused by non-coronary vascular conditions such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease

Note: All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in subjects with coexisting potentially fatal non-cardiac disease (e.g., cancer, infection) should be classified as cardiac.

Valve-related deaths are defined as:

- Any death caused by prosthetic valve dysfunction, valve thrombosis, embolism, bleeding event, or implanted valve endocarditis;
- Death related to reintervention on the operated valve.

3.3.11.3 Data Collection and Analysis Methods

A. Data Collection and Analysis

Data will be collected on a CEC adjudication form. For each endpoint, a Kaplan-Meier survival analysis will be performed for each treatment group, and the log-rank test will be used to compare the treatment groups.

B. Determination of Patients/Data for Analysis

This objective will be analyzed for the as treated population.

3.3.12 Secondary Objective #12 – Strokes and TIsAs

The number of subjects with strokes (of any severity) and TIsAs at 30 days, 6 months, 12 months and annually through five years will be reported.
3.3.12.1 Hypothesis and/or Parameters to Be Estimated

For each endpoint, the following hypotheses will be tested:

- \( H_0: S(t)_{\text{MCS TAVI}} = S(t)_{\text{SAVR}} \) for all \( t \)
- \( H_A: S(t)_{\text{MCS TAVI}} \neq S(t)_{\text{SAVR}} \) for at least one \( t \)

In the above expressions, \( S(t)_{\text{MCS TAVI}} \) and \( S(t)_{\text{SAVR}} \) denote the event-free survival functions for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

For each endpoint, event-free survival estimates for each treatment group will be provided at 30 days, 6 months, 12 months and annually through five years.

3.3.12.2 Endpoint Definition

Stroke and TIA will be defined according to the definition proposed by the Valve Academic Research Consortium (VARC) Consensus Report for Transcatheter Aortic Valve Implantation (TAVI); 2010-06-15

**Stroke Diagnostic Criteria**

- Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke
- Duration of a focal or global neurological deficit \( \geq 24 \) hours; OR \( < 24 \) hours, if therapeutic intervention(s) were performed (e.g. thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; OR the neurologic deficit results in death
- No other readily identifiable non-stroke cause for the clinical presentations (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences)*
- Confirmation of the diagnosis by at least one of the following:
  - Neurology or neurosurgical specialist
  - Neuroimaging procedure (MR or CT scan or cerebral angiography)
  - Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)

**Stroke Definitions**

- Transient Ischemic Attack
  - New focal neurologic deficit with rapid symptom resolution (usually 1-2 hours), always within 24 hours
  - Neuroimaging without tissue injury
- Stroke: (diagnosis as above, preferably with positive neuroimaging study)+
  - Minor (non-clinically important disability) - modified Rankin score \(< 2\) at 7 days or prior to discharge AND NIHSS score \(< 3\) (above baseline) at 7 days or prior to discharge and at 30-day assessment
  - Major (clinically important disability) - modified Rankin score \(\geq 2\) at 7 days or prior to discharge AND NIHSS score \(\geq 3\) (above baseline) at 7 days or prior to discharge and at 30-day assessment
Data will be collected on a CEC adjudication form. A separate analysis will be performed for each of the following:

- a composite of all strokes and TIAs
- major strokes only
- minor strokes only
- TIAs only

For each endpoint, a Kaplan-Meier survival analysis will be performed for each treatment group, and the log-rank test will be used to compare the treatment groups.

**B. Determination of Patients/Data for Analysis**

This objective will be analyzed for the as treated population.

### 3.3.13 Secondary Objective #13 - Index Procedure-Related MAEs

Index procedure related MAEs: Index procedure-related MAE events will be summarized and event rates will be provided at 30 days.

#### 3.3.13.1 Hypothesis and/or Parameters to Be Estimated

The endpoint is descriptive and no statistical hypothesis test will be performed. For each treatment group, the rate of index procedure-related MAE events will be summarized at 30 days.

#### 3.3.13.2 Endpoint Definition

The numerator will be the number of procedure-related MAE events experienced by the end of the 30-day follow-up visit, and the denominator will be the number of subjects evaluated at the 30-day follow-up visit plus the number of subjects not evaluated but who experienced a procedure-related MAE event prior to the end of the follow-up visit window.

#### 3.3.13.3 Data Collection and Analysis Methods

**A. Data Collection and Analysis**

Data regarding MAEs will be collected on a CEC adjudication form. For each treatment group, the event rate as described above will be calculated. Additionally, the percentage of subjects with a procedure-related MAE will be calculated in the same way, but allowing no more than one MAE per subject.

**B. Determination of Patients/Data for Analysis**

This objective will be analyzed for the as treated population.

### 3.3.14 Secondary Objective #14 - Length of Index Procedure Hospital Stay

Length of index procedure hospital stay

#### 3.3.14.1 Hypothesis and/or Parameters to Be Estimated

The endpoint is descriptive and no statistical hypothesis test will be performed. The mean length of index procedure hospital stay will be estimated.
3.3.14.2 **Endpoint Definition**

For each subject, the length of index procedure hospital stay will be calculated as the number of calendar days spanning the admission date to the discharge date on the discharge case report form; i.e., it will be calculated as (discharge date - admission date + 1).

3.3.14.3 **Data Collection and Analysis Methods**

A. **Data Collection and Analysis**

The admission date will be captured on the procedure form, and the discharge date will be captured on the discharge form. For each treatment group, the length of index procedure hospital stay will be summarized as with continuous data.

B. **Determination of Patients/Data for Analysis**

This objective will be analyzed for the as treated population.

3.3.15 **Secondary Objective #15 - Device Success**

Device success

3.3.15.1 **Hypothesis and/or Parameters to Be Estimated**

The endpoint is descriptive and no statistical hypothesis test will be performed. The rate of device success will be estimated.

3.3.15.2 **Endpoint Definition**

Device success is defined as follows:

- Successful vascular access, delivery and deployment of the device, and successful retrieval of the delivery system.
- Correct position of the device in the proper anatomical location (placement in the annulus with no impedance on device function).
- Intended performance of the prosthetic valve (aortic valve area > 1.2 cm² (by echocardiography using the continuity equation) and mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/sec, without moderate or severe prosthetic valve AR). Performance is assessed acutely in a resting state, either within 24-48 hours after the index procedure or before hospital discharge.
- Only one valve implanted in the proper anatomical location.

3.3.15.3 **Data Collection and Analysis Methods**

A. **Data Collection and Analysis**

The components of device success will be determined by the site and recorded on the procedure case report form. The numerator will be the number of subjects whose procedure resulted in device success, and the denominator will be the number of subjects with a procedure attempt.

B. **Determination of Patients/Data for Analysis**

This objective will be analyzed for the MCS TAVI cohort only in the as treated population.
3.3.16 Secondary Objective #16 - Procedural Success

Procedural success

3.3.16.1 Hypothesis and/or Parameters to Be Estimated
The endpoint is descriptive and no statistical hypothesis test will be performed. The rate of procedural success will be estimated.

3.3.16.2 Endpoint Definition
Procedural success is defined as device success and absence of in-hospital MACCE.

3.3.16.3 Data Collection and Analysis Methods
A. Data Collection and Analysis
Device success will be as determined in the previous objective. The components of MACCE will be recorded on a CEC adjudication form. In-hospital MACCE will include those events that have a date on or before the discharge date recorded on the discharge form. The numerator will be the number of subjects whose procedure resulted in procedural success, and the denominator will be the number of subjects with a procedure attempt.

B. Determination of Patients/Data for Analysis
This objective will be analyzed for the MCS TAVI cohort only in the as treated population.

3.3.17 Secondary Objective #17 - Prosthetic Valve Dysfunction

Evidence of prosthetic valve dysfunction at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

3.3.17.1 Hypothesis and/or Parameters to Be Estimated
The endpoint is descriptive and no statistical hypothesis test will be performed. Prosthetic valve dysfunction-free survival estimates will be provided at 30 days, 6 months, 12 months and annually through five years.

3.3.17.2 Endpoint Definition
Prosthetic valve dysfunction is a component of MAE and will be adjudicated by the CEC.

3.3.17.3 Data Collection and Analysis Methods
A. Data Collection and Analysis
Data will be collected on a CEC adjudication form. A Kaplan-Meier survival analysis will be performed.

B. Determination of Patients/Data for Analysis
This objective will be analyzed for the MCS TAVI cohort only in the implanted population.
3.3.18 Hierarchical Testing

Provided the 12-month non-inferiority mortality primary objective is met with a significant p-value, to keep the overall (familywise) Type I error rate at 0.05, a hierarchical test procedure will be applied to the 30-day (or hospital discharge, whichever is longer) MACCE powered secondary hypothesis and five of the secondary objective hypothesis tests. The goal of this hierarchical procedure is to make statistically valid claims of significance in the device labeling.

In this hierarchical test procedure, each objective is examined in the pre-specified order.
An objective is statistically significant only if that objective and all prior objectives have a significant p-value. The hierarchical testing order will be:

1. Change in transvalvular mean gradient from baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #9. The one-sided two-sample t-test will be used to test non-inferiority at a level of 0.05 the hypotheses:
   \[ H_0: \mu_{MCS\ TAVI} \leq \mu_{SAVR} -15 \]
   \[ H_A: \mu_{MCS\ TAVI} > \mu_{SAVR} -15 \]
   In the above expression \( \mu_{MCS\ TAVI} \) and \( \mu_{SAVR} \) denote the mean improvements in mean gradient from baseline to 12 months measured in mmHg.

2. Change in effective orifice area baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #9. The one-sided two-sample t-test will be used to test non-inferiority at a level 0.05 the hypotheses:
   \[ H_0: \mu_{MCS\ TAVI} \leq \mu_{SAVR} -0.375 \]
   \[ H_A: \mu_{MCS\ TAVI} > \mu_{SAVR} -0.375 \]
   In the above expression \( \mu_{MCS\ TAVI} \) and \( \mu_{SAVR} \) denote the mean improvements in effective orifice area from baseline to 12 months measured in cm².

3. Change in NYHA classification from baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #5. The one-sided two-sample t-test will be used to test non-inferiority at a level 0.05 the hypotheses:
   \[ H_0: \mu_{MCS\ TAVI} \leq \mu_{SAVR} -0.375 \]
   \[ H_A: \mu_{MCS\ TAVI} > \mu_{SAVR} -0.375 \]
   In the above expression \( \mu_{MCS\ TAVI} \) and \( \mu_{SAVR} \) denote the mean number of classification improvements in NYHA from baseline to 12 months.

4. Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score from baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #8. The one-sided two-sample t-test will be used to test non-inferiority at a level 0.05 the hypotheses:
   \[ H_0: \mu_{MCS\ TAVI} \leq \mu_{SAVR} -5 \]
   \[ H_A: \mu_{MCS\ TAVI} > \mu_{SAVR} -5 \]
   In the above expression \( \mu_{MCS\ TAVI} \) and \( \mu_{SAVR} \) denote the mean improvements in the KCCQ score from baseline to 12 months.

5. Powered Secondary Hypothesis: TAVI with the Medtronic CoreValve® System is superior to SAVR in binary rate of MACCE at 30 days or hospital discharge,
whichever is longer. This one-sided test will be carried out at the 0.025 level using the pooled z-test without correction for continuity to test the hypotheses:

\[ H_0: \pi_{MCS \text{TAVI}} = \pi_{SAVR} \]
\[ H_A: \pi_{MCS \text{TAVI}} < \pi_{SAVR} \]

In the above expression \( \pi_{MCS \text{TAVI}} \) and \( \pi_{SAVR} \) denote the binary rate of MACCE at 30 days or hospital discharge.

6. Change in SF-12 Physical Summary Scale from baseline to 30 days: TAVI vs. SAVR from secondary objective #8. The two-sided two-sample t-test will be used to test at a level 0.05 the hypotheses:

\[ H_0: \mu_{MCS \text{TAVI}} = \mu_{SAVR} \]
\[ H_A: \mu_{MCS \text{TAVI}} \neq \mu_{SAVR} \]

In the above expression \( \mu_{MCS \text{TAVI}} \) and \( \mu_{SAVR} \) denote the mean improvements in the SF-12 Physical Summary Scale from baseline to 30 days.

This hierarchical test procedure will be performed for the as treated population.

As the trial confirmation is not dependent on the secondary endpoints, multiplicity adjustments will not be made in the other analyses of the secondary endpoints. Summary data from other secondary objectives, such as device success and procedural success from secondary objectives #15 and #16, respectively, may be provided in the device labeling. However, no claims of statistical significance or other statistical inference will be made.

3.4 Additional Analyses

3.4.1 Poolability Analysis

3.4.1.1 Pooling of Small Sites

Sites contributing less than 3 treatment or 3 control subjects to the as treated analysis set will be considered “small sites” and ordered by the date of first enrollment in the as treated analysis set. Starting with the first “small site”, a pseudo-site will be created by adding subjects from successive “small sites”. If the number of subjects reaches or exceeds the size of the median enrollment of the “large sites”, then a second pseudo-site will be created. Additional pseudo-sites, if needed, would be created in the same manner.

3.4.1.2 Primary Endpoint by Site

The interaction between site or pseudosite and treatment on the probability of death at 12 months will be compared using logistic regression. If the resulting p-value is \( \leq 0.15 \), further exploratory analysis will attempt to identify covariates that may explain treatment effect differences among the sites, beginning in the next section. Otherwise, the data will be considered to be poolable across study sites.

3.4.1.3 Univariate Covariate Analysis

The following baseline characteristics will be examined individually as potential predictors of death at 12 months using logistic regression:
1. Gender
2. Age
3. Baseline NYHA
4. Logistic EuroSCORE
5. Baseline LVEF
6. Hypertension
7. Diabetes
8. Coronary artery disease
9. Prior stroke
10. Prior MI
11. Prior PCI

3.4.1.4 Multivariate Analysis

Covariates with p-value ≤ 0.20 from the previous section will be included along with site in a logistic regression model. If this multivariate logistic regression does not result in a significant (p-value ≤ 0.15) site by treatment interaction after adjustment for these baseline factors, then outcome results will again be considered poolable across study sites. If site by treatment interaction is still significant (p-value ≤ 0.15) after adjustment for these factors, results will be presented by site and the clinical significance of these differences will be assessed.

3.4.2 Gender Analysis

The primary endpoint and secondary endpoints #1-3 (MACCE, individual MACCE components, and MAE) will be examined for differences in outcome between genders. Additionally, tests for these outcomes will be performed to evaluate potential interactions between treatment and gender. These analyses will be performed on the as treated analysis set.

For the primary endpoint, the proportions of subjects who died at 12 months will be compared using logistic regression with gender as an independent variable on the complete case analysis. This analysis will be repeated with treatment and the treatment by gender interaction added to the model.

MACCE-free survival estimates for each gender will be provided at 30 days, 6 months, 12 months and annually through five years. MACCE-free survival between genders will be compared using the log-rank test. MACCE-free survival estimates for each gender and treatment combination will be provided at 30 days, 6 months, 12 months and annually through five years. A Cox proportional hazards model will be fit with predictors of gender, treatment, and treatment by gender interaction.

This analysis will be repeated for each individual component of MACCE and for MAE.

3.4.3 Access Site Analysis

The primary endpoint and secondary endpoints #1-3 (MACCE, individual MACCE components, and MAE) will be examined for differences in outcome between access sites (ilio-femoral or non-ilio-femoral). Additionally, tests for these outcomes will be performed to evaluate potential interactions between treatment
and access site. These analysis will be performed on the as treated analysis set. Per the as treated analysis set definition, TAVI subjects will be analyzed according to the access site on the procedure form, while SAVR subjects will be analyzed according to the stratified access site.

For the primary endpoint, the proportions of subjects who died at 12 months will be compared using logistic regression with access site as an independent variable on the complete case analysis. This analysis will be repeated with treatment and the treatment by access site interaction added to the model.

MACCE -free survival estimates for each gender will be provided at 30 days, 6 months, 12 months and annually through five years. MACCE-free survival between access sites will be compared using the log-rank test. MACCE -free survival estimates for each access site and treatment combination will be provided at 30 days, 6 months, 12 months and annually through five years. A Cox proportional hazards model will be fit with predictors of access site, treatment, and treatment by access site interaction.

This analysis will be repeated for each individual component of MACCE and for MAE.

4 REVISION PROCESS

The study statistician will be responsible for the execution of this statistical analysis plan, including any revisions and obtaining of appropriate approvals.

5 DISTRIBUTION

The study statistician will be responsible for execution of this statistical analysis plan and distribution of revisions to the appropriate clinical staff.

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CardioVascular Structural Heart Clinical Department

Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients)
Statistical Analysis Plan

Version 2
Date: 16 MAY 2011

IDE No. G100012
CIP No. MCV-US-2009-01 (High Risk Surgical)

Prepared by:

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Principal Statistician
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1 PURPOSE OF SAP

This Statistical Analysis Plan has been designed to document, before data are analyzed, the rationale for the study design, and the planned analyses that will be included in study reports. The design and analyses are consistent with the objectives of the Clinical Investigational Plan (CIP).

2 RATIONALE FOR STUDY DESIGN

The purpose of this study is to evaluate the safety and efficacy of the Medtronic CoreValve® System in the treatment of symptomatic severe aortic stenosis in subjects who have a predicted high risk for aortic valve surgery. High risk surgical subjects will be randomized to receive either transcatheter aortic valve implant (TAVI) with the Medtronic CoreValve® System (MCS) or surgical aortic valve replacement (SAVR) in a 1:1 ratio.

This statistical analysis plan is developed based on the Clinical Investigational Plan Version 5.0.

3 DESCRIPTION OF ANALYSIS

3.1 General Summaries

3.1.1 Description of Baseline Variables
Baseline demographic and clinical variables will be summarized for each of the treatment groups for the intent-to-treat, as treated, implanted, and per protocol populations. Refer to section 3.1.3.7 for definitions of these analysis sets. All continuous variables will be summarized with means, medians, standard deviations, interquartile ranges, minimums, and maximums and compared between treatment groups using a two-sample t-test or the non-parametric Wilcoxon rank-sum test. Categorical variables will be summarized with frequencies and percentages and compared between treatment groups using Pearson’s χ² test or Fisher’s exact test, as appropriate. Ordinal variables will be compared using Cochran-Mantel-Haenszel test with row mean scores.

Age will be calculated as the difference in days between the subject’s date of birth and the date of signing the informed consent, divided by 365.25.

3.1.2 Reports for which this Statistical Analysis Plan applies
This Statistical Analysis Plan applies to the study report for Pre-market Approval Application (PMA) to the Food and Drug Administration (FDA) and to the final report.
3.1.3 Special Considerations

3.1.3.1 Report Timing and Cutoff Dates

The PMA report will be generated after all enrolled subjects have completed their 12-month follow-up visit in-window or later (or, if early, have been followed for at least 365 days via a subsequent follow-up form), have died, or have exited from the study.

Cutoff dates will be applied to all site case report forms. A Visit Cutoff Date and a Received Cutoff Date will be used. The visit cutoff date will be the first date on which all enrolled subjects have been followed for 12 months, have died, or have exited from the study. The visit, assessment, and event dates will be used to determine which case report forms satisfy the visit cutoff date. The received cutoff date will be determined near the time of the database closure and will chosen to ensure that all known deaths, 12-month visits, and other forms of critical importance have been received while still allowing adequate time for data cleaning between the received cutoff date and the date of database closure. The "logints" log-in timestamp field will be used to determine which case report forms satisfy the received cutoff date.

Any forms which do not have a visit date directly on the form (e.g., the protocol deviation form) will use the visit date from the corresponding form for that entry. Forms with multiple dates (e.g., the protocol deviation form and the medication form) will apply cutoff dates to individual lines of data on the form.

The final report will be generated after all enrolled subjects have been followed for 5 years, have died, or have exited from the study. Because the intent is to report on all study data, it is not expected that cutoff dates will apply to the final report.

3.1.3.2 Missing Data

Unless specified in each objective, no statistical techniques will be used to impute missing data. If a subject’s data are missing for any reason, that subject will not be included in that portion of the analysis. The number of subjects included in each analysis will be reported so that the potential impact of missing data can be assessed. See sections 3.2.1.5 and 3.2.2.5 for the handling of missing data for the primary objective and powered secondary hypothesis, respectively.

In the case of partial dates, if only the month and year are known, the event or assessment will be analyzed as if it occurred on the 15th of that month. If only the year is known, the event or assessment will be analyzed as if it occurred on June 30th of that year. These resolutions of partial dates are subject to the restrictions that pre-procedure events and assessments must occur between the randomization date and the procedure date and post-procedure events and assessments must occur no earlier than the procedure date.

3.1.3.3 P-Values

All statistical tests and/or confidence intervals, as appropriate, will be performed at $\alpha=0.05$ (2-sided), except when specified otherwise. All reported p-values greater
than or equal to 0.001 will be rounded to three decimal places. P-values less than 0.001 will be displayed as “<0.001.”

3.1.3.4 Student’s t-Tests
For analyses of continuous data, given the sample sizes, it is expected that, even if the underlying data are not normal, that the sampling distributions of the sample means will be sufficiently normal to permit use of paired and 2-sample t-tests. Only in unusual cases will these be replaced with the Wilcoxon signed-rank and rank-sum tests, respectively.

For any two-sample t-test performed, the t-statistic will be calculated based on equal variances if the test for equality of variances is nonsignificant (p > 0.05). Otherwise, the t-statistic based on unequal variances will be used to compare the two samples.

3.1.3.5 Chi-Square Tests
For analyses of categorical data, chi-square tests will be used unless there are expected cell counts of less than 5. In those cases, Fisher’s exact test will be used.

3.1.3.6 Kaplan-Meier Analyses
Secondary objectives #1-4, #10-12, and #17 call for a Kaplan-Meier analysis of event-free rates at 30 days, 6 months, 12 months and annually through five years. For these analyses, these times correspond to 30 days, 183 days, 365 days, 730 days, 1095 days, 1460 days, and 1825 days, respectively. At each time point with data, the product-limit estimate of the event-free rate, the number of subjects at risk, the number of subjects with events, and the Peto standard error of the estimate will be presented.

For subjects without an event, the date of censoring will be the latest date of all follow-up visits, assessments, and events (including death).

3.1.3.7 Analysis Sets
There are four different analysis sets that are defined for this study. The primary analysis will be the “as treated” analysis. Data from roll-in patients will be presented separately with descriptive statistics.

3.1.3.7.1 Intent-to-Treat
The intent-to-treat population consists of all randomized subjects. Subjects will be analyzed according to the randomization assignment and the stratified access site (ilio-femoral or non-ilio-femoral), regardless of whether a procedure is actually attempted, which device the subject actually receives, and which access site is actually used. This population excludes roll-in patients. Because not all subjects in this population will have a procedure, time zero begins at the date of randomization.

3.1.3.7.2 As Treated
The as treated population consists of all randomized patients 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 (TAVI or SAVR). TAVI subjects will be analyzed according to the access site on the procedure form, while SAVR subjects will be analyzed according to the stratified access site. This population excludes roll-in patients. Time zero begins at the date of attempted procedure.

3.1.3.7.3 Implanted

The implanted population consists of all as treated subjects who are actually implanted with either the CoreValve device or a surgical valve. To be considered implanted, an MCS TAVI subject’s device disposition form must show at least one device with a final disposition of “Implanted,” while an SAVR subject’s procedure form must indicate the valve manufacturer and model as well as the suture method. Time zero begins at the date of the procedure.

3.1.3.7.4 Per Protocol

Based on the ICH E9 Statistical Principles for Clinical Trials\(^1\) recommendations, the per protocol population should satisfy the following:

1. The completion of a certain prespecified minimal exposure to the treatment regimen
2. The availability of measurements of the primary variable(s)
3. The absence of any major protocol violations, including the violation of entry criteria

To meet these requirements, the per protocol population will consist of all implanted subjects who were implanted according to their randomization and access site stratification and who have at least 12 months (365 days) of follow-up or have experienced the primary endpoint (death) prior to 12 months. These subjects must satisfy all inclusion/exclusion criteria. Time zero begins at the date of the procedure.

3.1.3.8 Interim Analysis

No formal interim analysis is planned, and there are no plans for early termination of the study due to superiority or futility of the investigational therapy.

3.1.3.9 Data Safety Monitoring Board (DSMB)

An independent, unblinded DSMB will be established and will be comprised of at least 3 experts, including a chairperson. The DSMB will have a minimum of one cardiac surgeon, one interventional cardiologist and one statistician, and will be independent of Medtronic and the trial investigators. Investigators participating in the trial may participate in the meetings to offer clarification surrounding events, but will not have voting privileges. Medtronic personnel may facilitate the DSMB meeting but will not have voting privileges. The DSMB will meet (via teleconference or in person) prior to the first subject enrollment to establish procedures for DSMB review, chairman appointment, and guidelines for trial recommendations. The full DSMB will meet on a periodic basis to perform a comprehensive data review, including at a minimum all adverse events and deaths, and will meet more frequently when needed. Primary and safety-related
secondary endpoints may also be reviewed at these meetings. Meetings will consist of both open and closed sessions.

The DSMB will also perform a supplemental review of, at a minimum, all serious adverse events and deaths and any other data requested by the DSMB on a more frequent periodic basis to ensure patient safety. DSMB members will review the report, and when necessary, provide recommendations about the conduct of the study and/or request a full DSMB meeting.

A DSMB charter will be developed and approved by Medtronic and the DSMB members. The committee will outline the criteria for both the full DSMB meeting and supplemental DSMB reviews within the DSMB charter.

Following each full DSMB meeting, the board will report to Medtronic in writing and may recommend changes in the conduct of the trial. These DSMB recommendations may include recommendations on trial status such as continuing the trial without modifications, continuing the trial with modifications, stopping the enrollment in the trial or a specific trial arm, or recommendations about trial conduct including recommendations around enrollment or protocol deviations.

In the case of UADEs, if Medtronic and the DSMB determine that the event presents an unreasonable risk to the participating subjects, Medtronic must terminate the clinical trial 5 working days after making that determination and not later than 15 working days after Medtronic first receives notice of the effect [21 CFR 812.46]. 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.

Additional details about the DSMB can be found in the DSMB charter.

### 3.2 Primary Objective

#### 3.2.1 Primary Objective

The primary objective is to demonstrate that the safety and effectiveness of the Medtronic CoreValve® System (MCS), as measured by all cause mortality rates at 12 months, is non-inferior to surgical aortic valve replacement (SAVR) in the treatment of symptomatic severe aortic stenosis in subjects who have a predicted high risk for aortic valve surgery.

#### 3.2.1.1 Hypothesis and/or Parameters to Be Estimated

Primary Hypothesis: TAVI with the Medtronic CoreValve® System is non-inferior to surgical aortic valve replacement (SAVR) in 12 month all-cause mortality:

- \( H_0: \pi_{MCS\ TAVI} \geq \pi_{SAVR} + 7.5\% \)
- \( H_A: \pi_{MCS\ TAVI} < \pi_{SAVR} + 7.5\% \)

In the above expression \( \pi_{MCS\ TAVI} \) and \( \pi_{SAVR} \) denote binary rates of all-cause mortality during a fixed follow-up of 12 months.
3.2.1.2 **Endpoint Definition**

The primary endpoint is the binary rate of all-cause mortality at 12 months. For each treatment group, the numerator will be the number of subjects who died at or before 12 months (365 days), and the denominator will be the number of subjects in the analysis cohort.

3.2.1.3 **Sample Size Methods and Assumptions**

A. **Sample Size Calculation and Methods**

The following are assumptions for the sample size estimate:

1:1 treatment allocation ratio

One-sided alpha = 0.05

\[ \pi_{SAVR} = 20.0\% \]

\[ \pi_{MCS\ TAVI} = 20.0\% \]

Power = >80%

Assuming 1:1 treatment allocation ratio between study device and surgical valve replacement and assuming the proportion of all-cause mortality at 12 months equal to 20% for both arms and a non-inferiority margin of 7.5%, Power Analysis and Sample Size (PASS) software calculates that a total of \textbf{355} subjects in each arm is required to attain 80% power in a Farrington and Manning test of non-inferiority of the study device at the 0.05 level of significance.
Accounting for 10% loss to follow-up, a total of \(395 + 395 = 790\) subjects is required.

**B. Rationale for Choice of Hypothesis**

The assumption for 12 month mortality for the SAVR arm is an estimate based on 12-month mortality as reported in the surgical literature for high risk AVR (table below). The subjects enrolled in this study are expected to have a higher mortality than observed in the surgical literature, as subjects enrolled in the High Risk Surgical Cohort must have an expected perioperative mortality of 15% (based on Investigator-estimated mortality or STS score >10).
Currently, the average patient undergoing surgery is older and has a greater number of comorbidities than the previously studied population. Given that the expected High Risk Surgical population will be older and at higher risk for surgery, it is estimated that the 12-month all-cause mortality rate among high risk SAVR subjects in the current study will be 20%.

3.2.1.4 Data Collection and Analysis Methods

A. Data Collection and Analysis

Death data will be collected on a CEC adjudication form.

The one-sided Farrington and Manning\textsuperscript{ii} test for non-inferiority of two binomial proportions will be carried out to assess statistical significance at the 0.05 level. The test statistic will be calculated as:

\[
 z = \frac{p_1 - p_2 - \delta_0}{\sqrt{\frac{\hat{p}_1 (1-\hat{p}_1)}{n_1} + \frac{\hat{p}_2 (1-\hat{p}_2)}{n_2}}} 
\]

Where \( p_1 \) and \( p_2 \) are the usual sample proportions, \( n_1 \) and \( n_2 \) are the sizes of the analysis cohorts, and \( \delta_0 = 0.075 \). In the calculation of the standard error, \( \hat{p}_1 \) and \( \hat{p}_2 \) are the maximum likelihood estimators under the constraint that the difference equals \( \delta_0 \), where that solution is given by

\[
\hat{p}_1 = 2u \cos(w) - b / 3a \\
\hat{p}_2 = \hat{p}_1 + \delta_0/3a 
\]

where

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Mortality at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elayda et al.\textsuperscript{iii}</td>
<td>1993</td>
<td>77</td>
<td>16%</td>
</tr>
<tr>
<td>Sundt et al.\textsuperscript{iv}</td>
<td>2000</td>
<td>133</td>
<td>20%</td>
</tr>
<tr>
<td>Chiappini et al.\textsuperscript{v}</td>
<td>2004</td>
<td>71</td>
<td>10%</td>
</tr>
<tr>
<td>Collart et al.\textsuperscript{vi}</td>
<td>2005</td>
<td>215</td>
<td>16%</td>
</tr>
<tr>
<td>Varadarajan et al.\textsuperscript{vii}</td>
<td>2006</td>
<td>80</td>
<td>13%</td>
</tr>
<tr>
<td>Melby et al.\textsuperscript{viii}</td>
<td>2007</td>
<td>105</td>
<td>18%</td>
</tr>
</tbody>
</table>
Assuming that non-inferiority is proven at the one-sided 0.05 level, a subsequent test for superiority will be performed using the above test statistic with $\delta_0 = 0$. Because this is a closed test procedure, no adjustment for multiplicity is needed.

Additionally, a 90% large sample confidence interval for the difference in proportions will be as:

$$\left( p_1 - p_2 \right) \pm z_{\alpha/2} \sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}}$$

### B. Determination of Patients/Data for Analysis

This objective will be analyzed for the intent-to-treat, as treated, implanted and per protocol populations.

#### 3.2.1.5 Missing Data

Every effort will be undertaken to minimize missing data. Since all-cause mortality is the primary endpoint for this trial, a minimal amount of missing data is anticipated. Subjects with any follow-up visits, assessments, or events on or after day 365 will be considered to have complete data for the purposes of this analysis, although only deaths occurring on or before 12 months (365 days) will count toward the primary endpoint. However, if outcome data are missing, Kaplan-Meier rates at 12 months will replace the binomial proportions in the calculation of the test statistic. The test statistic will then be calculated as:

$$z = \frac{(1-\hat{S}_1) - (1-\hat{S}_2) - \delta_0}{\sqrt{\hat{V}(\hat{S}_1) + \hat{V}(\hat{S}_2)}}$$

where $\hat{S}_1$ and $\hat{S}_2$ are the Kaplan-Meier survival estimates and $\hat{V}(\hat{S}_1)$ and $\hat{V}(\hat{S}_2)$ are the Greenwood variance estimates. Similarly, the 90% large sample confidence interval will then be calculated as:

$$\left( (1-\hat{S}_1) - (1-\hat{S}_2) \right) \pm z_{\alpha/2} \sqrt{\hat{V}(\hat{S}_1) + \hat{V}(\hat{S}_2)}$$
To assess the potential impact of any missing data, a sensitivity analysis will be conducted which will include a complete case (including only subjects whose status is known at 365 days), a best-case (assume missing MCS TAVI subjects are alive and SAVR subjects have died), a worst-case (assume missing MCS TAVI subjects have died and SAVR subjects are alive), and a tipping point analysis.

3.2.2 Powered Secondary Hypothesis

TAVI with the Medtronic CoreValve® System is superior to SAVR in binary rate of MACCE at 30 days or hospital discharge, whichever is longer.

3.2.2.1 Hypothesis and/or Parameters to Be Estimated

Powered Secondary Hypothesis: TAVI with the Medtronic CoreValve® System is superior to surgical aortic valve replacement (SAVR) in binary rate of MACCE at 30 days or hospital discharge, whichever is longer:

\[ H_0: \pi_{MCS\ TAVI} = \pi_{SAVR} \]
\[ H_A: \pi_{MCS\ TAVI} < \pi_{SAVR} \]

In the above expression, \( \pi_{MCS\ TAVI} \) and \( \pi_{SAVR} \) denote binary rates of MACCE at 30 days or hospital discharge, whichever is longer.

3.2.2.2 Endpoint Definition

The endpoint is the binary rate of MACCE at 30 days or hospital discharge, whichever is longer. For each treatment group, the numerator will be the number of subjects with a MACCE at 30 days or hospital discharge, whichever is longer, and the denominator will be the number of subjects in the analysis cohort. Refer to section 3.3.1.2 for the MACCE endpoint definition.

3.2.2.3 Sample Size Methods and Assumptions

A. Sample Size Calculation and Methods

The following are assumptions for the sample size estimate:

1:1 treatment allocation ratio

One-sided alpha = 0.025

\( \pi_{SAVR} = 20.0\% \)

\( \pi_{MCS\ TAVI} = 12.1\% \)

Power = >80%

For the secondary superiority hypothesis, assuming 1:1 treatment allocation ratio between study device and surgical valve replacement and assuming the proportion of MACCE at 30 days or hospital discharge, whichever is longer, equal to 20% in the surgical valve replacement arm and equal to 12.1% in the study device arm (39.5% relative treatment effect), PASS software calculates that 355 evaluable subjects per arm would yield 81.9% power for a one-sided test at the 0.025 level of significance.
B. Rationale for Choice of Hypothesis
Sundt et al., Collart et al., and Melby et al. reported MACCE rates at 30 days. From these studies, the MACCE (defined as a composite of all cause death, MI (Q-wave and non-Q-wave), emergent cardiac surgery, stroke, and reintervention) rate ranged from 15% to 31% with meta-analytic average of 20.1% (95% CI 16.5-23.8%). Thus, for the current study it is assumed that the expected MACCE rate at 30 days will be 20%.

3.2.2.4 Data Collection and Analysis Methods

A. Data Collection and Analysis
MACCE data will be collected on a CEC adjudication form.

The test statistic will be calculated using the pooled z-test without correction for continuity:

\[
z = \frac{p_{MCSTAVI} - p_{SAVR}}{\sqrt{p(1-p)(\frac{1}{n_{MCSTAVI}} + \frac{1}{n_{SAVR}})}}
\]
where $p$ is the pooled sample proportion:

$$p = \frac{n_{MCSTAVI} p_{MCSTAVI} + n_{SAVR} p_{SAVR}}{n_{MCSTAVI} + n_{SAVR}}$$

In the above expressions $p_{MCSTAVI}$ and $p_{SAVR}$ are the sample proportions of subjects having a MACCE by 30 days or discharge, whichever is longer, and $n_{MCSTAVI}$ and $n_{SAVR}$ are the numbers of subjects in each analysis cohort. The test is one-sided and the resulting $p$-value will be compared to 0.025.

### B. Determination of Patients/Data for Analysis

This objective will be analyzed for the intent-to-treat, as treated, implanted and per protocol populations.

#### 3.2.2.5 Missing Data

Every effort will be undertaken to minimize missing data. Because MACCE is a safety endpoint and because this endpoint is evaluated at 30 days, a minimal amount of missing data is anticipated for this secondary hypothesis. Subjects with any follow-up visits, assessments, or events on or after day 30 will be considered to have complete data for the purposes of this analysis. However, if outcome data are missing, Kaplan-Meier rates at 30 days will be used to calculate the test statistic. For subjects whose discharge date was after 30 days, any events prior to discharge will be treated as occurring on day 30. The test statistic is then calculated as:

$$z = \frac{(1 - \hat{S}_{MCSTAVI}) - (1 - \hat{S}_{SAVR})}{\sqrt{\hat{V}(\hat{S}_{MCSTAVI}) + \hat{V}(\hat{S}_{SAVR})}}$$

where $\hat{S}_{MCSTAVI}$ and $\hat{S}_{SAVR}$ are the Kaplan-Meier survival (event-free) estimates and $\hat{V}(\hat{S}_{MCSTAVI})$ and $\hat{V}(\hat{S}_{SAVR})$ are the Greenwood variance estimates.

To assess the potential impact of any missing data, a sensitivity analysis will be conducted which will include a complete case (including only subjects whose status is known at 30 days or discharge, whichever is longer), a best-case (assume missing MCS TAVI subjects are MACCE-free and SAVR subjects have a MACCE), a worst-case (assume missing MCS TAVI subjects have a MACCE and SAVR subjects are MACCE-free), and a tipping point analysis.

### 3.3 Secondary Objectives

#### 3.3.1 Secondary Objective #1 – MACCE

MACCE-free survival at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

#### 3.3.1.1 Hypothesis and/or Parameters to Be Estimated

The following hypotheses will be tested:
3.3.1.2 Endpoint Definition

MACCE is defined as a composite of:
- All-cause death
- Myocardial infarction (MI)
- All stroke
- Reintervention (defined as any cardiac surgery or percutaneous reintervention catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve)

MACCE components will be adjudicated by the Clinical Events Committee (CEC).

3.3.1.3 Data Collection and Analysis Methods

A. Data Collection and Analysis
Data will be collected on a CEC adjudication form. A Kaplan-Meier survival analysis will be performed for each treatment group, and the log-rank test will be used to compare the treatment groups.

B. Determination of Patients/Data for Analysis
This objective will be analyzed for the as treated population.

3.3.2 Secondary Objective #2 - Individual MACCE Components

The occurrence of individual MACCE components at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

3.3.2.1 Hypothesis and/or Parameters to Be Estimated

For each of individual MACCE components the following hypotheses will be tested:

\[ H_0: S(t)_{\text{MCS TAVI}} = S(t)_{\text{SAVR}} \text{ for all } t \]
\[ H_A: S(t)_{\text{MCS TAVI}} \neq S(t)_{\text{SAVR}} \text{ for at least one } t \]

In the above expressions \( S(t)_{\text{MCS TAVI}} \) and \( S(t)_{\text{SAVR}} \) denote the MACCE-free survival functions for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

MACCE-free survival estimates of individual MACCE components for each treatment group will be provided at 30 days, 6 months, 12 months and annually through five years.

3.3.2.2 Endpoint Definition

The four individual components of MACCE are all-cause death, myocardial infarction (MI), stroke, and reintervention.
3.3.2.3 **Data Collection and Analysis Methods**

A. **Data Collection and Analysis**
   Data will be collected on a CEC adjudication form. A Kaplan-Meier survival analysis will be performed for each of the four components for each of the treatment groups. The log-rank test will be used to compare the treatment groups for each component.

B. **Determination of Patients/Data for Analysis**
   This objective will be analyzed for the as treated population.

3.3.3 **Secondary Objective #3 – MAE**

MAE at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

3.3.3.1 **Hypothesis and/or Parameters to Be Estimated**

The following hypotheses will be tested:

- \( H_0: S(t)_{\text{MCS TAVI}} = S(t)_{\text{SAVR}} \) for all \( t \)
- \( H_A: S(t)_{\text{MCS TAVI}} \neq S(t)_{\text{SAVR}} \) for at least one \( t \)

In the above expressions, \( S(t)_{\text{MCS TAVI}} \) and \( S(t)_{\text{SAVR}} \) denote the MAE-free survival functions for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

MAE-free survival estimates for each treatment group will be provided at 30 days, 6 months, 12 months and annually through five years.

3.3.3.2 **Endpoint Definition**

Major adverse events (MAE) include:

- MACCE
- Acute kidney injury
- Cardiac tamponade
- Prosthetic valve dysfunction
- Cardiogenic shock
- Valve endocarditis
- Valve embolism
- Life-threatening, disabling or major bleeding
- Major vascular complication
- Cardiac perforation
- Device migration

MAE components will be adjudicated by the Clinical Events Committee (CEC).

3.3.3.3 **Data Collection and Analysis Methods**

A. **Data Collection and Analysis**
   Data will be collected on a CEC adjudication form. A Kaplan-Meier survival analysis will be performed for each treatment group, and the log-rank test will be used to compare the treatment groups.

B. **Determination of Patients/Data for Analysis**
   This objective will be analyzed for the as treated population.
3.3.4 Secondary Objective #4 - Conduction Disturbance Requiring Permanent Pacemaker Implantation

Conduction disturbance requiring permanent pacemaker implantation at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

3.3.4.1 Hypothesis and/or Parameters to Be Estimated

Separately for new onset and pre-existing conduction disturbance, the following hypotheses will be tested:

\[ H_0: S(t)_{MCS\ TAVI} = S(t)_{SAVR} \text{ for all } t \]
\[ H_A: S(t)_{MCS\ TAVI} \neq S(t)_{SAVR} \text{ for at least one } t \]

In the above expressions, \( S(t)_{MCS\ TAVI} \) and \( S(t)_{SAVR} \) denote the pacemaker implantation-free survival functions for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

Pacemaker implantation-free survival estimates for each treatment group will be provided at 30 days, 6 months, 12 months and annually through five years, separately for new onset and pre-existing conduction disturbance.

3.3.4.2 Endpoint Definition

Conduction disturbance requiring permanent pacemaker implantation is defined as any disturbance in the cardiac electrical conduction system that meets the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) Class I or IIa Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities for Acquired Atrioventricular Block in Adults or Permanent Pacing in Chronic Bifascicular Block. This endpoint will be adjudicated by an EKG core lab.

3.3.4.3 Data Collection and Analysis Methods

A. Data Collection and Analysis

Data will be collected on an EKG core lab adjudication form. Separately for new onset and pre-existing conduction disturbance, a Kaplan-Meier survival analysis will be performed for each treatment group, and the log-rank test will be used to compare the treatment groups.

B. Determination of Patients/Data for Analysis

This objective will be analyzed for the as treated population.

3.3.5 Secondary Objective #5 – NYHA

Change in NYHA class from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

3.3.5.1 Hypothesis and/or Parameters to Be Estimated

The following hypotheses will be tested at 30 days, 6 months, 12 months and annually thereafter up to 5 years:

\[ H_0: \mu_{MCS\ TAVI} = \mu_{SAVR} \]
\[ H_A: \mu_{MCS\ TAVI} \neq \mu_{SAVR} \]
In the above expressions $\mu_{\text{MCS TAVI}}$ and $\mu_{\text{SAVR}}$ denotes the mean change in NYHA classification from baseline, for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

The following hypotheses will also be tested at 30 days, 6 months, 12 months and annually thereafter up to 5 years:

\[
\begin{align*}
H_0: \mu_{\text{MCS TAVI}} &= 0 \\
H_A: \mu_{\text{MCS TAVI}} &\neq 0 \\
\end{align*}
\]

and

\[
\begin{align*}
H_0: \mu_{\text{SAVR}} &= 0 \\
H_A: \mu_{\text{SAVR}} &\neq 0 \\
\end{align*}
\]

Additionally, a test of non-inferiority at 12 months will be performed as part of a hierarchical test procedure. Refer to section 3.3.18 for more details.

### 3.3.5.2 Endpoint Definition

New York Heart Association (NYHA) class is a classification system for defining cardiac disease and related functional limitations into four broad categorizations:

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

For each subject with paired data, the number of classes changed from baseline (-2, -1, 0, 1, 2, or 3) will be calculated at 30 days, 6 months, 12 months and annually through five years.

### 3.3.5.3 Data Collection and Analysis Methods

#### A. Data Collection and Analysis

Data will be collected on follow-up visit forms. NYHA classifications will be summarized with frequencies and percentages at baseline, 30 days, 6 months, 12 months and annually through five years. Change in NYHA classification from baseline will be summarized both with frequencies and percentages and as continuous data at baseline, 30 days, 6 months, 12 months and annually through five years. For each treatment group, a paired t-test will be performed to evaluate change from baseline at 30 days, 6 months, 12 months and annually through five years. A two-sample t-test will be used to compare the change from baseline for the two groups at 30 days, 6 months, 12 months and annually through five years.
B. Determination of Patients/Data for Analysis
This objective will be analyzed for the as treated population.

3.3.6 Secondary Objective #6 - Six-Minute Walk Test

Change in distance walked during 6-minute walk test (6MWT) from baseline to 30 days and baseline to 12 months

3.3.6.1 Hypothesis and/or Parameters to Be Estimated

The following hypotheses will be tested at 30 days and 12 months:

\[ H_0: \mu_{\text{MCS TAVI}} = \mu_{\text{SAVR}} \]
\[ H_A: \mu_{\text{MCS TAVI}} \neq \mu_{\text{SAVR}} \]

In the above expressions \( \mu_{\text{MCS TAVI}} \) and \( \mu_{\text{SAVR}} \) denotes the mean change in 6-minute walk test distances from baseline, for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

The following hypotheses will also be tested at 30 days and 12 months:

\[ H_0: \mu_{\text{MCS TAVI}} = 0 \]
\[ H_A: \mu_{\text{MCS TAVI}} \neq 0 \]

and

\[ H_0: \mu_{\text{SAVR}} = 0 \]
\[ H_A: \mu_{\text{SAVR}} \neq 0 \]

3.3.6.2 Endpoint Definition

The 6-minute walk test distance is defined as the distance, in meters, that is walked in six minutes.

3.3.6.3 Data Collection and Analysis Methods
A. Data Collection and Analysis

Data will be collected on a separate six minute walk test form for each follow-up visit. Distance walked at each time point will be summarized as continuous data. For each treatment group, a paired t-test will be performed to evaluate change from baseline at 30 days and 12 months. A two-sample t-test will be used to compare the change from baseline for the two groups at 30 days and 12 months.

B. Determination of Patients/Data for Analysis

A six minute walk test per the American Thoracic Society Guidelines will be performed unless the subject is exempt due to any of the following conditions: postural hypotension, postural arrhythmia, resting systolic pressure less than 95 mmHg, non-ambulatory due to arthritis, neuromuscular disease or Peripheral Vascular Disease, Chronic Obstructive Pulmonary Disease with \( O_2 \) desaturation upon ambulation or oxygen dependent, or unstable angina. Subjects with any of these conditions will not undergo the test, but the reasons for not performing the test must be documented on the six minute walk test case report form. These subjects will be excluded from the analysis.
All subjects who are able to perform the six-minute walk evaluation; and those subjects who are unable to perform the walk evaluation due to heart failure symptoms at the time of the baseline or follow-up visit will be included in the analysis. Subjects who are unable to perform the walk evaluation due to heart failure symptoms at the time of the baseline or follow-up visit will be assigned a distance walked of zero meters.

This objective will be analyzed for the as treated population.

3.3.7 Secondary Objective #7 - Ratio of Days Alive Out of Hospital Versus Total Days Alive

Ratio of days alive out of hospital versus total days alive assessed at 12 months follow-up.

3.3.7.1 Hypothesis and/or Parameters to Be Estimated

The following hypotheses will be tested:

\[ H_0: \mu_{\text{MCS TAVI}} = \mu_{\text{SAVR}} \]
\[ H_A: \mu_{\text{MCS TAVI}} \neq \mu_{\text{SAVR}} \]

In the above expressions \( \mu_{\text{MCS TAVI}} \) and \( \mu_{\text{SAVR}} \) denotes the mean proportion of days alive out of hospital at 12 months, for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

For each treatment group, the mean proportion of days alive out of hospital will be estimated at 12 months.

3.3.7.2 Endpoint Definition

For each subject, the proportion of post-enrollment days alive out of hospital against total days alive will be calculated at 12 months. The numerator will be the number of days alive out of hospital, and the denominator will be the number of post-enrollment days alive as of the last follow-up date (the latest date of all follow-up visits, assessments, and events (including death)) or 365, whichever is smaller. All hospitalizations will be included in this analysis, including hospitalization for device implant.

3.3.7.3 Data Collection and Analysis Methods

A. Data Collection and Analysis

The admission date for the index procedure will be captured on the procedure form, and the discharge date will be captured on the discharge form. All other hospitalization dates will be collected on the hospitalization case report form. The proportion of days alive out of hospital will be summarized as with continuous data. A two-sample t-test will be used to compare the mean proportion for the two groups.

B. Determination of Patients/Data for Analysis

This objective will be analyzed for the as treated population.
3.3.8 Secondary Objective #8 - Quality of Life

Quality of Life (QoL) change from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

3.3.8.1 Hypothesis and/or Parameters to Be Estimated

For each QoL assessment, and for each follow-up time, the null hypothesis that the mean paired difference is the same for both treatment groups will be tested against the two-sided alternative that the mean paired difference is different.

Additionally, for each treatment group, for each QoL assessment, and for each follow-up time, the null hypothesis that the mean paired difference is zero will be tested against the two-sided alternative that the mean is not zero.

Finally, a test for the change in SF-12 Physical Summary Scale from baseline to 30 days and a test of non-inferiority for the Kansas City Cardiomyopathy Questionnaire (KCCQ) score at 12 months will be performed as part of a hierarchical test procedure. Refer to section 3.3.18 for more details.

3.3.8.2 Endpoint Definition

The Kansas City Cardiomyopathy Questionnaire (KCCQ), SF 12, and EuroQoL will be assessed at baseline, 30 days, 6 months, 12 months and annually through five years.

3.3.8.3 Data Collection and Analysis Methods

A. Data Collection and Analysis

Data will be collected on QoL questionnaires and entered in a separate database by a QoL core lab. For each treatment group, the changes in QoL scores will be evaluated using a paired t-test or Wilcoxon signed-rank test as appropriate. A two-sample t-test or Wilcoxon rank-sum test, as appropriate, will be used to compare the changes from baseline for the two groups.

B. Determination of Patients/Data for Analysis

All subjects completing the questionnaires will be evaluated and the reasons for missing data will be provided.

This objective will be analyzed for the as treated population.

3.3.9 Secondary Objective #9 - Echocardiographic Assessment of Valve Performance

Echocardiographic assessment of valve performance at discharge, 30 days, 6 months, 12 months and annually thereafter up to 5 years using the following measures:

- transvalvular mean gradient
- effective orifice area
- degree of aortic valve regurgitation (transvalvular and paravalvular)
3.3.9.1 **Hypothesis and/or Parameters to Be Estimated**

For both of the endpoints of transvalvular mean gradient and effective orifice area, the following hypotheses will be tested at discharge, 30 days, 6 months, 12 months and annually thereafter up to 5 years:

\[
\begin{align*}
H_0: & \quad \mu_{\text{MCS TAVI}} = \mu_{\text{SAVR}} \\
H_A: & \quad \mu_{\text{MCS TAVI}} \neq \mu_{\text{SAVR}}
\end{align*}
\]

In the above expressions, \( \mu_{\text{MCS TAVI}} \) and \( \mu_{\text{SAVR}} \) denote the mean change from baseline, for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

For both of the endpoints of transvalvular mean gradient and effective orifice area, the following hypotheses will also be tested at discharge, 30 days, 6 months, 12 months and annually thereafter up to 5 years:

\[
\begin{align*}
H_0: & \quad \mu_{\text{MCS TAVI}} = 0 \\
H_A: & \quad \mu_{\text{MCS TAVI}} \neq 0
\end{align*}
\]

and

\[
\begin{align*}
H_0: & \quad \mu_{\text{SAVR}} = 0 \\
H_A: & \quad \mu_{\text{SAVR}} \neq 0
\end{align*}
\]

For both of the endpoints of transvalvular and paravalvular degree of aortic valve regurgitation, at discharge, 30 days, 6 months, 12 months and annually thereafter up to 5 years:

\[
\begin{align*}
H_0: & \quad \mu_{\text{MCS TAVI}} = \mu_{\text{SAVR}} \\
H_A: & \quad \mu_{\text{MCS TAVI}} \neq \mu_{\text{SAVR}}
\end{align*}
\]

In the above expressions, \( \mu_{\text{MCS TAVI}} \) and \( \mu_{\text{SAVR}} \) now denote row mean scores for the ordinal regurgitation data, for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

Additionally, tests of non-inferiority for transvalvular mean gradient and effective orifice area at 12 months will be performed as part of a hierarchical test procedure. Refer to section 3.3.18 for more details.

3.3.9.2 **Endpoint Definition**

All echocardiograms will be analyzed by an echo core lab which will determine the values for these endpoints. Transvalvular mean gradient will be measured in mmHg. Effective orifice area will be measured in cm\(^2\). Degree of aortic valve regurgitation (transvalvular and paravalvular) will be described as mild, moderate, or severe.

3.3.9.3 **Data Collection and Analysis Methods**

A. **Data Collection and Analysis**

Data will be entered in a separate database by an echo core lab. For each treatment group, transvalvular mean gradient and effective orifice area at each time point will be summarized as with continuous data. For each treatment group, a paired t-test will be used to evaluate change from baseline at discharge, 30 days, 6 months, 12 months and annually through five years. A two-sample t-test will be used to compare the change from baseline for the two groups at 30 days, 6 months, 12 months and annually through five years.
Degree of aortic valve regurgitation will be summarized with frequencies and percentages at each time point. The two treatment groups will be compared using the Cochran-Mantel-Haenszel test with row mean scores.

B. Determination of Patients/Data for Analysis
All subjects undergoing echocardiography procedures will be evaluated.

This objective will be analyzed for the as treated and implanted populations.

3.3.10 Secondary Objective #10 - Aortic Valve Disease-Related Hospitalizations

Aortic valve disease related hospitalizations: the number of subjects re-hospitalized after the initial index procedure will be compared at 30 days, 6 months, 12 months and annually through five years.

3.3.10.1 Hypothesis and/or Parameters to Be Estimated
The following hypotheses will be tested:

\[ H_0: S(t)_{MCS\ TAVI} = S(t)_{SAVR} \text{ for all } t \]
\[ H_A: S(t)_{MCS\ TAVI} \neq S(t)_{SAVR} \text{ for at least one } t \]

In the above expressions \( S(t)_{MCS\ TAVI} \) and \( S(t)_{SAVR} \) denote the hospitalization-free survival functions for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

Hospitalization-free survival estimates for each treatment group will be provided at 30 days, 6 months, 12 months and annually through five years.

3.3.10.2 Endpoint Definition
Aortic valve disease hospitalizations are defined as a non-elective hospital admission for signs and symptoms related to aortic valve disease (as described below) that results in at least a two-night stay (i.e., where the admission date and the discharge date differ by at least two calendar days). For the purpose of the protocol, overnight stays at nursing home facilities or extended care facilities do not meet the protocol definition of hospitalization. This does include the administration or augmentation of intravenous heart failure therapy (e.g., inotropes, diuretics, and/or vasodilators).

Subjects with signs and symptoms related to aortic valve disease (as described below) who are hospitalized for less than two days or who are treated and released from the emergency department or an outpatient clinic (including treatment for intravenous heart failure therapy (e.g., inotropes, diuretics, and/or vasodilators)), will not be counted as aortic valve disease hospitalizations.

Aortic valve disease will be evaluated using documented evidence of the following signs and symptoms. An independent Clinical Events Committee (CEC) will review all available source documentation for all hospitalizations to determine if they are aortic valve disease hospitalizations. The CEC adjudication will be used for final analysis.

<table>
<thead>
<tr>
<th>Signs and Symptoms of Aortic Valve Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sign/Symptom</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>Definition</th>
</tr>
</thead>
</table>
### Aortic Valve Dysfunction

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortness of breath/dyspnea</td>
<td>A feeling of difficult or labored breathing that is out of proportion to the patient’s level of physical activity</td>
</tr>
<tr>
<td>Exercise intolerance</td>
<td>A condition where the patient is unable to do physical exercise at the level or for the duration that would be expected of someone in his/her general physical condition, or experiences unusually severe post-exercise pain, fatigue, or other negative effects</td>
</tr>
<tr>
<td>Dizziness/syncope</td>
<td>Lightheadedness or unsteadiness of gait or a partial or complete loss of consciousness with interruption of awareness of oneself and ones surroundings</td>
</tr>
<tr>
<td>Chest pain</td>
<td>Discomfort and soreness in and around the chest</td>
</tr>
</tbody>
</table>

### Worsening Heart Failure

#### Volume Overload

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthopnea</td>
<td>Dyspnea in which the person can breathe comfortably only when standing or sitting erect</td>
</tr>
<tr>
<td>Paroxysmal nocturnal dyspnea</td>
<td>Acute dyspnea caused by the lung congestion and edema that results from partial heart failure and occurring suddenly at night, usually an hour or two after the individual has fallen asleep.</td>
</tr>
<tr>
<td>Jugular venous distension</td>
<td>With the patient is positioned under 45°, and the filling level of the jugular vein determined. An abnormal response is more than 3 centimeters above the sternal angle.</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>Palpation of the edge of the liver below the edge of the ribs without inspiration</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>Swelling of tissues, usually in the lower limbs, due to the accumulation of fluids.</td>
</tr>
<tr>
<td>Pulmonary rales</td>
<td>Small clicking, bubbling, or rattling sounds in the lung associated with inspiration</td>
</tr>
<tr>
<td>Abdominal-jugular reflux</td>
<td>An elevation of venous pressure visible in the jugular veins and measurable in the veins of the arm, produced in active or impending congestive heart failure by firm pressure with the flat hand over the abdomen.</td>
</tr>
<tr>
<td>Radiographic evidence of pulmonary edema</td>
<td>NA</td>
</tr>
<tr>
<td>Elevated B-type natriuretic peptide level</td>
<td>NA</td>
</tr>
</tbody>
</table>

### Hypoperfusion

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Narrow pulse pressure</td>
<td>Pulse pressure &lt; 30 mmHg</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Systolic BP &lt; 90 systolic</td>
</tr>
<tr>
<td>Renal or hepatic dysfunction</td>
<td>• Rise in baseline creatinine by 25%</td>
</tr>
<tr>
<td></td>
<td>• Increase in LFT (SGOT, SGPT) &gt; 2 times normal</td>
</tr>
<tr>
<td>Low serum sodium concentration</td>
<td>Serum sodium &lt; 130 mEq/dL</td>
</tr>
</tbody>
</table>

#### 3.3.10.3 Data Collection and Analysis Methods

**A. Data Collection and Analysis**

Data will be collected on a CEC adjudication form. A Kaplan-Meier survival analysis will be performed for each treatment group, and the log-rank test will be used to compare the treatment groups.
B. Determination of Patients/Data for Analysis
   This objective will be analyzed for the as treated population.

3.3.11 Secondary Objective #11 - Cardiovascular Deaths and Valve-Related Deaths

Cardiovascular deaths and valve-related deaths: the number of cardiovascular deaths and valve-related deaths at 30 days, 6 months, 12 months and annually through five years will be reported.

3.3.11.1 Hypothesis and/or Parameters to Be Estimated
For each endpoint the following hypotheses will be tested:

\[ H_0: S(t)_{MCS\ TAVI} = S(t)_{SAVR} \text{ for all } t \]
\[ H_A: S(t)_{MCS\ TAVI} \neq S(t)_{SAVR} \text{ for at least one } t \]

In the above expressions \( S(t)_{MCS\ TAVI} \) and \( S(t)_{SAVR} \) denote the survival functions for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

For each endpoint, survival estimates for each treatment group will be provided at 30 days, 6 months, 12 months and annually through five years.

3.3.11.2 Endpoint Definition
Cardiovascular death will be defined, according to the definition proposed by the Valve Academic Research Consortium (VARC) Consensus Report for Transcatheter Aortic Valve Implantation (TAVI); 2010-06-15, as any one of the following:

- Any death due to proximate cardiac cause (e.g. MI, cardiac tamponade, worsening heart failure)
- Unwitnessed death and death of unknown cause
- All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure
- Death caused by non-coronary vascular conditions such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease

Note: All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in subjects with coexisting potentially fatal non-cardiac disease (e.g., cancer, infection) should be classified as cardiac.

Valve-related deaths are defined as:

- Any death caused by prosthetic valve dysfunction, valve thrombosis, embolism, bleeding event, or implanted valve endocarditis;
- Death related to reintervention on the operated valve.

3.3.11.3 Data Collection and Analysis Methods
A. Data Collection and Analysis
Data will be collected on a CEC adjudication form. For each endpoint, a Kaplan-Meier survival analysis will be performed for each treatment group, and the log-rank test will be used to compare the treatment groups.
B. Determination of Patients/Data for Analysis

This objective will be analyzed for the as treated population.

3.3.12 Secondary Objective #12 – Strokes and TIAs

The number of subjects with strokes (of any severity) and TIAs at 30 days, 6 months, 12 months and annually through five years will be reported.

3.3.12.1 Hypothesis and/or Parameters to Be Estimated

For each endpoint, the following hypotheses will be tested:

\[ H_0: S(t)_{MCS \ TAVI} = S(t)_{SAVR} \text{ for all } t \]
\[ H_A: S(t)_{MCS \ TAVI} \neq S(t)_{SAVR} \text{ for at least one } t \]

In the above expressions \( S(t)_{MCS \ TAVI} \) and \( S(t)_{SAVR} \) denote the event-free survival functions for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

For each endpoint, event-free survival estimates for each treatment group will be provided at 30 days, 6 months, 12 months and annually through five years.

3.3.12.2 Endpoint Definition

Stroke and TIA will be defined according to the definition proposed by the Valve Academic Research Consortium (VARC) Consensus Report for Transcatheter Aortic Valve Implantation (TAVI); 2010-06-15

**Stroke Diagnostic Criteria**

- Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke
- Duration of a focal or global neurological deficit ≥ 24 hours; OR < 24 hours, if therapeutic intervention(s) were performed (e.g. thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; OR the neurologic deficit results in death
- No other readily identifiable non-stroke cause for the clinical presentations (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences)*
- Confirmation of the diagnosis by at least one of the following:
  - Neurology or neurosurgical specialist
  - Neuroimaging procedure (MR or CT scan or cerebral angiography)
  - Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)

**Stroke Definitions**

- Transient Ischemic Attack
  - New focal neurologic deficit with rapid symptom resolution (usually 1-2 hours), always within 24 hours
  - Neuroimaging without tissue injury
- Stroke: (diagnosis as above, preferably with positive neuroimaging study)+
  - Minor (non-clinically important disability) - modified Rankin score < 2 at 7 days or
prior to discharge AND NIHSS score < 3 (above baseline) at 7 days or prior to discharge and at 30-day assessment
  o Major (clinically important disability) - modified Rankin score ≥ 2 at 7 days or prior to discharge AND NIHSS score ≥ 3 (above baseline) at 7 days or prior to discharge and at 30-day assessment

3.3.12.3 Data Collection and Analysis Methods

A. Data Collection and Analysis
Data will be collected on a CEC adjudication form. A separate analysis will be performed for each of the following:
  • a composite of all strokes and TIAs
  • major strokes only
  • minor strokes only
  • TIAs only
For each endpoint, a Kaplan-Meier survival analysis will be performed for each treatment group, and the log-rank test will be used to compare the treatment groups.

B. Determination of Patients/Data for Analysis
This objective will be analyzed for the as treated population.

3.3.13 Secondary Objective #13 - Index Procedure-Related MAEs

Index procedure related MAEs: Index procedure-related MAE events will be summarized and event rates will be provided at 30 days.

3.3.13.1 Hypothesis and/or Parameters to Be Estimated
The endpoint is descriptive and no statistical hypothesis test will be performed. For each treatment group, the rate of index procedure-related MAE events will be summarized at 30 days.

3.3.13.2 Endpoint Definition
The numerator will be the number of procedure-related MAE events experienced by the end of the 30-day follow-up visit, and the denominator will be the number of subjects evaluated at the 30-day follow-up visit plus the number of subjects not evaluated but who experienced a procedure-related MAE event prior to the end of the follow-up visit window.

3.3.13.3 Data Collection and Analysis Methods

A. Data Collection and Analysis
Data regarding MAEs will be collected on a CEC adjudication form. For each treatment group, the event rate as described above will be calculated. Additionally, the percentage of subjects with a procedure-related MAE will be calculated in the same way, but allowing no more than one MAE per subject.

B. Determination of Patients/Data for Analysis
This objective will be analyzed for the as treated population.
3.3.14 Secondary Objective #14 - Length of Index Procedure Hospital Stay

Length of index procedure hospital stay

3.3.14.1 Hypothesis and/or Parameters to Be Estimated
The endpoint is descriptive and no statistical hypothesis test will be performed. The mean length of index procedure hospital stay will be estimated.

3.3.14.2 Endpoint Definition
For each subject, the length of index procedure hospital stay will be calculated as the number of calendar days spanning the admission date to the discharge date on the discharge case report form; i.e., it will be calculated as (discharge date - admission date + 1).

3.3.14.3 Data Collection and Analysis Methods
A. Data Collection and Analysis
The admission date will be captured on the procedure form, and the discharge date will be captured on the discharge form. For each treatment group, the length of index procedure hospital stay will be summarized as with continuous data.

B. Determination of Patients/Data for Analysis
This objective will be analyzed for the as treated population.

3.3.15 Secondary Objective #15 - Device Success

Device success

3.3.15.1 Hypothesis and/or Parameters to Be Estimated
The endpoint is descriptive and no statistical hypothesis test will be performed. The rate of device success will be estimated.

3.3.15.2 Endpoint Definition
Device success is defined as follows:
- Successful vascular access, delivery and deployment of the device, and successful retrieval of the delivery system.
- Correct position of the device in the proper anatomical location (placement in the annulus with no impedance on device function).
- Intended performance of the prosthetic valve (aortic valve area > 1.2 cm² (by echocardiography using the continuity equation) and mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/sec, without moderate or severe prosthetic valve AR). Performance is assessed acutely in a resting state, either within 24-48 hours after the index procedure or before hospital discharge.
- Only one valve implanted in the proper anatomical location.

3.3.15.3 Data Collection and Analysis Methods
A. Data Collection and Analysis
The components of device success will be determined by the site and recorded on the procedure case report form. The numerator will be the number of subjects whose procedure resulted in device success, and the denominator will be the number of subjects with a procedure attempt.

B. Determination of Patients/Data for Analysis
This objective will be analyzed for the MCS TAVI cohort only in the as treated population.

3.3.16 Secondary Objective #16 - Procedural Success

Procedural success

3.3.16.1 Hypothesis and/or Parameters to Be Estimated
The endpoint is descriptive and no statistical hypothesis test will be performed. The rate of procedural success will be estimated.

3.3.16.2 Endpoint Definition
Procedural success is defined as device success and absence of in-hospital MACCE.

3.3.16.3 Data Collection and Analysis Methods
A. Data Collection and Analysis
Device success will be as determined in the previous objective. The components of MACCE will be recorded on a CEC adjudication form. In-hospital MACCE will include those events that have a date on or before the discharge date recorded on the discharge form. The numerator will be the number of subjects whose procedure resulted in procedural success, and the denominator will be the number of subjects with a procedure attempt.

B. Determination of Patients/Data for Analysis
This objective will be analyzed for the MCS TAVI cohort only in the as treated population.

3.3.17 Secondary Objective #17 - Prosthetic Valve Dysfunction

Evidence of prosthetic valve dysfunction at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

3.3.17.1 Hypothesis and/or Parameters to Be Estimated
The endpoint is descriptive and no statistical hypothesis test will be performed. Prosthetic valve dysfunction-free survival estimates will be provided at 30 days, 6 months, 12 months and annually through five years.

3.3.17.2 Endpoint Definition
Prosthetic valve dysfunction is a component of MAE and will be adjudicated by the CEC.
3.3.17.3 **Data Collection and Analysis Methods**

**A. Data Collection and Analysis**

Data will be collected on a CEC adjudication form. A Kaplan-Meier survival analysis will be performed.

**B. Determination of Patients/Data for Analysis**

This objective will be analyzed for the MCS TAVI cohort only in the implanted population.

3.3.18 **Hierarchical Testing**

Provided the 12-month non-inferiority mortality primary objective is met with a significant p-value, to keep the overall (familywise) Type I error rate at 0.05, a hierarchical test procedure will be applied to the 30-day (or hospital discharge, whichever is longer) MACCE powered secondary hypothesis and five of the secondary objective hypothesis tests. The goal of this hierarchical procedure is to make statistically valid claims of significance in the device labeling.

In this hierarchical test procedure, each objective is examined in the pre-specified order. An objective is statistically significant only if that objective and all prior objectives have a significant p-value. The hierarchical testing order will be:

1. Change in transvalvular mean gradient from baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #9. The one-sided two-sample t-test will be used to test non-inferiority at a level of 0.05 the hypotheses:
   \[ H_0: \mu_{MCS\ TAVI} \leq \mu_{SAVR} -15 \]
   \[ H_A: \mu_{MCS\ TAVI} > \mu_{SAVR} -15 \]
   In the above expression \( \mu_{MCS\ TAVI} \) and \( \mu_{SAVR} \) denote the mean improvements in mean gradient from baseline to 12 months measured in mmHg.

2. Change in effective orifice area baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #9. The one-sided two-sample t-test will be used to test non-inferiority at a level 0.05 the hypotheses:
   \[ H_0: \mu_{MCS\ TAVI} \leq \mu_{SAVR} -0.375 \]
   \[ H_A: \mu_{MCS\ TAVI} > \mu_{SAVR} -0.375 \]
   In the above expression \( \mu_{MCS\ TAVI} \) and \( \mu_{SAVR} \) denote the mean improvements in effective orifice area from baseline to 12 months measured in cm\(^2\).

3. Change in NYHA classification from baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #5. The one-sided two-sample t-test will be used to test non-inferiority at a level 0.05 the hypotheses:
   \[ H_0: \mu_{MCS\ TAVI} \leq \mu_{SAVR} -0.375 \]
   \[ H_A: \mu_{MCS\ TAVI} > \mu_{SAVR} -0.375 \]
   In the above expression \( \mu_{MCS\ TAVI} \) and \( \mu_{SAVR} \) denote the mean number of classification improvements in NYHA from baseline to 12 months.

4. Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score from baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #8. The
one-sided two-sample t-test will be used to test non-inferiority at a level 0.05 the hypotheses:
\[ H_0: \mu_{\text{MCS TAVI}} \leq \mu_{\text{SAVR}} -5 \]
\[ H_A: \mu_{\text{MCS TAVI}} > \mu_{\text{SAVR}} -5 \]
In the above expression $\mu_{\text{MCS TAVI}}$ and $\mu_{\text{SAVR}}$ denote the mean improvements in the KCCQ score from baseline to 12 months.

5. Powered Secondary Hypothesis: TAVI with the Medtronic CoreValve® System is superior to SAVR in binary rate of MACCE at 30 days or hospital discharge, whichever is longer. This one-sided test will be carried out at the 0.025 level using the pooled z-test without correction for continuity to test the hypotheses:
\[ H_0: \pi_{\text{MCS TAVI}} = \pi_{\text{SAVR}} \]
\[ H_A: \pi_{\text{MCS TAVI}} < \pi_{\text{SAVR}} \]
In the above expression $\pi_{\text{MCS TAVI}}$ and $\pi_{\text{SAVR}}$ denote the binary rate of MACCE at 30 days or hospital discharge.

6. Change in SF-12 Physical Summary Scale from baseline to 30 days: TAVI vs. SAVR from secondary objective #8. The two-sided two-sample t-test will be used to test at a level 0.05 the hypotheses:
\[ H_0: \mu_{\text{MCS TAVI}} = \mu_{\text{SAVR}} \]
\[ H_A: \mu_{\text{MCS TAVI}} \neq \mu_{\text{SAVR}} \]
In the above expression $\mu_{\text{MCS TAVI}}$ and $\mu_{\text{SAVR}}$ denote the mean improvements in the SF-12 Physical Summary Scale from baseline to 30 days.

This hierarchical test procedure will be performed for the as treated population.

As the trial confirmation is not dependent on the secondary endpoints, multiplicity adjustments will not be made in the other analyses of the secondary endpoints. Summary data from other secondary objectives, such as device success and procedural success from secondary objectives #15 and #16, respectively, may be provided in the device labeling. However, no claims of statistical significance or other statistical inference will be made.

### 3.4 Additional Analyses

#### 3.4.1 Poolability Analysis

##### 3.4.1.1 Pooling of Small Sites
Sites contributing less than 3 treatment or 3 control subjects to the as treated analysis set will be considered “small sites” and ordered by the date of first enrollment in the as treated analysis set. Starting with the first “small site”, a pseudo-site will be created by adding subjects from successive “small sites”. If the number of subjects reaches or exceeds the size of the median enrollment of the “large sites”, then a second pseudo-site will be created. Additional pseudo-sites, if needed, would be created in the same manner.
3.4.1.2 **Primary Endpoint by Site**

The interaction between site or pseudosite and treatment on the probability of death at 12 months will be compared using logistic regression. If the resulting p-value is $\leq 0.15$, further exploratory analysis will attempt to identify covariates that may explain treatment effect differences among the sites, beginning in the next section. Otherwise, the data will be considered to be poolable across study sites.

3.4.1.3 **Univariate Covariate Analysis**

The following baseline characteristics will be examined individually as potential predictors of death at 12 months using logistic regression:

1. Gender
2. Age
3. Baseline NYHA
4. Logistic EuroSCORE
5. Baseline LVEF
6. Hypertension
7. Diabetes
8. Coronary artery disease
9. Prior stroke
10. Prior MI
11. Prior PCI

3.4.1.4 **Multivariate Analysis**

Covariates with p-value $\leq 0.20$ from the previous section will be included along with site in a logistic regression model. If this multivariate logistic regression does not result in a significant (p-value $\leq 0.15$) site by treatment interaction after adjustment for these baseline factors, then outcome results will again be considered poolable across study sites. If site by treatment interaction is still significant (p-value $\leq 0.15$) after adjustment for these factors, results will be presented by site and the clinical significance of these differences will be assessed.

3.4.2 **Gender Analysis**

The primary endpoint and secondary endpoints #1-3 (MACCE, individual MACCE components, and MAE) will be examined for differences in outcome between genders. Additionally, tests for these outcomes will be performed to evaluate potential interactions between treatment and gender. These analyses will be performed on the as treated analysis set.

For the primary endpoint, the proportions of subjects who died at 12 months will be compared using logistic regression with gender as an independent variable on the complete case analysis. This analysis will be repeated with treatment and the treatment by gender interaction added to the model.

MACCE-free survival estimates for each gender will be provided at 30 days, 6 months, 12 months and annually through five years. MACCE-free survival between genders will be compared using the log-rank test. MACCE-free survival estimates for each gender and treatment combination will be provided at 30 days, 6 months, 12 months and annually through five years. A Cox proportional hazards
model will be fit with predictors of gender, treatment, and treatment by gender interaction.

This analysis will be repeated for each individual component of MACCE and for MAE.

3.4.3 Access Site Analysis

The primary endpoint and secondary endpoints #1-3 (MACCE, individual MACCE components, and MAE) will be examined for differences in outcome between access sites (ilio-femoral or non-ilio-femoral). Additionally, tests for these outcomes will be performed to evaluate potential interactions between treatment and access site. These analyses will be performed on the as treated analysis set. Per the as treated analysis set definition, TAVI subjects will be analyzed according to the access site on the procedure form, while SAVR subjects will be analyzed according to the stratified access site.

For the primary endpoint, the proportions of subjects who died at 12 months will be compared using logistic regression with access site as an independent variable on the complete case analysis. This analysis will be repeated with treatment and the treatment by access site interaction added to the model.

MACCE-free survival estimates for each gender will be provided at 30 days, 6 months, 12 months and annually through five years. MACCE-free survival between access sites will be compared using the log-rank test. MACCE-free survival estimates for each access site and treatment combination will be provided at 30 days, 6 months, 12 months and annually through five years. A Cox proportional hazards model will be fit with predictors of access site, treatment, and treatment by access site interaction.

This analysis will be repeated for each individual component of MACCE and for MAE.

4 REVISION PROCESS

The study statistician will be responsible for the execution of this statistical analysis plan, including any revisions and obtaining of appropriate approvals.

5 DISTRIBUTION

The study statistician will be responsible for execution of this statistical analysis plan and distribution of revisions to the appropriate clinical staff.

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The attached document is required to be approved by the following staff. After all required approvals are obtained; the attached document is approved for use.

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CardioVascular Structural Heart Clinical Department

Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients)

Statistical Analysis Plan

Version 3

Date: 06 NOV 2013

IDE No. G100012
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Prepared by:
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1 PURPOSE OF SAP

This Statistical Analysis Plan (SAP) has been designed to document, before data are analyzed, the clinical study design rationale for the Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients), and the planned analyses that will be included in study reports. The design and analyses are consistent with the objectives of the Clinical Investigational Plan (CIP). This SAP does not limit the analyses in reports, and additional analyses of the study data beyond this plan are expected.

2 RATIONALE FOR STUDY DESIGN

The purpose of this study is to evaluate the safety and efficacy of the Medtronic CoreValve® System in the treatment of symptomatic severe aortic stenosis in subjects who have a predicted high risk for aortic valve surgery. High risk surgical subjects will be randomized to receive either transcatheter aortic valve implant (TAVI) with the Medtronic CoreValve® System (MCS) or surgical aortic valve replacement (SAVR) in a 1:1 ratio.

This statistical analysis plan is developed based on the Clinical Investigational Plan Version 13.0.

3 DESCRIPTION OF ANALYSIS

3.1 General Summaries

3.1.1 Description of Baseline Variables

Baseline demographic and clinical variables will be summarized for each of the treatment groups for the intent-to-treat, as treated, and per protocol populations. All continuous variables will be summarized with means, medians, standard deviations, interquartile ranges, minimums, and maximums and compared between treatment groups using a two-sample t-test or the non-parametric Wilcoxon rank-sum test. Categorical variables will be summarized with frequencies and percentages and compared between treatment groups using Pearson’s χ² test or Fisher’s exact test, as appropriate. Ordinal variables will be compared using Cochran-Mantel-Haenszel test with row mean scores.

Age will be calculated as the difference in days between the subject’s date of birth and the date of signing the informed consent, divided by 365.25.

3.1.2 Reports for which this Statistical Analysis Plan applies

This Statistical Analysis Plan applies to the study report for Pre-market Approval (PMA) Application to the Food and Drug Administration (FDA) and to the final report.

This SAP applies to the main study manuscript, though not everything specified here will be included in the manuscript.
3.1.3 Special Considerations

3.1.3.1 Report Timing and Cutoff Dates

The PMA report will be generated after all enrolled subjects with 26, 29, and 31 mm valves have completed their 12-month follow-up visit in-window or later (or, if early, have been followed for at least 365 days via a subsequent follow-up form), have died, or have exited from the study.

Cutoff dates will be applied to all site case report forms. A Visit Cutoff Date and a Received Cutoff Date will be used. The visit cutoff date will be the first date on which all enrolled subjects have been followed for 12 months, have died, or have exited from the study. The visit, assessment, and event dates will be used to determine which case report forms satisfy the visit cutoff date. The received cutoff date will be determined near the time of the database closure and will be chosen to ensure that all known deaths, 12-month visits, and other forms of critical importance have been received while still allowing adequate time for data cleaning between the received cutoff date and the date of database closure. The “logints” log-in timestamp field will be used to determine which case report forms satisfy the received cutoff date.

Any forms which do not have a visit date directly on the form (e.g., the protocol deviation form) will use the visit date from the corresponding form for that entry. Forms with multiple dates (e.g., the protocol deviation form and the medication form) will apply cutoff dates to individual lines of data on the form.

The final report will be generated after all enrolled subjects have been followed for 5 years, have died, or have exited from the study. Because the intent is to report on all study data, it is not expected that cutoff dates will apply to the final report.

3.1.3.2 Missing Data

Unless specified in each objective, no statistical techniques will be used to impute missing data. If a subject’s data are missing for any reason, that subject will not be included in that portion of the analysis. The number of subjects included in each analysis will be reported so that the potential impact of missing data can be assessed. See sections 3.2.1.5 and 3.2.2.5 for the handling of missing data for the primary objective and powered secondary hypothesis, respectively.

In the case of partial dates, if only the month and year are known, the event or assessment will be analyzed as if it occurred on the 15th of that month. If only the year is known, the event or assessment will be analyzed as if it occurred on June 30th of that year. These resolutions of partial dates are subject to the restrictions that pre-procedure events and assessments must occur between the randomization date and the procedure date and post-procedure events and assessments must occur no earlier than the procedure date.

3.1.3.3 P-Values

All statistical tests and/or confidence intervals, as appropriate, will be performed at $\alpha=0.05$ (2-sided), except when specified otherwise. All reported p-values greater than or equal to 0.0001 and less than or equal to 0.9999 will be rounded to four
decimal places. P-values less than 0.0001 will be displayed as “<0.0001” and P-values greater than 0.9999 will be displayed as “>0.9999”.

3.1.3.4 Student’s t-Tests
For analyses of continuous data, given the sample sizes, it is expected that, even if the underlying data are not normal, that the sampling distributions of the sample means will be sufficiently normal to permit use of paired and 2-sample t-tests. Only in unusual cases will these be replaced with the Wilcoxon signed-rank and rank-sum tests, respectively.

For any two-sample t-test performed, the t-statistic will be calculated based on equal variances if the test for equality of variances is non-significant (p > 0.05). Otherwise, the t-statistic based on unequal variances will be used to compare the two samples.

3.1.3.5 Chi-Square Tests
For analyses of categorical data, chi-square tests will be used unless there are observed cell counts of less than 5. In those cases, Fisher’s exact test will be used.

3.1.3.6 Kaplan-Meier Analyses
Secondary objectives #1-4, #10-12, and #17 call for a Kaplan-Meier analysis of event-free rates at 30 days, 6 months, 12 months and annually through five years. For these analyses, these times correspond to 30 days, 183 days, 365 days, 730 days, 1095 days, 1460 days, and 1825 days, respectively. At each time point with data, the product-limit estimate of the event-free rate, the number of subjects at risk, the number of subjects with events, the Peto standard error of the estimate, and the loglog transformed 95% confidence interval using the Peto standard error will be presented.

For subjects without an event, the date of censoring will be the latest date of all follow-up visits, assessments, and events (including death in those objectives where death is not the endpoint).

3.1.3.7 Roll-in Cases
The first three successfully enrolled patients at each implanting site inclusive of both the High Risk Surgical and Extreme Risk patient populations will be considered “roll-in” subjects and will be automatically assigned to receive the Medtronic CoreValve® System. A maximum of three roll-in subjects is allowed per site. A successful roll-in subject is defined as the subject leaving the procedure room with one CoreValve® device in the correct position and not requiring emergency surgery. A site must have three successful roll-in subjects before they can be evaluated by the Training and Education Committee to move into the pivotal phase.

3.1.3.8 Enrolled Subject
An enrolled subject must sign informed consent, meet all of the inclusion and none of the exclusion criteria (with the exception of a percutaneous coronary or
Peripheral intervention and evidence of an acute myocardial infarction which must not occur within 30 days prior to the index procedure), have been assessed by the Screening Committee as being an appropriate candidate for enrollment, and have been assigned a patient identification number in the interactive voice/web randomization service (IXRS). Subjects will be considered enrolled into the trial at the time of randomization.

Randomization with an assignment to the treatment arm or control arm (MCS TAVI or SAVR) will be executed in a 1:1 ratio. Stratified randomization by investigational site and by intended access site (ilio-femoral or non-ilio-femoral) will be used to ensure subjects will be allocated to each comparison group proportionately.

3.1.3.9  Analysis Sets
There are four different analysis sets that are defined for this study. The primary analysis will be the “as treated” analysis. Analysis sets used for each objective are defined in the corresponding objective section. Data from roll-in patients will be presented separately with descriptive statistics.

3.1.3.9.1  Intent-to-Treat (ITT)
The intent-to-treat population consists of all randomized subjects. Subjects will be analyzed according to the randomization assignment and the stratified access site (ilio-femoral or non-ilio-femoral), regardless of whether a procedure is actually attempted, which device the subject actually receives, and which access site is actually used. This population excludes roll-in subjects. Because not all subjects in this population will have a procedure, time zero begins at the date of randomization.

3.1.3.9.2  As Treated (AT)
The as treated population 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. In the database, TAVI attempted procedure is defined by a non-missing MCS TAVI procedure date, and SAVR attempted procedure is defined by a non-missing SAVR procedure date. Subjects will be analyzed according to their first attempted procedure (TAVI or SAVR).

In addition, TAVI subjects will be analyzed according to the access site (ilio-femoral or non-ilio-femoral) on the first attempted procedure form, while SAVR subjects will be analyzed according to the stratified access site (ilio-femoral or non-ilio-femoral). This population excludes roll-in subjects. Time zero begins at the date of the first attempted procedure.

3.1.3.9.3  Implanted (IMP)
The implanted population consists of all as treated subjects who are actually implanted with either the MCS or a surgical valve. To be considered implanted, an MCS TAVI subject’s device disposition form must show at least one device with a final disposition of “Implanted,” while an SAVR subject’s procedure form must indicate the valve manufacturer and model as well as the suture method. Time zero begins at the date of the first attempted procedure.
3.1.3.9.4 **Per Protocol (PP)**

Based on the *ICH E9 Statistical Principles for Clinical Trials* recommendations, the per protocol population should satisfy the following:

1. The completion of a certain pre-specified minimal exposure to the treatment regimen
2. The availability of measurements of the primary variable(s)
3. The absence of any major protocol violations, including the violation of entry criteria

To meet these requirements, the per protocol population will consist of all implanted subjects who were implanted according to their randomization and access site stratification and who have at least 12 months (365 days) of follow-up or have experienced the primary endpoint (death) prior to 12 months. The per protocol population does not include those subjects crossing to a different type of procedure from their first attempted procedure types (MCS TAVI or SAVR) before their 12 month visits. These subjects must satisfy all inclusion/exclusion criteria. Time zero begins at the date of the first attempted procedure.

3.1.3.10 **23mm Valve**

The 23mm valve was not available until late in the study; therefore, if approximately 20 23mm CoreValve® implants have not occurred at the time of approximately 790 randomized subjects, the 23mm subjects will not be included in the primary analysis. Up to 40 additional subjects will be randomized with about 20 23mm CoreValve® implants. When 1 year data are available for the 23mm valve, the primary and secondary endpoint data will be summarized with descriptive statistics. If appropriate, the 23mm valve subjects will be pooled with the original 790 subjects in the primary analysis dataset and the primary and secondary endpoints will be recalculated. The primary endpoint and the secondary endpoints that include hypothesis testing will be analyzed without adjustments for multiple testing. The hierarchical test procedure will be performed the same way as described in section 3.3.18.

3.1.3.11 **Definition of Index Procedure**

TAVI Index Procedure: the first TAVI procedure that the Medtronic CoreValve® System delivery catheter is introduced.
SAVR Index Procedure: the first attempted SAVR procedure.

3.1.3.12 **Interim Analysis**

No formal interim analysis is planned, and there are no plans for early termination of the study due to superiority or futility of the investigational therapy.

3.1.3.13 **Data Safety Monitoring Board (DSMB)**

An independent, un-blinded DSMB will be established and will be comprised of at least 3 experts, including a chairperson. The DSMB will have a minimum of one cardiac surgeon, one interventional cardiologist and one statistician, and will be independent of Medtronic and the trial investigators. Investigators participating in the trial may participate in the meetings to offer clarification surrounding events, but will not have voting privileges. Medtronic personnel may facilitate the DSMB
meeting but will not have voting privileges. The DSMB will meet (via teleconference or in person) prior to the first subject enrollment to establish procedures for DSMB review, chairman appointment, and guidelines for trial recommendations. The full DSMB will meet on a periodic basis to perform a comprehensive data review, including at a minimum all adverse events and deaths, and will meet more frequently when needed. Primary and safety-related secondary endpoints may also be reviewed at these meetings. Meetings will consist of both open and closed sessions.

The DSMB will also perform a supplemental review of, at a minimum, all serious adverse events and deaths and any other data requested by the DSMB on a more frequent periodic basis to ensure patient safety. DSMB members will review the report, and when necessary, provide recommendations about the conduct of the study and/or request a full DSMB meeting.

A DSMB charter will be developed and approved by Medtronic and the DSMB members. The committee will outline the criteria for both the full DSMB meeting and supplemental DSMB reviews within the DSMB charter.

Following each full DSMB meeting, the board will report to Medtronic in writing and may recommend changes in the conduct of the trial. These DSMB recommendations may include recommendations on trial status such as continuing the trial without modifications, continuing the trial with modifications, stopping the enrollment in the trial or a specific trial arm, or recommendations about trial conduct including recommendations around enrollment or protocol deviations.

In the case of UADEs, if Medtronic and the DSMB determine that the event presents an unreasonable risk to the participating subjects, Medtronic must terminate the clinical trial 5 working days after making that determination and not later than 15 working days after Medtronic first receives notice of the effect [21 CFR 812.46]. 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.

Additional details about the DSMB can be found in the DSMB charter.

### 3.2 Primary Objective

#### 3.2.1 Primary Objective

The primary objective is to demonstrate that the safety and effectiveness of the Medtronic CoreValve® System (MCS), as measured by all-cause mortality rates at 12 months, is non-inferior to surgical aortic valve replacement (SAVR) in the treatment of symptomatic severe aortic stenosis in subjects who have a predicted high risk for aortic valve surgery.

#### 3.2.1.1 Hypothesis and/or Parameters to Be Estimated

Primary Hypothesis: TAVI with the Medtronic CoreValve® System is non-inferior to surgical aortic valve replacement (SAVR) in 12 month all-cause mortality:

H₀: π_{MCS TAVI} ≥ π_{SAVR} + 7.5%
Hₐ: π_{MCS TAVI} < π_{SAVR} + 7.5%

In the above expression, π_{MCS TAVI} and π_{SAVR} denote binary rates of all-cause mortality during a fixed follow-up of 12 months.

3.2.1.2 **Endpoint Definition**

The primary endpoint is the binary rate of all-cause mortality at 12 months. For each treatment group, the numerator will be the number of subjects who died at or before 12 months (365 days), and the denominator will be the number of subjects in the analysis cohort.

3.2.1.3 **Sample Size Methods and Assumptions**

**A. Sample Size Calculation and Methods**

The following are assumptions for the sample size estimate:

- 1:1 treatment allocation ratio
- One-sided alpha = 0.05
- $π_{SAVR} = 20.0\%$
- $π_{MCS TAVI} = 20.0\%$
- Power = 80%
- Non-inferiority margin = 7.5%

Assuming 1:1 treatment allocation ratio between study device and surgical valve replacement and assuming the proportion of all-cause mortality at 12 months equal to 20\% for both arms and a non-inferiority margin of 7.5\%, Power Analysis and Sample Size (PASS) software calculates that a total of 355 subjects in each arm is required to attain 80\% power in a Farrington and Manning test of non-inferiority of the study device at the 0.05 level of significance.
Accounting for 10% loss to follow-up, a total of $\frac{395+395}{2} = 790$ subjects is required.

B. Rationale for Choice of Hypothesis
The assumption for 12 month mortality for the SAVR arm is an estimate based on 12-month mortality as reported in the surgical literature for high risk AVR (table below). The subjects enrolled in this study are expected to have a higher mortality than observed in the surgical literature, as subjects enrolled in the High Risk Surgical Cohort must have an expected perioperative mortality of 15% (based on Investigator-estimated mortality or STS score >10).

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Mortality at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elayda et al.</td>
<td>1993</td>
<td>77</td>
<td>16%</td>
</tr>
<tr>
<td>Sundt et al.</td>
<td>2000</td>
<td>133</td>
<td>20%</td>
</tr>
<tr>
<td>Chiappini et al.</td>
<td>2004</td>
<td>71</td>
<td>10%</td>
</tr>
<tr>
<td>Collart et al.</td>
<td>2005</td>
<td>215</td>
<td>16%</td>
</tr>
<tr>
<td>Varadarajan et al.</td>
<td>2006</td>
<td>80</td>
<td>13%</td>
</tr>
<tr>
<td>Melby et al.</td>
<td>2007</td>
<td>105</td>
<td>18%</td>
</tr>
</tbody>
</table>
Currently, the average patient undergoing surgery is older and has a greater number of co-morbidities than the previously studied population. Given that the expected High Risk Surgical population will be older and at higher risk for surgery, it is estimated that the 12-month all-cause mortality rate among high risk SAVR subjects in the current study will be 20%.

3.2.1.4 Data Collection and Analysis Methods

A. Data Collection and Analysis

Death data will be collected on a CEC adjudication form.

The one-sided Farrington and Manning test for non-inferiority of two binomial proportions will be carried out to assess statistical significance at the 0.05 level. The test statistic will be calculated as:

\[
z = \frac{p_1 - p_2 - \delta_0}{\sqrt{\frac{1}{n_1} + \frac{1}{n_2}}} \sqrt{n_1 \left(1 - \frac{1}{n_1}\right) + n_2 \left(1 - \frac{1}{n_2}\right)}
\]

Where \( p_1 \) and \( p_2 \) are the usual sample proportions, \( n_1 \) and \( n_2 \) are the sizes of the analysis cohorts, and \( \delta_0 = 0.075 \). In the calculation of the standard error, \( \tilde{p}_1 \) and \( \tilde{p}_2 \) are the maximum likelihood estimators under the constraint that the difference equals \( \delta_0 \), where that solution is given by

\[
\tilde{p}_1 = 2u \cos(w) - b / 3a
\]

\[
\tilde{p}_2 = \tilde{p}_1 + \delta_0
\]

where

\[
w = (\pi + \cos^{-1}(v / u^3)) / 3
\]

\[
v = b^3 / (3a)^3 - bc / 6a^2 + d / 2a
\]

\[
u = \text{sign}(v)\sqrt{b^2 / (3a)^2 - c / 3a}
\]

\[
a = 1 + \theta
\]

\[
b = -(1 + \theta + p_1 + \theta p_2 - \delta_0 (\theta + 2))
\]

\[
c = \delta_0^2 - \delta_0 (2p_1 + \theta + 1) + p_1 + \theta p_2
\]

\[
d = p_1 \delta_0 (1 - \delta_0)
\]

\[\theta = n_2 / n_1\]

Assuming that non-inferiority is proven at the one-sided 0.05 level, a subsequent test for superiority will be performed using the above test statistic.
with $\delta_0 = 0$ at the one-sided 0.05 level. Because this is a closed test procedure, no adjustment for multiplicity is needed.

Additionally, a 90% large sample confidence interval for the difference in proportions will be calculated as:

$$\left( p_1 - p_2 \right) \pm z_{\alpha/2} \sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}}$$

**B. Determination of Patients/Data for Analysis**

This objective will be analyzed for the intent-to-treat, as treated, implanted and per protocol populations. The As Treated analysis will be the primary analysis for this objective.

**3.2.1.5 Missing Data**

Every effort will be undertaken to minimize missing data. Since all-cause mortality is the primary endpoint for this trial, a minimal amount of missing data is anticipated. Subjects with any follow-up visits, assessments, or events on or after day 365 will be considered to have complete data for the purposes of this analysis, although only deaths occurring on or before 12 months (365 days) will count toward the primary endpoint. However, if outcome data are missing, Kaplan-Meier rates at 12 months will replace the binomial proportions in the calculation of the test statistic. The test statistic will then be calculated as:

$$z = \frac{(1 - \hat{S}_1) - (1 - \hat{S}_2) - \delta_0}{\sqrt{\hat{V}(\hat{S}_1) + \hat{V}(\hat{S}_2)}}$$

where $\hat{S}_1$ and $\hat{S}_2$ are the Kaplan-Meier survival estimates and $\hat{V}(\hat{S}_1)$ and $\hat{V}(\hat{S}_2)$ are the Greenwood variance estimates. Similarly, the 90% large sample confidence interval will then be calculated as:

$$\left( (1 - \hat{S}_1) - (1 - \hat{S}_2) \right) \pm z_{\alpha/2} \sqrt{\hat{V}(\hat{S}_1) + \hat{V}(\hat{S}_2)}$$

To assess the potential impact of any missing data, a sensitivity analysis will be conducted which will include a complete case (including only subjects whose status is known at 365 days), a best-case (assume missing MCS TAVI subjects are alive at 12 months and missing SAVR subjects have died at the censoring time), a worst-case (assume missing MCS TAVI subjects have died at the censoring time and missing SAVR subjects are alive at 12 months), and a tipping point analysis if the conclusion is changed in the worst-case analysis.

**3.2.2 Powered Secondary Hypothesis**

TAVI with the Medtronic CoreValve® System is superior to SAVR in binary rate of MACCE at 30 days or hospital discharge, whichever is longer.
3.2.2.1 Hypothesis and/or Parameters to Be Estimated

Powered Secondary Hypothesis: TAVI with the Medtronic CoreValve® System is superior to surgical aortic valve replacement (SAVR) in binary rate of MACCE at 30 days or hospital discharge, whichever is longer:

\[ H_0: \pi_{\text{MCS TAVI}} = \pi_{\text{SAVR}} \]
\[ H_A: \pi_{\text{MCS TAVI}} < \pi_{\text{SAVR}} \]

In the above expression \( \pi_{\text{MCS TAVI}} \) and \( \pi_{\text{SAVR}} \) denote binary rates of MACCE at 30 days or hospital discharge, whichever is longer.

3.2.2.2 Endpoint Definition

The endpoint is the binary rate of MACCE at 30 days or hospital discharge, whichever is longer. For each treatment group, the numerator will be the number of subjects with a MACCE at 30 days or hospital discharge, whichever is longer, and the denominator will be the number of subjects in the analysis cohort. Refer to section 3.3.1.2 for the MACCE endpoint definition.

3.2.2.3 Sample Size Methods and Assumptions

A. Sample Size Calculation and Methods

The following are assumptions for the sample size estimate:

1:1 treatment allocation ratio

One-sided alpha = 0.025

\[ \pi_{\text{SAVR}} = 20.0\% \]

\[ \pi_{\text{MCS TAVI}} = 12.1\% \]

For the secondary superiority hypothesis, assuming 1:1 treatment allocation ratio between study device and surgical valve replacement and assuming the proportion of MACCE at 30 days or hospital discharge, whichever is longer, equal to 20% in the surgical valve replacement arm and equal to 12.1% in the study device arm (39.5% relative treatment effect), PASS software calculates that 355 evaluable subjects per arm would yield 81.9% power for a one-sided test at the 0.025 level of significance.
B. Rationale for Choice of Hypothesis
Sundt et al., Collart et al., and Melby et al. reported MACCE rates at 30 days. From these studies, the MACCE (defined as a composite of all cause death, MI (Q-wave and non-Q-wave), emergent cardiac surgery, stroke, and reintervention) rate ranged from 15% to 31% with meta-analytic average of 20.1% (95% CI 16.5-23.8%). Thus, for the current study it is assumed that the expected MACCE rate at 30 days will be 20%.

3.2.2.4 Data Collection and Analysis Methods

A. Data Collection and Analysis
MACCE data will be collected on a CEC adjudication form.

The test statistic will be calculated using the pooled z-test without correction for continuity:

\[
z = \frac{p_{MCSTAVI} - p_{SAVR}}{\sqrt{p(1-p)\left(\frac{1}{n_{MCSTAVI}} + \frac{1}{n_{SAVR}}\right)}}
\]

where \( p \) is the pooled sample proportion:

\[
p = \frac{n_{MCSTAVI}p_{MCSTAVI} + n_{SAVR}p_{SAVR}}{n_{MCSTAVI} + n_{SAVR}}
\]
In the above expressions \( p_{\text{MCS TAVI}} \) and \( p_{\text{SAVR}} \) are the sample proportions of subjects having a MACCE by 30 days or discharge, whichever is longer, and \( n_{\text{MCS TAVI}} \) and \( n_{\text{SAVR}} \) are the numbers of subjects in each analysis cohort. The test is one-sided and the resulting p-value will be compared to 0.025.

**B. Determination of Patients/Data for Analysis**

This objective will be analyzed for the intent-to-treat, as treated, implanted and per protocol populations. The As Treated analysis will be the primary analysis for this objective.

### 3.2.2.5 Missing Data

Every effort will be undertaken to minimize missing data. Because MACCE is a safety endpoint and because this endpoint is evaluated at 30 days, a minimal amount of missing data is anticipated for this secondary hypothesis. Subjects with any follow-up visits, assessments, or events on or after day 30 will be considered to have complete data for the purposes of this analysis. However, if outcome data are missing, Kaplan-Meier rates at 30 days will be used to calculate the test statistic. For subjects whose discharge date was after 30 days, any events prior to discharge will be treated as occurring on day 30. The test statistic is then calculated as:

\[
Z = \frac{(1 - \hat{S}_{\text{MCS TAVI}}) - (1 - \hat{S}_{\text{SAVR}})}{\sqrt{\hat{V}(\hat{S}_{\text{MCS TAVI}}) + \hat{V}(\hat{S}_{\text{SAVR}})}}
\]

where \( \hat{S}_{\text{MCS TAVI}} \) and \( \hat{S}_{\text{SAVR}} \) are the Kaplan-Meier survival (event-free) estimates and \( \hat{V}(\hat{S}_{\text{MCS TAVI}}) \) and \( \hat{V}(\hat{S}_{\text{SAVR}}) \) are the Greenwood variance estimates.

To assess the potential impact of any missing data, a sensitivity analysis will be conducted which will include a complete case (including only subjects whose status is known at 30 days or discharge, whichever is longer), a best-case (assume missing MCS TAVI subjects are MACCE-free at 30 days and missing SAVR subjects have a MACCE at the censoring time), a worst-case (assume missing MCS TAVI subjects have a MACCE at the censoring time and missing SAVR subjects are MACCE-free at 30 days), and a tipping point analysis if necessary.

### 3.3 Secondary Objectives

#### 3.3.1 Secondary Objective #1 – MACCE

MACCE-free survival at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

#### 3.3.1.1 Hypothesis and/or Parameters to Be Estimated

The following hypotheses will be tested:

- \( H_0: S(t)_{\text{MCS TAVI}} = S(t)_{\text{SAVR}} \) for all \( t \)
- \( H_A: S(t)_{\text{MCS TAVI}} \neq S(t)_{\text{SAVR}} \) for at least one \( t \)
In the above expressions $S(t)_{\text{MCS TAVI}}$ and $S(t)_{\text{SAVR}}$ denote the MACCE-free survival functions for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

MACCE-free survival estimates for each treatment group will be provided at 30 days, 6 months, 12 months and annually through five years.

### 3.3.1.2 Endpoint Definition

MACCE is defined as a composite of:

- All-cause death
- Myocardial infarction (MI)
- All stroke
- Reintervention (defined as any cardiac surgery or percutaneous reintervention catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve)

MACCE components will be adjudicated by the Clinical Events Committee (CEC).

### 3.3.1.3 Data Collection and Analysis Methods

#### A. Data Collection and Analysis

Data will be collected on a CEC adjudication form. A Kaplan-Meier survival analysis will be performed for each treatment group, and the log-rank test will be used to compare the treatment groups.

#### B. Determination of Patients/Data for Analysis

This objective will be analyzed for the as treated population.

### 3.3.2 Secondary Objective #2 - Individual MACCE Components

The occurrence of individual MACCE components at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

#### 3.3.2.1 Hypothesis and/or Parameters to Be Estimated

For each of individual MACCE components the following hypotheses will be tested:

$$H_0: S(t)_{\text{MCS TAVI}} = S(t)_{\text{SAVR}} \text{ for all } t$$
$$H_A: S(t)_{\text{MCS TAVI}} \neq S(t)_{\text{SAVR}} \text{ for at least one } t$$

In the above expressions $S(t)_{\text{MCS TAVI}}$ and $S(t)_{\text{SAVR}}$ denote the MACCE-free survival functions for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

MACCE-free survival estimates of individual MACCE components for each treatment group will be provided at 30 days, 6 months, 12 months and annually through five years.

#### 3.3.2.2 Endpoint Definition

The four individual components of MACCE are all-cause death, myocardial infarction (MI), stroke, and reintervention.
3.3.2.3 Data Collection and Analysis Methods

A. Data Collection and Analysis
Data will be collected on a CEC adjudication form. A Kaplan-Meier survival analysis will be performed for each of the four components for each of the treatment groups. The log-rank test will be used to compare the treatment groups for each component.

B. Determination of Patients/Data for Analysis
This objective will be analyzed for the as treated population.

3.3.3 Secondary Objective #3 – MAE

MAE at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

3.3.3.1 Hypothesis and/or Parameters to Be Estimated
The following hypotheses will be tested:
\[ H_0: S(t)_{\text{MCS TAVI}} = S(t)_{\text{SAVR}} \text{ for all } t \]
\[ H_A: S(t)_{\text{MCS TAVI}} \neq S(t)_{\text{SAVR}} \text{ for at least one } t \]
In the above expressions \( S(t)_{\text{MCS TAVI}} \) and \( S(t)_{\text{SAVR}} \) denote the MAE-free survival functions for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

MAE-free survival estimates for each treatment group will be provided at 30 days, 6 months, 12 months and annually through five years.

3.3.3.2 Endpoint Definition
Major adverse events (MAE) include:
- MACCE
- Acute kidney injury
- Cardiac tamponade
- Prosthetic valve dysfunction
- Cardiogenic shock
- Valve endocarditis
- Valve embolism
- Life-threatening, disabling or major bleeding
- Major vascular complication
- Cardiac perforation
- Device migration
MAE components will be adjudicated by the Clinical Events Committee (CEC).

3.3.3.3 Data Collection and Analysis Methods

A. Data Collection and Analysis
Data will be collected on a CEC adjudication form. A Kaplan-Meier survival analysis will be performed for each treatment group, and the log-rank test will be used to compare the treatment groups.

B. Determination of Patients/Data for Analysis
This objective will be analyzed for the as treated population.
3.3.4 Secondary Objective #4 - Conduction Disturbance Requiring Permanent Pacemaker Implantation

Conduction disturbance requiring permanent pacemaker implantation at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

3.3.4.1 Hypothesis and/or Parameters to Be Estimated
Separately for new onset and pre-existing conduction disturbance, the following hypotheses will be tested:

\[ H_0: S(t)_{MCS \ TAVI} = S(t)_{SAVR} \text{ for all } t \]
\[ H_A: S(t)_{MCS \ TAVI} \neq S(t)_{SAVR} \text{ for at least one } t \]

In the above expressions \( S(t)_{MCS \ TAVI} \) and \( S(t)_{SAVR} \) denote the pacemaker implantation-free survival functions for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

Pacemaker implantation-free survival estimates for each treatment group will be provided at 30 days, 6 months, 12 months and annually through five years, separately for new onset and pre-existing conduction disturbance.

3.3.4.2 Endpoint Definition
Conduction disturbance requiring permanent pacemaker implantation is defined as any disturbance in the cardiac electrical conduction system that meets the American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) Class I or IIa Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities for Acquired Atrioventricular Block in Adults or Permanent Pacing in Chronic Bifascicular Block. This endpoint will be adjudicated by an EKG core lab.

3.3.4.3 Data Collection and Analysis Methods

A. Data Collection and Analysis
Data will be collected on an EKG core lab permanent pacemaker implant adjudication form. Separately for new onset and pre-existing conduction disturbance, a Kaplan-Meier survival analysis will be performed for each treatment group, and the log-rank test will be used to compare the treatment groups. The event date is the date of permanent pacemaker implantation.

B. Determination of Patients/Data for Analysis
This objective will be analyzed for the as treated population.

3.3.5 Secondary Objective #5 – NYHA

Change in NYHA class from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years.

3.3.5.1 Hypothesis and/or Parameters to Be Estimated
The following hypotheses will be tested at 30 days, 6 months, 12 months and annually thereafter up to 5 years:

\[ H_0: \mu_{MCS \ TAVI} = \mu_{SAVR} \]
HA: $\mu_{\text{MCS TAVI}} \neq \mu_{\text{SAVR}}$

In the above expressions $\mu_{\text{MCS TAVI}}$ and $\mu_{\text{SAVR}}$ denotes the mean change in NYHA classification from baseline, for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

The following hypotheses will also be tested at 30 days, 6 months, 12 months and annually thereafter up to 5 years:

$H_0: \mu_{\text{MCS TAVI}} = 0$

$H_A: \mu_{\text{MCS TAVI}} \neq 0$

and

$H_0: \mu_{\text{SAVR}} = 0$

$H_A: \mu_{\text{SAVR}} \neq 0$

Additionally, a test of non-inferiority at 12 months will be performed as part of a hierarchical test procedure. Refer to section 3.3.18 for more details.

3.3.5.2 Endpoint Definition

New York Heart Association (NYHA) class is a classification system for defining cardiac disease and related functional limitations into four broad categorizations:

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

For each subject with paired data, the number of classes changed from baseline (-2, -1, 0, 1, 2, or 3) will be calculated at 30 days, 6 months, 12 months and annually through five years.

3.3.5.3 Data Collection and Analysis Methods

A. Data Collection and Analysis

Data will be collected on follow-up visit forms. NYHA classifications will be summarized with frequencies and percentages at baseline, 30 days, 6 months, 12 months and annually through five years. Change in NYHA classification from baseline will be summarized both with frequencies and percentages and as continuous data at baseline, 30 days, 6 months, 12 months and annually through five years. For each treatment group, a paired t-test will be performed to evaluate change from baseline at 30 days, 6 months, 12 months and annually through five years. A two-sample t-test will be used to compare the change from baseline for the two groups at 30 days, 6 months, 12 months and annually through five years.
B. Determination of Patients/Data for Analysis
This objective will be analyzed for the as treated population.

3.3.6 Secondary Objective #6 - Six-Minute Walk Test

Change in distance walked during 6-minute walk test (6MWT) from baseline to 30 days and baseline to 12 months

3.3.6.1 Hypothesis and/or Parameters to Be Estimated

The following hypotheses will be tested at 30 days and 12 months:

\[ H_0: \mu_{MCS\ TAVI} = \mu_{SAVR} \]
\[ H_A: \mu_{MCS\ TAVI} \neq \mu_{SAVR} \]

In the above expressions \( \mu_{MCS\ TAVI} \) and \( \mu_{SAVR} \) denotes the mean change in 6-minute walk test distances from baseline, for the TAVI with the Medtronic CoreValve \textsuperscript{®} System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

The following hypotheses will also be tested at 30 days and 12 months:

\[ H_0: \mu_{MCS\ TAVI} = 0 \]
\[ H_A: \mu_{MCS\ TAVI} \neq 0 \]

and

\[ H_0: \mu_{SAVR} = 0 \]
\[ H_A: \mu_{SAVR} \neq 0 \]

3.3.6.2 Endpoint Definition

The 6-minute walk test distance is defined as the distance, in meters, that is walked in six minutes.

3.3.6.3 Data Collection and Analysis Methods

A. Data Collection and Analysis

Data will be collected on a separate six minute walk test form for each follow-up visit. Distance walked at each time point will be summarized as continuous data. For each treatment group, a paired t-test will be performed to evaluate change from baseline at 30 days and 12 months. A two-sample t-test will be used to compare the change from baseline for the two groups at 30 days and 12 months.

B. Determination of Patients/Data for Analysis

A six minute walk test per the American Thoracic Society Guidelines will be performed unless the subject is exempt due to any of the following conditions: postural hypotension, postural arrhythmia, resting systolic pressure less than 95 mmHg, non-ambulatory due to arthritis, neuromuscular disease or Peripheral Vascular Disease, Chronic Obstructive Pulmonary Disease with \( O_2 \) desaturation upon ambulation or oxygen dependent, or unstable angina. Subjects with any of these conditions will not undergo the test, but the reasons for not performing the test must be documented on the six minute walk test case report form. These subjects will be excluded from the analysis.
All subjects who are able to perform the six-minute walk evaluation will be included in the analysis.
This objective will be analyzed for the as treated population.

3.3.7 Secondary Objective #7 - Ratio of Days Alive Out of Hospital Versus Total Days Alive

Ratio of days alive out of hospital versus total days alive assessed at 12 months follow-up.

3.3.7.1 Hypothesis and/or Parameters to Be Estimated

The following hypotheses will be tested:
\[ H_0: \mu_{\text{MCS TAVI}} = \mu_{\text{SAVR}} \]
\[ H_A: \mu_{\text{MCS TAVI}} \neq \mu_{\text{SAVR}} \]

In the above expressions \( \mu_{\text{MCS TAVI}} \) and \( \mu_{\text{SAVR}} \) denotes the mean proportion of days alive out of hospital at 12 months, for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

For each treatment group, the mean proportion of days alive out of hospital will be estimated at 12 months.

3.3.7.2 Endpoint Definition

For each subject, the proportion of post-procedure days alive out of hospital against total days alive will be calculated at 12 months. The numerator will be the number of days alive out of hospital, and the denominator will be the number of post-procedure days alive as of the last follow-up date (the latest date of all follow-up visits, assessments, and events (including death)) or 365, whichever is smaller. All hospitalizations will be included in this analysis, including hospitalization for device implant.

3.3.7.3 Data Collection and Analysis Methods

A. Data Collection and Analysis

The admission date for the Medtronic CoreValve® implant procedure will be captured on the procedure form, and the discharge date will be captured on the discharge form. All other hospitalization dates will be collected on the hospitalization case report form. The proportion of days alive out of hospital will be summarized as with continuous data. A two-sample t-test will be used to compare the mean proportion for the two groups.

B. Determination of Patients/Data for Analysis

This objective will be analyzed for the as treated population.

3.3.8 Secondary Objective #8 - Quality of Life

Quality of Life (QoL) change from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years.
3.3.8.1 Hypothesis and/or Parameters to Be Estimated

For each QoL assessment, and for each follow-up time, the null hypothesis that the mean paired difference is the same for both treatment groups will be tested against the two-sided alternative that the mean paired difference is different.

Additionally, for each treatment group, for each QoL assessment, and for each follow-up time, the null hypothesis that the mean paired difference is zero will be tested against the two-sided alternative that the mean is not zero.

Finally, a test for the change in SF-12 Physical Summary Scale from baseline to 30 days and a test of non-inferiority for the Kansas City Cardiomyopathy Questionnaire (KCCQ) score at 12 months will be performed as part of a hierarchical test procedure. Refer to section 3.3.18 for more details.

3.3.8.2 Endpoint Definition

The Kansas City Cardiomyopathy Questionnaire (KCCQ), SF 12, and EuroQoL will be assessed at baseline, 30 days, 6 months, 12 months and annually through five years.

3.3.8.3 Data Collection and Analysis Methods

A. Data Collection and Analysis

Data will be collected on QoL questionnaires and entered in a separate database by a QoL core lab. For each treatment group, the changes in QoL scores will be evaluated using a paired t-test or Wilcoxon signed-rank test as appropriate. A two-sample t-test or Wilcoxon rank-sum test, as appropriate, will be used to compare the changes from baseline for the two groups.

B. Determination of Patients/Data for Analysis

All subjects completing the questionnaires will be evaluated and the reasons for missing data will be provided.

This objective will be analyzed for the as treated population.

3.3.9 Secondary Objective #9 - Echocardiographic Assessment of Valve Performance

Echocardiographic assessment of valve performance at discharge, 30 days, 6 months, 12 months and annually thereafter up to 5 years using the following measures:

- transvalvular mean gradient
- effective orifice area
- degree of aortic valve regurgitation (transvalvular and paravalvular)

3.3.9.1 Hypothesis and/or Parameters to Be Estimated

For both of the endpoints of transvalvular mean gradient and effective orifice area, the following hypotheses will be tested at discharge, 30 days, 6 months, 12 months and annually thereafter up to 5 years:

\[ H_0: \mu_{\text{MCS TAVI}} = \mu_{\text{SAVR}} \]
HA: $\mu_{\text{MCS TAVI}} \neq \mu_{\text{SAVR}}$

In the above expressions $\mu_{\text{MCS TAVI}}$ and $\mu_{\text{SAVR}}$ denotes the mean change from baseline, for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

For both of the endpoints of transvalvular mean gradient and effective orifice area, the following hypotheses will also be tested at discharge, 30 days, 6 months, 12 months and annually thereafter up to 5 years:

\[ H_0: \mu_{\text{MCS TAVI}} = 0 \]
\[ H_A: \mu_{\text{MCS TAVI}} \neq 0 \]

and

\[ H_0: \mu_{\text{SAVR}} = 0 \]
\[ H_A: \mu_{\text{SAVR}} \neq 0 \]

For both of the endpoints of transvalvular and paravalvular degree of aortic valve regurgitation, at discharge, 30 days, 6 months, 12 months and annually thereafter up to 5 years:

\[ H_0: \mu_{\text{MCS TAVI}} = \mu_{\text{SAVR}} \]
\[ H_A: \mu_{\text{MCS TAVI}} \neq \mu_{\text{SAVR}} \]

In the above expressions $\mu_{\text{MCS TAVI}}$ and $\mu_{\text{SAVR}}$ now denote row mean scores for the ordinal regurgitation data, for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

Additionally, tests of non-inferiority for transvalvular mean gradient and effective orifice area at 12 months will be performed as part of a hierarchical test procedure. Refer to section 3.3.18 for more details.

### 3.3.9.2 Endpoint Definition

All echocardiograms will be analyzed by an echo core lab which will determine the values for these endpoints. Transvalvular mean gradient will be measured in mmHg. Effective orifice area will be measured in cm$^2$. Degree of aortic valve regurgitation (transvalvular and paravalvular) will be described as none, trace, mild, moderate, or severe.

Transvalvular mean gradient is the measure of Mean Gradient across Aortic Valve ($\text{MGV}_2$) by CW Doppler. Effective orifice area (EOA) will be derived by the formula:

\[ \text{EOA} = \frac{\text{LVOT Long Axis diameter}^2 \times 0.785 \times (\text{VTI}_{v1})}{\text{VTI}_{v2}}. \]

Where: LVOT Long Axis diameter is the measure of LVOT long-axis diameter mid-systole in mm, $\text{VTI}_{v1}$ is the Velocity time integral of LVOT velocity by PW in cm, and $\text{VTI}_{v2}$ is the Velocity time integral across Aortic valve by CW Doppler in cm.

### 3.3.9.3 Data Collection and Analysis Methods

#### A. Data Collection and Analysis

Data will be entered in a separate database by an echo core lab. For each treatment group, transvalvular mean gradient and effective orifice area at each time point will be summarized as with continuous data. For each treatment group, a paired t-test will be used to evaluate change from baseline at discharge, 30 days, 6 months, 12 months and annually through five years. A
two-sample t-test will be used to compare the change from baseline for the two groups at 30 days, 6 months, 12 months and annually through five years.

Degree of aortic valve regurgitation will be summarized with frequencies and percentages at each time point. The two treatment groups will be compared using the Cochran-Mantel-Haenszel test with row mean scores.

B. Determination of Patients/Data for Analysis
All subjects undergoing echocardiography procedures will be evaluated.

The primary analysis for this objective will be based on the implanted population, but this objective will be analyzed for the as treated population as well.

3.3.10 Secondary Objective #10 - Aortic Valve Disease-Related Hospitalizations

Aortic valve disease related hospitalizations: the number of subjects re-hospitalized after the first attempted procedure will be reported at 30 days, 6 months, 12 months and annually through five years. The aortic valve disease related hospitalization-free survival functions will be compared between the two groups.

3.3.10.1 Hypothesis and/or Parameters to Be Estimated

The following hypotheses will be tested:

\[ H_0: S(t)_{MCS\ TAVI} = S(t)_{SAVR} \] for all t
\[ H_A: S(t)_{MCS\ TAVI} \neq S(t)_{SAVR} \] for at least one t

In the above expressions \( S(t)_{MCS\ TAVI} \) and \( S(t)_{SAVR} \) denote the hospitalization-free survival functions for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

Hospitalization-free survival estimates for each treatment group will be provided at 30 days, 6 months, 12 months and annually through five years.

3.3.10.2 Endpoint Definition

Aortic valve disease hospitalizations are defined as a non-elective hospital admission for signs and symptoms related to aortic valve disease (as described below) that results in at least a two-night stay (i.e., where the admission date and the discharge date differ by at least two calendar days). For the purpose of the protocol, overnight stays at nursing home facilities or extended care facilities do not meet the protocol definition of hospitalization. This does include the administration or augmentation of intravenous heart failure therapy (e.g., inotropes, diuretics, and/or vasodilators).

Subjects with signs and symptoms related to aortic valve disease (as described below) who are hospitalized for less than two days or who are treated and released from the emergency department or an outpatient clinic (including treatment for intravenous heart failure therapy (e.g., inotropes, diuretics, and/or vasodilators)), will not be counted as aortic valve disease hospitalizations.
Aortic valve disease will be evaluated using documented evidence of the following signs and symptoms. An independent Clinical Events Committee (CEC) will review all available source documentation for all hospitalizations to determine if they are aortic valve disease hospitalizations. The CEC adjudication will be used for final analysis.

<table>
<thead>
<tr>
<th>Sign/Symptom</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aortic Valve Dysfunction</strong></td>
<td></td>
</tr>
<tr>
<td>Shortness of breath/dyspnea</td>
<td>A feeling of difficult or labored breathing that is out of proportion to the patient's level of physical activity</td>
</tr>
<tr>
<td>Exercise intolerance</td>
<td>A condition where the patient is unable to do physical exercise at the level or for the duration that would be expected of someone in his/her general physical condition, or experiences unusually severe post-exercise pain, fatigue, or other negative effects</td>
</tr>
<tr>
<td>Dizziness/syncope</td>
<td>Lightheadedness or unsteadiness of gait or a partial or complete loss of consciousness with interruption of awareness of oneself and ones surroundings</td>
</tr>
<tr>
<td>Chest pain</td>
<td>Discomfort and soreness in and around the chest</td>
</tr>
<tr>
<td><strong>Worsening Heart Failure</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Volume Overload</strong></td>
<td></td>
</tr>
<tr>
<td>Orthopnea</td>
<td>Dyspnea in which the person can breathe comfortably only when standing or sitting erect</td>
</tr>
<tr>
<td>Paroxysmal nocturnal dyspnea</td>
<td>Acute dyspnea caused by the lung congestion and edema that results from partial heart failure and occurring suddenly at night, usually an hour or two after the individual has fallen asleep.</td>
</tr>
<tr>
<td>Jugular venous distension</td>
<td>With the patient is positioned under 45°, and the filling level of the jugular vein determined. An abnormal response is more than 3 centimeters above the sternal angle.</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>Palpation of the edge of the liver below the edge of the ribs without inspiration</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>Swelling of tissues, usually in the lower limbs, due to the accumulation of fluids.</td>
</tr>
<tr>
<td>Pulmonary rales</td>
<td>Small clicking, bubbling, or rattling sounds in the lung associated with inspiration</td>
</tr>
<tr>
<td>Abdominal-jugular reflux</td>
<td>An elevation of venous pressure visible in the jugular veins and measurable in the veins of the arm, produced in active or impending congestive heart failure by firm pressure with the flat hand over the abdomen.</td>
</tr>
<tr>
<td>Radiographic evidence of pulmonary edema</td>
<td>NA</td>
</tr>
<tr>
<td>Elevated B-type natriuretic peptide level</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Hypoperfusion</strong></td>
<td></td>
</tr>
<tr>
<td>Narrow pulse pressure</td>
<td>Pulse pressure &lt; 30 mmHg</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Systolic BP &lt; 90 systolic</td>
</tr>
<tr>
<td>Renal or hepatic dysfunction</td>
<td>Rise in baseline creatinine by 25%</td>
</tr>
<tr>
<td>Low serum sodium concentration</td>
<td>Serum sodium &lt; 130 mEq/dL</td>
</tr>
</tbody>
</table>
### 3.3.10.3 Data Collection and Analysis Methods

**A. Data Collection and Analysis**

Data will be collected on a CEC adjudication form. A Kaplan-Meier survival analysis will be performed for each treatment group, and the log-rank test will be used to compare the treatment groups.

**B. Determination of Patients/Data for Analysis**

This objective will be analyzed for the as treated population.

### 3.3.11 Secondary Objective #11 - Cardiovascular Deaths and Valve-Related Deaths

Cardiovascular deaths and valve-related deaths: the number of cardiovascular deaths and valve-related deaths at 30 days, 6 months, 12 months and annually through five years will be reported.

#### 3.3.11.1 Hypothesis and/or Parameters to Be Estimated

For each endpoint the following hypotheses will be tested:

\[ H_0: S(t)_{MCS\ TAVI} = S(t)_{SAVR} \text{ for all } t \]

\[ H_A: S(t)_{MCS\ TAVI} \neq S(t)_{SAVR} \text{ for at least one } t \]

In the above expressions \( S(t)_{MCS\ TAVI} \) and \( S(t)_{SAVR} \) denote the survival functions for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

For each endpoint, survival estimates for each treatment group will be provided at 30 days, 6 months, 12 months and annually through five years.

#### 3.3.11.2 Endpoint Definition

Cardiovascular death will be defined, according to the definition proposed by the Valve Academic Research Consortium (VARC) Consensus Report for Transcatheter Aortic Valve Implantation (TAVI); 2010-06-15, as any one of the following:

- Any death due to proximate cardiac cause (e.g. MI, cardiac tamponade, worsening heart failure)
- Unwitnessed death and death of unknown cause
- All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure
- Death caused by non-coronary vascular conditions such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease

Note: All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established. Specifically, any unexpected death even in subjects with coexisting potentially fatal non-cardiac disease (e.g., cancer, infection) should be classified as cardiac.

Valve-related deaths are defined as:

- Any death caused by prosthetic valve dysfunction, valve thrombosis, embolism, bleeding event, or implanted valve endocarditis;
• Death related to reintervention on the operated valve.

3.3.11.3 Data Collection and Analysis Methods

A. Data Collection and Analysis
Data will be collected on a CEC adjudication form. For each endpoint, a Kaplan-Meier survival analysis will be performed for each treatment group, and the log-rank test will be used to compare the treatment groups.

B. Determination of Patients/Data for Analysis
This objective will be analyzed for the as treated population.

3.3.12 Secondary Objective #12 – Strokes and TIAs

The number of subjects with strokes (of any severity) and TIAs at 30 days, 6 months, 12 months and annually through five years will be reported.

3.3.12.1 Hypothesis and/or Parameters to Be Estimated
For each endpoint, the following hypotheses will be tested:

\[ H_0: S(t)_{MCS\ TAVI} = S(t)_{SAVR} \text{ for all } t \]
\[ H_A: S(t)_{MCS\ TAVI} \neq S(t)_{SAVR} \text{ for at least one } t \]

In the above expressions, \( S(t)_{MCS\ TAVI} \) and \( S(t)_{SAVR} \) denote the event-free survival functions for the TAVI with the Medtronic CoreValve® System (MCS TAVI) and surgical aortic valve replacement (SAVR) treatment arms, respectively.

For each endpoint, event-free survival estimates for each treatment group will be provided at 30 days, 6 months, 12 months and annually through five years.

3.3.12.2 Endpoint Definition
Stroke and TIA will be defined based on the definition published in the European Heart Journal; January 6, 2011, titled "Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium".

<table>
<thead>
<tr>
<th>Stroke Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke</td>
</tr>
<tr>
<td>• Duration of a focal or global neurological deficit ≥ 24 hours; OR &lt; 24 hours, if therapeutic intervention(s) were performed (e.g. thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; OR the neurologic deficit results in death</td>
</tr>
<tr>
<td>• No other readily identifiable non-stroke cause for the clinical presentations (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences)*</td>
</tr>
<tr>
<td>• Confirmation of the diagnosis by at least one of the following:</td>
</tr>
<tr>
<td>o Neurology or neurosurgical specialist</td>
</tr>
<tr>
<td>o Neuroimaging procedure (MR or CT scan or cerebral angiography)</td>
</tr>
<tr>
<td>o Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)</td>
</tr>
</tbody>
</table>
### Stroke Definitions

- **Transient Ischemic Attack**
  - New focal neurologic deficit with rapid symptom resolution (usually 1-2 hours), always within 24 hours
  - Neuroimaging without tissue injury

- **Stroke**: (diagnosis as above, preferably with positive neuroimaging study)^
  - Minor (non-clinically important disability) - modified Rankin score < 2 at 30 and 90 days
  - Major (clinically important disability) - modified Rankin score ≥ 2 at 30 and 90 days

*Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies

+ Major and Minor stroke will be adjudicated and analyzed using the MRS at 90 days only.

#### 3.3.12.3 Data Collection and Analysis Methods

**A. Data Collection and Analysis**

Data will be collected on a CEC adjudication form. A separate analysis will be performed for each of the following:

- a composite of all strokes and TIAs
- major strokes only
- minor strokes only
- TIAs only

For each endpoint, a Kaplan-Meier survival analysis will be performed for each treatment group, and the log-rank test will be used to compare the treatment groups.

**B. Determination of Patients/Data for Analysis**

This objective will be analyzed for the as treated population.

#### 3.3.13 Secondary Objective #13 - Index Procedure-Related MAEs

Index procedure related MAEs: Index procedure-related MAE events will be summarized and event rates will be provided at 30 days.

**3.3.13.1 Hypothesis and/or Parameters to Be Estimated**

The endpoint is descriptive and no statistical hypothesis test will be performed. For each treatment group, the rate of index procedure-related MAE events will be summarized at 30 days.

**3.3.13.2 Endpoint Definition**

The numerator will be the number of procedure-related MAE events experienced by the end of the 30-day follow-up visit, and the denominator will be the number of subjects evaluated at the 30-day follow-up visit plus the number of subjects not evaluated but who experienced a procedure-related MAE event prior to the end of the follow-up visit window.

**3.3.13.3 Data Collection and Analysis Methods**

**A. Data Collection and Analysis**
Data regarding MAEs will be collected on a CEC adjudication form. For each treatment group, the event rate as described above will be calculated. Additionally, the percentage of subjects with a procedure-related MAE will be calculated in the same way, but allowing no more than one MAE per subject.

B. Determination of Patients/Data for Analysis
This objective will be analyzed for the as treated population with an index procedure. All subjects who are evaluated at the 30-day follow-up visit (or a later follow-up), or are not evaluated but have experienced a procedure-related MAE event prior to the end of the follow-up visit window will be included in the analysis.

3.3.14 Secondary Objective #14 - Length of Index Procedure Hospital Stay

Length of index procedure hospital stay

3.3.14.1 Hypothesis and/or Parameters to Be Estimated
The endpoint is descriptive and no statistical hypothesis test will be performed. The mean length of index procedure hospital stay will be estimated.

3.3.14.2 Endpoint Definition
For each subject, the length of index procedure hospital stay will be calculated as the number of calendar days spanning the admission date to the discharge date on the discharge case report form; i.e., it will be calculated as (discharge date - admission date).

3.3.14.3 Data Collection and Analysis Methods
A. Data Collection and Analysis
The admission date will be captured on the procedure form, and the discharge date will be captured on the discharge form. For each treatment group, the length of index procedure hospital stay will be summarized as with continuous data.

B. Determination of Patients/Data for Analysis
This objective will be analyzed for the as treated population with an index procedure.

3.3.15 Secondary Objective #15 - Device Success

Device success (only for Medtronic CoreValve® System (MCS TAVI) cohort)

3.3.15.1 Hypothesis and/or Parameters to Be Estimated
The endpoint is descriptive and no statistical hypothesis test will be performed. The rate of device success will be estimated.

3.3.15.2 Endpoint Definition
Device success is defined as follows:
- Successful vascular access, delivery and deployment of the device, and successful retrieval of the delivery system.
• Correct position of the device in the proper anatomical location (placement in the annulus with no impedance on device function).
• Intended performance of the prosthetic valve (aortic valve area > 1.2 cm² for 26, 29, and 31 mm valves, > 0.9 cm² for 23 mm valve (by echocardiography using the continuity equation) and mean aortic valve gradient < 20 mmHg or peak velocity < 3 m/sec, without moderate or severe prosthetic valve AR). Performance is assessed acutely in a resting state, either within 24-48 hours after the index procedure or before hospital discharge.
• Only one valve implanted in the proper anatomical location.

3.3.15.3 Data Collection and Analysis Methods

A. Data Collection and Analysis
   The components of device success will be determined by the site and recorded on the procedure case report form. The numerator will be the number of subjects whose index procedure resulted in device success, and the denominator will be the number of subjects with an index procedure and an evaluable device success.

B. Determination of Patients/Data for Analysis
   This objective will be analyzed for the MCS TAVI cohort only in the as treated population with an index procedure and an evaluable device success.

3.3.16 Secondary Objective #16 - Procedural Success

Procedural success (only for Medtronic CoreValve® System (MCS TAVI) cohort)

3.3.16.1 Hypothesis and/or Parameters to Be Estimated
   The endpoint is descriptive and no statistical hypothesis test will be performed. The rate of procedural success will be estimated.

3.3.16.2 Endpoint Definition
   Procedural success is defined as device success and absence of in-hospital MACCE.

3.3.16.3 Data Collection and Analysis Methods

A. Data Collection and Analysis
   Device success will be as determined in the previous objective. The components of MACCE will be recorded on a CEC adjudication form. In-hospital MACCE will include those events that have a date on or before the discharge date recorded on the discharge form. The numerator will be the number of subjects whose index procedure resulted in procedural success, and the denominator will be the number of subjects with an index procedure and an evaluable procedural success.

B. Determination of Patients/Data for Analysis
   This objective will be analyzed for the MCS TAVI cohort only in the as treated population with an index procedure and an evaluable procedural success.
3.3.17 Secondary Objective #17 - Prosthetic Valve Dysfunction

Evidence of prosthetic valve dysfunction at 30 days, 6 months, 12 months and annually thereafter up to 5 years. (only for Medtronic CoreValve® System (MCS TAVI) cohort)

3.3.17.1 Hypothesis and/or Parameters to Be Estimated

The endpoint is descriptive and no statistical hypothesis test will be performed. Prosthetic valve dysfunction-free survival estimates will be provided at 30 days, 6 months, 12 months and annually through five years.

3.3.17.2 Endpoint Definition

Prosthetic valve dysfunction is a component of MAE and will be adjudicated by the CEC.

3.3.17.3 Data Collection and Analysis Methods

A. Data Collection and Analysis

Data will be collected on a CEC adjudication form. A Kaplan-Meier survival analysis will be performed.

B. Determination of Patients/Data for Analysis

This objective will be analyzed for the MCS TAVI cohort only in the implanted population.

3.3.18 Hierarchical Testing

Provided the 12-month non-inferiority mortality primary objective is met with a significant p-value, to keep the overall (familywise) Type I error rate at 0.05, a hierarchical test procedure will be applied to the 30-day (or hospital discharge, whichever is longer) MACCE powered secondary hypothesis and five of the secondary objective hypothesis tests. The goal of this hierarchical procedure is to make statistically valid claims of significance in the device labeling.

In this hierarchical test procedure, each objective is examined in the pre-specified order.

An objective is statistically significant only if that objective and all prior objectives have a significant p-value. The hierarchical testing order will be:

1. Change in transvalvular mean gradient from baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #9. The one-sided two-sample t-test will be used to test non-inferiority at a level of 0.05 the hypotheses:

   \[ H_0: \mu_{MCS\ TAVI} \leq \mu_{SAVR} -15 \]

   \[ H_A: \mu_{MCS\ TAVI} > \mu_{SAVR} -15 \]

   In the above expression \( \mu_{MCS\ TAVI} \) and \( \mu_{SAVR} \) denote the mean improvements in mean gradient from baseline to 12 months measured in mmHg.

2. Change in effective orifice area baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #9. The one-sided two-sample t-test will be used to test non-inferiority at a level 0.05 the hypotheses:

   \[ H_0: \mu_{MCS\ TAVI} \leq \mu_{SAVR} -0.375 \]
HA: $\mu_{\text{MCS TAVI}} > \mu_{\text{SAVR}} -0.375$

In the above expression $\mu_{\text{MCS TAVI}}$ and $\mu_{\text{SAVR}}$ denote the mean improvements in effective orifice area from baseline to 12 months measured in cm$^2$.

3. Change in NYHA classification from baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #5. The one-sided two-sample t-test will be used to test non-inferiority at a level 0.05 the hypotheses:

H$_0$: $\mu_{\text{MCS TAVI}} \leq \mu_{\text{SAVR}} -0.375$

H$_A$: $\mu_{\text{MCS TAVI}} > \mu_{\text{SAVR}} -0.375$

In the above expression $\mu_{\text{MCS TAVI}}$ and $\mu_{\text{SAVR}}$ denote the mean number of classification improvements in NYHA from baseline to 12 months. For subjects with NYHA categories at both baseline and 12 month visit, the NYHA classification improvements will be calculated as $\text{NYHA}_{12\text{month}} - \text{NYHA}_{\text{baseline}}$.

4. Change in Kansas City Cardiomyopathy Questionnaire (KCCQ) score from baseline to 12 months: MCS TAVI vs. SAVR from secondary objective #8. The one-sided two-sample t-test will be used to test non-inferiority at a level 0.05 the hypotheses:

H$_0$: $\mu_{\text{MCS TAVI}} \leq \mu_{\text{SAVR}} -5$

H$_A$: $\mu_{\text{MCS TAVI}} > \mu_{\text{SAVR}} -5$

In the above expression $\mu_{\text{MCS TAVI}}$ and $\mu_{\text{SAVR}}$ denote the mean improvements in the KCCQ score from baseline to 12 months.

5. Powered Secondary Hypothesis: TAVI with the Medtronic CoreValve® System is superior to SAVR in binary rate of MACCE at 30 days or hospital discharge, whichever is longer. This one-sided test will be carried out at the 0.025 level using the pooled z-test without correction for continuity to test the hypotheses:

H$_0$: $\pi_{\text{MCS TAVI}} = \pi_{\text{SAVR}}$

H$_A$: $\pi_{\text{MCS TAVI}} < \pi_{\text{SAVR}}$

In the above expression $\pi_{\text{MCS TAVI}}$ and $\pi_{\text{SAVR}}$ denote the binary rate of MACCE at 30 days or hospital discharge.

If there are missing data for this endpoint, Kaplan-Meier rates at 30 days will be used to calculate the test statistic.

6. Change in SF-12 Physical Summary Scale from baseline to 30 days: TAVI vs. SAVR from secondary objective #8. The two-sided two-sample t-test will be used to test at a level 0.05 the hypotheses:

H$_0$: $\mu_{\text{MCS TAVI}} = \mu_{\text{SAVR}}$

H$_A$: $\mu_{\text{MCS TAVI}} \neq \mu_{\text{SAVR}}$

In the above expression $\mu_{\text{MCS TAVI}}$ and $\mu_{\text{SAVR}}$ denote the mean improvements in the SF-12 Physical Summary Scale from baseline to 30 days.

This hierarchical test procedure will be performed for the as treated population, except that #1 and #2 tests will be performed for the implanted population.

As the trial confirmation is not dependent on the secondary endpoints, multiplicity adjustments will not be made in the other analyses of the secondary endpoints. Summary data from other secondary objectives, such as device success and procedural success from secondary objectives #15 and #16, respectively, may be
provided in the device labeling. However, no claims of statistical significance or other statistical inference will be made.

### 3.4 Additional Analyses

All the following additional analyses will be analyzed for the as treated population.

#### 3.4.1 Poolability Analysis

##### 3.4.1.1 Pooling of Small Sites

Sites contributing less than 3 treatment or 3 control subjects to the as treated analysis set will be considered “small sites” and ordered by the date of first enrollment in the as treated analysis set. Starting with the first “small site”, a pseudo-site will be created by adding subjects from successive “small sites”. If the number of subjects reaches or exceeds the size of the median enrollment of the “large sites”, then a second pseudo-site will be created. Additional pseudo-sites, if needed, would be created in the same manner. If the total enrollment number in the last pseudo-site is less than half of the median enrollment of the “large sites”, the last pseudo-site will be combined to the second last pseudo-site.

##### 3.4.1.2 Primary Endpoint by Site

The interaction between site or pseudo-site and treatment on the probability of death at 12 months will be compared using logistic regression if there are no missing data for the primary endpoint. In case there are missing data, Cox proportional hazard model will be used. If the resulting p-value for the interaction is \( < 0.15 \), further exploratory analysis will attempt to identify covariates that may explain treatment effect differences among the sites, beginning in the next section. Otherwise, the data will be considered to be poolable across study sites.

##### 3.4.1.3 Univariate Covariate Analysis

The following baseline characteristics might be examined individually as potential predictors of death at 12 months using the logistic model or Cox proportional hazard model as appropriate. Additional baseline characteristics might be added later.

1. Gender
2. Age
3. Baseline NYHA
4. STS score
5. Logistic EuroSCORE
6. Baseline LVEF
7. Hypertension
8. Diabetes
9. Coronary artery disease
10. Prior stroke
11. Prior MI
12. Prior PCI
13. Chronic Lung Disease/COPD
14. Does not live independently
15. BMI<21kg/m
16. Unplanned weight loss
17. Falls in past 6 months
18. KATZ>=3
19. Charlson co-morbidity score of 5
20. Immunosuppressive therapy

3.4.1.4 **Multivariate Analysis**

Covariates with p-value ≤ 0.20 from the previous section will be included along with site in the model. If this multivariate analysis does not result in a significant (p-value ≤ 0.15) site by treatment interaction after adjustment for these baseline factors, then outcome results will again be considered poolable across study sites. If site by treatment interaction is still significant (p-value ≤ 0.15) after adjustment for these factors, results will be presented by site and the clinical significance of these differences will be assessed.

3.4.2 **Gender Analysis**

The primary endpoint and secondary endpoints #1-3 (MACCE, individual MACCE components, and MAE) will be examined for differences in outcome between genders. Additionally, tests for these outcomes will be performed to evaluate potential interactions between treatment and gender. These analyses will be performed on the as treated analysis set.

For the primary endpoint, the proportions of subjects who died at 12 months will be compared using logistic regression with gender, treatment and the treatment by gender interaction in the model. In case there are missing data for the primary endpoint, the Cox proportional hazard model will be applied instead.

MACCE-free survival estimates for each gender and treatment combination will be provided at 30 days, 6 months, 12 months and annually through five years. A Cox proportional hazards model will be fitted with predictors of gender, treatment, and treatment by gender interaction.

This analysis will be repeated for each individual component of MACCE and for MAE.

3.4.3 **Access Site Analysis (Ilio-femoral and Non-ilio-femoral)**

The primary endpoint and secondary endpoints #1-3 (MACCE, individual MACCE components, and MAE) will be examined for differences in outcome between access sites (ilio-femoral or non-ilio-femoral). Additionally, tests for these outcomes will be performed to evaluate potential interactions between treatment and access site. These analyses will be performed on the as treated analysis set. Per the as treated analysis set definition, TAVI subjects will be analyzed according to the access site on the procedure form, while SAVR subjects will be analyzed according to the stratified access site.

For the primary endpoint, the proportions of subjects who died at 12 months will be compared using logistic regression with access site, treatment and the treatment by access site interaction in the model. In case there are missing data for the primary endpoint, the Cox proportional hazard model will be applied instead.
MACCE-free survival estimates for each access site and treatment combination will be provided at 30 days, 6 months, 12 months and annually through five years. A Cox proportional hazards model will be fitted with predictors of access site, treatment, and treatment by access site interaction.

This analysis will be repeated for each individual component of MACCE and for MAE.

4 REVISION PROCESS

The study statistician will be responsible for the execution of this statistical analysis plan, including any revisions and obtaining of appropriate approvals.

5 DISTRIBUTION

The study statistician will be responsible for execution of this statistical analysis plan and distribution of revisions to the appropriate clinical staff.

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Addendum to Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients) Statistical Analysis Plan Version 3

Required Approvers:

Sharla Chenoweth, Date 21 Jan 2014
Sr. Prin. Statistician

Victoria Hench, Date January 21, 2014
Sr. Statistics Manager

Gloria Toledo, Date 21 Jan 2014
Clinical Research Manager

Tim Patterson, Date 21 Jun 2014
Principal Clinical Quality Specialist
Addendum to Medtronic CoreValve® U.S. Pivotal Trial (High Risk Surgical Patients) Statistical Analysis Plan Version 3

The purpose of this addendum is to document the analysis for enrolled Pivotal HR subjects with 23 mm valves in the Medtronic Pivotal HR PMA clinical study report (CSR).

Based on the results from Medtronic CoreValve® clinical trials (Extreme Risk, Japan, etc.) and FDA 2010 Draft Heart Valve Guidance, Medtronic decided to include those enrolled HR subjects with 23 mm valves in all the analyses in Pivotal HR PMA CSR.

This decision won’t change the analysis timing for the HR PMA, which was pre-specified in the HR SAP V3. The HR PMA report will be generated after all enrolled subjects that were candidates for 26, 29, and 31 mm valves have completed their 12-month follow-up visit in-window or later (or, if early, have been followed for at least 365 days via a subsequent follow-up form), have died, or have exited from the study.

Here is the rationale supporting Medtronic’s decision on the enrolled HR subjects with 23 mm valves:

- FDA 2010 Draft Heart Valve Guidance:
  - The 15 subjects implanted per size per position criterion is based on statistical calculations for echocardiographic effective orifice area (EOA) data. These calculations show that in order to assure a sufficiently narrow 95% confidence interval, the minimum number of subjects implanted with each valve size is 15.

- The HR and ER sub-studies occurred in parallel at the same clinical centers and using the same echo core lab;

- The minimum number of subjects for the valve size requirement was met in the ER sub-study allowing for adequate assessment of the hemodynamic performance of the 23 mm valve;

- The hemodynamic performance of all valve sizes was compared between high risk and extreme risk subjects. The results did not show major difference between the risk stratification. Therefore, the data collected in the ER sub-study effectively validated the performance of the valve for both submissions.
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<th>Reason for change</th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>3.2.1.5 Missing Data</td>
<td>However, if outcome data are missing, Kaplan-Meier rates at 12 months will replace the binomial proportions in the calculation of the Farrington and Manning test statistic.</td>
<td>However, if outcome data are missing, Kaplan-Meier rates at 12 months will replace the binomial proportions in the calculation of the test statistic. The test statistic will then be calculated as: [ z = \frac{(1 - \hat{S}_1) - (1 - \hat{S}_2) - \delta_0}{\sqrt{\hat{V}(\hat{S}_1) + \hat{V}(\hat{S}_2)}} ] where ( \hat{S}_1 ) and ( \hat{S}_2 ) are the Kaplan-Meier survival estimates and ( \hat{V}(\hat{S}_1) ) and ( \hat{V}(\hat{S}_2) ) are the Greenwood variance estimates. Similarly, the 90% large sample confidence interval will then be calculated as: [ \left(\frac{(1 - \hat{S}_1) - (1 - \hat{S}_2)}{1 - \hat{S}<em>1} \right) \pm z</em>{0.05} \sqrt{\hat{V}(\hat{S}_1) + \hat{V}(\hat{S}_2)} ]</td>
<td>Clarification regarding how the primary endpoint will be calculated if there are any subjects whose status is unknown at 365 days post-procedure.</td>
</tr>
<tr>
<td>2.</td>
<td>3.2.2.5 Missing Data</td>
<td>However, if outcome data are missing, Kaplan-Meier rates at 30 days will replace the binomial proportions in the calculations above. For subjects whose discharge date was after 30 days, any events prior to discharge will be treated as occurring on day 30.</td>
<td>However, if outcome data are missing, Kaplan-Meier rates at 30 days will be used to calculate the test statistic. For subjects whose discharge date was after 30 days, any events prior to discharge will be treated as occurring on day 30. The test statistic is then calculated as: [ z = \frac{(1 - \hat{S}<em>{MCSTAY}) - (1 - \hat{S}</em>{SAVR})}{\sqrt{\hat{V}(\hat{S}<em>{MCSTAY}) + \hat{V}(\hat{S}</em>{SAVR})}} ] where ( \hat{S}<em>{MCSTAY} ) and ( \hat{S}</em>{SAVR} ) are the Kaplan-Meier survival (event-free) estimates and ( \hat{V}(\hat{S}<em>{MCSTAY}) ) and ( \hat{V}(\hat{S}</em>{SAVR}) ) are the Greenwood variance estimates.</td>
<td>Clarification regarding how the powered secondary endpoint will be calculated if there are any subjects whose status is unknown at 30 days post-procedure.</td>
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<td>3.</td>
<td>3.1.3.1 Report Timing and Cutoff Dates</td>
<td>The PMA report will be generated after all enrolled subjects with have completed their 12-month follow-up visit in-window or later (or, if early, have been followed for at least 365 days via a subsequent follow-up form), have died, or have exited from the study.</td>
<td>The PMA report will be generated after all enrolled subjects with <strong>26, 29, and 31 mm valves</strong> have completed their 12-month follow-up visit in-window or later (or, if early, have been followed for at least 365 days via a subsequent follow-up form), have died, or have exited from the study.</td>
<td>Clarify that analysis will be performed when all candidates for 26, 29, or 31 mm CoreValve have been followed for 1 year.</td>
</tr>
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<td>4.</td>
<td>3.1.3.6 Kaplan-Meier Analyses</td>
<td>At each time point with data, the product-limit estimate of the event-free rate, the number of subjects at risk, the number of subjects with events, and the Peto standard error of the estimate will be presented. For subjects without an event, the date of censoring will be the latest date of all follow-up visits, assessments, and events (including death).</td>
<td>At each time point with data, the product-limit estimate of the event-free rate, the number of subjects at risk, the number of subjects with events, the Peto standard error of the estimate, <strong>and the loglog transformed 95% confidence interval using the Peto standard error</strong> will be presented. For subjects without an event, the date of censoring will be the latest date of all follow-up visits, assessments, and events (including <strong>death in those objectives where death is not the endpoint</strong>).</td>
<td>Clarify that the loglog transformed 95% confidence interval using the Peto standard error will be presented.</td>
</tr>
<tr>
<td>5.</td>
<td>3.1.3.7 Roll-in Cases</td>
<td>NA</td>
<td>The first three successfully enrolled patients at each implanting site inclusive of both the High Risk Surgical and Extreme Risk patient populations will be considered “roll-in” subjects and will be automatically assigned to receive the Medtronic CoreValve® System. A maximum of three roll-in subjects is allowed per site. A successful roll-in subject is defined as the subject leaving the procedure room with one CoreValve® device in the correct position and not requiring emergency surgery. A site must have three successful roll-in subjects before they can be evaluated by the Training and Education Committee to move into the pivotal phase.</td>
<td>Clarification of the definition of a Roll-in subject</td>
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### Revised version (changes are bolded)

An enrolled subject must sign informed consent, meet all of the inclusion and none of the exclusion criteria (with the exception of a percutaneous coronary or peripheral intervention and evidence of an acute myocardial infarction which must not occur within 30 days prior to the index procedure), have been assessed by the Screening Committee as being an appropriate candidate for enrollment, and have been assigned a patient identification number in the interactive voice/web randomization service (IXRS). Subjects will be considered enrolled into the trial at the time of randomization.

Randomization with an assignment to the treatment arm or control arm (MCS TAVI or SAVR) will be executed in a 1:1 ratio. Stratified randomization by investigational site and by intended access site (iliofemoral or non-ilio-femoral) will be used to ensure subjects will be allocated to each comparison group proportionately.

### Reason for change

Clarification of the definition of a Enrolled subject

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<tr>
<td>6.</td>
<td>3.1.3.8 Enrolled Subject</td>
<td>NA</td>
<td>An enrolled subject must sign informed consent, meet all of the inclusion and none of the exclusion criteria (with the exception of a percutaneous coronary or peripheral intervention and evidence of an acute myocardial infarction which must not occur within 30 days prior to the index procedure), have been assessed by the Screening Committee as being an appropriate candidate for enrollment, and have been assigned a patient identification number in the interactive voice/web randomization service (IXRS). Subjects will be considered enrolled into the trial at the time of randomization. Randomization with an assignment to the treatment arm or control arm (MCS TAVI or SAVR) will be executed in a 1:1 ratio. Stratified randomization by investigational site and by intended access site (iliofemoral or non-ilio-femoral) will be used to ensure subjects will be allocated to each comparison group proportionately.</td>
<td>Clarification of the definition of a Enrolled subject</td>
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<td>7.</td>
<td>3.1.3.9.2 As Treated (AT)</td>
<td>The as treated population consists of all randomized patients 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 (TAVI or SAVR). TAVI subjects will be analyzed according to the access site on the procedure form, while SAVR subjects will be analyzed according to the stratified access site. This population excludes roll-in patients. Time zero begins at the date of attempted procedure.</td>
<td>The as treated population consists of all ITT subjects patients 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. In the database, TAVI attempted procedure is defined by a non-missing MCS TAVI procedure date, and SAVR attempted procedure is defined by a non-missing SAVR procedure date. Subjects will be analyzed according to their first attempted procedure (TAVI or SAVR). In addition, TAVI subjects will be analyzed according to the access site (ilio-femoral or non-ilio-femoral) on the first attempted procedure form, while SAVR subjects will be analyzed according to the stratified access site (ilio-femoral or non-ilio-femoral). This population excludes roll-in subjects. Time zero begins at the date of the first attempted procedure.</td>
<td>Clarification of the definition of an as-treated subject</td>
</tr>
<tr>
<td>8.</td>
<td>3.1.3.10 23mm Valve</td>
<td>NA</td>
<td>The 23mm valve was not available until late in the study; therefore, if approximately 20 23mm CoreValve® implants have not occurred at the time of approximately 790 randomized subjects, the 23mm subjects will not be included in the primary analysis. Up to 40 additional subjects will be randomized with about 20 23mm CoreValve® implants. When 1 year data are available for the 23mm valve, the primary and secondary endpoint data will be summarized with descriptive statistics. If appropriate, the 23mm valve subjects will be pooled with the original 790 subjects in the primary analysis dataset and the primary and secondary endpoints will be recalculated. The primary endpoint and the secondary endpoints that include hypothesis testing will be analyzed without adjustments for multiple testing. The hierarchical test procedure will be performed the same way as described in section 3.3.18.</td>
<td>The 23mm CoreValve was added to the protocol after 1 year of enrollment had been completed, therefore enrollment for 23mm valve will continue after the 790 subjects were enrolled.</td>
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<td>9.</td>
<td>3.1.3.11 Definition of Index Procedure</td>
<td>NA</td>
<td>TAVI Index Procedure: the first TAVI procedure that the Medtronic CoreValve® System delivery catheter is introduced. SAVR Index Procedure: the first attempted SAVR procedure.</td>
<td>Define index procedure</td>
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<td>10.</td>
<td>3.3.7.2 Endpoint Definition</td>
<td>For each subject, the proportion of post-enrollment days alive out of hospital against total days alive will be calculated at 12 months. The numerator will be the number of days alive out of hospital, and the denominator will be the number of post-enrollment days alive as of the last follow-up date (the latest date of all follow-up visits, assessments, and events (including death)) or 365, whichever is smaller. All hospitalizations will be included in this analysis, including hospitalization for device implant.</td>
<td>For each subject, the proportion of post-procedure days alive out of hospital against total days alive will be calculated at 12 months. The numerator will be the number of days alive out of hospital, and the denominator will be the number of post-procedure days alive as of the last follow-up date (the latest date of all follow-up visits, assessments, and events (including death)) or 365, whichever is smaller. All hospitalizations will be included in this analysis, including hospitalization for device implant.</td>
<td>Clarify that ratio days alive is based on number of days from procedure not number of days from enrollment</td>
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<td>11.</td>
<td>3.3.9.2 Endpoint Definition</td>
<td>All echocardiograms will be analyzed by an echo core lab which will determine the values for these endpoints. Transvalvular mean gradient will be measured in mmHg. Effective orifice area will be measured in cm². Degree of aortic valve regurgitation (transvalvular and paravalvular) will be described as mild, moderate, or severe.</td>
<td>All echocardiograms will be analyzed by an echo core lab which will determine the values for these endpoints. Transvalvular mean gradient will be measured in mmHg. Effective orifice area will be measured in cm². Degree of aortic valve regurgitation (transvalvular and paravalvular) will be described as none, trace, mild, moderate, or severe.</td>
<td>Clarification of formulas used for mean gradient, EOA, and aortic regurgitation</td>
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Transvalvular mean gradient is the measure of Mean Gradient across Aortic Valve (MGV) by CW Doppler. Effective orifice area (EOA) will be derived by the formula: EOA = LVOT Long Axis diameter² × 0.785 × (VTI₄₅) / VTI₃₂. Where: LVOT Long Axis diameter is the measure of LVOT long-axis diameter mid-systole in mm, VTI₄₅ is the Velocity time integral of LVOT velocity by PW in cm, and VTI₃₂ is the Velocity time integral across Aortic valve by CW Doppler in cm.
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<td>12</td>
<td>3.3.10</td>
<td>Secondary Objective #10 - Aortic Valve Disease-Related Hospitalizations</td>
<td>Aortic valve disease related hospitalizations: the number of subjects re-hospitalized after the initial index procedure will be compared at 30 days, 6 months, 12 months and annually through five years.</td>
<td>Clarify the definition of aortic valve related hospitalizations.</td>
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<td>Aortic valve disease related hospitalizations: the number of subjects re-hospitalized after the first attempted procedure will be reported at 30 days, 6 months, 12 months and annually through five years. The aortic valve disease related hospitalization-free survival functions will be compared between the two groups.</td>
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<td>13</td>
<td>3.3.12.2</td>
<td>Endpoint Definition</td>
<td>Stroke and TIA will be defined according to the definition proposed by the Valve Academic Research Consortium. (VARC) Consensus Report for Transcatheter Aortic Valve Implantation (TAVI); 2010-06-15</td>
<td>Updated the stroke definition to correspond to VARC-I and the protocol</td>
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<td>Stroke: (diagnosis as above, preferably with positive neuroimaging study)+</td>
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<td>Minor (non-clinically important disability) - modified Rankin score &lt; 2 at 7 days or prior to discharge AND NIHSS score &lt; 3 (above baseline) at 7 days or prior to discharge and at 30-day assessment</td>
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<tr>
<td></td>
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<td></td>
<td>O Major (clinically important disability) - modified Rankin score ≥ 2 at 7 days or prior to discharge AND NIHSS score ≥ 3 (above baseline) at 7 days or prior to discharge and at 30-day assessment</td>
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<td>Stroke: (diagnosis as above, preferably with positive neuroimaging study)+</td>
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<td>Minor (non-clinically important disability) - modified Rankin score &lt; 2 at 30 and 90 days</td>
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<td></td>
<td>Major (clinically important disability) - modified Rankin score ≥ 2 at 30 and 90 days</td>
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<td>*Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies + Major and Minor stroke will be adjudicated and analyzed using the MRS at 90 days only.</td>
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<td>14</td>
<td>3.3.13.3</td>
<td>Data Collection and Analysis Methods</td>
<td>This objective will be analyzed for the as treated population.</td>
<td>Clarification procedure analysis is based on the as-treated cohort that also had index procedure.</td>
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<td>This objective will be analyzed for the as treated population with an index procedure. All subjects who are evaluated at the 30-day follow-up visit (or a later follow-up), or are not evaluated but have experienced a procedure-related MAE event prior to the end of the follow-up visit window will be included in the analysis.</td>
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<tr>
<td>15</td>
<td>3.3.14.3</td>
<td>Data Collection and Analysis Methods</td>
<td>This objective will be analyzed for the as treated population.</td>
<td>Clarification procedure analysis is based on the as-treated cohort that also had index procedure.</td>
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<td>This objective will be analyzed for the as treated population with an index procedure.</td>
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<td>16</td>
<td>3.3.15.2 Endpoint</td>
<td>Intended performance of the prosthetic valve (aortic valve area &gt; 1.2 cm² (by echocardiography using the continuity equation) and mean aortic valve gradient &lt; 20 mmHg or peak velocity &lt; 3 m/sec, without moderate or severe prosthetic valve AR). Performance is assessed acutely in a resting state, either within 24-48 hours after the index procedure or before hospital discharge.</td>
<td>Intended performance of the prosthetic valve (aortic valve area &gt; 1.2 cm² for 26, 29, and 31 mm valves, &gt; 0.9 cm² for 23 mm valve (by echocardiography using the continuity equation) and mean aortic valve gradient &lt; 20 mmHg or peak velocity &lt; 3 m/sec, without moderate or severe prosthetic valve AR). Performance is assessed acutely in a resting state, either within 24-48 hours after the index procedure or before hospital discharge.</td>
<td>Add the device success requirements for the 23mm CoreValve</td>
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<td>17</td>
<td>3.3.15.3 Data</td>
<td>The components of device success will be determined by the site and recorded on the procedure case report form. The numerator will be the number of subjects whose procedure resulted in device success, and the denominator will be the number of subjects with a procedure attempt. This objective will be analyzed for the MCS TAVI cohort only in the as treated population.</td>
<td>The components of device success will be determined by the site and recorded on the procedure case report form. The numerator will be the number of subjects whose index procedure resulted in device success, and the denominator will be the number of subjects with an index procedure and an evaluable device success. This objective will be analyzed for the MCS TAVI cohort only in the as treated population with an index procedure and an evaluable device success.</td>
<td>Clarified analysis is for subjects with an index procedure.</td>
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<tr>
<td>18</td>
<td>3.3.16 Secondary</td>
<td>Device success will be as determined in the previous objective. The components of MACCE will be recorded on a CEC adjudication form. In-hospital MACCE will include those events that have a date on or before the discharge date recorded on the discharge form. The numerator will be the number of subjects whose procedure resulted in procedural success, and the denominator will be the number of subjects with a procedure attempt. This objective will be analyzed for the MCS TAVI cohort only in the as treated population.</td>
<td>Device success will be as determined in the previous objective. The components of MACCE will be recorded on a CEC adjudication form. In-hospital MACCE will include those events that have a date on or before the discharge date recorded on the discharge form. The numerator will be the number of subjects whose index procedure resulted in procedural success, and the denominator will be the number of subjects with an index procedure and an evaluable procedural success. This objective will be analyzed for the MCS TAVI cohort only in the as treated population with an index procedure and an evaluable procedural success.</td>
<td>Clarified analysis is for subjects with an index procedure.</td>
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| 19.| 3.4.1.3 Univariate Covariate Analysis | The following baseline characteristics will be examined individually as potential predictors of death at 12 months using logistic regression:  
1. Gender  
2. Age  
3. Logistic EuroSCORE  
6. Baseline LVEF  
7. Hypertension  
8. Diabetes  
9. Coronary artery disease  
10. Prior stroke  
11. Prior MI  
12. Prior PCI | The following baseline characteristics might be examined individually as potential predictors of death at 12 months using the logistic **model** or Cox proportional hazard model as appropriate.  
Additional baseline characteristics might be added later:  
1. Gender  
2. Age  
3. Baseline NYHA  
4. **STS** score  
5. Logistic EuroSCORE  
6. Baseline LVEF  
7. Hypertension  
8. Diabetes  
9. Coronary artery disease  
10. Prior stroke  
11. Prior MI  
12. Prior PCI  
13. Chronic Lung Disease/COPD  
14. Does not live independently  
15. BMI<21kg/m  
16. Unplanned weight loss  
17. Falls in past 6 months  
18. KATZ>3  
19. Charlson co-morbidity score of 5  
20. Immunosuppressive therapy | Provide comprehensive list of baseline characteristics that will be evaluated as potential predictors. |
| 20.| Addendum for 23mm CoreValve | NA | All candidates for the 23mm CoreValve are included in all analysis. | Document that the analysis for the 23mm CoreValve will not be following Version 3 of the SAP with the justification. |