# Medtronic CoreValve® U.S. Pivotal Trial

CLINICAL STUDY PLAN SYNOPSIS

**IDE No.** G100012
**CIP No.** MCV-US-2009-01 (High Risk Surgical)
**CIP No.** MCV-US-2009-01 (Extreme Risk)

## Sponsor

Medtronic CardioVascular
Clinical Research
Mailstop: MVS82
Mounds View South
8200 Coral Sea St NE
Mounds View, MN 55112

*For more information refer to www.clinicaltrials.gov and www.AorticStenosisTrial.com*

CAUTION – Investigational device. Limited by United States law to investigational use.

| | High Risk Surgical Patients | Extreme Risk Patients |
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| **Purpose** | The purpose of the trial 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. | The purpose of the trial is to evaluate the safety and efficacy of the Medtronic CoreValve® System in the treatment of symptomatic severe aortic stenosis in subjects necessitating aortic valve replacement, with predicted operative mortality or serious, irreversible morbidity risk of ≥ 50% at 30 days. |
| **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). | This is a prospective, non-randomized clinical trial. All enrolled patients will be assigned to transcatheter aortic valve implant (TAVI) with the Medtronic CoreValve® System (MCS). |
| **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. | The primary objective of the trial is to demonstrate the safety and effectiveness of the Medtronic CoreValve® System (MCS), as measured by a composite of all-cause death or major stroke at 12 months, in subjects necessitating aortic valve replacement, with predicted operative mortality or serious, irreversible morbidity risk of ≥ 50% at 30 days. |
| **Primary Endpoint(s)** | All-cause mortality at 12 months. | All-cause death or major stroke at 12 months. |
| **Secondary Endpoints** | 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:<br>• all-cause death<br>• myocardial infarction (MI)<br>• all stroke, and<br>• reintervention (defined as any cardiac surgery or percutaneous reintervention catheter procedure that repairs, otherwise alters or adjusts, or replaces a previously implanted valve)<br>2. The occurrence of individual MACCE components at 30 days, 6 months, 12 months and annually thereafter up to 5 years.<br>3. Major Adverse Events (MAE) at 30 days, 6 months,12 months and annually thereafter up to 5 years.<br>4. Conduction disturbance requiring permanent pacemaker implantation at 30 days, 6 months, 12 months and annually thereafter up to 5 years.<br>5. Change in NYHA class from baseline at 30 days, 6 months, 12 months and annually thereafter up to 5 years.<br>6. Change in distance walked during 6-minute walk test (6MWT) from baseline to 30 days and baseline to 12 months. | |

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| **Secondary Endpoints (continued)** | 7. Ratio of days alive out of hospital versus total days alive assessed at 12 months follow-up.<br>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:<br>• Kansas City Cardiomyopathy<br>• Questionnaire (KCCQ)<br>• SF-12, and<br>• EuroQoL<br>9. Echocardiographic assessment of prosthetic valve performance at discharge, 30 days, 6 months, 12 months and annually thereafter up to 5 years usingthe following measures:<br>• transvalvular mean gradient<br>• effective orifice area<br>• degree of prosthetic aortic valve regurgitation (transvalvular and paravalvular)<br>10. Aortic valve disease hospitalization at 30 days, 6 months, 12 months and annually thereafter up to 5 years.<br>11. Cardiovascular deaths and valve-related deaths at 30 days, 6 months, 12 months and annually thereafter up to 5 years.<br>12. Strokes (of any severity) and TIAs at 30 days, 6 months, 12 months and annually thereafter up to 5 years.<br>13. Index procedure related MAEs.<br>14. Length of index procedure hospital stay. | |
| | The following secondary endpoints will be assessed for the MCS TAVI cohort subjects only:<br>15. Device success defined as follows:<br>• Successful vascular access, delivery and deployment of the device, and successful retrieval of the delivery system<br>• correct position of the device in the proper anatomical location (placement in the annulus with no impedance on device function),<br>• Intended performance of the prosthetic valve[1] (aortic valve area > 1.2 $cm^2$ (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)<br>• Only one valve implanted in the proper anatomical location<br>[1]assessed acutely in a resting state, either within 24-48 hours after the index procedure or before hospital discharge<br>16. Procedural success, defined as device success and absence of in-hospital MACCE.<br>17. Evidence of prosthetic valve dysfunction at 30 days, 6 months, 12 months and annually thereafter up to 5 years. | 15. Device success defined as follows:<br>• Successful vascular access, delivery and deployment of the device, and successful retrieval of the delivery system<br>• correct position of the device in the proper anatomical location (placement in the annulus with no impedance on device function),<br>• Intended performance of the prosthetic valve[1] (aortic valve area > 1.2 $cm^2$ (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)<br>• Only one valve implanted in the proper anatomical location<br>[1]assessed acutely in a resting state, either within 24-48 hours after the index procedure or before hospital discharge<br>16. Procedural success, defined as device success and absence of in-hospital MACCE.<br>17. Evidence of prosthetic valve dysfunction at 30 days, 6 months, 12 months and annually thereafter up to 5 years. |

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| **Trial Sites** | The trial will be conducted at up to 40 sites in the United States. | |
| **Sample Size** | 790 subjects*<br>• 395 MCS TAVI<br>• 395 SAVR<br>**790 inclusive of ilio-femoral and non-iliofemoral subjects* | 487 ilio-femoral subjects. (MCS TAVI)<br>Up to 100 non-ilio-femoral subjects. (MCS TAVI) |
| **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. | Subjects with symptomatic severe aortic stenosis (AS), necessitating aortic valve replacement, with 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. | 1. Subject must have co-morbidities such that one cardiologist and two cardiac surgeons agree that medical factors preclude operation, based on a conclusion that the probability of death or serious morbidity exceeds the probability of meaningful improvement. Specifically, the predicted operative risk of death or serious, irreversible morbidity is ≥ 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 $cm^2$ (or aortic valve area index ≤ 0.5$cm^2/m^2$) by resting echocardiogram.<br>3. Subject is symptomatic from his/her aortic valve stenosis, as demonstrated by NYHA Functional Class II or greater.<br>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.<br>5. The subject and the treating physician agree that the subject will return for all required postprocedure follow-up visits. | |

## Exclusion Criteria — Clinical

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| 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. | 2. Any percutaneous coronary or peripheral interventional procedure performed within 30 days prior to the MCS TAVI procedure. |
| 3. Blood dyscrasias as defined: leukopenia (WBC <1000 $mm^3$), thrombocytopenia (platelet count <50,000 cells/$mm^3$), history of bleeding diathesis or coagulopathy, or hypercoagulable states.<br>4. Untreated clinically significant coronary artery disease requiring revascularization.<br>5. Cardiogenic shock manifested by low cardiac output, vasopressor dependence, or mechanical hemodynamic support.<br>6. Need for emergency surgery or any reason.<br>7. Severe ventricular dysfunction with left ventricular ejection fraction (LVEF) <20% as measured by resting echocardiogram.<br>8. Recent (within 6 months) cerebrovascular accident (CVA) or transient ischemic attack (TIA).<br>9. End-stage renal disease requiring chronic dialysis or creatinine clearance <20 cc/min.<br>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:<br>• aspirin<br>• heparin (HIT/HITTS)<br>• nitinol (titanium or nickel)<br>• ticlopidine and clopidogrel<br>• contrast media | 11. A known hypersensitivity or contraindication to any of the following which cannot be adequately pre-medicated:<br>• aspirin<br>• heparin (HIT/HITTS) and bivalirudin<br>• nitinol (titanium or nickel)<br>• ticlopidine and clopidogrel<br>• contrast media |
| 12. Ongoing sepsis, including active endocarditis.<br>13. Subject refuses a blood transfusion.<br>14. Life expectancy <12 months due to associated non-cardiac, co-morbid conditions.<br>15. Other medical, social, or psychological conditions that in the opinion of an Investigator precludes the subject from appropriate consent.<br>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).<br>17. Currently participating in an investigational drug or another device trial.<br>18. Symptomatic carotid or vertebral artery disease. | |
| 19. Subject has been offered surgical aortic valve replacement but declined. | |

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| **Exclusion Criteria — Anatomical** | 20. Native aortic annulus size < 20 mm or > 27 mm per the baseline diagnostic imaging.<br>21. Pre-existing prosthetic heart valve in any position.<br>22. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation (3-4+)).<br>23. Severe mitral (3-4+) or severe tricuspid regurgitation.<br>24. Moderate to severe mitral stenosis.<br>25. Hypertrophic obstructive cardiomyopathy.<br>26. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.<br>27. Severe basal septal hypertrophy with an outflow gradient.<br>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).<br>29. Ascending aorta diameter > 43 mm unless the aortic annulus is 20-23 mm in which case the ascending aorta diameter > 40 mm.<br>30. Congenital bicuspid or unicuspid valve verified by echocardiography. | 19. Native aortic annulus size < 20 mm or > 27 mm per the baseline diagnostic imaging.<br>20. Pre-existing prosthetic heart valve in any position.<br>21. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation (3-4+)).<br>22. Severe mitral (3-4+) or severe tricuspid regurgitation.<br>23. Moderate to severe mitral stenosis.<br>24. Hypertrophic obstructive cardiomyopathy.<br>25. Echocardiographic evidence of intracardiac mass, thrombus or vegetation.<br>26. Severe basal septal hypertrophy with an outflow gradient.<br>27. 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).<br>28. Ascending aorta diameter > 43 mm unless the aortic annulus is 20-23 mm in which case the ascending aorta diameter > 40 mm.<br>29. Congenital bicuspid or unicuspid valve verified by echocardiography. |
| **Exclusion Criteria — Vascular** | 31. Transarterial access not able to accommodate an 18Fr sheath. | 30. Transarterial access not able to accommodate an 18Fr sheath. |
| **Follow-up Schedule** | 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. | |

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Medtronic

**www.medtronic.com**

**World Headquarters**
Medtronic, Inc.
710 Medtronic Parkway
Minneapolis, MN 55432-5604
USA
Tel: (763) 514-4000
Fax: (763) 514-4879

Medtronic USA, Inc.
Toll-free: 1 (800) 328-2518
(24-hour technical support for physicians and medical professionals)